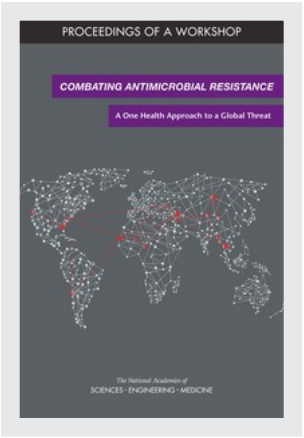

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COMBATING ANTIMICROBIAL RESISTANCE

A One Health Approach to a Global Threat

PROCEEDINGS OF A WORKSHOP

Ceci Mundaca-Shah, V. Ayano Ogawa, and Anna Nicholson, *Rapporteurs*

Forum on Microbial Threats

Board on Global Health

Health and Medicine Division

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Acronyms and Abbreviations

AAVMC	Association of American Veterinary Medical Colleges
APHIS	Animal and Plant Health Inspection Service
APLU	Association of Public and Land-grant Universities
BEARI	Behavioral Economics to improve treatment of Acute Respiratory Infection
BMGF	Bill & Melinda Gates Foundation
BQA	Beef Quality Assurance
CARE	Collective Antimicrobial Resistance Ecosystem
CDC	U.S. Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
COP	colonizing opportunistic pathogen
CRE	carbapenem-resistant Enterobacteriaceae
DRI	drug-resistant infection
EHR	electronic health record
ESBL	extended spectrum beta-lactamase
ESKAPE	*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterobacter*
FAO	Food and Agriculture Organization of the United Nations
FDA	U.S. Food and Drug Administration

GARDP	Global Antibiotic Research & Development Partnership
GDF	Global Drug Facility
GFSI	Global Food Safety Initiative
GHSA	Global Health Security Agenda
GLASS	Global Antimicrobial Resistance Surveillance System
GP	general practitioner
HAI	health care–associated infection
IACG	Interagency Coordinating Group on Antimicrobial Resistance
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
IHR	International Health Regulations
IMI	Innovative Medicines Initiative
IV	intravenous
MDR	multidrug resistant
MDR-TB	multidrug-resistant tuberculosis
MI	microbiome index
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
MTB	*Mycobacterium tuberculosis*
NAE	no-antibiotics-ever
NARMS	National Antimicrobial Resistance Monitoring System
NIFA	National Institute of Food and Agriculture
OIE	World Organisation for Animal Health
PAVE	Priority Antimicrobial Value and Entry
PCV	pneumococcal conjugate vaccine
RIF	rifampin
SHEA	Society for Health Care Epidemiology of America
SSAFE	Safe Supply of Affordable Food Everywhere
TB	tuberculosis
UN	United Nations
USDA	U.S. Department of Agriculture

VFD	Veterinary Feed Directive
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

1

Introduction

As of 2017, the emergence and spread of antimicrobial resistance continues unabated around the world, leaving devastating health and economic outcomes in its wake. Those consequences will multiply if collaborative global action is not taken to address the spread of resistance. An influential report released in 2016 estimated that each year at least 700,000 people across the world die from infections that are resistant to current antibiotics, and by 2050, drug-resistant infections will take an estimated 10 million lives per year (Review on Antimicrobial Resistance, 2016). The same report further predicts that the economic cost of lost global production caused by antimicrobial resistance will amount to approximately $100 trillion between now and 2050 if antimicrobial resistance is not tackled. Despite this crisis, there are very few prospects for new antibiotics in the development pipeline that are likely to receive regulatory approval; new drugs will be critical as existing antibiotics lose their effectiveness against infections at an escalating rate. Additionally, improved antimicrobial stewardship practices that promote appropriate use of antimicrobials may be needed to be adopted widely in reducing drug resistance and achieving better patient outcomes. As the burden of resistance to antibiotics grows, even routine medical conditions and procedures will become life threatening because of the risk of untreatable infection. International multilateral organizations have recognized the threat of antimicrobial resistance and have developed plans for action, but there is an urgent need for the immediate implementation of collective actions. "Imagine the emergence of a rapidly spreading bacteria resistant to all known antibiotics. . . . We need to act

now or run the risk of entering a postantibiotic era," warned Victor Dzau, president of the National Academy of Medicine.

WORKSHOP OBJECTIVES

Major drivers of antimicrobial resistance in humans have been accelerated by inappropriate antimicrobial prescribing in health care practices; the inappropriate use of antimicrobials in livestock; and the promulgation of antibiotic resistance genes in the environment. The National Academies of Sciences, Engineering, and Medicine have been engaged with the issue of antimicrobial resistance for nearly two decades (IOM, 1998, 2010, 2011). To build on this work, to explore developments since the last workshop was convened, and to help parlay knowledge into immediate action, an ad hoc planning committee,[1] under the auspices of the Forum of Microbial Threats at the National Academies, planned the 2-day public workshop Combating Antimicrobial Resistance: A One Health Approach to a Global Threat.

The workshop explored issues of antimicrobial resistance through the lens of One Health, which is a collaborative approach of multiple disciplines—working locally, nationally, and globally—for strengthening systems to counter infectious diseases and related issues that threaten human, animal, and environmental health, with an end point of improving global health and achieving gains in development. The approach can be used to examine how factors across those three domains of human, animal, and environmental health converge and contribute to the emergence and spread of antimicrobial resistance. A concerted effort across these three domains can help strengthen the fight against the threat of antimicrobial resistance. Furthermore, the workshop was convened to explore immediate and short-term actions and research needs that will have the greatest effect on reducing antimicrobial resistance, while taking into account the complexities of bridging different sectors and disciplines to address this global threat. Topics explored during the workshop include the following[2]:

- The implications and effects on human health of the movement of resistance genes across different ecosystems;

[1] The planning committee's role was limited to planning the workshop, and this Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

[2] The full Statement of Task is available in Appendix A.

- The expected effect of new regulatory policies and waste management techniques in the United States regarding the use of antimicrobials in animal agriculture;
- The role and effectiveness of antibiotic stewardship programs in reducing and preventing antimicrobial resistance;
- The importance of data availability and data sharing to monitor and evaluate strategies' implementation and progress;
- Strategies for maintaining the effectiveness of existing drugs, for developing new drugs and diagnostics, and for implementing disease prevention strategies, including vaccine use and the alternatives to antibiotics; and
- The need for national and international collaboration and coordination mechanisms across the One Health domains for prevention, control, and research and development.

The 2-day workshop was held on June 20 and 21, 2017, in Washington, DC, and was chaired by Lonnie King, professor and dean emeritus of The Ohio State University College of Veterinary Medicine. Workshop speakers and discussants contributed perspectives from government, academia, private, and nonprofit sectors. The workshop comprised 2 keynote addresses and 25 speaker presentations over 4 sessions. During the final session, speakers and discussants broke out into four groups to identify impactful short-term actions that are feasible and cost-effective against antimicrobial resistance.

ORGANIZATION OF THE PROCEEDINGS OF A WORKSHOP

In accordance with the policies of the National Academies, the workshop did not attempt to establish any conclusions or recommendations about needs and future directions, focusing instead on information presented, questions raised, and improvements recommended by individual workshop participants. Chapter 2 includes highlights from the keynote addresses that discuss harnessing the global momentum to prioritize a strategy for immediate action to combat antimicrobial resistance. Chapter 3 focuses on microbial and genetic movements across the One Health domains. It discusses approaches to strengthening the knowledge and evidence base for surveillance of antimicrobial resistance and for the effect of antimicrobials in the environment. Chapter 4 features strategies for applying social and behavioral sciences to help improve responsible use of antimicrobials. It delves into achieving desired behavioral changes toward antimicrobial use through stewardship programs, incentives, and policies, as well as education and prevention measures. Chapter 5 covers research and development actions aimed at reducing antimicrobial use, specifically

examining strategies to accelerate and prioritize basic and applied research and development for vaccines and diagnostics, and funding mechanisms to promote such investments. Chapter 6 lays out the importance of partnerships and collaboration in combating antimicrobial resistance. Chapter 7 provides an overview of the actions suggested during the four breakout groups' discussions that took place as the final session of the workshop, as well as the subsequent discussion and general synthesis.

2

The Global Momentum to Counter Antimicrobial Resistance

To provide some context for the workshop's presentations and discussions, Keiji Fukuda, director and clinical professor at the University of Hong Kong School of Public Health, and Sally Davies, chief medical officer for England in the United Kingdom Department of Health, provided their perspectives on harnessing the current global momentum to combat antimicrobial resistance.

