ADDRESSING ANTIMICROBIAL RESISTANCE

A Report of the Aspen Health Strategy Group

Foreword by Kathleen Sebelius and Tommy G. Thompson

Edited by Alan R. Weil and Rachel Dolan

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The mission of the **Aspen Health Strategy Group** is to promote improvements in policy and practice by providing leadership on important and complex health issues. The group is comprised of 23 senior leaders across influential sectors including health, business, media, and technology, and is part of the Health, Medicine and Society Program at the Aspen Institute. Co-chaired by Kathleen Sebelius and Tommy G. Thompson, both former governors and former US Secretaries of Health and Human Services, the Aspen Health Strategy Group tackles one health issue annually through a year-long, in-depth study. This book is a collection of papers on the group's fourth subject: antimicrobial resistance (AMR). The papers provide an overview of AMR and address topics related to human demand, animal- and environmental-health factors, and drug pipeline challenges, and includes a final consensus report based on the group's work.

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It is my pleasure to introduce the fourth annual report of the Aspen Health Strategy Group (AHSG), which focuses on antimicrobial resistance and offers a package of "Big Ideas" for confronting this growing threat. This publication emerges from an intensive and thought-provoking research and discussion process that allowed experts and leaders across disciplines to reach consensus on opportunities to protect one of the great lifesaving advances of modern medicine: antibiotics.

The AHSG tradition began in 2015. Every year since, members have explored a single pressing health topic in depth. Its three prior reports -- on end-of-life care, the opioid epidemic, and chronic diseases -- have made significant contributions to the national health policy and practice conversation. I am confident the insights and recommendations here will do the same. The need is urgent: antimicrobial resistance results in some 35,000 deaths every year in the U.S. alone.

The AHSG is one of the signature projects of the Health, Medicine and Society Program, the Aspen Institute's domestic health initiative. Kathleen Sebelius and Tommy G. Thompson, who have both served as US Secretaries of Health and Human Services and as state governors, are the co-chairs. Joining them around the table are 23 leaders of major corporations, health systems, professional associations, and foundations, as well as innovative thinkers in academic settings. Five former HHS secretaries are ex officio members of the group.

We thank all of them deeply for the commitment they have made to the AHSG, and to the rigorous, nonpartisan tradition of the Aspen Institute. Their respect for the power of evidence to inform sound decision-making, and their contribution to turning ideas into action, point the way to a healthier future for all.

All the best,

Dan Porterfield
President and CEO
The Aspen Institute

Contents

Foreword

Kathleen Sebelius
AHSG Co-Chair

Tommy G. Thompson
AHSG Co-Chair

This is our fourth year as co-chairs of the Aspen Health Strategy Group, and we are proud of the group's success in promoting improvements in policy and practice by providing leadership on important and complex health issues.

This year we selected antimicrobial resistance as our topic. Antimicrobial resistance (AMR) is a serious threat to public health. There is no system in place to track antibiotic resistance globally. According to estimates from the Centers for Disease Control and Prevention, 35,000 Americans with resistant infections die each year. Antimicrobial resistance puts every single person at risk. It threatens the effective treatment of cancer, tuberculosis, HIV, malaria and other serious health conditions. In June 2019, the Aspen Health Strategy Group met for three days and took on hard questions related to this critically important issue.

We are pleased to present the final report from our work, based upon our group's rich discussion. In the tradition of the thought-provoking conversations and dialogue on how to address critical societal issues -- the hallmark of the Aspen Institute -- the report includes five Big Ideas to address antimicrobial resistance. In our discussions, we relied heavily upon four background papers, prepared by subject matter experts. Those papers are included in this compendium as well.

Each background paper was written by a subject matter expert. Ramanan Laxminarayan, provided the background on antimicrobial resistance in the US as well as global context. Helen Boucher summarized current efforts at antimicrobial

stewardship and highlighted the need for increased effectiveness. Lonnie King described a One Health approach, which acknowledges the interconnected nature of humans, animals and the environment. Muhammad Zaman and Katie Clifford explained the failures in the market for antibiotics and promising efforts to address the need for future drugs. We were fortunate to have four of the authors present for the discussion in Aspen, in addition to Mollyann Brodie from the Henry J. Kaiser Family Foundation, who provided again this year, valuable data regarding public opinion on antibiotic resistance. We also heard from Charles (Chuck) Daley, MD, Chief, Division of Mycobacterial and Respiratory Infections, at Jewish National Health, and Taiwo Oduala, a patient of Dr. Daley's, who shared the reality of antibiotic resistance with us.

Before our meeting we issued a broad call to the public for their ideas for how to address antimicrobial resistance. We benefited from all of the ideas, but we particularly want to acknowledge the following individuals and organizations: Marcia Angell (Harvard Medical School); Mary Faith Harty; Abhilasha Karkey (Oxford University); Martha Kendrick (Stop Sepsis, Save Lives Coalition); Jeffrey Klausner (University of California, Los Angeles); Shawn Walker (Dark Horse Advisors); and Hua Wang (The Ohio State University).

We are also grateful to the three organizations that provided funding to make this work possible. We received generous financial support from the Robert Wood Johnson Foundation, the Laurie M. Tisch Illumination Fund and HCA Healthcare. The perspectives expressed in this report are those of the authors and do not necessarily reflect the views of any of these organizations. On behalf of the Aspen Health Strategy Group and all those associated with its activities in 2019, we thank them for their support and continued commitment to this effort.

AHSG Co-Chairs

Dedication

This report is dedicated to Bernard J. Tyson,
an AHSG member since its inception. As head of Kaiser Permanente,
Bernard understood that quality and access to health care are compatible with
cost-efficiency and that healing does not end at the hospital's walls.

We will miss his wisdom, insight, and kindness.

Bernard J. Tyson, AHSG Member, 2016 - 2019

ASPEN HEALTH STRATEGY GROUP REPORT

Five Big Ideas on Addressing Antimicrobial Resistance

Part 1

"The federal government should designate a single body to oversee the nation's response to the growing AMR threat and to serve as a point of accountability for progress in implementing that response."

– THE ASPEN HEALTH STRATEGY GROUP

Five Big Ideas on Addressing Antimicrobial Resistance

Introduction

Antibiotics have transformed the practice of medicine and save millions of lives each year. Yet, all we have come to expect from antibiotics is at risk. Antimicrobial resistance (AMR) -- the phenomenon whereby antibiotics lose their effectiveness due to mutations in the pathogens they are designed to treat -- is on the rise.[1] Resistance is a natural phenomenon, but it is much accelerated due to overuse and misuse of antibiotics in human, animal, and agricultural applications. In 2019, the Centers for Disease Control and Prevention (CDC) estimated that 35,000 deaths and at least 2.8 million illnesses each year in the US are due to antibiotic resistance. The United States, and the world, need creative approaches and big ideas to reverse this ominous trend.

The Aspen Health Strategy Group selected antimicrobial resistance as its topic for discussion in 2019, its fourth year. This group of leaders in and outside health care spent three days considering the topic with the assistance of subject matter experts who prepared four background papers to frame the conversation. The group emerged with five big ideas to tackle antimicrobial resistance.

1 Antibiotic resistance occurs when an antibiotic is no longer able to kill the targeted bacteria. Antimicrobial resistance describes a broader phenomenon that includes viruses, fungi, and other microbes. Despite their scientific differences, the issues involved in these two phenomena are identical and this report uses the terms interchangeably.

The Aspen Health Strategy Group's goal is to promote improvements in policy and practice by providing leadership on important and complex health issues. Co-chaired by Kathleen Sebelius and Tommy Thompson, both former governors and former US Secretaries of Health and Human Services, the group is composed of 23 senior leaders across sectors including health, business, media, and technology. More information about the Aspen Health Strategy Group can be found on the Aspen Institute website (aspeninstitute/aspen-health-strategy-group.org). This report captures the deliberations of the group, but no specific proposal or statement in the report should be considered to represent the opinion of any individual member of the group.

Background

"Antibiotics are pivotal in treating and preventing common infections in modern medicine, but their overuse and misuse have contributed to an alarming increase in antibiotic resistance worldwide," writes Ramanan Laxminarayan in "Antimicrobial Resistance: An Overview."

As noted above, the CDC has estimated that 35,000 deaths each year in the United States are attributable to AMR. The true burden of antimicrobial resistance is difficult to measure because illness and exposure to resistant microbes are correlated. Indeed, AMR is never listed as a patient's cause of death, as resistance is a characteristic of the microbe. Inability to kill a strain of bacteria causes a cascade of illnesses and, potentially, organ failure, which is the proximate cause of death. Tracing the illness back to a resistant microbe is an imperfect process and is likely undercounted.

Resistance is a natural phenomenon that arises from microbial mutations. But the rate of mutation is dramatically accelerated when the microbe is repeatedly exposed to antibiotics. Antimicrobial exposure is a primary driver of resistance through appropriate use as well as sub-therapeutic levels of antibiotics and poor quality antibiotics. Per capita use of antibiotics in the US is among the highest in the world. Globally, sales of antibiotics for human use increased 65% between 2000 and 2015, with low-and middle-income countries (LMICs) comprising four of the six countries with the highest consumption rate (Klein et al., 2018).

Laxminarayan concludes by noting: "After decades of neglect, AMR has captured the attention and concern of the public health community and global leaders." We have moved from an era of niche reports arising from scientific bodies to high-level discussion of the issue in global settings such as the World Economic Forum and the World Health Assembly. The United States must lead on the AMR agenda while supporting global efforts as well.

In "Reducing Human Demand for Antimicrobials," Helen Boucher describes "two categories of interventions designed to reduce inappropriate use of antibiotics: infection prevention and antibiotic stewardship. Preventing infections eliminates the need to use antibiotics at all, while stewardship assures that antibiotics are used optimally," she writes.

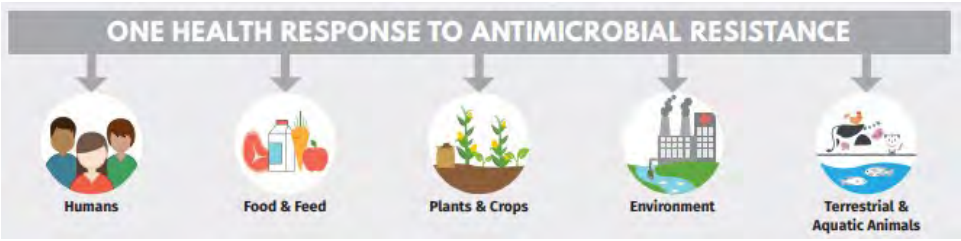
Successful infection prevention and antibiotic stewardship programs require leadership, resources, and proper staffing and training. Implementation depends upon behavior change by clinicians and patients. Standardized methods of measurement must be in place to monitor progress and guide resources to where they are most needed.

The initial focus of stewardship has been in inpatient hospital settings, but improved measurement and capacity in ambulatory and post-acute settings is also vital. Boucher notes that effective practices related to prevention and stewardship have been identified for a number of health care settings, but implementation has lagged. Innovative payment methods will be needed to properly target funds to the institutions that need to take action.

"We live in a world that is rapidly changing, complex and progressively interconnected. The convergence of people, animals and their products in our environment has resulted in an unprecedented 21st century mixing bowl. This convergence has created a new dynamic, one in which the health of the human, animal and environmental domains are threatened simultaneously and interdependently," writes Lonnie King in "Addressing Antimicrobial Resistance Through a One Health Approach."

The Food and Drug Administration (FDA) estimates that more than 60,000 tons of antibiotics were used globally in animal agriculture in 2010, and one-quarter of that was used in the US. As the global population continues to increase, particularly in low- and middle-income countries, demand on food production will continue to grow. Antibiotics have been used for growth promotion and gains in efficiency, yet most of these antibiotics are excreted as waste and then may be transmitted through the water supply.

According to King, to adequately address AMR in such an interconnected environment, a "One Health" approach is necessary. "One Health can be defined as the collaborative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment." A successful application of this approach requires new thinking, data sharing and cooperation across domains.



"The need for new antibiotics, in addition to global partnership on One Health and reduced antibiotics in hospitals, homes and farms, is critical. The innovation pipeline, at the moment, does not look promising," write Muhammad Zaman and Katie Clifford in "The Dry Pipeline: Overcoming Challenges in Antibiotics Discovery and Availability." The cost of developing antibiotics has increased, yet sales of new antibiotics will be limited since new drugs must be used sparingly to preserve their efficacy, creating a classic case of market failure. There are also technical challenges to discovering new and effective antimicrobials, as methods for discovery used in the 20th century have been exhausted. Many new drugs fail at the stage of clinical trials because they do not perform better than existing drugs.

New and creative ideas will be needed to overcome the prevailing market headwinds. Possible market approaches include public-private partnerships to increase investment in discovery, bring drugs to market, and ensure their ongoing availability to patients. Technical approaches include pursuing alternatives to antibiotics, such as bacteriophages and vaccines. Zaman and Clifford note that global partnerships will be critical to this effort; despite the US leading on drug innovation and discovery, antimicrobial resistance is a global issue and other countries can provide lessons for innovation.

Framing the Issue

Five themes emerged in the group's discussions that helped guide the development of this year's big ideas. The themes are:

- **Antimicrobial resistance is a staggering global problem**

  Antimicrobial resistance puts every single person at risk of disease or death. Exposure to a resistant microbe can occur at any place and at any time. Those who are exposed are subject to increasingly burdensome treatment, often with significant side effects and lasting health consequences. While many people can be cured of resistant infections after receiving extensive treatment, infants, the elderly, and those who are medically fragile or immu-

no-compromised may be unable to tolerate additional treatment or may not respond to that treatment. Even people without any previous health limitations may succumb to resistant infections.

Official estimates of the number of people sickened or killed by resistant microbes may provide a false sense of calm. At an estimated 35,000 deaths per year in the United States, AMR does not even approach the top ten causes of death. The experts we heard from consider this estimate to be conservative and the risk of future acceleration of death rates to be significant.

Growing rates of AMR threaten our ability to benefit from clinical advances made over the past decades. Risk of infection is always a consideration when contemplating a medical intervention such as surgery or chemotherapy. The growing risk of a resistant infection may fundamentally alter the calculus. Substantially increasing the risks associated with common procedures such as Cesarean section deliveries and joint replacement could ultimately undermine the benefits of these and other commonplace surgeries.

Increased global trade and travel and the interconnectedness of global economies and societies means that AMR is a problem on a global scale. While tens of thousands die each year in the US due to antibiotic resistance, this

number is much higher in other countries. According to the United Nations, antimicrobial resistance causes more than 700,000 deaths per year globally, (IACG, 2019) much of which is due to drug-resistant tuberculosis.

Each country acting to reduce its antibiotic consumption individually is necessary but not sufficient to address the problem. Resistant strains can travel globally among humans as well as between humans and their environment. Developing countries continue to face food pressures leading to increased use of antibiotics in animals to meet demand. Lack of adequate sanitation practices and wastewater treatment in low- and middle-income countries leads to increased risk of infection and contamination. AMR is a global phenomenon that requires a global response.

- **There has been significant but uneven and insufficient progress in stewardship**

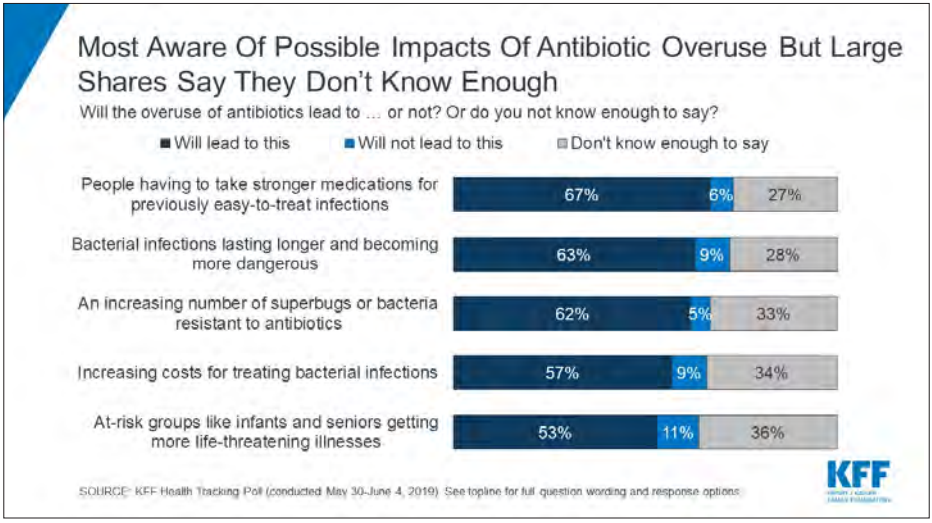
  Elevating the issue of antimicrobial resistance and stewardship has led to progress, but much more must be done. The most significant progress in the US has occurred in two arenas: animal production and inpatient hospitals. In the wake of new guidance from the Food and Drug Administration, in combination with shifting demand from consumers, the FDA reports a 43% reduction in the use of medically important antibiotics (those that also are used in human medicine) in animal production. New federal standards, guidance from accreditation organizations, and financial incentives associated with infection control have combined to improve practices in hospitals. Indeed, the CDC attributes the 18% decline in AMR deaths between 2013 and 2019 largely to hospital-based infection prevention efforts (CDC, 2019a). In addition, long-awaited conditions of participation requirements regarding antibiotic stewardship in hospitals that receive funds from Medicare and/or Medicaid (essentially all hospitals) have recently been promulgated by the Centers for Medicare & Medicaid Services (CMS).

  Yet, there are significant gaps in our response to AMR. The focus on inpatient hospital settings does not extend to the outpatient setting — whether hospital, clinic, or doctor's office. For example, more than 270 million antibiotic prescriptions were written in outpatient settings in 2016 (CDC, 2018). The CDC estimates that 30% of antibiotics prescribed in doctors' offices and emergency departments are unnecessary (CDC, 2019a). Nursing homes and rehabilitation hospitals are similarly behind in their attention to infection control and antimicrobial stewardship. Dentists routinely prescribe antibiotic prophylaxis despite guidelines recommending limited use.

Even as we reduce antibiotic use for food production, use remains high and there is significant overuse when it comes to companion animals. A very small fraction of antibiotics are used in food crops and trees, but growing concerns are arising regarding anti-fungal use, which can create untreatable conditions in the same manner as occurs with resistant bacteria.

- **Awareness and understanding of the problem and solutions are low**

  Awareness is a necessary precondition to action, yet awareness is low among clinicians, patients, and the general public. Even when awareness is present, there is reluctance to change practices that would reduce the potential for harm. Likely the highest-profile practice change has been the emphasis on handwashing, but compliance with this basic practice is modest (CDC, 2019b). Doctors continue to prescribe broad spectrum antibiotics to treat certain diseases despite guidelines to the contrary.



While the major cause of the increase in AMR is unnecessary use of antibiotics, the reasons for unnecessary use are myriad and not fully understood. In the inpatient setting, many antibiotics could be avoided through better infection control techniques. In the outpatient setting, better, faster, and inexpensive diagnostics may be required to alter the default behavior of prescribing broad-spectrum antibiotics when a patient presents with symptoms that are only moderately likely to arise from a bacterial infection. Patients who move from the hospital to a rehabilitation center or from the hospital to home are

particularly susceptible to unnecessary, or unnecessarily long, courses of antibiotic treatment.

The general public has little understanding of the issue (Wellcome Trust, 2019). More than half of Americans incorrectly believe viral infections can be cured by antibiotics or they are unsure if they can be (Muñana et al., 2019). One-third of Americans don't feel they know enough to say that antibiotic overuse can lead to increased drug resistance (Muñana et al., 2019).

- **The antibiotic discovery trajectory is too slow to meet future needs**

  As resistance grows, the need for new antibiotics grows as well. Yet, the discovery pipeline is far too limited to meet anticipated future needs. There are technical and economic reasons for this. Traditional methods for finding antibiotics have essentially been exhausted. New and creative approaches are needed, and those approaches depend on human and financial capital that is in short supply.

  The economic model for drug development -- publicly-funded basic science followed by private investment that brings drugs to market at prices designed to recover that investment -- does not work for antibiotics. Existing antibiotics are cheap, and stewardship demands that new antibiotics be used sparingly. Some antibiotics are narrowly targeted to certain strains of microbes. Most antibiotics are taken for a period of days or week. In this context there is no viable business model for major investment to bring new antibiotics to market.

  Similar issues arise relative to preventive therapies and diagnostics. Preventive therapies eliminate the infection before it occurs, thereby avoiding not only the need for an antibiotic, but also reducing the incremental risk of a drug resistant mutation that arises from every antibiotic use. Diagnostics enable more precise identification of the microbe, which, in turn, enables use of a narrower-spectrum antibiotic, or realization that an antibiotic is not needed at all. Better diagnostics preserve broad-spectrum antibiotics for when they are needed and reduce the likelihood of drug resistant mutations. Yet, so long as antibiotics are inexpensive, the economics of prevention and diagnosis are such that there is little reason for any company to invest in their development and testing.

- **Domestic leadership is deficient**

  At times in the past when the country has faced complex risks, decision-making authority has been vested in an individual or select group of senior officials whose work is coordinated. Antibiotic stewardship has been elevated at the federal level in the US with the creation of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), whose role is now embodied in federal law. This is a tremendous step forward and provides a multidisciplinary focal point for discussing and recommending an appropriate response.

  While PACCARB has created an action plan, there is no locus of accountability for adoption, implementation, and measurement of progress against that plan. The group has no formal authority. It can (and does) make policy recommendations, but adoption of those recommendations is dependent upon the individual priorities and actions of myriad public and private actors. PACCARB is also missing a critical element: its action plan does not incorporate the US Environmental Protection Agency (EPA), and it has no representation from the EPA.

Five Big Ideas to Address Antimicrobial Resistance

1. Health systems must be accountable for antibiotic stewardship

The growing crisis of AMR cries out for leadership from the health sector. Individual clinicians and health institutions must embrace the core tenets of stewardship -- infection prevention and parsimonious use of existing antibiotics -- as guiding practices. Like other quality initiatives in health care, responsibility for antibiotic stewardship must emerge from its infectious diseases silo and become woven into the fabric of the overall enterprise and be embraced by health system leadership.

It is time to move from a modest number of antibiotic-related HEDIS (Healthcare Effectiveness Data and Information Set) measures associated with specific conditions to ambitious goals related to all aspects of stewardship with data collected across all settings and reported publicly. Similarly, all payers and regulatory bodies must incorporate the full spectrum of stewardship activities into their requirements for providers and their payment systems.

Building from the progress we have made and the lessons we have learned from the inpatient setting, next steps include:

- Professional societies and regulators should develop metrics applicable to all settings where antibiotic stewardship is warranted, including outpatient, rehabilitative, long-term care, telehealth, dental, and companion veterinary settings. These metrics must include all elements of effective stewardship: infection control, accurate diagnosis, appropriate prescribing, and timely cessation. Based on the limited effects of handwashing mandates, regulators and accreditors should view the adoption of change management strategies as a necessary component of any mandates for behavior change.

- Professional societies should develop best practices and standard care pathways that embody antibiotic stewardship for the clinical presentation of diseases. In conjunction with these practices, the societies should develop training modules that demonstrate how to change workflows to facilitate adherence to these practices. Training on these matters should be built into the medical, nursing, pharmacy, veterinary and dental curricula. Accountability for adhering to these practices should extend beyond the infectious disease specialists typically responsible for infection control.

- Measured rates of infection control, diagnosis, and treatment should be used for quality improvement purposes within institutions and reported publicly for use by patients and payers to drive demand for improvement.

- Effective antibiotic stewardship should be an element of accreditation, conditions of participation, and other regulatory aspects of the health care enterprise as they apply to all provider types. A commitment to stewardship must be demonstrated throughout an organization's management structure.

- Payers, including CMS, should develop financial incentives that support antibiotic stewardship. One element of those incentives could be realigning payment polices so that the use of diagnostics, and de-escalating use of antibiotics when bacterial culture results are negative, are financially viable relative to immediate prescribing of broad-spectrum antibiotics. Another element could be direct payment to cover the staff and systems costs associated with antibiotic stewardship efforts, rather than expecting them to compete for resources within an institution. Rewards for effective antibiotic stewardship should be built into existing and new value-based payment initiatives.

2. The nation must adopt a unified One Health response

The federal government should designate a single body to oversee the nation's response to the growing AMR threat and to serve as a point of accountability for progress in implementing that response.

The federal government should consolidate review of policy regarding the use of antibiotics in humans, animals and agriculture into a single locus within the Department of Health and Human Services. Policies across different agencies and divisions, including the National Institutes of Health (NIH), FDA, CMS, US Department of Agriculture (USDA), and EPA, should be coordinated regarding surveillance, antibiotic approval, antibiotic use, reporting, and investment. Policy regarding antibiotics should be developed using a One Health perspective that considers the interrelationship of human, animal and environmental health.

The current PACCARB approach has similarities to the Federal Interagency Task Force on Antimicrobial Resistance which developed and released an action plan in 2001. With representation from a broad range of federal agencies (including EPA, Department of Defense (DOD), and US Agency for International Development (USAID)), the Task Force's Public Health Action Plan to Combat Antimicrobial Resistance focused on surveillance, prevention and control, research, and product development. Now, as then, the challenge was resources and a sustained commitment to implementing the entirety of the plan (Knobler et al., 2003).

The US government's coordinated approach should interface with existing global efforts targeted at AMR.

3. Redesign antibiotic development

Business as usual simply perpetuates the market failures associated with antibiotic development described above. Novel approaches are required to build a strong antibiotic pipeline through mechanisms that change the financial incentives associated with antibiotic development and accelerate the scientific learning necessary to develop new drugs.

Borrowing from lessons related to vaccine development and orphan drugs, new approaches are needed that include the following elements:

- NIH should increase its investment in the basic science behind antibiotic development and related therapies such as antifungals.
- Various models to reduce the financial risk associated with bringing new antibiotics to market should be explored. These include:
    - > Direct public investment in later stages of drug development with subsequent sharing of profits received from antibiotic sales.
    - > Awarding of financial "prizes" for successful development of drugs that can substitute for reliance upon high levels of sales.

  - > Pooling of funds to be deployed rapidly for the most promising science, with CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) as an existing model.
  - > Reducing the financial risk associated with regulatory approval for new antibiotics.
  - > Applying artificial intelligence and other "big data" approaches to accelerate drug discovery.
- Similar models should be deployed for drugs that prevent infections and diagnostics that enable more appropriate antibiotic prescribing. These clinical advances face some of the same financial challenges as antimicrobial development. Funding and funding models for diagnostics should align with funding for new antibiotics so they can be deployed in tandem to maximum effect.

4. Invest in research

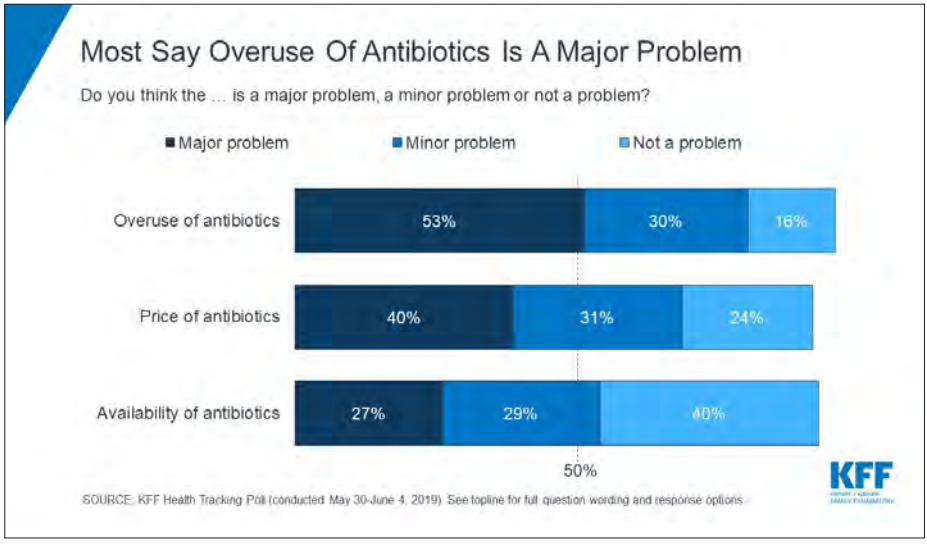
The federal government should make targeted investments in research to improve our understanding of AMR and how to respond. In particular:

- Additional research is required on the scope and expression of antimicrobial resistance. We need better estimates of its prevalence, its consequences, and a better understanding of how and where people are exposed to resistant microbes.
- Basic information regarding antibiotic use across industries and within the health sector is lacking. For a challenge of this scale, transparency of data is essential for research and discovery.
- Research should be expanded regarding the environmental presence and persistence of antimicrobials. This includes better understanding of the effects of antibiotic use in animals and appropriate dosing for animals.
- Research is needed on rapid diagnostics that are used at the point of care in order to reduce over-prescribing for the sole reason that the identity of the microbe is unknown.
- Research is needed in system improvement, design, and engineering to maximize the adoption of infection prevention and infection control practices in all health care settings.

5. Engage the public

Clinicians and public health leaders should engage the public in efforts to reduce consumer demand for antibiotics. Engagement needs to occur at a number of levels:

- Clinicians, during training and on an ongoing basis, need information regarding AMR so they can advocate effectively for appropriate patient care and engage their patients in that care.
- Clinicians, at the time of care, need tools to explain circumstances where antibiotics are and are not warranted and that there are risks associated with inappropriate antibiotic use.
- All health care institutions engaged in patient care that involves antibiotics need internal curricula for their staff and patient education resources that clinical staff are expected to use when interacting with patients.
- Patients who have experienced the effects of having a resistant infection need support in sharing their stories with clinicians, patients, and the population as a whole, to motivate behavior change in this area.
- In all of these efforts, the focus must be on the risks posed by the resistant pathogen, not the person who carries the pathogen. This will minimize the likelihood of stigma associated with resistant infection, which would be harmful to patients and efforts to improve care.



Moving Forward

Antimicrobial resistance is not currently receiving the attention it deserves relative to the threat that it poses. The Aspen Health Strategy Group, with its multi-sector membership, has developed these ideas to address the emerging threat of antimicrobial resistance. We hope they will serve as catalysts for changes in policy and practice.

We will take our call for a multi-sector response to those we mention in this report. With our focus on health care, we will share this report with officials in the US Department of Health and Human Services, which houses the Centers for Medicare & Medicaid Services, the National Institutes of Health, the Centers for Disease Control and Prevention, the Food and Drug Administration, and other agencies. We will also reach out to other sectors, particularly agriculture and environmental, both of which have a significant role to play in responding to this crisis.

The Aspen Health Strategy Group members have also committed to examining steps we can take within our own institutions and organizations. We look forward to working with all who share our goal of responding to the growing burden of antimicrobial resistance.

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BACKGROUND PAPERS

Antimicrobial Resistance: An Overview

Ramanan Laxminarayan, Ph.D., M.P.H.

Reducing Human Demand for Antimicrobials

Helen W. Boucher, M.D., F.A.C.P., F.D.S.A.

Part 2

Addressing Antimicrobial Resistance Through a One Health Approach

Lonnie King, D.V.M., M.S., M.P.A., D.A.C.V.P.M.

The Dry Pipeline: Overcoming Challenges in Antibiotics Discovery and Availability

Muhammad H. Zaman, Ph.D. and Katie Clifford, M.P.H., M.B.A.

Carbapenem-resistant *Enterobacteriaceae* (CRE)

"Much of what we consider modern medicine, whether the ability to ensure that premature babies survive, or women get timely Cesarean sections, or the elderly are able to undergo transplants and joint replacements, depends on effective antibiotics…. The loss of an important enabler of modern medicine could lead to many patients not reaping the benefits of medical advances made over the last century."

– RAMANAN LAXMINARAYAN, PH.D.

Antimicrobial Resistance: An Overview

Ramanan Laxminarayan, Ph.D., M.P.H.

Introduction

The introduction of antibiotics, along with public health improvements from sanitation, hygiene, and safe drinking water, has been associated with a decline in infectious disease-related mortality in the United States during the 20th century (Armstrong et al., 1999; Jayachandran et al., 2010). Clinical studies have shown that antibiotics reduce mortality by 10% for skin infections and as much as 75% for bacterial endocarditis (Spellberg et al., 2011). Antibiotics have been pivotal in treating and preventing common infections in modern medicine, but their overuse and misuse have contributed to an alarming increase in antibiotic resistance worldwide. With every use of any antibiotic, whether appropriate or not, we eliminate bacteria that are susceptible to the antibiotic leaving behind only bacteria that are resistant to the antibiotic. Over time, more and more infections are caused by these resistant bacteria. With declining choice of antibiotics, we have entered a "post-antibiotic" era where many infections are not treatable with any available antibiotic (Carlet et al., 2012; WHO, 2014).

Antibiotic resistance is the classic evergreen problem. The first *in vitro* study of resistance to penicillin was published in 1940 by Ernst Chain and colleagues, two years before the first patient was even treated with penicillin. In the decades that followed, experts and the media continued to warn about an impending crisis of resistance but were largely ignored by the public and policymakers who seemed convinced that, despite much smoke, there was no fire. All that changed when resistance became clinically relevant. In the mid-1990s, methicillin-resistant *Staphylococcus*

aureus (MRSA), a pathogen that had not been encountered outside health care settings, became common in patients who had not been hospitalized. New antibiotics have been developed to treat resistant organisms, but the pharmaceutical industry has been unable to keep up with the pace at which resistance is developing. New strains of enterobacteriaceae that are resistant to carbapenem, a drug of last resort in these instances, cause infections that are not treatable with any available antibiotic.