MOVING FROM KNOWLEDGE TO ACTION

During his keynote address, Fukuda reflected on how the issue of antimicrobial resistance has evolved since the 20th century. The discovery of penicillin in 1928 and the introduction of sulfonamides in 1937 ushered in an intense period of scientific discovery related to microbial infections, antimicrobial resistance, and drug development that continues today, said Fukuda. He noted that the 1950s through the 1970s was the "golden period" of antibiotic development, discovery, and production that spawned many of today's current classes of antibiotics. Since the identification of transferable resistance in the 1950s, he said, an estimated 200,000 articles related to the concept have been published (Davies and Davies, 2010). The same period saw the emergence of national and international efforts to provide scientific guidance and perspectives on resistance, said Fukuda. In 1959, the World Health Organization (WHO) scientific group on antibiotics research first recommended studies on resistance (WHO, 1960), and in 1981, a scientific working group on antimicrobial resistance released a report including guidelines for the appropriate use of antibiotics (WHO,

1981). In 2001, WHO released its Global Strategy for Containment of Antimicrobial Resistance (WHO, 2001). Fukuda added that the Transatlantic Taskforce on Antimicrobial Resistance was formed in 2009, and 2011 saw the release of the European Action Plan,[1] the Jaipur Declaration,[2] and the World Health Day "Antimicrobial resistance: no action today, no cure tomorrow" policy package.[3]

The outcome of this scientific work, said Fukuda, has been a plethora of scientific knowledge and guidelines—from WHO, from the World Organisation for Animal Health (OIE), and from the Food and Agriculture Organization of the United Nations (FAO), among others—about preserving the efficacy of antimicrobials. The 1998 World Health Assembly resolution WHA51.17 (Emerging and other communicable diseases: antimicrobial resistance)[4] brought to the forefront issues that are only beginning to be grappled with today, he said. Fukuda explained that the resolution formalized concerns about the rapid emergence and spread of human pathogens resistant to available antibiotics, about the increasing inefficacy of available antibiotics and the high cost of the new-generation antimicrobials, and about the potential for extensive use of antibiotics in food production to further accelerate the development of resistance.

There have been major gains in scientific knowledge, concepts, and professional guidance related to antimicrobial resistance, said Fukuda. However, he observed that the issue has been positioned as a complex phenomenon of primarily medical relevance. Although the recent adoption of the One Health approach has broadened its relevance to other fields, he said, the expectation that science will provide an endless supply of new antibiotic drugs remains prevalent. The reality is that the pharmaceutical industry has been losing interest in delivering new medicines because new antibiotic drugs are not financially viable, he cautioned, which is juxtaposed with the continued increase in antimicrobial resistance trends worldwide. The first global survey of antimicrobial resistance that was conducted by WHO in 2014, explained Fukuda, examined a group of hospital and community infections and resistance patterns to study the magnitude of antimicrobial resistance across all WHO regions and countries. The report found high levels of antimicrobial resistance in all regions, he said, as well as significant gaps in surveillance data and underreporting of key concerns

[1] The European One Health Action Plan against Antimicrobial Resistance is available at ec.europa.eu/health/amr/sites/amr/files/amr_action_plan_2017_en.pdf (accessed July 31, 2017).

[2] The Jaipur Declaration on Antimicrobial Resistance is available at www.searo.who.int/entity/regional_committee/64/rc64_jd.pdf (accessed July 31, 2017).

[3] The World Health Day "Antimicrobial resistance: no action today, no cure tomorrow" policy package is available at www.who.int/world-health-day/2011/en (accessed July 31, 2017).

[4] World Health Assembly resolution WHA51.17 is available at archives.who.int/prioritymeds/report/append/microb_wha5117.pdf (accessed July 31, 2017).

such as multidrug-resistant tuberculosis. The report underscored the need for active strategic change and extending engagement beyond the health and science sector, he said, because current approaches are essential but not sufficient.

The One Health approach provides a collaborative concept to broaden engagement beyond the realm of health and science, Fukuda said. FAO, OIE, and WHO are partnering around the One Health concept and actively targeting champions at the highest possible levels in political, economic, security, and business sectors around the world. He reported that these efforts have affected meaningful change by broadening, publicizing, and socializing the discussion about antimicrobial resistance. He pointed to WHO's global action plan on antimicrobial resistance (WHO, 2015b) as a key development. Although it is essentially a repackaging of principles and guidance that had been created years previously, he said, it represents the outcome of focused diplomatic effort to engage across sectors and with countries at all levels of development. It also laid the foundation for a milestone high-level meeting of the G20 and the United Nations (UN) in 2016, which increased the issue's legitimacy and formalized countries' commitment to address antimicrobial resistance. The meeting also mandated an Interagency Coordinating Group on Antimicrobial Resistance (IACG), which is composed of high-level representatives of relevant UN agencies, other international organizations, and individual experts across different sectors, to provide practical guidance for approaches needed to ensure sustained effective global action to address antimicrobial resistance. The gains achieved are political and time limited, Fukuda warned, unless they are built upon through institutional commitment and cooperation across nonhealth public sectors and catalyze further action in the private sector.

Fukuda considered how to capitalize on the momentum of efforts to date and move from knowledge about antimicrobial resistance to the next phase of action. The high-level aims remain unchanged, he said: achieving the lowest possible sustained levels of antimicrobial resistance; developing and producing reliable new technologies, including essential medicines; and providing affordable and equitable access to those technologies. According to Fukuda, there are several foundational elements to emphasize. He noted that antimicrobial resistance needs to become a high-profile social issue—like cancer, tobacco control, or HIV/AIDS—to provide the necessary fuel to drive change. Antimicrobial resistance needs to be familiar and personally relevant to the average person, he added, and not an abstract, far-removed issue that people assume science will remedy. "Socialization" of antimicrobial resistance must be the fundamental driver, Fukuda argued, because popular concern and support will be needed to enable new policies, initiatives, and funding. He reflected, "The concrete challenge is how do you take something that in general is seen as abstract, technical, and distant, almost

like science fiction, and . . . make that personal? How do you humanize it? How do you make it seem like something that has to be dealt with now?" He suggested employing multiple voices, including civil society and media, to recraft the concept as personal, urgent, and potentially reversible with appropriate action.

Fukuda remarked that accelerating the pace of change will require closing certain knowledge gaps. He observed that in public health, evidence sometimes drives action, but insufficient evidence is often cited as justification for slow progress. Critical gaps in information, he said, include the need for a more holistic picture of the epidemiology and the etiology of resistance across the One Health domains, which will allow better allocation of resources and responsibilities. Understanding which interventions are most cost-effective is another gap, he said, as well as strategies for transitioning past the use of antimicrobials for growth promotion in agriculture.

Moving forward, Fukuda urged key groups to be visibly active in their efforts to address antimicrobial resistance. He suggested the following:

- The UN's IACG should actively engineer cooperation and coordination among sectors.
- FAO, OIE, WHO, and other international organizations should keep the issue of antimicrobial resistance at the forefront, provide strategic advice in addition to technical guidance, and continue to exemplify the One Health approach to partnering.
- Governments should take leadership roles and broaden the involvement of nonhealth agencies, as well as introducing legislation and providing financing. Additionally, the health and agriculture sectors on the national level should work to make knowledge about antimicrobial resistance and best practices normative and to separate profit from the provision of antibiotics.
- Civil society can serve as society's conscience, scrutinizing and organizing efforts around the inappropriate use of antimicrobials.
- Industry should find ways back into antimicrobial drug production and should internalize access to drugs as an operational concept of production, not a separate issue.
- Funders and academia should drive large-scale, multidisciplinary, impact-based research to close the knowledge gaps.

DEVISING AND PRIORITIZING A STRATEGY FOR IMMEDIATE ACTION AND IMPLEMENTATION

Davies warned that action on the ground against antimicrobial resistance will require evidence; research to gather evidence, she added, requires the appropriate policy and funding, which can only be obtained through

political and civil engagement. She remarked that "If we don't get this right, not only will there be an impact with people dying of infection and that will alter modern medicine, but it will impact global health security and agricultural livelihoods and our environment."

Davies emphasized that antimicrobial resistance is a complex, intricate problem that is not easily visible and understood by the public. However, the reality is that drug-resistant infections cause nearly one death every 45 seconds around the world—with the young, the old, the immunocompromised, and the pregnant disproportionately affected (Review on Antimicrobial Resistance, 2016). If the tide is not stemmed, the rate will increase to one death every 3 seconds, and 28 million people, mostly in developing countries, will be pushed into extreme poverty by 2050 (World Bank, 2017). With the ability of antimicrobial resistance to contribute to increased mortality and poverty worldwide and to affect the global economy, she added, achieving the UN's Sustainable Development Goals will require antimicrobial resistance to be addressed.