Although resistance rates increased sharply in the United States between 2000 and 2010, they seem to have plateaued in the case of some bacterial pathogens, including MRSA. However, resistance is rising for other bacterial pathogens, including carbapenem-resistant *enterobacteriaceae* (CRE). In 2012, 4.6% of acute-care hospitals reported at least one CRE health care associated infection (short-stay hospitals, 3.9%; long-term acute-care hospitals, 17.8%). The proportion of that was CRE increased from 1.2% in 2001 to 4.2% in 2011 (CDC, 2013). Although these increases seem modest, given the lack of therapeutic options to treat *enterobacteriaceae* infections (with the exception of a highly toxic drug, colistin) this report prompted the director of the Centers for Disease Control and Prevention (CDC), Dr. Tom Frieden, to warn of "nightmare bacteria" that would seriously cripple our ability to deal with bacterial infections in health care settings. Similar data from other countries have prompted global leaders including President Barack Obama, Prime Minister David Cameron, and Chancellor Angela Merkel to start talking about the problem.

This period of increased resistance has coincided with a drought in new antimicrobials. By the early 2000s, as existing drugs were failing, there were no new compounds to take their place. With one exception, the only antimicrobial introductions in the 2000s were variations of existing drugs. Meanwhile, aging populations and increased frequency of procedures have created a situation where resistance is now firmly established across health care institutions in the United States and around the world.

The Consequences of Anti-Microbial Resistance (AMR)

Antibiotic-resistant infections are associated with increased morbidity, mortality, and higher costs of treatment (Cosgrove, 2006; Geissler et al., 2003; Roberts et al., 2009; Shorr, 2009) (see Table 1 for estimated ranges derived from multiple studies). Estimates of the disease burden attributable to antibiotic resistant infections (Cosgrove et al., 2003; Shorr, 2009) and of the economic burden of antibiotic resistance (Cohen et al., 2010) vary widely (Smith and Coast, 2013).

Table 1: Excess Costs Due to Infections with Resistant Organisms Versus Infections with Susceptible Organisms

Resistant Organism	Control	Range of Excess Cost
Methicillin-resistant *S. aureus*	Methicillin-susceptible *S. aureus*	$695–$29,030
Vancomycin-resistant *Enterococcus*	Vancomycin-susceptible *Enterococcus*	$16,711–$60,988
Resistant *P. aeruginosa*	Susceptible *P. aeruginosa*	$627–$45,256
Resistant *A. baumannii*	Susceptible *A. baumannii*	$5,336–$126,856
Multiple organisms	Susceptible	$9,372–$18,990
ESBL *Enterobacteriaceae*	Non-ESBL *Enterobacteriaceae*	$3,658-$4,892

Source: Gandra et al., 2014

In the United States, an estimated 23,000 deaths each year are caused by AMR, but a new report expected to be released by the CDC is likely to show a much greater burden of resistance. A widely cited report by The Review on Antimicrobial Resistance projects over 10 million global deaths from AMR each year, exceeding those from cancer (The Review on Antimicrobial Resistance, 2016). But these numbers are flawed in multiple respects. First, most of these projected deaths come from resistant malaria and TB infections under the assumption the world will do absolutely nothing as drugs fail. The estimate also assumes no progress in research and development on vaccines and in development of new drugs. These unrealistic assumptions make the projections meaningless to serious AMR experts, but they have played an advocacy role by focusing the attention of politicians on the problem.

The burden associated with resistance is difficult to measure. Estimating the morbidity and mortality-related costs of drug resistance is problematic because of the bi-directional causality between disease severity and resistance (Howard et al., 2001). Sicker patients are more likely to stay in the hospital longer and are more likely to contract a resistant infection during that stay due to their reduced immunity. At the same time, patients with resistant infections are likely to be sicker. Many studies fail to control for the severity of the patient's underlying illness, which results in an overestimation of the morbidity and mortality due to drug resistance (Rubin et al., 1999; Abramson and Sexton 1999). For this reason, studies on the burden of drug resistance have been difficult to carry out and the degree of bias introduced by bi-directional causality is unknown.

Much of what we consider modern medicine, whether the ability to ensure that premature babies survive, or women get timely Cesarean sections, or the elderly are able to undergo transplants and joint replacements, depends on effective antibiotics. In the US alone, more than one million knee and hip joint replacement surgeries are performed annually; the number is expected to exceed four million by 2030. Available evidence suggests that rates of surgical site infection associated with colorectal surgeries in the United States have gone up by a factor of 2.5 since 1980, a trend that is likely due to reductions in the efficacy of antibiotic prophylaxis (Gandra et al., 2019). Model-based analyses have shown that a 30% reduction in the efficacy of antibiotic prophylaxis for ten common surgical procedures and cancer chemotherapy in the United States could result in 120,000 additional infections and 6,300 additional infection-related deaths per year (Teillant et al., 2015). We know less about how many patients forego surgeries and transplants because of the risk of infection. The loss of an important enabler of modern medicine could lead to many patients not reaping the benefits of medical advances made over the last century.

Drivers of Resistance in Humans

Antimicrobial consumption is a primary driver of resistance. Global sales of antibiotics for human consumption increased by 36% between 2000 and 2011 with Brazil, Russia, India, China, and South Africa accounting for 76% of the increase (Klein et al., 2018). Significant increases in consumption rates were also noted for two "last-resort" classes of antibiotics, carbapenems (45%) and polymixins (13%).

In the US, there are large geographical variations in prescribing. One study found that an increase of one standard deviation in the number of physician offices per capita was associated with a 25.9% increase in prescriptions per capita. Socio-economic conditions have also been identified as important determinants of prescription rates (Klein et al. 2015). In areas with higher poverty rates, access to providers drives the prescribing rate. However, in wealthier areas, where access is less of a problem, a higher density of providers and clinics increases the prescribing rate. Both antibiotic consumption and resistance are greatest in the US Southeast and Northeast, while the lowest rates are on the West Coast. The average person in Alaska consumes less than half the antibiotics each year than the average person in West Virginia or Tennessee.

Antibiotic consumption in animals and in the environment also likely contribute to overall resistance, but the precise attribution of resistant infections in humans

to use in animals and in the environment is unknown. Evolutionary biology suggests that resistance can arise in any setting where antibiotics are used, whether in humans or in animals. That said, transmission of resistant pathogens plays a strong role in determining the burden of resistance. If infection control in health care settings were uniformly and exceptionally high there would be less potential for resistant genes generated in the environment to affect sick patients. In the absence of effective infection control, it is natural that resistant genes find their way through air, water, food and humans to cause harm to those with weakened immunity.

The drivers of resistance are not uniform worldwide. Although antibiotic consumption has been correlated with resistance in high-income countries, environmental factors such as access to water and sanitation, education levels, and indicators of good governance are more likely to predict resistance in low- and middle-income countries (Collignon et al., 2018).

Current Action on AMR in the United States

Until 2014, there was inconsistent attention paid to AMR. Reports by the erstwhile Office of Technology Assessment, and the National Academies of Sciences were read by experts but failed to have much of an effect on government policy. In 2014, President Obama requested his Council of Advisors on Science and Technology to form a group to report on actions that the US government could take on AMR. That report informed the 2015 National Action Plan for Combatting Antibiotic Resistant Bacteria (CARB) (White House, 2015a). The plan designated a role for all relevant federal agencies in addressing the issue along dimensions of sustainable use of existing antibiotics; creating incentives for development of new antibiotics, vaccines and diagnostics; and working internationally to address the problem. The CARB action plan was also tied to the creation of a Presidential Advisory Council on Combatting Antibiotic Resistant Bacteria (PACCARB), which served to raise the profile of the issue within the federal government. In the same year, a White House order created a preference in federal acquisitions for meat and poultry produced according to responsible antibiotic-use policies served or sold in all federal facilities (White House, 2015b). This measure, which has been seldom discussed, suddenly opened up a tremendous market for antibiotic-free meat in the United States.

PACCARB
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

Federal budgets to address AMR went up from under $1 million in 2014 to nearly $1 billion in the space of just two years. Two-thirds of this money was allocated to the Biomedical Advanced Research and Development Authority (BARDA) within the Department of Health and Human Services and the National Institute of Allergy and Infectious Diseases (NIAID) to encourage the development of new antibiotics. About 15% of the dollars went to the CDC for programs to assist states in antibiotic stewardship. A key feature of the CARB plan was its emphasis on One Health, which is a balanced approach that respects the perspectives of human, animal and environmental health.

Although the United States lagged Europe in addressing AMR, much progress has been made during the last four years in ensuring greater coordination among federal agencies in addressing AMR, greater research spending on new solutions to AMR on drugs, vaccines and diagnostics, and improved incentives for using antibiotics appropriately. However, much remains to be done. Per capita antibiotic consumption levels in the United States remain among the highest in the world.

The Root of the Problem: Missing Incentives

Although often viewed through a clinical lens, antibiotic resistance is fundamentally a problem of managing an open access resource like fisheries or oil (Laxminarayan and Brown, 2001). Individual patients, doctors, hospitals and even countries have little incentive to use antibiotics judiciously because they both contribute to and are affected by antibiotic overuse and misuse by others (Laxminarayan et al., 2007). Maintaining antibiotic effectiveness in the long term requires a balance between conservation of existing antibiotic effectiveness and innovation and new drug development to replenish antibiotic effectiveness. Making better use of existing antibiotics is accomplished by reducing the need for antibiotics (through new vaccines, wider use of existing vaccines and infection control); reducing the unnecessary use of antibiotics (through better diagnostics, improved incentives for clinicians to prescribe fewer antibiotics, greater restrictions on access to newer, powerful antibiotics, and public education); and innovation to reduce the impact of antibiotic use on resistance (such as absorbents that prevent active antibiotic residues from reaching the gastro-intestinal flora (Fantin et al., 2009)). Innovation requires discovery, testing and development of new antibiotics. Measures to improve antibiotic stewardship are likely to decrease incentives for investing in new

antibiotics. Similarly, investments in new antibiotics reduce incentives for antibiotic stewardship because physicians believe that there will be a new drug to save the day.

As a demonstration of the problem, a survey of physicians showed they were most likely to choose the broadest-spectrum agent to treat pneumonia despite guideline recommendations to the contrary; a drug's potential to promote resistance rated lowest among seven determinants of their choices (Metlay et al., 2002). Another study showed that 87% of physicians surveyed believed antimicrobial resistance was a national problem, but only 55% believed it was a problem at their institution (Wester et al., 2002). The upshot is that antibiotics are prescribed to a greater extent than would be in society's overall best interests. And it is not just physicians who lack incentives to slow the spread of resistance. Market failures also appear in infection control practices, vaccination programs, and use of diagnostics. We may not be paying enough attention to preventing or correctly diagnosing infections, and, therefore, antibiotics are used more than if there were a socially appropriate level of infection control or diagnosis.

Two avenues for regulation can ensure the continued availability of effective, affordable antibiotics. One is to increase incentives for conservation of antibiotic effectiveness, and the other is to increase incentives for finding new antibiotics and bringing them to market.

Incentives for Conservation

In most countries, antibiotics are used in outpatient settings, in health care facilities, and for veterinary purposes. Antibiotics in the community are most often prescribed for bronchitis, sinusitis, and acute otitis media — indications for which the value of antibiotics is questionable (Zoorob et al., 2012). They are also used in cases of viral influenzas and colds, where they have no value at all (Zoorob et al., 2012). Influenzas are easily preventable through an annual vaccination. Nevertheless, rates of seasonal influenza vaccination remain low in the United States. Antibiotic use is often tied to physicians' incentives to write a prescription. Many physicians see antibiotics as a substitute for time spent explaining to a patient why antibiotics are unnecessary (Teixeira Rodrigues et al., 2013).

The only published study to have evaluated the effect of cost sharing on antibiotic use is the RAND Health Insurance Experiment, a randomized controlled trial of cost sharing in health care conducted between 1974 and 1982 (Foxman et al., 1987). Consumers in the free care plan, where all medical expenses were covered by insurance, used 85% more antibiotics than consumers in plans that required consumers to pay a portion of their medical bills. Cost sharing did not appear to differentially reduce antibiotic prescriptions for conditions that were primarily viral, indicating that cost sharing reduced both "appropriate" and "inappropriate" consumption. In theory, health plans could vary cost sharing amounts based on patients' diagnoses and the appropriateness of the prescription, but this would be difficult to implement in practice.

Another limitation of using cost sharing to reduce antibiotic prescriptions is that most common antibiotics are fairly inexpensive, and at current copayment levels consumers are already paying a large share of the price, if not the entire amount, out of pocket. For off-patent antibiotics, patients' copayments typically exceed the wholesale price of the drug. Cost sharing could induce a switch from newer, more expensive antibiotics to older drugs, but evidence on the real-world effects of such a change is lacking. Clinical guidelines frequently recommend that broad-spectrum drugs be held in reserve, though this policy diminishes incentives for research and development of new antibiotics and may even contribute to the development of antibiotic resistance by loading selection pressure on a handful of older drugs.

In hospitals, antibiotics are used intensively to treat infections that occur as a consequence of hospitalization. Antibiotics serve as substitutes for infection control. Although the costs of antibiotics are reimbursable and can be billed to individual patients, the costs of infection control are not. Consequently, antibiotics are a more cost-effective approach to controlling infections (from the hospital's perspective) than investing in direct infection control measures such as barrier protection (caps, gloves, and gowns). Subsidizing hospital infection control and taxing the number of infections that are contracted in hospitals are potential approaches to reducing the use of antibiotics to treat easily prevented infections.

The greatest quantities of antibiotics in the United States are used in agriculture (Laxminarayan et al., 2007). Whereas an antibiotic purchase for human use requires a prescription from a registered medical practitioner, no

such prescription is required to purchase antibiotics in bulk for veterinary or agricultural use. In fact, it is easy to purchase pharmacy-quality antibiotics, even for use in home fish tanks, over the Internet. In recent years, the use of medically important antibiotics in agriculture declined by 33% between 2016 and 2017, potentially as a result of the Food and Drug Administration's Veterinary Feed Directive, under which medicated feed is permissible only under the professional supervision of a licensed veterinarian (American Veterinary Medical Association, 2019). However, the use of antibiotics that are not considered important for human medicine remains high and could be curtailed using a combination of hygiene, herd health and vaccines.

Evidence from the European Union, where antibiotic use for growth promotion is banned, shows that most animal operations were able to make do without antibiotics (Cogliani et al., 2011). Only farms that had poor ventilation and hygiene and excessive crowding of animals had to resort to low-dose antibiotics to compensate for poor growth (Speksnijder et al., 2015). Just as in the case of hospitals, antibiotics are a lower-cost substitute for better hygiene and infection control that would prevent disease in the first place (Shallcross and Davies, 2014).

If we are to use antibiotics more judiciously, it may be necessary to create a system that stresses the economic value of preserving the effectiveness of the drugs. In the language of economists, antibiotic resistance is a negative "externality" associated with antibiotic use, much as pollution is an undesirable externality associated with the generation of power at a thermal power plant. Neither the user of antibiotics nor power plants has an incentive to take into account the negative impact of their actions on the rest of society. Efforts to restrict antibiotic use in outpatient settings have been much less successful than in hospitals because no central agent (such as a hospital administrator or infection control committee) can enforce an antibiotic policy (Durkin et al., 2018). Also, the high cost of malpractice lawsuits may induce doctors to err on the side of using stronger and broader-spectrum antibiotics than may be called for (Sakoulas et al., 2009). This tendency has the effect of increasing the level of resistance throughout the community, but the impact of each individual prescription is so small that the benefit perceived by the doctor of prescribing antibiotics often outweighs the small uncertain costs associated with increasing resistance. One solution would be to design guidelines that use community data to minimize the overall total cost of treatment and future resistance.

From a patient's perspective, the decision to request an antibiotic is based on two factors: the benefit of quickly recovering from an infection and the cost (minimized by insurance coverage) of taking the medication. But patients may not be aware of studies that have demonstrated conclusively that prior use of antibiotics increases a person's risk of acquiring a resistant infection (WHO, 2014). Patients who are educated about the risks of antibiotics may be more careful about demanding such medication from the doctor. In addition, policymakers may want to consider such economic instruments as taxes, subsidies, and redesigned prescription drug insurance programs to ensure that incentives faced by both doctors and patients are aligned with the interests of society.

Incentives for New Drug Development

A separate paper for this meeting focuses on drug development, but a few points appear here. Like with other open access resources, the pricing of antibiotics does not reflect its scarcity value, and the cost of finding new antibiotics. As a result, antibiotics are used too frequently while their low price discourages innovation. A number of studies have examined the economic benefits of antibiotics, but these have largely ignored the broader value provided by these drugs in enabling complex surgeries, transplants and procedures on immune-compromised patients (Smith and Coast, 2013).

Since antibiotics are given only for a few days at a time and do not require the life-long adherence that most medication for chronic disease requires, they are seen as less profitable than medications for chronic disease. This perception of lower value from insurance companies and purchasers is reflected in the relatively low rates of reimbursement for antibiotics (Laxminarayan et al., 2007). There is a further problem with antibiotic pricing. Since there are many antibiotics (often close substitutes for each other) on the market, the added economic value of new antibiotics with new mechanisms of action are not perceived until other antibiotics start failing. Moreover, new antibiotics with novel mechanisms of action not only bring value in terms of being able to treat previously untreatable infections, but also in reducing the selection pressure for resistance in existing antibiotics (Laxminarayan and Weitzman, 2002). In the absence of a perceived value and willingness-to-pay for new antibiotics, reimbursements remain low and there is insufficient investment in new antibiotic development by the pharmaceutical sector.

At its heart, the market failure associated with the lack of development of new antibiotics is caused by reimbursement limits for new antibiotics. Allowing the price of new antibiotics to reflect the true opportunity cost of resources to bring them into existence focuses attention on the need to invest in conservation of the antibiotics we currently have.

Concluding Thoughts

After decades of neglect, AMR has captured the attention and concern of the public health community and global leaders. A series of reports drawing attention to the topic has reaffirmed the global and serious nature of declining antibiotic effectiveness, uniting rich and poor countries (PCAST, 2014; Laxminarayan et al., 2013; CMO, 2013). In 2015, AMR was featured at the G7 heads of state, the World Economic Forum in Davos, and the World Health Assembly, where a key resolution was passed requiring the World Health Organization to take a more active stance to combat the problem, and for member countries to prepare national action plans to conserve antimicrobial effectiveness (WHA, 2015). The United States can and should do more to support efforts to combat resistance in other countries. Experience gained in the US on infection control practices and antibiotic stewardship should be shared widely, since resistance generated in any country will soon appear here.

A case in point is colistin resistance. Plasmid-mediated colistin resistance encoded by *mcr-1* was first documented in China during the routine surveillance of food animals. This has been followed by similar reports across a wide geographic area in humans, animals, and the environment. The *mcr-1* gene has been reported among human isolates in 29 countries, related to environmental samples in four countries, and in food animals and other animals in 28 countries. More recently, a second gene encoding resistance, mcr-2, has been isolated from porcine and bovine *Escherichia coli* (Al-Tawfiq et al., 2017).

What might a future with respect with AMR look like? Drug resistance is a numbers game. Even though a vanishingly small proportion of infections cannot be treated with available antibiotics, that translates to a large number of cases of infections and deaths because bacterial infections are so common. Unless the current system of developing antibiotics is somehow modified, the price of any new antibiotic will be in the tens of thousands of dollars. While that will drive up the cost of health care for those who can pay this price, for many, especially those without insurance or financial access, it will be a death sentence. We need to change incentives for how antibiotics are used and conserved. Smart regulation

will combine conservation incentives and incentives for new drug development. Approaches that reward new drug innovation but do not reward conservation are unlikely to be long-term solutions. While antibiotics have few substitutes in the short term, in the long term, there will be therapeutic alternatives that may be less susceptible to resistance. However, we have no visibility into what these alternatives will look like, when they will be available, and what they will cost.

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Clostridioides difficile (C. difficile)

"Best practices for infection prevention and antimicrobial stewardship have been identified for many different health care settings, yet uptake remains low and we are far from meeting our goals of decreasing antibiotic consumption. In many cases, the appropriate guidelines are in place, but adherence is lacking."

– HELEN W. BOUCHER, M.D., F.AC.P., F.I.D.S.A.

Reducing Human Demand for Antimicrobials

Helen W. Boucher, M.D., F.A.C.P., F.I.D.S.A.

Introduction

While microbes develop resistance in nature, overuse of antibiotics is the major driver of antimicrobial resistance (AMR) in the United States today. This paper describes two categories of interventions designed to reduce inappropriate use of antibiotics: infection prevention and antibiotic stewardship. Preventing infections eliminates the need to use antibiotics at all, while stewardship assures that antibiotics are used optimally. For each intervention the paper discusses the status of the approach, the knowledge gaps that serve as barriers to progress, and the next steps needed to make further progress. It then turns to awareness, which underpins all efforts to address AMR.

Much of the leadership on AMR in the United States has come from the Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB, of which the author is a member). The 2015 Combatting Antimicrobial Resistant Bacteria National Action Plan (NAP) set the stage, defined the problem, and developed an initial set of goals for combatting AMR. The United States has made significant progress, and a great deal of research has been conducted (Boucher et al., 2016; PACCARB, 2016). The focus now is on research and implementation of programs and approaches that are demonstrated to be effective at promoting judicious use of antibiotics, paired with measurement of implementation.

Infection Prevention

Importance

The best infection is the one that never happens. The field of infection prevention started with a focus on hospital acquired infections (HAIs) and has grown to include long-term care facilities, nursing homes and outpatient facilities, which is why the "H" in HAIs now refers to "health care." Hospital infection prevention goals have been incorporated into legislation as well as payment strategies (Dixon and CDC, 2011). Payment penalties associated with excessive rates of certain "reasonably preventable" HAIs were incorporated into the Value Based Purchasing program of the *Patient Protection and Affordable Care Act* enacted by Congress in 2010 (ACA, 2010), and public reporting of certain HAIs to the Centers for Disease Control and Prevention (CDC) was required beginning in 2011 (Dixon and CDC, 2011). The CDC, Agency for Healthcare Research and Quality (AHRQ), the National Institutes of Health (NIH) and the Centers for Medicare & Medicaid (CMS) have all established goals for reductions in a number of HAIs including catheter associated urinary tract infections (CAUTI), specific surgical site infections (SSIs), methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, and infections caused by *Clostridioides difficile (C. difficile)* (United States Office of Disease Prevention and Health Promotion, 2019). Similarly, the Joint Commission includes HAIs in their annual national patient safety goals (Joint Commission, 2019). All states have HAI reduction plans tied to receipt of their CDC Preventive Health and Health Services Block Grants (CDC, 2019).

As we consider infection prevention, hand hygiene serves as a cautionary tale. It is the most important, and perhaps simplest, infection prevention measure, yet we continue to fall short of goals, just for washing our hands. CDC estimates that health care workers clean their hands less than half the time they should (CDC, 2019). Countless efforts, campaigns and strategies have been employed, but results remain disappointing. Grayson and colleagues recently reported their experience implementing the Australian national hand hygiene initiative. They demonstrated sustained improvement in compliance as well as a decrease in hospital-acquired *S. aureus* bloodstream infections: for every 10% increase in compliance they observed a 15% reduction in incidence of infection. This is the most impactful evidence of the effectiveness of hand hygiene currently available. They also showed

that "securing and maintaining compliance" requires culture change throughout organizations as much or more than changing individual behavior (Gould et al., 2018; Grayson et al., 2018).

With limited resources available for infection prevention, there is tension between conducting surveillance for the purposes of reporting infections and investments in culture change and process improvement to reduce infections. Mandatory reporting can make it appear that the number of infections has increased, when, in fact, it is only the rate of reporting that has gone up. Financial penalties for excessive infection rates can motivate improvement, but can contribute to a culture of blame that is counterproductive, or to underreporting which makes performance appear better than it actually is.

Knowledge Gaps

Infection control metrics were originally developed for the hospital setting. Different metrics are appropriate for other care settings, but those metrics are not as well developed. Not enough is known about how to conduct infection prevention outside of the acute care hospital setting and how to coordinate activities across all health care settings, especially across care sites that are not part of the same system with a shared electronic health record. Studies are also needed to determine appropriate levels of front-line staffing (e.g., nurses and aides) in post-acute care that will allow timely delivery of needed patient care services and adherence to infection prevention protocols. Finally, research is needed to understand which implementation approaches lead to sustained behavior and practice change.

Next Steps

Delivery of actionable infection prevention programs requires people, time and infrastructure. Infection prevention personnel require specific training in implementation and leadership. Change requires getting out to the site of direct patient contact and interacting with people to reinforce good behavior. Once there are well-vetted estimates of staffing requirements in different health care settings, standards should be developed and adherence to these standards assured by accrediting organizations and health care payers (PACCARB, 2018).

CMS supports a variety of quality improvement networks designed to serve as resources for care and practice improvements. PACCARB recommended expanding the role of and resources available to Hospital Improvement Innovation Networks (HIINs) and Quality Innovation Network-Quality Improvement Organizations (QIN/QIOs) and argued that they should be contractually required to staff appropriately trained individuals with specific expertise in infection prevention and implementation science to ensure that the programs they coordinate provide maximum benefit across acute, post-acute, and ambulatory settings. In addition, HIINs and QIN/QIOs should work in close collaboration with state health departments to implement infection prevention efforts, including assessments of the presence and quality of activities in all health care settings and wide dissemination of effective initiatives. For example, QIN/QIOs could perform site visits at dialysis centers and ambulatory surgery centers to ensure that appropriate strategies are in place and could provide mechanisms to track antibiotic use and clinical outcomes using CMS data in the ambulatory setting (PACCARB, 2018).

Financial resources are needed to ensure adequate infection prevention measures in combatting AMR. PACCARB called for expanding the Antibiotic Resistance Solutions Initiative (ARSI) funding made available to CDC to encourage the adoption and execution of infection prevention programs. The CDC's ARSI serves to support national infrastructure to detect, respond, contain, and prevent resistant infections across health care settings, food, and communities. More funding for this initiative will allow for the expansion of activities of state health departments in their efforts to track multiple drug resistant organisms in all health care settings and intervene to prevent their spread.

Financial penalties imposed on hospitals with higher HAI rates remove resources needed to make improvements to prevent infection and optimize antibiotic use. PACCARB recommended that CMS investigate novel reimbursement strategies that target provision of funds to hospitals and post-acute care institutions to enhance antibiotic stewardship and infection control (PACCARB, 2018).

Antibiotic Stewardship

Importance

Antibiotic stewardship programs (ASPs) provide "coordinated interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration" (Society for Healthcare

Epidemiology of America, Infectious Diseases Society of America, & Pediatric Infectious Diseases Society, 2012). The benefits of antibiotic stewardship include improved patient outcomes, reduced adverse events including *C. difficile* infection, improved rates of bacterial susceptibility to targeted antibiotics, and optimized resource utilization. The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America believe that ASPs are best led by infectious disease physicians with additional stewardship training (Ostrowsky et al., 2018). CDC developed core elements of ASP for hospitals in 2014, then for long-term care and outpatient facilities in 2015 (CDC, 2016a; CDC, 2016b). The Joint Commission published a new antimicrobial stewardship standard, effective January 2017, that requires hospitals, critical access hospitals, and nursing care centers to establish and maintain ASPs that are aligned with the CDC core elements (Joint Commission, 2016).

The 2015 NAP called for establishment of ASPs in all US hospitals by 2020 and for CMS to issue a Condition of Participation that participating hospitals (virtually every US hospital) develop programs based on recommendations from the CDC. The NAP also recommended expanding stewardship activities to ambulatory surgery centers, dialysis centers, nursing homes and other long-term care facilities, and emergency departments and outpatient settings (Barlam et al., 2016). The NAP called for reporting antibiotic use to CDC to allow for generation of estimates of state and national antibiotic use as well as to form the basis for measuring appropriateness (PACCARB, 2016). To date, a very small number of facilities report, far below the NAP goal of 95% of hospitals by 2020 (PACCARB, 2018).

Precise knowledge of the cause of an infection helps physicians guide appropriate therapy and care for infected patients. Tests can help detect specific pathogens, determine appropriate and optimal therapy, monitor response to therapy, and aid in disease surveillance. Effective use of diagnostic tests is a key component of antimicrobial stewardship. Despite the increased use of rapid tests and the availability of molecular and proteomics-based tests, diagnostics are not optimally integrated into clinical care (Caliendo et al., 2013).

Diagnostic tools require stewardship as well (Madden et al., 2018). Unnecessary testing can lead to unnecessary antibiotic treatment. Performing urine cultures

in patients without urinary symptoms is perhaps the most common example. In these cases, positive test results do not represent true infection, but may meet criteria for HAI and require reporting, even when the physician recognizes the false positive and avoids treatment. This leads to financial and reputational cost for the hospital and can be discouraging to the infection prevention team members.

Knowledge Gaps

Research gaps for ASPs include understanding more precisely the optimal use of antibiotics, including the identification of patients who do not need antibiotics, determining the shortest effective duration of a course of therapy and how to de-escalate therapy, identifying regimens that have the least impact on the microbiome, and optimal methods of administration (e.g., IV vs oral).

A major knowledge gap surrounds the implementation of antibiotic stewardship in outpatient settings. While the initial focus on antibiotic stewardship in inpatient health care settings provided a good start, promoting optimal antibiotic use by outpatient prescribers, particularly those not affiliated with a health system, is an especially important challenge that requires further evaluation and implementation. Greater understanding is needed of current factors that may serve as disincentives to antibiotic stewardship (e.g., the influence of patient satisfaction surveys when patients expect to receive antibiotics, and the high cost of diagnostics versus the relatively low cost of antibiotics).

Additional implementation research is needed, particularly focused on behavior and culture change across the health care continuum. Prescribers in hospitals, long-term care facilities and outpatient settings behave differently. Study of regional differences in prescribing practices and approaches leading to improved prescribing is needed. Tools to improve communication between prescribers and patients who request or demand antibiotics and those to sustain culture change should be sought.

With respect to diagnosis, urgent needs include point-of-care tests with short turn-around times (10-15 minutes), tests that distinguish viral from bacterial infections, and determining where diagnostic tests fit into overall care algorithms

(Caliendo et al., 2013; PACCARB, 2018). More work is needed to better understand how to increase uptake of testing and motivate clinicians to stop antibiotics or switch to a narrower spectrum when a test indicates that is the appropriate treatment (Caliendo et al., 2013).

Particular progress is needed with respect to antimicrobial susceptibility tests – tests that determine if a particular antibiotic is effective against a particular bacteria or fungus. Such tests need to be developed in conjunction with, and contemporaneous with, development of new antibiotics.

Next Steps

In order to deliver effective stewardship, we need to maintain and expand the infectious disease physician and pharmacist workforce with expertise in antibiotic use and resistance. This workforce will, in turn, facilitate the establishment and maintenance of accountable ASPs in all health care settings. Workforce development will require innovative strategies, including enhanced training and education, new payment models for infectious disease physicians performing stewardship, expanded support for funding of pharmacy residency training programs in infectious diseases, and use of telemedicine (Ostrowsky et al., 2018; PACCARB, 2018; Siddiqui et al., 2017). A suite of incentives, including loan repayment, early career grant mechanisms, and improved reimbursement should be implemented (Ostrowsky et al., 2018; PACCARB, 2018; Siddiqui et al., 2017).

The Infectious Diseases Society of America supports appropriate and evidence-based use of telehealth and telemedicine technologies to provide up-to-date, timely, cost-effective subspecialty care to resource-limited populations and to provide continuing education and longitudinal support to infectious diseases, physicians. Telehealth programs provide potential for cost savings, on both an individual patient level and for the health care system in general.

PACCARB recommendations include:

- CMS should immediately finalize the Medicare conditions of participation requirements for antibiotic stewardship programs, as proposed in June of 2016, in hospitals and critical access hospitals. In addition, CMS should develop detailed interpretive guidelines that include all aspects of CDC's Core Elements of Hospital ASPs. CMS should develop training to ensure that surveyors are able to assess the quality and outcomes of ASPs (PACCARB, 2018).

- CMS should enforce the Medicare conditions of participation requirements for antibiotic stewardship and infection control programs in long-term care facilities that went into effect in November 2017 and the expanded requirements for infection control programs that also went into effect in November 2017 (PACCARB, 2018).
- Develop new federal policies, standards, and payment methods to support antibiotic stewardship (PACCARB, 2018).
- Make reporting of antibiotic use measures a mandatory component of the Merit-based Incentive Payment System (MIPS) for outpatient prescribers. Several antibiotic use measures are currently optional in the MIPS. CMS should explore making the antibiotic use measures required for all specialties for which measures currently exist, and evaluate additional antibiotic use measures for specialties for which none currently exists (PACCARB, 2018).
- Determine approaches to require and incentivize activities to improve stewardship in ambulatory settings where patients are particularly vulnerable to infection, including in ambulatory surgical centers, dialysis centers, clinics that provide complex care to immunocompromised patients and where patients receive outpatient therapy through central catheters (PACCARB, 2018).
- Develop reimbursement approaches specifically for antibiotic stewardship activities for hospitals and post-acute care institutions (PACCARB, 2018).
- Develop a timeline for mandatory hospital data reporting of antibiotic use and resistance to CDC (PACCARB, 2018).
- Develop an appropriate risk-adjustment method for any antibiotic resistance measures prior to integrating such measures into pay for performance programs (PACCARB, 2018).