Despite this need to address antimicrobial resistance, Davies reported that there have been no new classes of antibiotics in routine clinical practice since the 1980s because the market has failed. Not only have companies withdrawn from the market, but also the research environment is barren, she said. Reliance on new drugs is not the complete answer though, reminded Davies, as other efforts such as surveillance and interdisciplinary work, including contributions from economists, are also crucial. With all this said, she also pointed out that more people die worldwide from lack of access to antimicrobials than to resistance, and so handling the tension between lack of access with excess use is critical.

Davies remarked on the push for global action on antimicrobial resistance over the past few years. Repeating what Fukuda mentioned earlier in his presentation, Davies said that significant diplomatic efforts to engage across sectors and countries have helped achieve progress. She particularly highlighted the importance of the 71st session of the UN General Assembly high-level meeting in 2016 that Fukuda alluded to, where heads of state adopted a political declaration calling for coordinated global action—an agreement that had been negotiated among member states under the leadership of the Permanent Representative of Mexico. Several countries, including China, Germany, the Netherlands, Sweden, and the United Kingdom, also played key leadership positions, she added. There was also progress with the G20 in 2017 with a communique to be put forth a few weeks after the workshop by G20 leaders on commitment to combating antimicrobial resistance (G20 Leaders, 2017). Davies said negotiations continue on the diplomatic level.

Davies provided further details on the IACG, which she directs the

work of as one of the three conveners.[5] IACG is supported by the tripartite secretariat of FAO, OIE, and WHO, has membership from all UN agencies, brings together experts across difference sectors including the environment, and is cochaired by the WHO director general and the UN deputy secretary-general. She was optimistic that the IACG will serve as a useful mechanism for driving action through the following terms of reference (IACG, 2017):

- Raise awareness and support implementation of major global priorities, tools, and standards for reducing antimicrobial resistance, including WHO's global action plan and supporting the Sustainable Development Goals.
- Coordinate mapping of actions being taken by UN agencies, other organizations, and key stakeholders toward achieving measurable results, and identify opportunities for collaboration, as well as gaps, redundancies, and duplication.
- Promote, plan, and facilitate collaborative action to align activities so gaps are closed and resources are optimally distributed.
- Explore the feasibility of developing global goals and ambitions related to antimicrobial resistance for UN agencies, component members, and, where appropriate, other stakeholders, for priorities set out in the declaration.
- Regularly report on progress and on IACG meetings and issue a full report to the UN General Assembly at its 73rd session in 2018, through the secretary-general, keeping member states, stakeholders, and the governing bodies of FAO, OIE, and WHO fully apprised of progress.

Davies reported that the IACG's initial work plan includes aligning with the Sustainable Development Goals and WHO's global action plan; reviewing work ongoing by FAO, OIE, and WHO; and mapping a framework for action. Making progress on metrics—surveillance, monitoring, and evaluation—is also a priority for Davies. Progress is being made, she noted, with the plans for the Institute of Health Metrics and Evaluation to include antimicrobial resistance into the Global Burden of Disease resource, which provides a tool to quantify health loss from diseases, injuries, and risk factors so health systems can be improved. Furthermore, 90 percent of the world's population is now covered by national action plans against resistance (WHO, 2017a). However, plans are meaningless without action, Davies noted, and implementing plans will require more funding, which may need more coordination on the national and global levels. Interna-

[5] The other two conveners are Junshi Chen and Martha Lutterodt.

tional push funding has increased dramatically since 2014, she said, but more pull funding will be needed for diagnostics and therapeutics.[6] Davies concluded her presentation by encouraging the audience to play a key role in the fight against antimicrobial resistance by following infection prevention and control practices, such as handwashing, which can reduce antibiotic consumption.

[6] Push incentives, such as research grants, subsidized loans, and tax credits, aim to reduce industry's costs to help stimulate research and development through the basic research, preclinical, and clinical trial phrases, whereas pull incentives, such as add-on payments, market exclusivity, and intellectual property protections, are provided during the approval process and the post-market period to create viable market demand.

3

Microbial and Genetic Movements Across the One Health Domains

During session I of the workshop, speakers and discussants explored microbial and genetic movements across health, agriculture, and environmental compartments. The session's first half, moderated by Rima Khabbaz, deputy director of infectious diseases at the U.S. Centers for Disease Control and Prevention (CDC), covered knowledge gaps and opportunities to strengthen the evidence base, with a focus on surveillance of antimicrobial resistance. It opened with an overview of the National Antimicrobial Resistance Monitoring System (NARMS) by Patrick McDermott, director of NARMS at the U.S. Food and Drug Administration (FDA). Paula Cray, professor and head of the Department of Population Health and Pathobiology at North Carolina State University-Raleigh, followed with a review of the quality of antimicrobial surveillance across countries at differing levels of development. James Tiedje, university distinguished professor of microbiology and molecular genetics and of plant, soil, and microbial sciences at Michigan State University, discussed environmental surveillance for antimicrobial resistance and identifying horizontal gene exchange as the point of control. The effect of antimicrobials in the environment was the focus of the session's second half, moderated by Jeffrey Silverstein, deputy administrator of animal production and protection with the U.S. Department of Agriculture (USDA) Agricultural Research Service. Lance Price, professor at The George Washington University Milken Institute School of Public Health, explained how resistance determinants on microbes are transmitted between human and animal hosts. Ed Topp, principal research scientist at Agriculture and Agri-Food Canada, described how human activities can potentiate antimicrobial resistance within the

environmental reservoir of microorganisms. Lisa Durso, a microbiologist with the USDA Agricultural Research Service, evaluated management and mitigation strategies for reducing the transfer of antimicrobials to the environment. The session's final speaker, Steve Brooks, vice president of environment, health, and safety at Pfizer Inc., provided a manufacturing perspective and outlined the biopharmaceutical industry's road map to reduce the environmental impact of antibiotic production.

STRENGTHENING THE KNOWLEDGE AND EVIDENCE BASE

National Antimicrobial Resistance Monitoring System

McDermott explained that NARMS was established in 1996 as a collaboration among CDC, FDA, and USDA. At its outset, NARMS was tasked with integrated surveillance of antimicrobial resistance in foodborne bacteria, which he defined as

> the coordinated sampling and testing of bacteria from food animals, foods, and clinically ill humans and the subsequent evaluation of antimicrobial resistance trends throughout the food production and supply chain using harmonized methods.

In the years since, he said, the concept of integrated surveillance has shifted to One Health surveillance, which includes an environmental component. He described the key function of each agency in NARMS today. USDA carries out randomized, nationally representative sampling of food animals at slaughter, which is providing new insights into the ecology of resistance. FDA works with state partners to test samples of the retail meat supply annually. CDC performs susceptibility sampling on 5 percent of the nontyphoidal *Salmonella* samples collected by participating state public health departments, with plans to begin annual whole genome sequencing on every isolate collected.

Value of One Health Surveillance

One Health surveillance is foundational to all national action plans and to the World Health Organization (WHO) recommendations for combating antimicrobial resistance, said McDermott. He emphasized that the approach has value across multiple dimensions. It is used to establish baseline levels of pathogens and resistance in different reservoirs and to describe the spread of resistant bacterial strains and genes across ecosystems. When temporal and spatial resistance trends are identified, they underpin hypotheses about the sources and reservoirs of resistant bacteria, he said. Link-

BOX 3-1
New U.S. Food and Drug Administration (FDA) Policy on Use of Antimicrobial Drugs in Food Animal Production

McDermott described a new FDA policy on the use of antibiotics in food animal production as part of its efforts to combat antimicrobial resistance. In January 2017, FDA completed the implementation of Guidance for Industry #213, which eliminates the use of antibiotics with importance in human medicine for growth promotion purposes in food animal production. In addition, the use of medically important antibiotics in feed and drinking water of food animals has been transitioned to veterinary oversight. Seven classes of antibiotics are affected: aminoglycosides, lincosamides, macrolides, penicillins, streptogramins, sulfonamides, and tetracyclines. Because the affected classes are already being tracked as part of the National Antimicrobial Resistance Monitoring System, he said, there is a large body of phenotypic data currently being analyzed with new metagenomic sequencing technology to establish prepolicy baseline levels. McDermott was optimistic that those baseline levels, which come from sample sources of different food animals and resistances, will serve as reliable reference points for evaluating the effect of this new policy.