CDC should develop approaches to obtain and benchmark data on antibiotic use from post-acute and ambulatory settings and track use across settings (e.g., in patients who move from acute to long-term to home care). This will require capacity building in these sites to make the electronic collection of antibiotic use data possible. In addition, metrics to assess the quality and appropriateness of antibiotic use should be developed. These measures need to be collected as close to real-time as possible to facilitate feedback to prescribers. Approaches to expand the capacity for reporting of antibiotic resistance should occur in conjunction with those to expand the reporting of antibiotic use (PACCARB, 2018).

Additional steps are required to overcome barriers to the development and deployment of antibiotic susceptibility tests. Funding for the development of new antibiotics should always include the development of a concomitant rapid antibiotic susceptibility test. Antibiotic developers should be encouraged to share drug formulation with diagnostics companies as early in drug development as possible. Reimbursement methods for tests should include additional payments that create incentives for using the most sensitive test. Reimbursement should also be available for tests for infection prevention because of the public health importance (PACCARB, 2018).

Awareness

All efforts to combat AMR depend upon awareness of the problem. The first objective of the World Health Organization (WHO) Global Action Plan is to improve awareness and understanding of antimicrobial resistance through effective communication, education and training (WHO, 2016). CDC led the call to action in the US Government. The 2013 CDC Threat Report, *Antibiotic Resistance Threats in the United States,* served to increase awareness of the threat that antibiotic resistance poses and the consequences of inaction, and to encourage immediate action to address the threat (CDC, 2013).

The Infectious Diseases Society of America (IDSA) has led the way in terms of advocacy for AMR. In July 2004, the IDSA released its *Bad Bugs, No Drugs* report, which documented the magnitude of the problem and made recommendations to address the complex issues underlying the lack of antibiotic development (IDSA, 2004). As one of the first organizations to detect, delineate and raise awareness of the threats posed by pathogens growing resistant to treatments, IDSA is committed to combating AMR by driving advances in science, patient care, public health and public policy. In 2011, IDSA released *Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,* and many of the policy proposals outlined in this report were ultimately adopted by the PACCARB NAP (IDSA et al., 2011).

Infectious diseases physicians are on the frontlines of this effort, leading antimicrobial stewardship and infection prevention programs in their hospitals;

conducting research, including clinical trials for new antibiotics and diagnostics; caring for patients infected with multidrug resistant organisms; and informing public health interventions. More than 700 IDSA physician members have signed on to join the 2018 CDC AMR Challenge. IDSA's efforts include ongoing work to:

- lead advocacy promoting US federal investment in infection prevention, antimicrobial stewardship, and AMR surveillance and data collection across human health, animal health and the environment in the US and globally;
- promote the development and uptake of safe and effective vaccines;
- elevate antibiotic stewardship as a universal component of medical practice;
- lead advocacy and scientific efforts that drive innovation in antimicrobial drug and diagnostic development;
- feature the latest AMR science at the joint IDSA/HIV Medicine Association/ Society of Healthcare Epidemiology of America and Pediatric Infectious Diseases Society IDWeek 2018, with more than one-third of this year's sessions covering diverse aspects of AMR; and
- educate the next generation of infectious diseases leaders to combat AMR (IDSA, 2018).

The PACCARB and its National Action Plan call for AMR education at multiple levels, especially for pre-professional and professional health care (medical, veterinary, nursing, etc.) students. Leaders at CDC and members of PACCARB, among others, recognize opportunities for public education and the importance of engaging all citizens in the fight against AMR. Work is underway to develop

model curricula for high school, college, pre-professional and professional students. Goals include building model infection prevention and antimicrobial stewardship curricula that will be required by accrediting bodies. IDSA recently launched a new stewardship curriculum for all infectious diseases fellows; the interactive CORE curriculum will be launched in summer, 2019 and curriculum for stewardship leaders will follow (IDSA, 2019).

Recommendations include securing funding and developing mechanisms to promote graduate, medical, pharmacy, and nursing school education directed at infectious diseases specialties through additional grants, scholarships, and fellowships. The WHO Global AMR Action Plan recommends including the use of antimicrobial agents and resistance in school curricula to promote a better understanding and awareness from an early age (WHO, 2016). We recommend promotion of the inclusion of formalized education as part of any future mandates linked to federal funding.

A model curriculum that provides standardized content should be developed from existing identified core competencies such as the CDC's Healthcare Infection Control Practices Advisory Committee Core Infection Prevention and Control Practices (CDC, n.d.). Antibiotic resistance is a complex subject requiring a core curriculum that stresses systems dynamics, problem solving, and systems thinking, training which is not currently integrated uniformly in medical, pharmacy, or nursing schools. It is important to develop, plan, integrate, and deliver model curricula for medical, pharmacy, and nursing schools across didactic, laboratory, clinical, and practice-based education programs. Academic institutions should be tasked to develop a curriculum that better integrates infection prevention and stewardship learning across disciplines, course offerings, and various pedagogy, including inter-professional education. To ensure the curriculum is used consistently, it must be made a required component by accreditation bodies (PACCARB, 2018).

Educational programs should also incorporate strategies for how to engage the patient and the lay public regarding infection prevention, vaccination, and appropriate antibiotic use across the health care continuum.

Conclusion

Best practices for infection prevention and antimicrobial stewardship have been identified for many different health care settings, yet uptake remains low and we are far from meeting our goals of decreasing antibiotic consumption. In

many cases, the appropriate guidelines are in place, but adherence is lacking. A focus on long-term care and outpatient health care settings is a priority, with an emphasis on implementation and direct reimbursement for infection prevention and antibiotic stewardship activities. To effect lasting change and decrease demand for antimicrobials, we need a robust and well trained workforce and an educated public.

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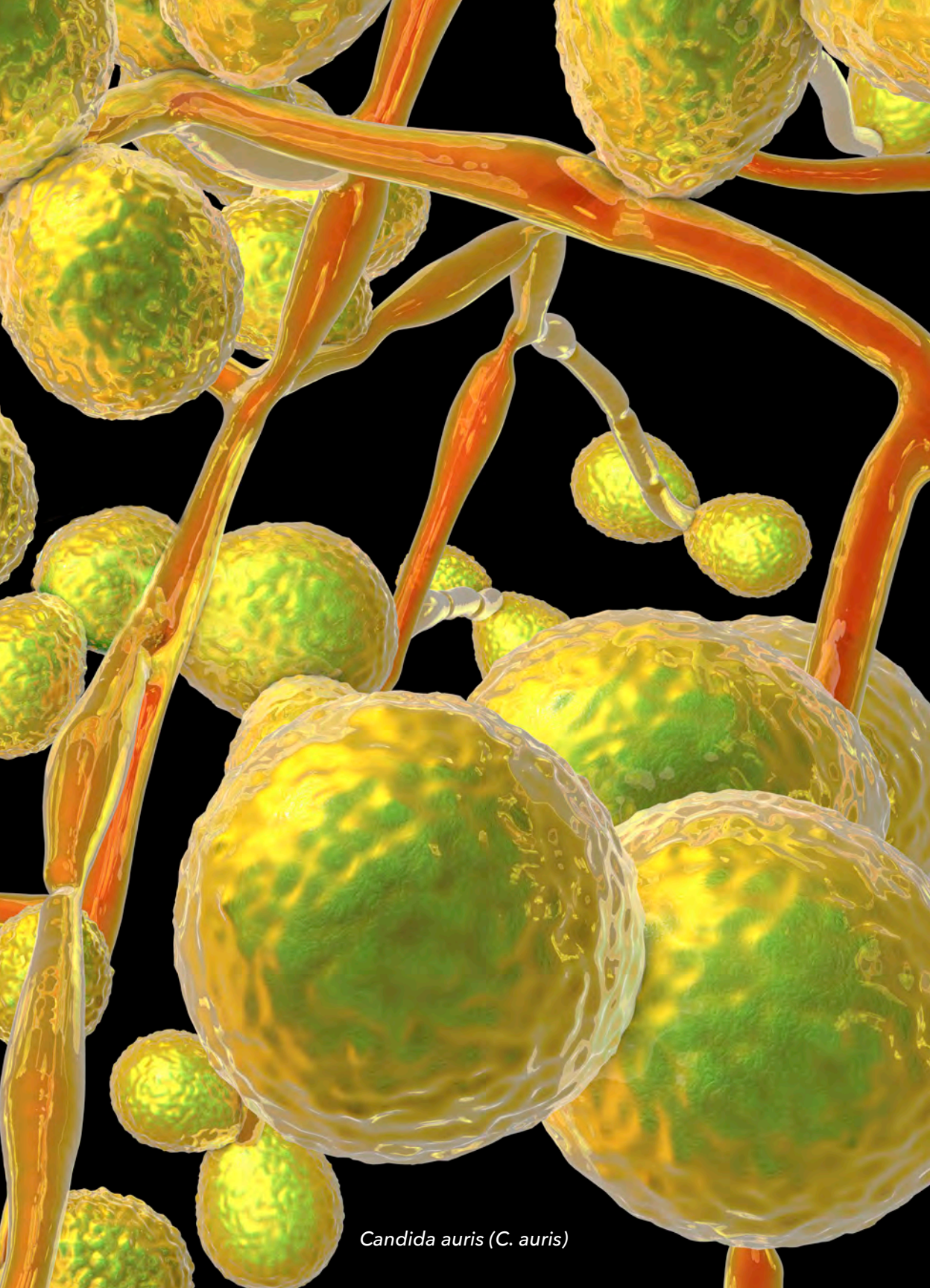


Candida auris (C. auris)

"AMR is the quintessential One Heath issue and recognizes that the health of people is closely connected to the health of animals and the environment. … A sound understanding of the roles of each domain in the emergence, spread and persistence of AMR genes and resistant pathogens requires an integrated and holistic view. One Health brings together a broad, multidisciplinary group of scientists, researchers and practitioners to create a foundation for the design, implementation, and evaluation of AMR programs and policies."

– LONNIE KING, D.V.M., M.S., M.P.A., D.A.C.V.P.M.

Addressing Antimicrobial Resistance Through a One Health Approach

Lonnie King, D.V.M., M.S., M.P.A., D.A.C.V.P.M.

**"When one tugs at a single thing in nature,
he finds it is attached to the rest of the world." – John Muir, 1912**

Introduction

Antimicrobial resistance (AMR) is one of the most daunting health problems of this century. This paper discusses the complex human, animal, and environmental factors that make AMR such a vexing issue. It explains how the "One Health" framework improves our understanding of AMR and serves as the foundation for interventions to address the problem. This paper focuses on the animal and environmental domains of One Health, discussing current progress and remaining issues primarily within these domains.

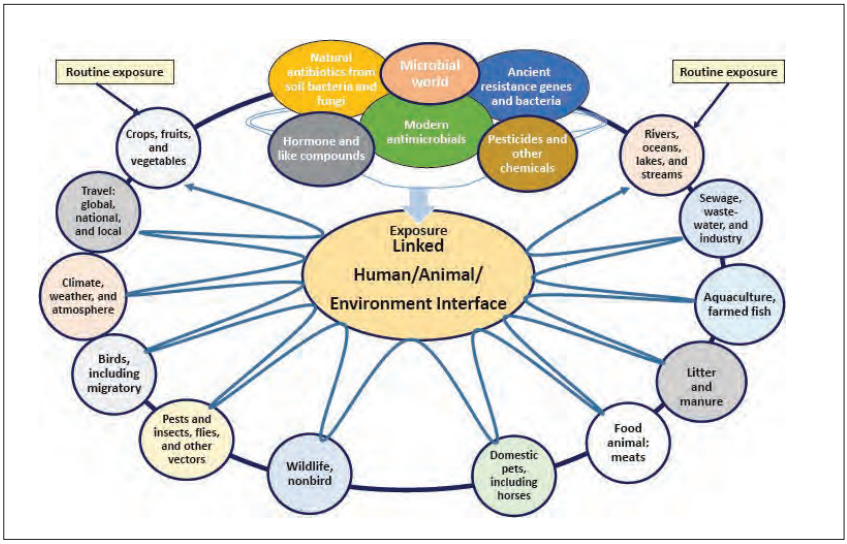
We live in a world that is rapidly changing, complex and progressively interconnected. The convergence of people, animals and their products in our environment has resulted in an unprecedented 21st century mixing bowl. This convergence has created a new dynamic, one in which the human, animal and environmental domains of health are threatened simultaneously and interdependently. As the number of people and animals continue to undergo rapid growth, our human-animal-environment interfaces are accelerating and becoming increasingly consequential for everyone's health.

The Animal, Environment, and Human Health Relationship

The ecology of AMR within the environment is complex and massive in scope and scale. Human activities can lead to contamination via wastewater, sewage, surface water, and discharges from manufacturing plants and health care facilities. Animals and how we raise them contaminate the environment through manure, run-off, land fertilization, aquaculture, food, pets and even aerosol exposures in

intensified animal production facilities. Figure 1 depicts the many interrelated factors that form the ecosystem of humans, animals and the environment.

Figure 1: The Collective Antimicrobial Resistance Ecosystem (CARE Model)



Source: National Academies of Sciences, Engineering and Medicine (2017). (with permission of Dr. Paula Cray)

AMR and multi-drug resistant organisms emerge when resistant genes are influenced by key anthropogenic factors including pollution, antimicrobial production, wastewater treatment, and animal agriculture. Together these factors create an "organismal soup" consisting of resistant genes, mobile genetic materials, pathogens and related organisms. Within the dynamics of the "soup," the key drivers of AMR are selection, growth conditions, cell density and cell contact. (National Academies of Sciences, Engineering and Medicine, 2017, pp. 20-23). The proliferation of antibiotics throughout the environment throws more ingredients into the soup, increasing opportunities for resistant mutations and transmission among animals and humans along dimensions that are not fully understood.

Animals and Antibiotics

In 2016, roughly 25-30 billion food animals were produced (excluding aquaculture) and over 340 million tons of meat are consumed globally each year (Ritchie and Rosen, 2017). In 2010, the Food and Drug Administration (FDA)

estimated that 63,151 tons of antibiotics were used in animal agriculture globally and that about one-quarter of this was in the US (FDA, 2010). It is estimated that approximately 75% of antibiotics used in animals are excreted in either urine or feces, mostly unmetabolized (United Nations, 2017).

The key relationship and linkage between animals and people is through environmental contamination, especially through water. Surface water, ground water, wastewater and streams are all vehicles of potential transmission and most contain various levels of antimicrobials, their metabolites, AMR genes and resistant organisms (Marshall and Levy, 2011). Research has demonstrated that AMR genes can persist in the environment for months (Kummerer, 2004). In a recent study, scientists were able to identify and measure AMR genes in highly polluted air in several Chinese cities (Zhang et al., 2019). Resistant bacteria, resistant genes and mobile genetic materials that are associated with antibiotic use in animals make their way to humans through food, direct contact with animals, and indirectly through environmental contamination.

There is evidence that agroecosystems in general, and water in particular, are important sources of bacterial transmission to animals as well (Williams-Nguyen et al., 2016). Wildlife are also exposed to antibiotics, AMR genes and pathogens through environmental sources. It is well documented that wildlife harbor AMR organisms and genes, even though little is known about antibiotics' direct effects on wildlife health (Allen et al., 2010). Wildlife, including migrating birds, may represent an under-appreciated source of both exposure to and transmission of AMR agents.

Farm Agriculture

Crop and tree agriculture account for less than one-half percent of all antibiotics used (Stockwell and Duffy, 2012). Crops and ornamental plants are commonly infected with fungi and farmers use antifungal agents and copper to counter these infections. There is growing concern that fungi are becoming resistant to the most common antifungal agents, particularly the azole class of anti-fungicides and pesticides (Dalhoff, 2018), which account for about one-third of

all antifungals used today and are commonly found in the environment (Meis et al., 2016). Human hospitals are now experiencing an explosive epidemic of the fungus *Candida auris,* which is resistant to azoles and other antifungal agents (CDC, 2016). Although only a hypothesis, some scientists are concerned that this pathogen may be linked to the overuse of azoles on crops worldwide.

Growing Antimicrobial Resistance

Various studies have shown effects of antibiotic use and exposure on the gut microbiota, which reduces the abundance of microbes in the gut and increases the number of resistant genes (Blaser, 2016). The perturbation of normal gut microbiota, or microbiome, may adversely affect the health of an individual (Casals-Pascual et al., 2018). Other studies support the evidence that risks appear greatest for young children and may be responsible for serious problems later in life including obesity, diabetes, inflammatory bowel diseases, allergies and asthma. Changes in the gut microbiome after treatment with a course of antibiotics may alter the diversity of the microbiome for weeks to months (Blaser, 2016).

While still lacking more critical studies, there are indications that travel, diet, natural environmental exposures and animal use of antimicrobials can impact the diversity of AMR genes in an individual's gut microbiome and can then confer resistance to both pathogens and commensal organisms (Baron et al., 2018). With this knowledge and emerging studies, the sources and levels of antibiotics and AMR genes in the environment has taken on a new interest and research focus.

We have entered a new era of emerging and re-emerging diseases. Over the last six decades, an estimated 335 new diseases have been identified, with the number in each decade larger than the one before. Of these new diseases, almost 21% have been classified as antimicrobial resistant pathogens (Jones et al., 2008). Almost 75% of these diseases are classified as zoonotic, meaning they are transmitted between animals and humans (Taylor et al., 2001).

Tie to Human Activity

Human activity underlies the dynamics that lead to growing antimicrobial resistance. These activities include global trade and commerce; transportation;

changing food and production systems; economic development; changing land use; technology and industrial advances; and movements and rapid growth in human and animal populations (Smolinski et al., 2003). In order to fully understand and effectively respond to AMR, we must fully appreciate and take into consideration the contributions and dynamics of these forces.

The driving forces just listed are more likely to increase than decrease over time. Today's global human population of 7.6 billion is expected to reach perhaps 10 billion by mid-century (United Nations, 2015) as we add approximately 10,000 people daily to the earth's human community. Of this rapid growing and expanding population, almost 90% of the growth will occur in low- and middle-income countries (LMICs).

Concurrently, global food production will need to increase by approximately 70% to meet global demands (FAO, 2017). The United Nation's Food and Agricultural Organization (FAO) now projects that the demand for protein from animal sources and food animals themselves will increase by 50% over the next several decades and many will be associated with production in more intensified systems (FAO, 2003). This remarkable projection for more protein and more animals is driven by the fact that as less developed countries make economic gains their populations have a seemingly insatiable appetite for proteins from animal sources.

Food production in LMICs relies heavily upon antibiotics for growth promotion and gains in feed efficiencies for food animals. The Center for Disease Dynamics, Economics and Policy estimates that there will be a 67% increase is consumption of antibiotics by animal populations by 2030 due to the rapid increase in both numbers of animals and more intensified production systems that traditionally rely on a greater use of antibiotics (Van Boeckel et al., 2015).

About 80% of the world has no wastewater treatment and perhaps a billion people lack clean water and basic sanitation (United Nations, 2017). Globally, the fastest growing populations are in peri-urban or slum settings in large cities in LMICs. These populations are especially vulnerable to emerging infections, AMR diseases and serious environmental contamination and degradation. Therefore, the great 21st century mixing bowl will be both enlarged and intensified.

Our Knowledge Is Limited

While we know a great deal, we still lack understanding of how antibiotics, genes, mobile genetic elements and AMR organisms circulate, persist, and transfer

resistance among the domains of human, animal, and environment. We do not understand the potential impact accumulating antimicrobials in the soil and water will have on microbial diversity and how that may translate into broader environmental effects. We also do not know the precise levels of hazard or risk to people or animals associated with the presence of specific antimicrobial agents in the environment.

One Health: A New Construct For AMR

One Health can be defined as the collaborative effort of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and the environment (King, 2008). The scope of One Health is impressive, broad, and growing. AMR is the quintessential One Heath issue and recognizes that the health of people is closely connected to the health of animals and the environment (Robinson et al., 2016). A sound understanding of the roles of each domain in the emergence, spread and persistence of AMR genes and resistant pathogens requires an integrated and holistic view. One Health brings together a broad, multidisciplinary group of scientists, researchers and practitioners to create a foundation for the design, implementation, and evaluation of AMR programs and policies. When we tug on anything related to AMR, we find it is attached to the world of the other domains; thus, our response also needs to be coordinated.

The recognition of both the AMR global crisis and the One Health framework has been influential in the political and societal acknowledgement of the AMR issue and has led to a new conversation among stakeholders. The G-7 and G-20 countries, along with the General Assembly of the United Nations, have made strong recommendations in support of One Health strategies to help address AMR. The World Health Organization (WHO), Food and Agriculture Organization and the World Animal Health Organization (OIE) have pledged to work together and share expertise across the animal, human and environmental health domains. (WHO, 2008).

Progress in Animal Agriculture

Animal agriculture in the US is a vast enterprise that represents 40% of total farm receipts across the country. Food animals also consume over 30% of all crops grown and are responsible for one of the country's main export markets. Today, there are about 2.2 million farms in the US on 910 million acres and two-thirds of

these farms and ranches rear livestock and poultry (USDA, 2012). There are literally tens of millions of food animals produced annually in a complex and multifaceted industry consisting of different production practices, markets and use of antibiotics.

Antibiotics in animal agriculture are used for the treatment, control and prevention of diseases and, until recently, for growth promotion and feed efficiencies by using antibiotics at low doses for prolonged periods of time. The practice of using antibiotics in animal agriculture has changed dramatically in the last several years based on recent FDA policy changes and the changing demands and preferences of consumers. Since January 1, 2017, the FDA has emphasized the judicious use of medically important drugs in food animals based on the issuance of two pieces of guidance. One bans the use of medically-important antibiotics (i.e., those commonly used in human medicine to treat serious infections) to enhance growth or improve feed efficiency of food animals (FDA, 2012). The second directs pharmaceutical companies to change the labels and claims on these products accordingly (FDA, 2013). The FDA also expanded the scope of its existing Veterinary Feed Directive (VFD) by bringing the use of antibiotics in feed and water under the oversight of licensed veterinarians for the prevention, control and treatment of diseases (FDA, 2015). Antibiotics used for growth promotion were banned in the European Union in 2006 but are still commonly used in other parts of the world (European Commission, 2016).

Today, retailers and other sectors of the food system are dictating how antibiotics are used (or not used) for production. In some developed countries, food animal products are differentiated and marketed based on societal preferences and values associated with how they are produced. Animal products, especially some poultry brands, are now marketed and sold as produced "without antibiotics" or labeled "no antibiotics ever." There are some questions today about whether this practice is a social good or just a marketing strategy and whether it actually has any effect on human health.

Reducing the Use of Antimicrobials in Food Animals in the US

Significant progress is being made in animal agriculture to reduce the use of medically important antibiotics by adopting new processes and taking effective

actions. Activities have focused on the five steps of the US government's National Action Plan (NAP) to combat antibiotic resistant bacteria (CDC, 2015). These steps consist of establishing stewardship programs; improving and broadening surveillance; discovering diagnostics and using them sensibly; expanding research and development with a focus on the discovery and approval of new antibiotics; and, becoming strong and engaged partners with the global community. The NAP is focused on federal government programs and is based on a One Health framework.

Of the critical steps being promoted to address AMR in animal agriculture, two activities have the highest priority. The first is stewardship, which is defined as a set of coordinated strategies to improve the use of antimicrobials to ensure the goals of enhanced patient outcomes, reduced resistance and limited selection pressure, and reduced costs of care due to suboptimal use (Society for Healthcare Epidemiology of America, 2012). The second priority is reducing or eliminating the need for antibiotics through infection prevention and control (IP&C) and the development of alternatives to antibiotics.

The stewardship programs have shown the greatest progress to date. The FDA reports a 43% reduction in the use of medically important antibiotics in animal agriculture since its directives to eliminate antibiotic use for growth promotion and feed efficiency went into force (FDA, 2017). One reason stewardship efforts have succeeded is that many are built on the platform of quality assurance programs that have been in place for several decades. These programs have grown into effective education and certification programs promoting good husbandry practices, animal well-being and food safety. The food-animal associations and veterinary organizations have been active in creating contemporary stewardship programs and these groups have been collaborating to share best practices.

Reducing Need for Antibiotics

There is also a new emphasis on reducing or eliminating the need to use antibiotics based on implementation of effective and proven on-farm IP&C. While such strategies have been used for decades, they have often lacked documentation of their contributions to health due to a lack of evaluation criteria, limited cost-effectiveness analyses, and inconsistent implementation. There is a wide range of options and levels of sophistication for IP&C and often the larger, more intensified production systems have more stringent and reliable practices. Sanitation and hygiene, biosecurity, health management for transportation, facilities and health monitoring, improving the host immunological response, vaccines, and the reduction of environmental contamination are common strategies, although these methods are not fully evaluated.

Another emerging area of importance is the development and use of alternatives to antibiotics. Both public and private researchers are actively exploring new and innovative products. New vaccines, phages, lysins, phytochemicals, pre- and probiotics, new molecules, natural products, immunomodulators, immunoglobulins and peptides are some examples. There is an essential need to better understand how these practices and products reduce or prevent diseases, reduce the need for antibiotics, reduce resistance and decrease the cost of food production.

Barriers to Additional Progress

Financial Incentives

Before the FDA ban, low level and constant use of antibiotics was a method to achieve a faster and greater rate of gain and improved efficiency of feed conversion. Many US producers believe that the use of antibiotics for growth promotion was cost beneficial and reduced the cost of food animal products for consumers. While the FDA ban was expected, some farmers and producers believe that antibiotic use in animals has not been proven to be a key driver of resistance or a source of AMR human infections. Animal agriculture is not a monolith and there is a heterogeneity of cultures, production systems,

perceptions, anti-government sentiments, behaviors and incentives. Whether one is accepting or skeptical of the evidence behind the FDA ban, the prohibition against using antibiotics to improve yield goes against the financial incentives that underlie animal production. However, the return on this investment has not been well documented or measured.

Uneven Government Response

Over the last few years, the US Department of Health and Human Services, especially the CDC and National Institutes of Health (NIH), have deservedly received significant budget increases for AMR activities and have demonstrated excellent progress based on these new funding levels. However, the ratio of human health funding to animal health funding has been approximately 40:1 (HHS, 2016). With the recognition of One Health and the need to incorporate the animal and environmental domains in the national plan to combat antimicrobial resistance, federal agencies with animal and environmental programs, are not receiving support commensurate with the risks and threats of these two domains.

Differences in Industry Response

Although US food animal producers are complying with the FDA guidance, there remain differences across the animal industries regarding the belief that mandated AMR programs are needed. These industries lack national leadership and a collective voice, and their progress, which is variable, is primarily accomplished within their own sectors and not as a national strategy, except when regulations push them forward.

Animal agriculture consists of multiple industries and commodities such as dairy, swine, beef, broilers, layers, turkeys, sheep, goats and aquaculture. These segments of the industry are integrated into a complex food and fiber global system and are often associated with multiple specialties and subgroups. Production systems can be further classified into small independent producers and large intensified operations which are often part of vertically integrated businesses. These industries have different markets, retailer influences and production practices including how they use antibiotics and adopt stewardship and infection prevention activities.

Reluctance to Share Data

Surveillance and subsequent data sharing are key goals under the NAP. Surveillance is an important tool that helps inform appropriate public and animal health interventions and evaluate the success of existing AMR activities. While much of today's conversation is about reducing and preventing AMR in people, there are similar concerns about resistance in animal populations which can only be evaluated through surveillance and sharing critical results. However, producers and animal health officials are concerned that the collection and sharing of data on AMR and antibiotic use from farms and ranches could result in financial penalties or unnecessary trade restrictions. In addition, many producers view on-farm surveillance as an infringement of the right to privacy and a form of unnecessary government intrusion. Important data may be shared within the confines of the industries themselves to help determine appropriate antibiotic use. State animal health diagnostic labs and private diagnostic labs help support producers and food system companies but mostly keep data confidential.

Veterinary Shortages

As part of the FDA ban, the agency also promulgated changes to the existing Veterinary Feed Directive (FDA, 2015). The VFD now authorizes only licensed veterinarians to use medically important antibiotics when needed for a specific animal health purpose and further requires veterinarians to use this prescribing authority only within the context of a valid veterinarian-client-patient-relationship (VCPR) (AVMA, 2017a; AVMA, 2017b). With thousands of farms and ranches across the US and many in rural settings, establishing a VCPR has become somewhat problematic because of the national shortage of food animal veterinarians.

Differences Between Global Public and Animal Health Organizations

Recently the World Health Organization went beyond recommending that medically important antibiotics not be used for growth promotion to state that they should not be used in healthy animals at all (CIDRAP, 2018b). The WHO's recommendation takes professional judgment out of the hands of veterinarians and would eliminate using antibiotics to control or prevent diseases. This has become a controversial topic for the US animal health and

veterinary communities and the FDA has not supported this recommendation. For licensed veterinarians, this is inconsistent with their definition of stewardship and established medical practices committed to support animal welfare, health and food security. Conditions commonly exist where animals are exposed to diseases or predictably will be exposed based on the movements and complexities of animal production systems. The use of medically important antibiotics may prevent an outbreak or substantially reduce morbidity and, thus, decrease the potential antibiotic use for a larger number of animals that may become infected. This view is not inconsistent with how human medical clinicians treat their patients. Withholding antibiotics from animals with diseases resulting in their suffering or contrary to their wellbeing is considered unethical and a violation of the veterinary code of practice.

Antiquated Research Models

Like other comprehensive research and operational strategies, One Health research faces the barriers of old academic and government structures and narrow funding models. A new National Institute of Antimicrobial Resistance Research and Education (NIAMRRE) has recently been created that is a contrast to the old model (Association of Public and Land Grant Universities & Association of American Veterinary Medical Colleges, 2018). Based at Iowa State University, NIAMRRE employs a One Health model designed to bring academic and governmental organizations together to share resources, work collaboratively and prioritize national activities.

Like human medicine, animal health is suffering from a progressively smaller pipeline of new antibiotics and diagnostics. The failing business model for antimicrobial development is also a major barrier for animal agriculture and needs to be resolved along with the issue in human health.

The urgent and critical question for producers is: can US poultry, livestock and aquaculture be produced safely, humanely and profitably without using medically important antibiotics for growth promotion and feed efficiency and with the judicious use of antibiotics limited to treatment, control and prevention under veterinary supervision? The answer to this question requires a more holistic approach to research than has existed in the past.

Consumer Confusion

Parts of the industry, led by national poultry brands, restaurant chains and retailers, are advocating and marketing their meat as “antibiotic free” or “no

antibiotics ever" (NAE). These labels and practices are contrary to most of the industry and to veterinary practitioners who promote the judicious use of antibiotics. The American Veterinary Medical Association defines judicious use as when the decision is reached to use antimicrobials for treatment, control or prevention of disease, veterinarians should strive to optimize therapeutic efficiency and minimize resistance to antimicrobials to protect public and animal health and well-being (AVMA, 2017a). "Antibiotic free" labels may confuse the public. For example, all animals that receive antibiotics must undergo a delayed period or withdrawal period before they can be marketed to avoid any drug residues and are then deemed safe for consumers by the FDA. In addition, NAE and antibiotic free labels do not mean that companies and producers never use antibiotics in any of their animals; rather they mean that antibiotics were not used to produce meat under that label, but other animals that were treated are marketed elsewhere under a different label. (National Academies of Sciences, Engineering and Medicine, 2017).

Lagging Progress in Companion Animal Medicine

FDA regulations target food animals because food safety and public health issues have been the impetus for recent changes in AMR programs for this sector. However, this is not the case for companion animals and veterinary practices supporting this group of animals. There are approximately 94 million cats and 90 million dogs in the US along with countless other types of pets (AVMA, 2018); these pets are intimately associated with their owners. Companion animal practitioners commonly use medically important antibiotics with few if any restrictions. In a survey of companion animal practitioners, only 45% of the group was concerned about AMR infections; 62% believed that they impacted AMR; and 88% were unaware of existing guidelines to treat common infections (Banfield Pet Hospital, 2017). The next FDA five-year plan has targeted this group of practitioners and sets out goals to implement stewardship programs, follow established guidelines and better educate this segment of the veterinary profession (FDA, 2018).

The Challenge of Global Food Animal Production

The world is experiencing unprecedented growth in both human and animal populations and an unparalleled demand for animal-derived foods. The human-animal interface will intensify and expand globally. The growth in worldwide production systems, especially in LMICs, the expanding global food system, the movement of people through immigration and travel especially those infected with AMR pathogens, the further expansion of the trade of animals and their products and the growing connection and contamination of the environment ensures that antibiotics, metabolites, AMR genes, and AMR microbes will continue to be exchanged at rates we have not previously experienced.