SOURCE: McDermott presentation, June 20, 2017.

ing those sources and reservoirs to specific antibiotic-use practices helps to shape more informed and targeted interventions through risk analysis. One Health surveillance also provides information about the burden of illness, he noted, including the risk factors and clinical outcomes related to resistant infections versus antibiotic-susceptible ones. Furthermore, he added, it generates critical data to inform decisions about actions taken to mitigate resistance when emerging trends are identified. McDermott said that NARMS data are central to FDA's regulatory processes (see Box 3-1 for information on a new FDA policy) and other evidence-based policies regarding judicious antibiotic use. Pre-harvest surveillance data support risk analysis of foodborne antimicrobial resistance hazards as part of the qualitative risk assessment process for preapproving new animal antibiotics. Post-harvest data contribute to identifying interventions to contain resistance and to evaluating the effectiveness of antibiotics after approval.[1] Finally, he said that One Health surveillance data are used to evaluate

[1] As examples, he cited FDA's withdrawal of fluoroquinolones for use in poultry and its prohibition of extra-label use of third-generation cephalosporins; the latter has had a measurable and fairly immediate effect in both human and animal isolates, he said.

whether an evidence-based intervention has achieved its intended effect—that is, establishing a new baseline—at which point this cycle begins anew.

Potential Challenges of One Health Surveillance

Based on his experience with NARMS, McDermott outlined a set of challenges faced in One Health surveillance. He noted gathering accurate information and bacterial isolates is expensive, laborious, and requires sustainable commitment from government and public health sectors. Maintaining a sound sampling scheme along the food chain and environment is challenging, albeit critical, for valid trend analysis, he added. McDermott said that silos hinder collaboration and data sharing among the agriculture, industry, and public health sectors, as well as among microbiologists, epidemiologists, and other specialists within and across sectors. In that vein, he reflected, fostering international harmonization and cooperation is becoming increasingly important. Publishing complex findings in a manner that is timely and appropriate for different audiences is a continuous challenge, he said. A related challenge is using the data to formulate sound public health policy, because there are conflicting opinions about how much evidence is sufficient to act upon. He noted that calls for more data represent a major cause of delay.

Lessons Learned from NARMS

McDermott reflected on lessons learned from the 20-year history of NARMS. He explained that some nontyphoidal *Salmonella* are more adept than others at acquiring multidrug-resistant plasmids; therefore, resistance to critically important antibiotics differs by serotype.[2] He reported that since NARMS began, the overall susceptibility picture for all serotypes on its current 15-drug panel has steadily improved. Resistance to three or more classes of drugs (multidrug resistance) among human isolates declined between 1996 and 2014 in the United States (see Figure 3-1). Among the critically important antibiotics—ceftriaxone, azithromycin, and ciprofloxacin—only ceftriaxone resistance is material in human isolates. According to McDermott, the rates of resistance to quinolones and third-generation cephalosporins in human nontyphoidal *Salmonella* isolates in the United States are comparable to the best susceptibility situations in the European Union. Among nontyphoidal *Salmonella* isolates in broiler meat

[2] Antimicrobials are deemed critically important if they are (1) sole therapies or one of few alternatives to treat serious human disease, and (2) used to treat diseases caused by either organisms that may be transmitted to humans from nonhuman sources, or human diseases causes by organisms that may acquire resistance genes from nonhuman sources (WHO, 2012).

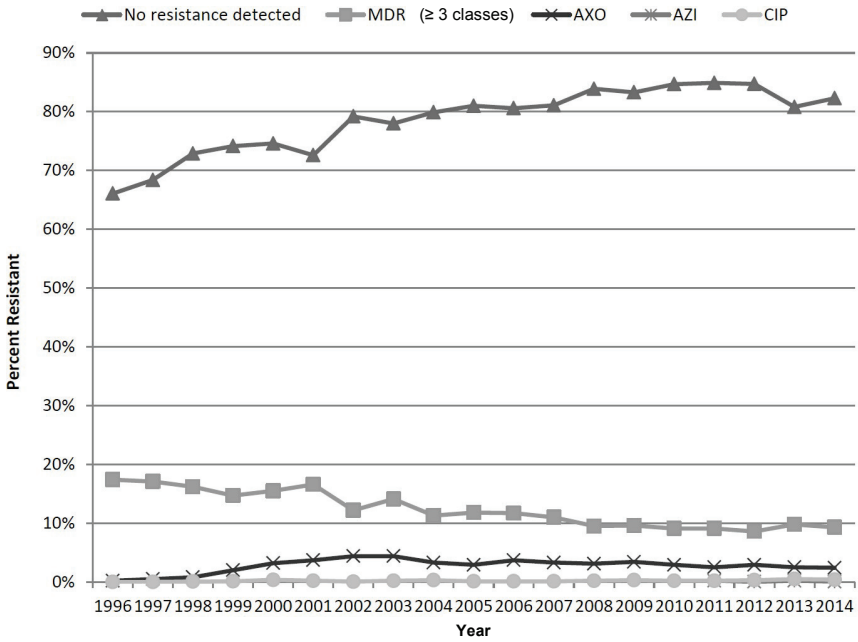


FIGURE 3-1 Resistance to critically important antibiotics in nontyphoidal *Salmonella* in the United States (1996–2014).
NOTE: AXO = ceftriaxone; AZI = azithromycin; CIP = ciprofloxacin; MDR = multidrug resistance.
SOURCE: McDermott presentation, June 20, 2017.

supply in the United States, antibiotic resistance is roughly on par with the European Union.

Whole genome sequencing is affecting a sea change in surveillance, observed McDermott. It provides comprehensive genomic information on resistance-related genes and is thus proving to be a good surrogate for traditional in vitro susceptibility testing, per several recent studies on resistance genotype–phenotype correlations for target food-borne pathogens. For example, a clinically resistant strain of *Salmonella enterica* will have a known resistance determinant (genotype–phenotype correlation) in around 99 percent of cases (Zankari et al., 2013; McDermott et al., 2016). A One Health approach is essential because resistance is a problem that transcends national borders, cautioned McDermott. Plasmids are transmitted readily around the world, and those that accumulate resistance genes do so rapidly and spread to other pathogens within the same family. To illustrate, he noted that the history of accumulated resistance is recapitulated in some

modern strains. One particular plasmid backbone (IncA/C2 plasmid backbone 113,320 bp), now fairly widespread in U.S. agriculture, is 99 percent identical to a plasmid from a child in Madagascar who had plague in 1997. McDermott said that NARMS provides comprehensive genomic information on its website,[3] and it is preparing to launch a data dashboard tool for real-time reporting that will enable resistance tracking.

McDermott concluded with reference to some existing gaps in One Health surveillance. NARMS needs to incorporate programs for food animal and companion animal pathogen surveillance, he said, as well as for on-farm testing to assess husbandry practices on resistance. He said that an environmental surveillance piece is needed to complete the One Health platform and to better understand the movement of pathogens and resistance genes, both in the United States and worldwide. He predicted that the tide will shift toward microbiome-type surveillance, but he cautioned against allowing the sheer volume of data generated by new genomic approaches to impede or delay the most critical step—taking appropriate action to mitigate resistance.

Quality of One Health Surveillance in Developed and Developing Countries

Cray reviewed the quality of antimicrobial surveillance across the One Health domains, with a focus on the respective challenges faced by countries at differing levels of development. She is involved in developing guidance documents to frame the minimal requirements for establishing a surveillance system for antimicrobial resistance. Efforts in developing countries may face different challenges than efforts in developed countries, she said. To illustrate the practical reality of data collection fieldwork in parts of some developing countries,[4] she described work carried out by her graduate students in Uganda. Cray noted they tend to face lengthy delays caused by impassable roads, frequent power outages, and a poor laboratory infrastructure that renders bacterial culture curation and procurement of supplies challenging. Very few translators are available to enable communication across Uganda's 14 different dialects and to help surmount cultural differences for her students, she added.

[3] For more information, see www.cdc.gov/narms/index.html (accessed July 31, 2017).

[4] Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization, commented to Cray that her generalization about developing countries may be sending the wrong message—not all countries in Latin America, Asia, and other areas lack infrastructure and standards. Rather, the main problem in many of those countries is the lack of political will to build capacity. She responded that if time permitted, she would have included a third category for transitioning countries and regions.

Potential Opportunities to Improve Surveillance Data Integration

Most current surveillance, especially in developing countries, primarily involves country-based and human-focused systems, said Cray. However, there is an ongoing shift from site-specific monitoring toward continuous, long-term, multisectoral monitoring systems. She noted that this shift has underscored the need for improved data collection and integration across the human, animal, retail, and environmental spheres. This research gap is evident in the "infinitesimally small" number of total publications on antimicrobial surveillance systems—relative to its critical importance—in the past 45 years, she noted. Sampling methodologies for antimicrobial susceptibility testing are not consistent within and between different countries, said Cray, so improving quality control and harmonizing culture-sampling methodologies will be crucial for better data integration. Current activities aimed at this goal include global- and national-level action plans led by WHO and its Advisory Group on Integrated Surveillance of Antimicrobial Resistance,[5] by the Food and Agriculture Organization of the United Nations (FAO), and by the World Organisation for Animal Health (OIE). WHO's Global Antimicrobial Resistance Surveillance System is working to coordinate how data are captured,[6] she said, but only for human surveillance and not for animal, veterinary, retail, or environmental surveillance at this time. Other immediate needs, she added, include harmonizing the ways that data are analyzed and reported as well as supporting and enhancing the WHO, OIE, and FAO programs.

Cray called for creating a real-time global databank of existing data sets that could include, for example, antimicrobial resistance, infectious disease, sequencing, climate, wildlife migration, and migratory birds. The databank could be compiled, assimilated, and analyzed to identify gaps, promote innovation, and take collaborative action against antimicrobial resistance. She recommended framing this work within a new paradigm—the Collective Antimicrobial Resistance Ecosystem (CARE) (see Figure 3-2). The paradigm is predicated on continual exposures to multiple types of resistance determinants at the interface of humans, animals, and the environment. To conclude, she suggested that hurricanes, floods, droughts, fires, and volcanic eruptions represent unique opportunities to study antimicrobial resistance after the environment has been "reset," observing: "Once we have homeostasis again in the environment, if we begin sampling, can we then watch at a true evolutionary development of resistance and bacterial gene movement over time?"

[5] For more information, see www.agisar.org (accessed July 31, 2017).

[6] For more information, see www.who.int/antimicrobial-resistance/publications/surveillance-system-manual/en (accessed July 31, 2017).

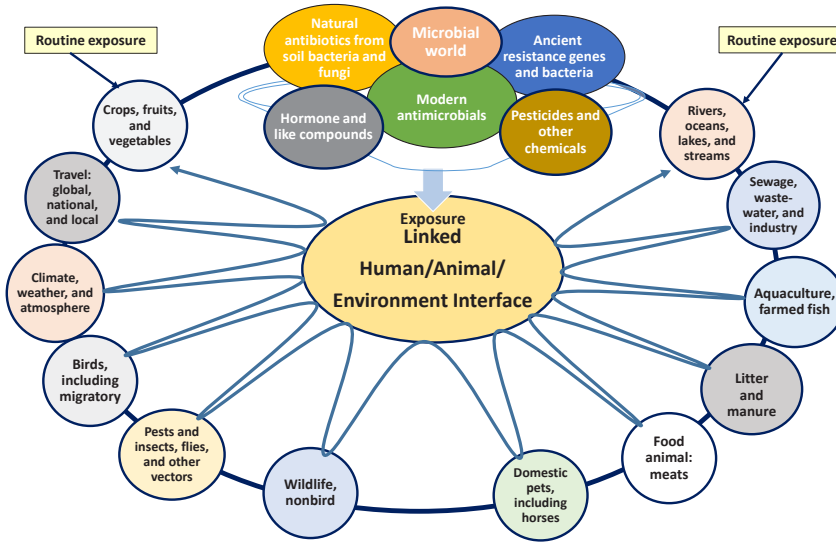


FIGURE 3-2 The Collective Antimicrobial Resistance Ecosystem (CARE) model.
SOURCES: Cray presentation, June 20, 2017; adapted from USDA, 2014.

Antimicrobial Surveillance in the Environment

According to Tiedje, better understanding of antibiotic resistance genes and antibiotic-resistant bacteria in the environment is a high-priority knowledge gap. This includes their survival rates, survival conditions, and treatment methods, as well as their transport, growth substrates, growth conditions, and the microbial ecology of manure and commensal hosts. In a commensal relationship between bacteria and host microorganisms, the bacteria benefit from the relationship while the hosts remain unaffected. Further research on horizontal gene exchange is a specific priority for Tiedje, because it is the point of control of antimicrobial resistance.

Horizontal Gene Exchange

To explain the process of horizontal gene exchange, Tiedje described the continuum through which multidrug-resistant organisms emerge. Every gram of soil in the native resistome, which is a collection of all the antimicrobial resistance genes in a microbial environment, contains antibiotic resistance in its microbes, which can be steered in a problematic direction

by anthropogenic factors such as general pollution, antibiotic production, wastewater treatment plants, animal agriculture, and aquaculture. Horizontal gene exchange occurs in the "organismal soup" that arises out of this environmental selection, he said. The soup contains commensals that can carry antibiotic resistance genes, mobile genetic elements, and pathogens. However, the elements in the soup that are critical in driving the creation of multidrug-resistant organisms are selection, growth conditions, cell density, and cell contact, Tiedje added. Managing those elements, he said, is the key to minimizing horizontal gene exchange and the creation of resistant pathogens. Ample evidence demonstrates this process of horizontal gene exchange, Tiedje said. He cited a study on the abundance of antibiotic resistance genes in the metagenomes of different environments (Li et al., 2015). The abundances in natural environments, such as sediments, soils, and river water, were up to three orders of magnitude smaller than total abundances found in environments that were seriously affected by anthropogenic environmental selection, such as feces and wastewater from animal agriculture.

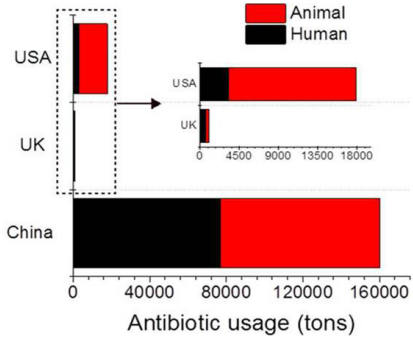
Resistance Clusters and Coselection

Resistance clusters and coselection for antibiotics, heavy metals, and disinfectants are key parts of the resistance problem, said Tiedje. Evidence suggests strong correlations between certain antibiotic resistance genes and mobile genetic elements, he said. Clusters of identical sequences found in three different pig farms in different regions of China indicate that genes are transferring globally and in particular clusters (Johnson et al., 2016). He noted that the same study analyzed the "growth" of one cluster in compost from a single Chinese farm. In manure, it appears that coselection occurs for the growth of organisms with certain types of resistance genes, he said, which seem to be genetically linked in a resistance cluster.

Strategies for Environmental Surveillance

Tracking the volume of antibiotic use, production, and emission around the world will be critical for enacting a targeted strategy for action, Tiedje argued. He quoted Rai Kookana, an expert from Commonwealth Scientific and Industrial Research Organisation in antibiotic quantification, as attributing the majority of the world's production to China and India. Kookana suggested that strategies target Asia, because the necessary components for horizontal gene exchange and selection are highly prevalent in that region (Kookana et al., 2014) (see Figure 3-3).

Tiedje cautioned that each sector, such as dairy, pig, chicken, fish, wastewater treatment plants, and antibiotic production facilities, as well



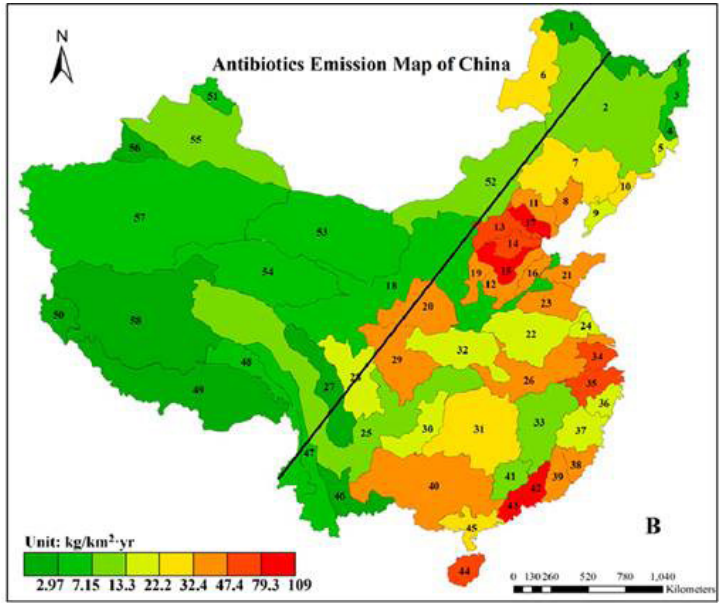


FIGURE 3-3 Surveillance of antibiotic use in China.
Top: Comparison of antibiotic usage among China, the United Kingdom, and the United States.
Bottom: Density of antibiotics emissions in river basins of China.
SOURCES: Tiedje presentation, June 20, 2017; Ying et al., 2017; Zhang et al., 2015. Reprinted (adapted) with permission from Ying, G. G., L. Y. He, A. J. Ying, Q. Q. Zhang, Y. S. Liu, and J. L. Zhao. 2017. China must reduce its antibiotic use. *Environmental Science and Technology* 51(3):1072–1073. Copyright (2017) American Chemical Society; Reprinted (adapted) with permission from Zhang, Q. Q., G. G. Ying, C. G. Pan, Y. S. Liu, and J. L. Zhao. 2015. Comprehensive evaluation of antibiotics emission and fate in the river basins of China: Source analysis, multimedia modeling, and linkage to bacterial resistance. *Environmental Science and Technology* 49(11):6772–6782. Copyright (2015) American Chemical Society.