The need for a One Health global approach is demonstrated by experience with the *mcr-1* gene. The *mcr-1* gene confers resistance to colistin, which is considered an antibiotic of last resort for a number of bacterial infections (Liu et al., 2016). *Mcr-1* was first reported and isolated in China from swine and now has been found on numerous pathogens and plasmids in people across five continents. Colistin had been commonly used in China for growth promotion in livestock. (Meinersmann et al., 2017). Recently the *mcr-1* gene was isolated in the US in several people and pigs. It was identified through the National Antimicrobial Resistance Monitoring System (NARMS), one of the only One Health surveillance systems in the US, that compares bacteria isolated from humans with AMR infections (CDC), retail meats (FDA) and isolates from animal slaughtering plants (USDA). As new AMR organisms and genes continue to emerge and move globally, One Health surveillance systems will take on a new level of importance.

One Health Requires New Thinking

Insights from the One Health framework have disclosed the remarkable interconnectedness of people, animals and their products, and the environment, and have helped to explain the complexities and dynamics of AMR. To understand AMR is to understand convergence: the convergence of the three domains of One Health (human, animal, environment), and convergence of distinct sciences, disciplines and technologies to create innovative strategies and transformative synergies not possible by using any of these disciplines alone (MIT, 2016). One Health is an appropriate example of convergence science and holds great promise as both a construct to understand AMR and an application to address AMR.

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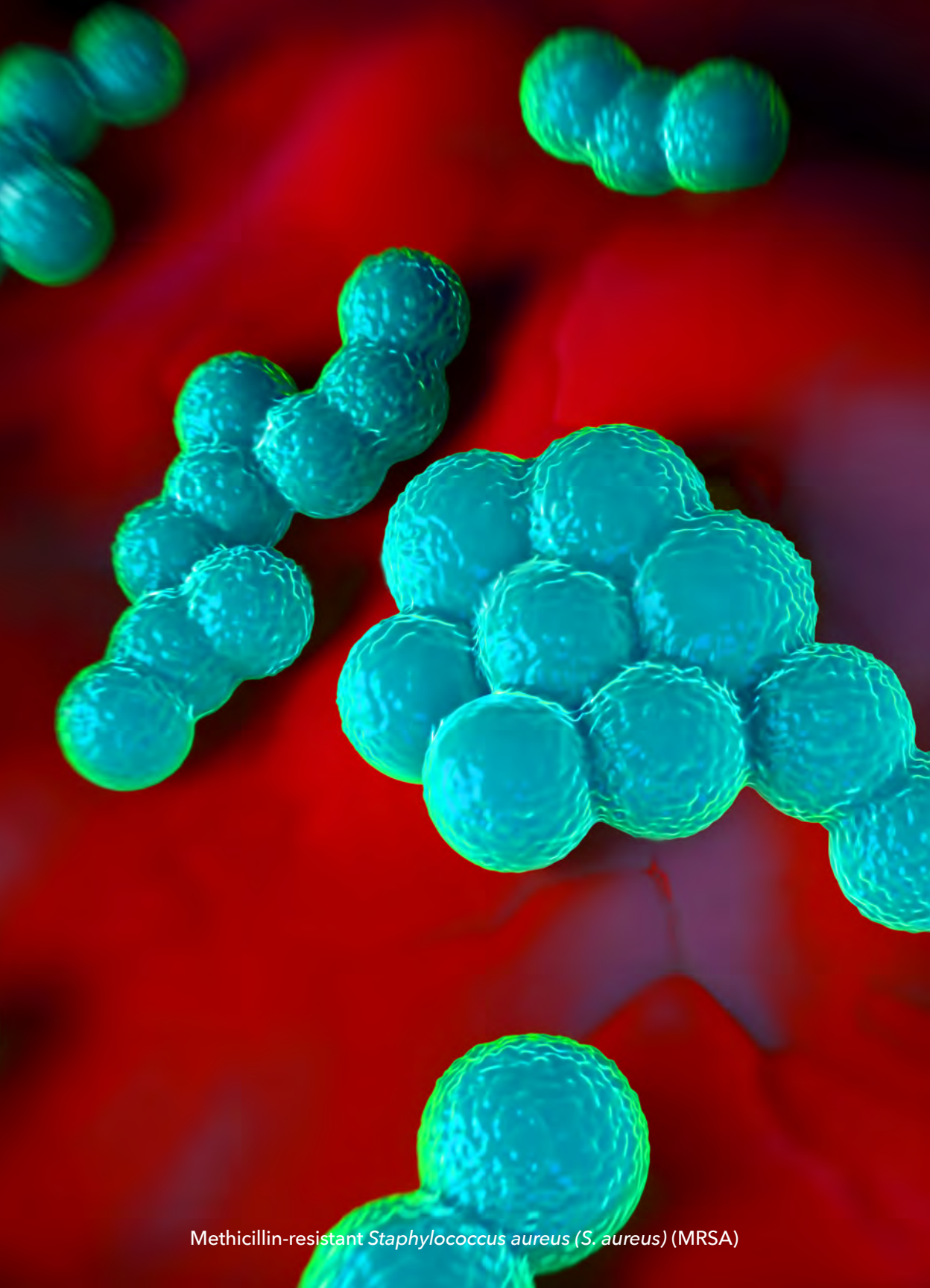


Methicillin-resistant *Staphylococcus aureus (S. aureus)* (MRSA)

"The need for new antibiotics, in addition to global partnership on One Health and reduced antibiotics in hospitals, homes and farms, is critical. The innovation pipeline, at the moment, does not look promising. A single strategy is unlikely to work."

– MUHAMMAD H. ZAMAN, PH.D., AND KATIE CLIFFORD, M.P.H., M.B.A.

The Dry Pipeline: Overcoming Challenges in Antibiotics Discovery and Availability

Muhammad H. Zaman, Ph.D., and Katie Clifford, M.P.H., M.B.A.

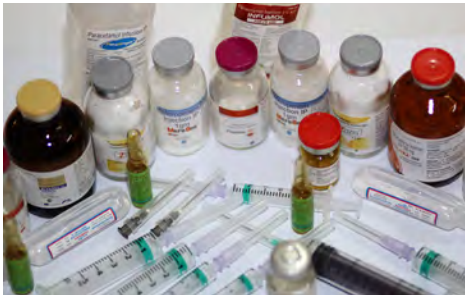
Discovery, Optimism and Decline

Mould Juice – that is what Sir Alexander Fleming called his discovery of penicillin (Rosen, 2017). While the story about an open window and Sir Fleming's coming back to his lab in London from vacation to find clear spots on *Staphylococcus* plates is debated by historians (Hare, 1982), there is little debate that Fleming made the discovery. Going from the mould juice to a form that could be used in a patient took over a decade as a team from the Oxford Dunn School had to work with a shoestring budget and improvise all kinds of apparatus (Lax, 2004).

The first human trial, on Albert Alexander in Oxford, was simultaneously a success and a failure. It was a success, for the infection that was oozing puss did get under control; a failure because the Oxford team ran out of the drug (due to its high impurity) and Albert died a month after the trial (Markel, 2013).

Penicillin, while discovered in the UK, came to the market largely through a combination of help from the US war effort, the US Department of Agriculture, and pharmaceutical companies in the US. Its arrival on the world stage was at an opportune time: just as the first cases of resistance to widely used sulfa drugs were being reported. Penicillin was a wonder drug, one that in many ways changed the course of World War II and created a massive interest in the antibiotic market (Quinn, 2013). The Soviet Union, in its national research labs, was making its own version of penicillin, and while it had some early success, the efficacy and potency remained weak. Ultimately they ended up procuring the drug from countries on the other side of the Iron Curtain (Kirchhelle, 2018).

The penicillin miracle soon started to wane, and with excess use of the drug, hospitals in London and beyond were starting to see emergence of resistance (Bud, 2007).



Despite the early signs of resistance, the period immediately following the war was one of high optimism in pharmaceutical companies. While soil scientists had known for quite some time about the vast reserves in nature, the big discovery of Streptomycin by Waksman and Schatz at Rutgers University opened up the possibility of harnessing soil (Kingston, 2004). Erythromycin, discovered in soil in the Philippines, and Vancomycin, from soil deep in the jungles of Borneo, further strengthened the belief that soil samples contained infinite reserves of antibiotics, and it was only a matter of looking hard enough (McKenna, 2017). The discovery of Methicillin through an academia-industry partnership (the collaboration between Sheehan at the Massachusetts Institute of Technology (MIT) and Doyle at Beecham (Graham, 2009)), suggested that there were new opportunities for antibiotic discovery by synthetic modifications of naturally occurring chemotherapeutics.

The discoveries continued to come in at a steady rate in the 1950s and early 1960s. However, with several hospital outbreaks of resistant infections in the UK, Australia, Canada, Denmark and the US, there was an increasing realization of the need for rational use and for newer antibiotics that would combat resistant infection (Chambers and Deleo, 2010). Committees and reports, in both the human sector (Barrett et al., 1968) and the animal sector (Wise, 2007) took a harsh stance against pharmaceutical companies and their aggressive marketing and sales tactics. This was around the same time as some of the earlier patents were expiring.

As the discoveries started to dry up, along with calls for stewardship and restrictions, the business models of pharmaceutical companies started to become strained. Demand for higher profits, increased competition from international generics (partly due to change in the Indian patent laws and a mushrooming of Indian pharmaceutical companies in the 1970s and 1980s), and better margins in non-communicable disease drugs for cancer, cardiovascular ailments, and diabetes led to a precipitous decline in antibiotic drugs coming to market (Falagas et al., 2006; Jawadekar, 2016; Khanna and Zaman, forthcoming). The last major class of antibiotics came out over 30 years ago in the mid-1980s (Conly and Johnston, 2005).

Before 2013, the last time a new class of drug for Gram negative resistant infections was discovered was 1962 with the development of quinolones (Tacconelli et al., 2018). It wasn't until recently that antimicrobials against Gram negative bacteria entered the development pipeline, with nine in development; however, of those nine, all are in Phase I clinical trials and none uses a novel mechanism of action (Boucher et al., 2013). Since the mid-1980s, the number of new antibiotics approved by the Food and Drug Administration (FDA) has continued to decline. For example, the number of antibiotics approved by the FDA in the four-year period of 1983-1987 was 16; the number from 2008-2012 was just two (Boucher et al., 2013). At the moment, there are 42 drugs in the antibiotic pre-clinical pipeline in the US, and they are primarily focused on urinary tract infection, nosocomial pneumonia, resistant *Staph* infection and uncomplicated gonorrhea (Pew Charitible Trusts, 2019).

It is important to note that all of the drugs brought to the market in the last 30 years have been variants of existing drugs discovered by 1984 (Jinks, 2017). Of all the major pharmaceutical companies, only four (GlaxoSmithKline (GSK), Merck, Roche and Pfizer) have active antibiotic pipelines (Hu, 2018). Novartis, the Swiss company, with an annual revenue of $51.9 billion (Novartis, 2018), was the latest multi-national pharmaceutical company to pull out of the antibiotic market in July 2018 while it had 32 products in the pipeline (Renwick and Mossialos, 2018). Two months prior to the Novartis announcement, Allergan, an Irish pharmaceutical company, divested its $1.5 billion dollar infectious diseases unit (Erman, 2018). According to recent data, only 4.7% of the total venture capital investment in pharmaceuticals between 2003-2013 was geared toward antibiotics (Renwick et al., 2016).

The Drug Development Process

Before we discuss the challenges with the dry pipeline of antibiotics, it is worthwhile to give a synopsis of the drug development process. The typical model for drug development is a five stage process (FDA, 2018b). In most cases it begins with a discovery in a lab followed by pre-clinical studies with animal models. Testing of the molecule in animal models is followed by submission of an investigation new drug (IND) application to the FDA; if approved, clinical research involving human patients can commence, evaluating safety and dosage (Phase I) and efficacy and side effects (Phases II – IV) (FDA, 2018b). Successful human trials enable the company making the drug to file for a new drug to FDA (or to a similar agency in Europe or elsewhere). This is followed by a comprehensive FDA review of safety and efficacy. The final stage of the process involves post-market surveillance and periodic oversight for continued safety.

During the early era of antibiotic discovery the first phases of this process were routinely carried out in-house in pharmaceutical companies. These days the first two steps are typically conducted in small biotech and pharmaceutical companies separate from the large multinational pharmaceutical companies. There is strong evidence that nearly all novel drugs that are approved are dependent on public funds in the early phase of discovery (Cleary et al., 2018).

Challenges Underlying the Dry Antibiotic Pipeline

Three challenges underlie the weak antibiotic pipeline: (1) technical challenges in discovery; (2) the cost of bringing products to market; and (3) the limited profitability of new drugs.

Technical Challenges in Discovery

The model of sifting through the soil that worked so well decades ago is no longer promising. While the number of antibiotics that are discovered are few, only a small fraction of those few are able to perform better in late-stage clinical trials than existing drugs on the market (Sukkar, 2013). While there are a number of promising candidates in the early R&D pipeline, particularly in the CARB-X portfolio, very few have moved past Phase I at this time, so efficacy has not been thoroughly evaluated (CARB-X, n.d.).

The spread of resistance has also made discovery more challenging. New discoveries that show promise against specific pathogens may be unable to tackle resistant strains. This means additional burden on discovery and trials, which acts as a disincentive for development. On average, less than 2% of antibiotics in preclinical development reach the market (Science Business, 2019). However, once those few antibiotics reach the clinical trial stage, their likelihood of ap-

proval improves. As of December 2018, there were 44 drugs in the global antibiotic pipeline, with 14 drugs in Phase I, 11 drugs in Phase II, 13 drugs in Phase III, three submitted for New Drug Application, and three approved (Pew Charitable Trusts, 2019). Of the three antibiotics approved, all were active on the same target and all were effective against Gram-negative ESKAPE pathogens.

Cost of Bringing Products to Market

Antibiotic development costs have gone up from $231 million in 1987 to $802 million in 2001 (Katz et al., 2006). Increased global resistance means that pharmaceutical companies have to conduct more extensive clinical trials than they did decades ago. The costs of trials have gone up, and the majority of research for new molecule discovery is happening at small to mid-size pharmaceutical companies that do not have the financial means to carry the drugs through the expensive stages of clinical trials (Science Business, 2019; Sukkar, 2013). Limited public funding is available to these companies for clinical trials (Renwick and Mossialos, 2018).

There is also a high burden to prove efficacy, through demonstration that the drug in clinical trials is equally or more efficacious than either a placebo, if it's a first in class drug, or existing therapies, if there is already a standard of treatment used (FDA, 2018a; Sukkar, 2013). The duration of the indication is also much shorter than chronic diseases, making it difficult to find and enroll patients in a clinical trial (Renwick and Mossialos, 2018). In addition, the timeline for clinical trials adds risk as, by the time the drug reaches the market, there is a chance that there may already be signs of resistance against the molecule (Satyanarayana, 2018).

Limited Profitability

The timeline for development is relevant for another reason. Any major new drug would most likely be used sparingly to preserve its clinical efficacy, leading to limited sales in the early years due to stewardship efforts. This was the case for the antibiotic Teflaro (Allergan), which entered the market in 2016 and was effective against multidrug resistant infection. With average annual sales of just $130 million, compared to $1.4 billion for the company's leading oncology drug, Allergan

decided to cut its antibiotic R&D arm in 2018 (Coukell and Boucher, 2019). This would also mean that the period of exclusivity for a pharmaceutical company during which its profits are the highest could be undercut significantly by very limited sales. Revision of guidelines from the US Patent and Trade office in 2001, in response to criticism that patentability was defined too liberally, has also affected the number of patent applications for new antibiotics (Katz et al., 2006).

While the demand for antibiotics in low- and middle-income countries is high, large pharmaceutical companies and their products have a smaller footprint in these places compared to generic manufacturers. The necessary push for stewardship to preserve the efficacy of antibiotics, both in animals and humans, means that there will be fewer antibiotics sold in the future, compared to chronic diseases, where the market growth looks significantly stronger (Sukkar, 2013). Additionally, the fact that not all antibiotics can be sold freely, and some are reserved for exceptional circumstances, further diminishes the interest of pharmaceutical companies (Jinks, 2017). There are also concerns by pharmaceutical companies, operating in the global marketplace, that antibiotics are often underpriced (McKenna, 2018).

Ultimately, the case for investment in R&D for antibiotics is significantly weaker than for chronic diseases. For example, the net present value (NPV) for investment in R&D for antibiotics is negative $50 million, suggesting that, on average, a company investing in antibiotics will lose money (Renwick and Mossialos, 2018). In comparison, NPV for oncology drugs is $300 million, musculoskeletal disease is $1,150 million and for neurologic disease it is $720 million (Renwick and Mossialos, 2018). Of the 16 brand name antibiotics approved since 2000, only five were able to generate profits of $100 million annually (McManus, 2018). This has an impact on where pharmaceutical companies invest their funds: as of 2014, there were 800 oncology drugs in clinical trials, compared to 50 antibiotics in the R&D pipeline (Villanueva and Fanjul, 2017).

Exploring Solutions

Innovation for discovery of new antibiotics is essential. This section explores mechanisms to increase investments in discovery, reduce the cost to bring a new antibiotic to the market, and develop alternatives to antibiotics.

Increasing Investment in Discovery

There is a need for increasing funding not just at the basic science level but also for later-stage translation. Eighty-five percent of the current funding earmarked for antibiotics in the EU, for example, goes toward basic research with limited funding for expensive clinical trials (Renwick and Mossialos, 2018). There are calls to pool some of the disparate early-phase funding and redirect it to more focused later-stage funding to increase the chance of success later in the pipeline. There are also possibilities of increasing tax credits for companies that invest in R&D for antibiotics (Sukkar, 2013).

Various innovative funding models have been created. These include public-private partnerships, such as CARB-X, a $550 million consortium based at Boston University and funded through a joint partnership among the US Department of Health and Human Services' (HHS) Biomedical Advanced Research and Development Authority (BARDA); the Wellcome Trust; Germany's Federal Ministry of Education and Research (BMBF); the UK government's Global Antimicrobial Resistance Innovation Fund (UK GAMRIF); the Gates Foundation and receiving in-kind support from the National Institute of Allergy and Infectious Diseases (NIAID) (CARB-X, n.d.). CARB-X started in 2016 and aims to fund promising "best science and most promising early development R&D projects anywhere in the world" and is focused on supporting early-stage antibiotic development projects that will attract private or public funding for clinical development. The model is based on non-dilutive funding for pre-clinical and early development antibiotic therapies and diagnostics, where founders would not have to give up ownership of their company in order to secure investment. At the moment, CARB-X has 33 projects in seven different countries with five projects in Phase I clinical trials.

CARB-X
Combating Antibiotic-Resistant Bacteria

A more recent example of the potential of public-private partnerships in accelerating antibiotic development can be seen in the collaboration between the US Departments of Defense (DoD) and HHS with VenatoRx Pharmaceuticals (Johnson, 2019). HHS and DoD will partner with VenatoRx in their efforts to commercialize VNRX-5133, a compound that will combine with antibiotic cefepime to treat the increasing number of drug-resistant urinary tract infections. This two-year engagement will provide VenatoRx with $30 million in funding from HHS and DoD to apply for FDA approval of the drug and for additional studies to test the drug's efficacy in relation to bioterrorist threats (Johnson, 2019). All parties recognize the need for a more robust antibiotic pipeline, with the director of BARDA stating that new antibiotics are "essential to national health security and global health efforts to combat antibiotic-resistant infection" (Johnson, 2019). With the funding support from the federal government, VenatoRx will begin Phase III clinical trials in August 2019.

Another model of supporting private sector R&D efforts for much-needed antimicrobials is the Global Antibiotic Research and Development Partnership (GARDP) (GARDP, n.d.). Established by the World Health Organization (WHO) and Drugs for Neglected Disease Initiative in 2016, GARDP is a non-profit that focuses on development of and improved access to novel antibiotic therapies. Focused on developing therapies for sexually-transmitted infections, neonatal sepsis, and pediatric pneumonia, GARDP partners with corporations and other organizations to conduct research on novel antibiotic compounds as well as revisit previously abandoned early stage research. GARDP has recently partnered with pharmaceutical companies Takeda and Eisai, gaining access to those companies' chemical libraries where they can screen for potentially promising antibiotic compounds against pathogens on the WHO global priority list. In addition to accessing these valuable compound libraries, this partnership keeps both Takeda and Eisai engaged in antimicrobial R&D efforts.

Reducing Cost to Market

The need for a more robust antibiotic pipeline that is able to effectively treat increasingly resistant infections is well known. Still, this unmet need and increasing demand has not yet translated to an increased investment by drug makers in antibiotic R&D. While there have been a number of pre-market, "push" incentives over the past decade, led by organizations such as BARDA, CARB-X, and the National Institutes of Health, private sector investment in antibiotics still lags (Coukell and Boucher, 2019).

To ensure a sustainable antibiotic pipeline, "pull" incentives are needed to restructure how the market for antibiotics functions and to attract continued pharmaceutical sector investment. Effective "pull" incentives must be structured to direct R&D investment toward the most pressing pathogen threats, to balance a growing antibiotic portfolio with stewardship and surveillance, and to reliably reward companies that bring novel antibiotics to market (Coukell and Boucher, 2019). Bringing drugs to market requires tremendous initial investment, and the market is not currently built to reward those who invest in novel and much needed antibiotic drug development. Just recently, Melinta and Achaogen, two public companies with approved antibiotics coming to market, were facing serious financial difficulties, with Achaogen filing for bankruptcy in April 2019.

One method of incentivizing investment in antibiotic R&D efforts is to address the issue of high costs of clinical trials, particularly through allowing for smaller trials to be run. Recognizing that the cost of large clinical trials is a disincentive for antibiotic development, the European Medicines Agency issued updated guidelines in 2013, allowing for smaller clinical trials to be used for new antibiotics targeting drug resistant infection while maintaining the same efficacy standards (Sukkar, 2013). While previously, clinical trials required thousands of patients, the new guidelines allow antibiotic clinical trials to enroll a few hundred patients, reducing the cost and time burden substantially.

Legal scholars have argued for creating market entry rewards (MERs) in the form of a monetary prize upon successfully licensing a novel, therapeutically efficacious antibiotic, provided it also meets criteria for patient access, safety and sustainability (Anders, 2018; Renwick and Mossialos, 2018). The MERs would be linked to R&D costs and/or public health value, and not sales volume, to overcome the sales problems described earlier. Given the high pay-out needed as an incentive (on the order of $1-2 billion USD), and the global market for efficacious antibiotics, these pay-outs would need to be internationally coordinated. The UK National Institute of Health and Care Excellence (NICE) is looking into a similar mechanism that would pay pharmaceutical corporations for antibiotics on the basis of their clinical value, rather than sales (ProductLife Group, 2019).

Another idea is to create an Options Market for Antibiotics (OMA) where developers sell options to a broad group of interested stakeholders (international agencies, government, inter-government agencies, other NGOs), which would fund part of the R&D. Those investors would then get a discounted price should the antibiotic reach the market (Renwick and Mossialos, 2018).

A critical issue faced by companies that may produce novel antibiotics is that they will confront limited sales due to calls for preserving the most potent antibiotics for the most acute needs. One avenue to address this would be to reimburse companies for unsold medications (Anders, 2018).

There is risk associated with all of the above approaches. Small and medium enterprises with potential targets would need substantial support (well beyond the grants available from CARB-X and similar endeavors) to move along the pipeline, assuming that their candidates continue to perform well in subsequent stages of the trials. While MER and OMA mechanisms increase incentives for development, the likelihood of any potential drug candidate reaching the market is still low, keeping the risk elevated for corporate investors (in the case of MER) and other stakeholders (in the case of OMA). Pooling of resources across multiple agencies and governments, from high-income countries, along with public private partnerships, may decrease these risks.

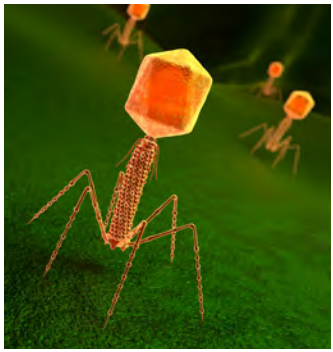
Pursuing Alternatives to Antibiotics

Since the weak pipeline for new antibiotics classes is a major concern, there has been increasing discussion of alternative approaches to tackle and treat drug resistant infection. Two main avenues in this sector merit discussion.

First, bacteriophages, discovered in 1915 by British microbiologist Frederick Twort, and subsequently by Canadian-French scientist Felix d'Herelle, are being discussed again (Keen, 2015). Bacteriophages are viruses that reside inside a bacterium, can commandeer bacterial machinery for replication, and cause bacterial death. Prior to the use of sulfa drugs and penicillin, bacteriophages had become a global sensation for infectious diseases and clinical trials were conducted from Algeria to Vietnam, India to Indiana. Phages fascinated not only public health professionals and doctors, but also artists and literary figures. Lewis Sinclair's Pulitzer Prize winning book, *Arrowsmith*, is about a doctor who discovers phage therapy and goes against the scientific establishment to cure the disenfranchised (Lewis, 1988). There was significant interest in the therapy from the former Soviet Union with the establishment of an institute in Tbilisi, Georgia that continues to function to this day and recently celebrated its 100 years of work (Parfitt, 2005).

With limited efficacy against a broad spectrum of diseases (Loc-Carrillo and Abedon, 2011), a decline in funding for phages (Boodman, 2018a), and the ease with which antibiotics could be produced and shipped, interest in phages started to wane. Since the late 1980s, however, the interest in phages has once again

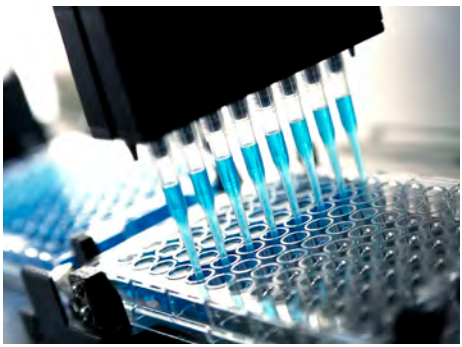
gained momentum due to better understanding of virus-host interaction and advancement in the field of bacterial genetics. Recent interest and investment in phage therapy seems promising, including interest from the US Navy (Boodman, 2018b). Discussion in scientific magazines, and non-fiction science literature, has further fueled public interest in the topic. However, despite the potential, robust human clinical trial data for phages remains very limited. There are some data in early Phase I clinical trials that seem promising (Keen, 2015; Salmond and Fineran, 2015), but scant data for Phases II and III for phage therapies suggest that broad use of phage therapy may not happen in the very near future.



The second alternative approach being proposed is the use of vaccines. Researchers argue that there are several reasons to invest in vaccination as a potent approach against drug resistant infections. While resistance against an antibiotic is a natural and evolutionary process, vaccines do not have the same resistance challenges (Bloom et al., 2018) because they are prophylactic and decrease the incidence of the disease. If children globally received a vaccine against *Streptococcus* pneumoniae, which causes meningitis, ear infection and pneumonia, the WHO estimates there would be a reduction of 11 million days of antibiotic use annually (WHO, 2016). Furthermore, vaccines target pathogens in a variety of ways, and for a pathogen to become resistant against those would require a series of specific selective mutations, the likelihood of which remains small.

A broad analysis of vaccines versus antibiotics would suggest that while the golden period of antibiotic discovery was in the 1950s and 1960s, the golden era of vaccines is the present time (Mroz, 2017). As of October 2017, there were 144 infectious disease vaccines in the R&D pipeline, with the most common targets being influenza, HIV, RSV and Ebola (Shen and Cooke, 2019). Still, there are a few vaccines in development targeting bacterial agents, such as *C. difficile* and meningococcal, and both are in Phase III trials (Shen and Cooke, 2019). The WHO believes that vaccines are a promising means of slowing antibiotic resistance, and are calling for vaccine development for *Streptococcus* (strep throat), tuberculosis, *Klebsiella* pneumoniae (pneumonia and urinary tract) and *Staphylococcus aureus* (staph infection), which hold great potential for reducing the overuse and misuse of antibiotics worldwide (WHO, 2016).

The uptick in vaccine development is largely due to decreasing cost of vaccine production through a number of new technologies (Sederstrom, 2018). However, vaccine development is very consolidated, with 90% of vaccine sales being driven by four large pharmaceutical companies – GSK, Merck, Pfizer and Sanofi (Shen and Cooke, 2019). The use of vaccines also means that antibiotic consumption would decrease, due to lower incidence of overall and bacterial-specific illness in the population, resulting in a reduction of cases of resistance driven by overuse and misuse of antimicrobials (Klugman and Black, 2018; Shen and Cooke, 2019). Last, but not least, vaccines also preserve the microbiome, unlike antibiotics that can have a disruptive impact on the microbiome, especially that of children.



Despite these potential upsides, vaccine development for all resistant infections is unlikely. For example, the WHO has noted a vaccine for *S. aureus* would hold great public health impact; however, the ability of the pathogen to evade the immune system has seriously complicated vaccine development efforts (Giersing et al., 2016). Furthermore, vaccines, unfortunately, continue to suffer from anti-vaccination movements that are putting many lives at risk (Board, 2019). An increase in vaccine research, therefore, will also need to be combined with an awareness movement to allay concerns among certain segments of society about vaccines.

Learning from India, China and Europe

While the US continues to lead in innovation and discovery, there are important lessons to learn from research and development efforts in Europe, India, and China. In the case of China, there is a strong public investment in innovation, with support for antimicrobial resistance coming directly from President Xi Jinping (Xiao and Li, 2016). The UK-China partnership, established in 2016, aims to create bilateral funding support mechanisms for research, discovery and innovation in the context of drug discovery and development. The "Made in China 2025" campaign also aims to transform the Chinese pharmaceutical sector, with strong public-private partnership and tax incentives (L.E.K. Consulting, 2018). In addition, China is making it possible for non-Chinese companies to conduct clinical trials in China with fewer hurdles and bureaucracy, although policy change is in early stages (Sami, 2017).

The case with India is different, as India has been a world leader in generic pharmaceuticals for a few decades, but lags behind in new and innovative pharmaceutical discovery (Differding, 2017). However, recent partnerships of Sanofi (Palmer, 2016), Merck (Van Arnum, 2011), Bristol Meyers-Squibb (Bristol-Myers Squibb, 2007), and GSK (GlaxoSmithKline, 2009) with Indian manufacturers suggest a hybrid model where multi-national companies and generics can partner together to create new vaccines or novel molecules.

The European Union also has created policies and incentives which may provide meaningful examples to the US. These include the "Innovative Medicines Initiative" (IMI) which is a large-scale public-private partnership between the European Commission and the European Federation of Pharma Industries and Association to screen new molecules (Goldman, 2012). The aim of this initiative is to mitigate risk, increase efficiency by pooling resources, and create a culture of collaboration for discovery. The funding for the initiative is a joint public-private venture with pharmaceutical companies contributing over $3 billion, and the public sector adding $1 billion (Reichman and Simpson, 2016). Several projects such as Drive AB and New Drugs for Bad Bugs (Outterson et al., 2015) are under the IMI initiative. Correspondingly, there are stronger intellectual property laws approved by the EU that encourage drug development (Annemans et al., 2011).

Finally, and perhaps most important, the European Medicines Agency (EMA) (a parallel of the US FDA) has revised its clinical trials policy to make it easier for pharmaceutical companies to gain approval for new antibiotic drugs across large global markets. In early 2019, EMA published revised guidelines on the evaluation of antimicrobial clinical trials in an effort to align regulatory requirements with that of the FDA and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) (Kent, 2019). This policy change is meant to reduce the amount of duplicate work that is required of pharmaceutical companies during clinical trials, effectively reducing associated trial costs and allowing them to enter the EU, US and Japanese markets earlier. These guidelines are currently in a six-month public consultation period, and will go into effect at the end of July 2019 (ProductLife Group, 2019).

Conclusion

The need for new antibiotics, in addition to global partnership on One Health and reduced antibiotics in hospitals, homes and farms, is critical. The innovation pipeline, at the moment, does not look promising. A single strategy is unlikely to work. A multi-pronged strategy that involves investment not just in basic science, but also in clinical trials, is needed. This should be combined with market entry incentive structures and a parallel pursuit of alternative treatment and prophylactic strategies including phages and vaccines. Most important, no country can do this alone. There is much that the US has to offer, but equally important, the US can learn from other models and strategies in other parts of the world. AMR is a problem facing the entire world; it requires a solution that is global in its structure, character and scope.

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ADDRESSING ANTIMICROBIAL RESISTANCE

A Report of the Aspen Health Strategy Group

The mission of the Aspen Health Strategy Group is to promote improvements in policy and practice by providing leadership on important and complex health issues. The group is comprised of 23 senior leaders across influential sectors including health, business, media, and technology, and is part of the Health, Medicine and Society Program at the Aspen Institute. Co-chaired by Kathleen Sebelius and Tommy G. Thompson, both former governors and former US Secretaries of Health and Human Services, the Aspen Health Strategy Group tackles one health issue annually through a year-long, in-depth study. This book is a collection of papers on the group's fourth subject: antimicrobial resistance (AMR). The papers provide an overview of AMR and address topics related to human demand, animal- and environmental-health factors, and drug pipeline challenges, and includes a final consensus report based on the group's work.

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