as each region needs a tailored strategy for surveillance, because each faces different issues with respect to development, income level, rural or urban settings, and level of antibiotic production. Operations are rapidly changing owing to technological advancements, for example, that allow larger-scale farmers to use management strategies including infrared infection detection, saliva monitoring, and behavioral monitoring to quickly isolate and treat animals. He explained that surveillance data will help to validate the relationships among quantitative polymerase chain reaction data, metagenomic data, isolate data, and residue data. Another of Tiedje's actionable priorities was sector-specific education and training about resistance, such as the "Pork Checkoff" campaign in the United States, which provides resources for young people on antimicrobial use and regulations among other educational tools.[7]

Given the volume of molecular data becoming available, Tiedje said, improvements in data integration, data mining, and epidemiology are needed for developing quantitative risk-assessment models to guide action against resistance. Furthermore, he argued that there is a strong economic incentive for a NARMS-style system that provides real-time data monitoring (cow-side, for example) that can be linked to risk and allow users to make better decisions, to save money, and to promote less resistance. Tiedje also suggested that integrating environmental surveillance data with clinical data from hospitals would help to identify links and perform real-time risk analyses. As an example, he noted that Stedtfeld et al. (2016) have developed an antimicrobial resistance dashboard application designed to geospatially map antibiotic resistance genes and antibiotic-resistant bacteria from environments and clinics.

DISCUSSION

David Rizzo, chair of the Department of Plant Pathology, University of California, Davis, asked about the practice of spraying antibiotics on plants and its impact on soil. Cray said that her model plans to capture the use of antimicrobials and pesticides on plant crops, because there is particularly selective pressure at the bacterial level. Tiedje commented that such use on plants is very low in the United States, at 0.1 percent of total use.

Jeffrey Duchin, health officer and chief of Communicable Disease Epidemiology and Immunization Section for Public Health for Seattle and King County, Washington, asked if there are drivers of resistance in humans, besides the administration of antibiotics, that can be identified through the food production chain, such as pre- or postharvest animal husbandry prac-

[7] For more information, see www.pork.org/production-topics/antibiotics-resource-center (accessed September 18, 2017).

tices, and if there are key points at which the resistance problem is exacerbated that are analogous to horizontal gene transfer hot spots. McDermott said that genomic data can reveal links with antimicrobial resistance traits that the surveillance system does not test for, such as quaternary ammonium compounds used in carcass washing during animal processing, so those types of processing steps warrant closer consideration. Tiedje noted that copper and zinc resistance are important co-selectors being used more widely as the use of antibiotics decreases. Cray added that practices for moving animals could even be drivers: it can increase animals' stress and thus the recrudescence of shedding, which increases the distribution of bacteria in the population.

Peter Daszak, president of EcoHealth Alliance, asked if the livestock industry still uses growth promoters that are clinically significant antimicrobial drugs in human health. McDermott clarified that in the United States, the use of any antibiotics that are classified as medically important can no longer be used for growth promotion as of January 2017; however, that does not include ionophores, which are a class of antibiotics used to slow the growth and reproduction of parasites in animals. Tiedje suggested that tetracycline, used very heavily in animals, could be a critical driver of coselecting the important human resistances. Cray noted that tetracycline use is common in human dermatology; in Denmark, an increase in one bacterial population's resistance to tetracycline was attributed primarily to increased human use (Lomholt and Kilian, 2014).

David Relman, professor of medicine at Stanford University, suggested designing specific studies to better understand the microenvironments in which gene flow is most significant and asked about the best possible study design for capturing and interpreting genetic information. McDermott recommended using longitudinal studies that capture national use data as well as biological (and ultimately metagenomic) samples. When coupled with data on variable practices nationwide, he predicted, those studies will help clarify which of those practices are driving resistance. Cray reiterated the value of conducting a study after the environment has been reset—for example, after a flood affecting agricultural land, sewage treatment plants, and hospital wastewater treatment plants.

ANTIMICROBIALS IN THE ENVIRONMENT

Interface and Pathways of Gene Transfer

Many current antibiotic-resistant infections are the result of very rare genetic events, said Price, so the overarching goal should be reducing the opportunity for these rare genetic events to occur, for example, in billions of food animals worldwide. He added that intervening effectively requires

microbial-level understanding of how resistance determinants can be transmitted between hosts.

Transmission of Resistance Determinants

Some resistance determinants can be "hardwired" into a microbe's genome, said Price, and some resistance determinants are located on mobile elements that can move around within the genome of that organism. Furthermore, some types of mobile elements can jump around within an organism's genome, while others sit on different kinds of mobile elements that can be passed between bacteria. Both hardwired and mobile elements are implicated in amplifying resistance in food animals and ultimately threatening human health, he said. Bacteria with hardwired resistance determinants can emerge in food animals and jump to humans, causing antibiotic-resistant infections. The same transmission scenario holds for bacteria with mobile resistant determinants. In another transmission scenario, bacteria with mobile resistance determinants can emerge in food animals, jump to humans, and transfer their resistance determinants to another bacterium that causes antibiotic-resistant infections. Finally, he said, bacteria with hardwired resistant determinants can emerge in food animals, jump to humans, and transfer the resistance determinant via transformation or transduction.

Resistance Transmission in Salmonella and Campylobacter Bacteria

New multidrug resistance determinants in *Salmonella* have been associated with the introduction of antibiotics to animals, said Price. The reverse scenario, rapid decrease in resistance, has also been observed when antibiotics have been removed from food animal production. For example, when the Canadian government asked Quebecois broiler producers to stop injecting broiler chicken eggs with cephalosporins, Price said, there was an immediate and precipitous decrease in cephalosporin-resistant *Salmonella* in poultry products.[8] In parallel, he said, there was a direct positive effect on human health: a precipitous decrease in cephalosporin-resistant *Salmonella* infections in people and a decrease in cephalosporin-resistant *Escherichia coli*. In another example, ciprofloxacin-resistant *Campylobacter* infections increased rapidly in humans after the introduction of enrofloxacin (the animal version of ciprofloxacin) in broiler chicken production, according to Price. This evidence spurred FDA to block the use of enrofloxacin

[8] For more information, see www.canada.ca/content/dam/canada/public-health/migration/publications/drugs-products-medicaments-produits/antibiotic-chicken-industry-surveillance-resistance-antibiotique-industrie-poulet/alt/pub-eng.pdf (accessed July 31, 2017).

in broiler chicken production,[9] Price said, but removing the drug did not cause a rapid decrease in resistance (Nelson et al., 2007). The rates merely flattened out, he explained, because resistance was coded by a single-point mutation in a housekeeping gene hardwired in the genome. Because there was no measurable metabolic cost to the organism to carry the mutation, there was no counterselection to eliminate it.[10]

Resistance Transmission in Colonizing Opportunistic Pathogens

As of 2013, CDC estimated that there were about 410,000 drug-resistant infections by *Salmonella* and *Campylobacter* each year in the United States (CDC, 2013b); however, this figure has not been sufficient to induce aggressive policy actions. He surmised that "body counts" are more powerful than infection statistics for catalyzing action among policy makers, and the number of deaths for those two bacterial infections was estimated at less than 1,000. Furthermore, he said, infectious disease doctors in general do not focus on *Salmonella* and *Campylobacter* in the context of superbugs, but rather tend to think about colonizing opportunistic pathogens (COPs) instead. According to Price, these COPs include

- *Klebsiella pneumoniae*, including carbapenem-resistant Enterobacteriaceae (CRE);
- Extraintestinal pathogenic *Escherichia coli*, including CRE;
- *Enterococcus*, including vancomycin-resistant *Enterococcus*; and
- *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA).

COPs are more difficult to study than foodborne pathogens, said Price, because they cause "insidious epidemics" spanning human, animal, and environmental hosts. They also have indefinite and asymptomatic colonization periods and are transmitted silently (asymptomatically) from person to person.

Next-generation DNA sequencing and other new tools are revealing more about coresistance and horizontal gene transfer in COPs, said Price. An example from the Netherlands illustrates how coresistance can fuel the spread of resistance in the absence of profligate antibiotic use. In 2004, a new strand of livestock-associated MRSA (ST398) was found in an infant and traced to the family's pig farm, and a survey of livestock throughout

[9] For more information, see www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm (accessed July 31, 2017).

[10] He cautioned that in Spain, they continued to use cipro-enrofloxacin until virtually all of their *Campylobacter* was resistant to ciprofloxacin.

Europe found the strain was already spreading rapidly (Voss et al., 2005). Whole-genome sequencing was applied to understand the evolutionary history of its epidemiology, which originated as methicillin-susceptible *Staphylococcus aureus* (MSSA) that had made a host jump from humans to animals. Heavy antibiotic use mediated the transition from human MSSA to pig MRSA, which began spreading back to people working in the agricultural industry, mainly through direct exposure. Price warned that farmers, farm workers, and veterinarians—and their families—are on the frontline of livestock-associated MRSA, which can be fatal to a susceptible host. An important cautionary example of horizontal gene transfer, said Price, is mobilized colistin resistance (see Box 3-2).

Future Directions for Research in Resistance Transmission

Going forward, said Price, whole-genome phylogenetic analyses will help to trace host jumps and the natural history of mobile element acquisition. Bayesian molecular clock analyses can be used to estimate the point of time in prehistory when two or more life forms diverged; he suggested that it will also help to estimate the timing of when mobile elements jump

BOX 3-2
A Critical Threat of Horizontal Gene Transfer

An example of horizontal gene transfer comes from China, said Price. In 2016, a new mobile element—mobilized colistin resistance (*mcr-1*)—was discovered in China. It codes for resistance to colistin, one of the last drugs that works against certain strains of carbapenem-resistant Enterobacteriaceae (CRE). Chinese livestock producers were using colistin heavily, and the gene was found in *Escherichia coli* colonizing food animals, and to a lesser degree, humans through contaminated meat. Fortunately, the power of genome sequence laboratories enabled quick recognition of the gene in other countries where colistin is used routinely in livestock. This example also underscores the value of older antibiotics, said Price, which will increase as resistance spreads to newer antibiotics. He warned that *mcr-1* is a promiscuous triple threat. It flows seamlessly between hosts, because the gene itself is mobilizable and it sits on a mobilizable plasmid. The plasmids are carried by *Escherichia coli*, which has an extremely broad host range. Evidence has confirmed that *mcr-1* can be found on multiple plasmids and in different strains of *Escherichia coli*, he said. Price noted that it is very likely that *mcr-1* will eventually find its way into a successful CRE strain: "We now know that the last card in the CRE royal flush is in play—horizontal transfer is a critical threat."

SOURCE: Price presentation, June 20, 2017.

between animals and people. However, mobile genetic elements are often noisy, with much recombination and little reliable phylogenetic signal. He said that longer-read sequencing methods may help address this challenge, but it will require significant investment to define the clouds of genetic diversity that can exist even on a single farm. Furthermore, it is not yet possible to quantify the proportion of antibiotic-resistant human infections that are caused by antibiotic use in livestock production, be it historic or contemporary. Addressing antibiotic resistance will require ensuring transparency, obtaining source samples, closing the routine disease prevention loophole, and raising animals and people in ways that promote health and obviate the need for antibiotics, he concluded.

Environmental Reservoirs of Antimicrobial Resistance and Effects of Antibiotic Residues

The One Health framework has three key elements, said Topp: humans who receive antibiotics; animals and fish that receive antibiotics; and the terrestrial and aquatic environments. Microorganisms in the environment represent a reservoir of genes that confer resistance to antibiotics, he explained, and those genes can be recruited into pathogens of significance to human or animal health. The environment also represents a way for these antibiotic-resistant organisms to transmit to humans, to animals, and between humans and animals. Pathogenic organisms can carry antibiotic resistance genes, he said, but commensal organisms can also carry antibiotic resistance genes that ultimately can be transmitted to pathogens. He presented Figure 3-4, which articulates the sources and transmission pathways of antimicrobial resistance within the One Health framework.

Impact of Anthropogenic Activities on the Environmental Reservoir

From a One Health perspective, Topp said, a major concern is that anthropogenic activities are potentiating an environment conducive to resistance transmission. Researchers are working on multiple fronts to mitigate this effect. Most work is focused on the increasing abundance of antibiotic resistance genes *in* the environment, which entails an undesirable increase in exposure to these genes *through* the environment. Another concern is the promotion of resistance to new antibiotics as they are brought to market, he said. Evidence suggests that bacteria in environments exposed to certain chemicals have an accelerated evolution rate. Another focus is whether the association between antibiotic resistance genes and elements that confer mobility is increasing, which would accelerate the speed at which human pathogens recruit those genes. Yet another focus is whether resistance genes get "stacked," thus increasing the probability of resistance to multiple

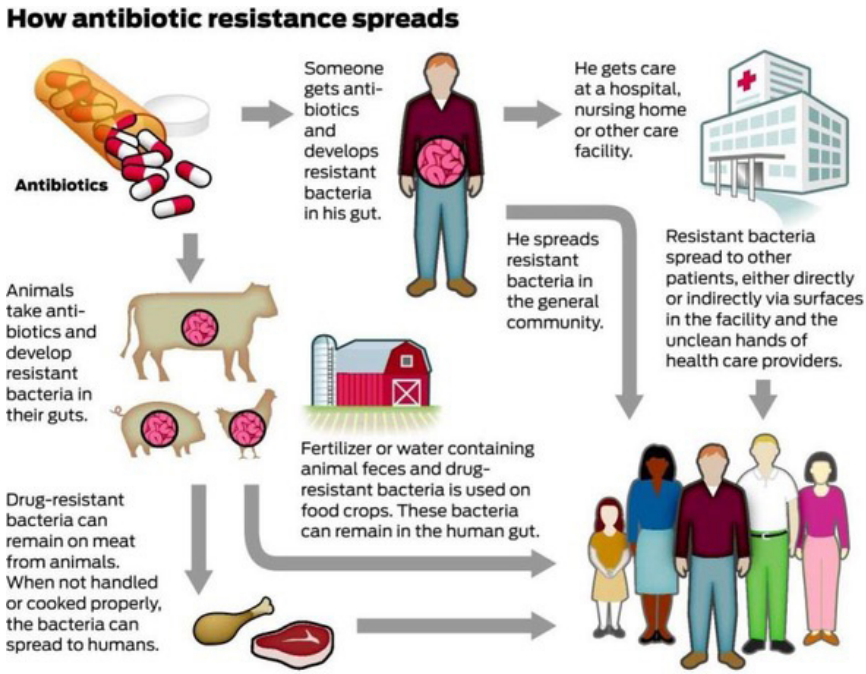


FIGURE 3-4 The spread of antibiotic resistance through various vehicles. SOURCES: Topp presentation, June 20, 2017; Todd Trumbull/San Francisco Chronicle/Polaris; adapted from CDC, 2013a.

classes of antibiotics. Genes conferring multiple types of resistance that are dispersed in different bacteria are of less concern than those on a single bacterium that can be exchanged to other bacteria, he said.

Being able to identify the source of waterborne antimicrobial resistance is particularly critical in low-income countries without adequate infrastructure for potable water or wastewater treatment, Topp said. Some bacteria, such as *Escherichia coli* O157:H7 bovine, have reservoirs that are specific enough to trace if detected in water. Water can contain fecal source markers as well. Caffeine or human/veterinary pharmaceuticals are human-specific chemical markers, he said, and biological markers include host-specific DNA from Bacteroidales bacteria or mitochondrial DNA from fecal material.

Biological Contaminants in the Resistome

Many anthropogenic activities can potentiate the environmental resistome, said Topp. People who are medicated excrete antibiotic residues

and bacteria that have been selected in their digestive tracts, so human waste streams are a primary threat. Human waste streams also include effluents from wastewater treatment plants that enter directly into aquatic environments, such as through irrigation with reclaimed water or land application of recovered biosolids. Animal waste streams from livestock production systems also contain excreted antibiotic residues and resistant bacteria selected within the animals, he said. This can potentiate the environmental resistome when manure is recycled onto crop production ground. In aquaculture, direct application of drugs to water is a major concern. Manufacturing plants that fabricate antibiotics in many parts of the world also produce effluents that contaminate the environment with high concentrations of drugs, he said. Establishing minimal selective concentrations of antibiotics, said Topp, will require better understanding the relationship between environmentally relevant concentrations of antibiotics and whether those concentrations are high enough to select for resistance.

Chemical Contaminants in the Resistome

In addition to antibiotic-resistant bacteria from biological contaminants, Topp explained, waste streams also contain organic or inorganic chemicals such as copper and zinc that can coselect for resistance (Song et al., 2017). Mounting evidence shows that livestock animal fecal matter is enriched for antibiotic-resistant bacteria and that crop ground fertilized with these materials become enriched with antibiotic resistance genes (Marti et al., 2013). Researchers are investigating whether those genes will appear in crops grown on those soils, he said, and whether consumption of those crops by humans or animals represents a route of transmission from the environment.

Environmental Persistence of Antibiotic Resistance Genes

Antibiotic resistance genes can persist for at least months in crop ground through commercial-scale application of animal manures, said Topp. Whether all antibiotic resistance genes in soil behave consistently with respect to their persistence in dynamics remains unknown, but evidence suggests that certain proxies or sentinel DNA markers may represent many antibiotic resistance genes, he said. For example, class 1 integrons seem to be highly correlated with the abundance of many antibiotic resistance genes (Gillings et al., 2015). Topp explained that when antibiotic residues are applied to the ground, their persistence varies widely. For example, beta-lactams are quickly destroyed in soil or water, but fluoroquinolones are quite persistent because they are “sticky” to soil and their

bioavailability is reduced.[11] Environmental factors such as aeration and tilling can affect persistence, he said, as can different exposure scenarios (e.g., punctual manure application versus constant effluent from wastewater).

Topp concluded by recommending a shift in focus from exposure to risk:

> In the realm of environmental science related to antimicrobial resistance, the state of the science right now is exposure assessments. We can measure, we can quantify antibiotic resistance genes or bacteria, but we really have very little understanding of the significance of that to human health in a risk assessment context. So we really need to make the leap from exposure to hazard to risk.

Some Management Strategies for Reducing the Transfer of Antimicrobials to the Environment

Durso opened her presentation by drawing a conceptual distinction between the term *resistance* as used in environmental versus clinical settings. In clinical settings, she described, antibiotic resistance is a function of a pathogenic bacterial isolate and is often linked directly to treatment failure. In environmental settings, she said, the term is not consistently defined and it can be applied either to an isolate or to an entire community of bacteria. Relationships are generally indirect; most bacteria are not pathogens and pathogenicity of zoonotic and opportunistic bacteria is assumed, but not known. Durso's first priority is the need for more precise vocabulary for discussing environmental antibiotic resistance, both within the field and across the One Health triad. This would strengthen problem-solving efforts and allow for resources to be allocated where they will have the most impact, she suggested.

Evaluating Strategies for Mitigating Antimicrobial Resistance

To evaluate the efficacy of mitigation strategies to reduce the transfer of antibiotic resistance, Durso said, three categories of targets can be used: drugs and bioactive drug breakdown products, bacteria that can grow in a predetermined drug concentration, or any part of any target gene or resistance determinant. Different targets tell different stories, she warned. Different conclusions about resistance can be drawn from the same sample, because each of those categories has multiple subtargets that can

[11] Among pharmaceutical chemical contaminants in a Canadian sample, Topp reported, the biocide triclocarban had the highest concentration of dry weight in biosolids. Ciprofloxacin's concentration was also high, as were concentrations of other fluoroquinolones, tetracyclines, and macrolide antibiotics.

be measured and there are various ways to present and analyze the data. Establishing a reasonable goal for reduction, she said, requires being able to assess native or naturally occurring (background) resistance and reference (baseline) levels of resistance prior to a mitigation treatment. Data from manure, soil, water, and air reveal that the relationship between drugs and antibiotic resistance is complex, she said. Sometimes there are clear links between drugs and the resistance measure, in line with the current assumption that "more drugs equal more resistance" (Zwonitzer et al., 2016). However, because there are other drivers of resistance in the environment, other studies have found that increases in antibiotic drug concentrations are not necessarily correlated with increasing measures of the resistance target being measured (Dalkmann et al., 2012).

Drivers of Resistance Beyond Drug Use

Durso explained that antibiotic resistance transfer from agricultural to human settings is an issue deeply entwined with—and confounded by—the idea that agricultural antibiotic drug use is the primary or sole driver of resistance. However, studies carried out in organic and drug-free systems may help to begin disentangling these two separate questions. She cited a study reporting that resistance persisted in organically raised swine even in the absence of farm use of antibiotics (Stanton et al., 2011). A growing body of evidence from this and other studies, she said, suggests that reducing resistant bacterial populations will require strategies in addition to prudent use of antibiotics, such as the manure management strategies described in the next section. Realistic mitigation targets for drug residues, bacteria, and genes should reflect the fact that resistance occurs both naturally and as a result of historical and current anthropogenic activities, she argued. She further argued that from the perspective of long-term risk reduction, the source of the target is of little importance to achieving the goal of reducing transfer within and outside of agricultural systems. From the regulatory perspective, however, she conceded that identifying the source of the target does matter. The working assumption that antibiotic use is the primary driver of resistance on farms and in the surrounding water, soil, and air is untested, she noted. While drug use is a strong driver of antibiotic resistance in the animal gut, she said, increasing evidence suggests the need to revisit that assumption and identify the factors—other than drug use—that drive the transfer of antimicrobial-resistant drugs, bacteria, and genes out of the agricultural system.

Manure Management Strategies

Durso surveyed current management options for reducing resistance transfer in manure. The main types of manure are ground-deposited feces

from grazed beef and dairy animals, solid manure collected from the surface of feedlot pens or from inside of poultry houses, and physically contained liquid manure slurries. Application methods include liquid irrigation, slurry injected beneath the soil surface, and dry product applied to the soil surface. She reported that several manure management strategies have shown promise for mitigating some measure of antibiotic resistance, including wood chip bioreactors, composting, land application, and anaerobic digestion (for more detail, see Box 3-3).

A Manufacturing Perspective on Reducing the Environmental Impact of Antimicrobials

Brooks provided a manufacturing perspective on reducing the environmental impact of antimicrobial production. He began his presentation by highlighting that maintaining a supply of affordable, accessible antibiotics is essential to global public health and yields huge societal benefits. Manufacturing and the (proper or improper) use and disposal of medicine,

BOX 3-3
Promising Manure Management Strategies

Wood chip bioreactors and thermal processing are two promising strategies for mitigating antibiotic resistance, said Durso. In Iowa, a study on wood chip bioreactors in tile drain systems is using metagenomics to track antibiotic-resistant bacteria and antibiotic resistance genes from the point at which manure is applied to the land, through its transport in the soil, and onto its potential leeching into the tile drain water. Significant amounts of sulfamethazine (70 percent), enrofloxacin (90 percent), and monensin (80 percent) were found to be retained in the wood chips (Ilhan et al., 2011). Durso noted that wood chip systems are already in use, mostly for nutrient purposes, and they represent a ready-to-go mitigation strategy that can be implemented immediately.

Thermal processing is another promising option, Durso said, for achieving the ideal goals of eliminating resistance in a sample and ultimately eliminating the transfer of resistance out of agricultural systems. She described a case study of applying thermal processing to livestock mortalities. Hydrothermal carbonization (a combination of high temperature and pressure) was applied to sick animals that had been treated and had robust antibiotic-resistant flora. Thermal processing eliminated all of the antibiotic-resistant bacteria and, even more importantly, Durso added, it completely eliminated all of the microbially derived DNA (i.e., antibiotic resistance genes). After treatment, no plasmid was recovered and no DNA fragments were amplifiable (Ducey et al., 2017).

SOURCES: Durso presentation, June 20, 2017; Ilhan et al., 2011; Ducey et al., 2017.

he continued, are potential sources of antimicrobials in the environment, but there are many other sources as well (see Figure 3-5). While antimicrobial resistance in the environment is ancient and predates the industrial-scale use of antibiotics (D'Costa et al., 2011), Brooks acknowledged that the phenomenon at hand may indeed be accelerated, and many stakeholders in the industry recognize the elevated levels of antimicrobials in environmental samples.

The industry's supply chain for established antibiotics is complex and global, he said, stating that it has a significant footprint; it has also raised concerns of environmental pollution from some drug manufacturing companies in emerging markets such as China and India. A recent influential study on antimicrobial resistance asserted a link between manufacturing pollution and antimicrobial resistance and called for better control of manufacturing effluent (Review on Antimicrobial Resistance, 2016). Brooks explained that active pharmaceutical ingredients can be found in

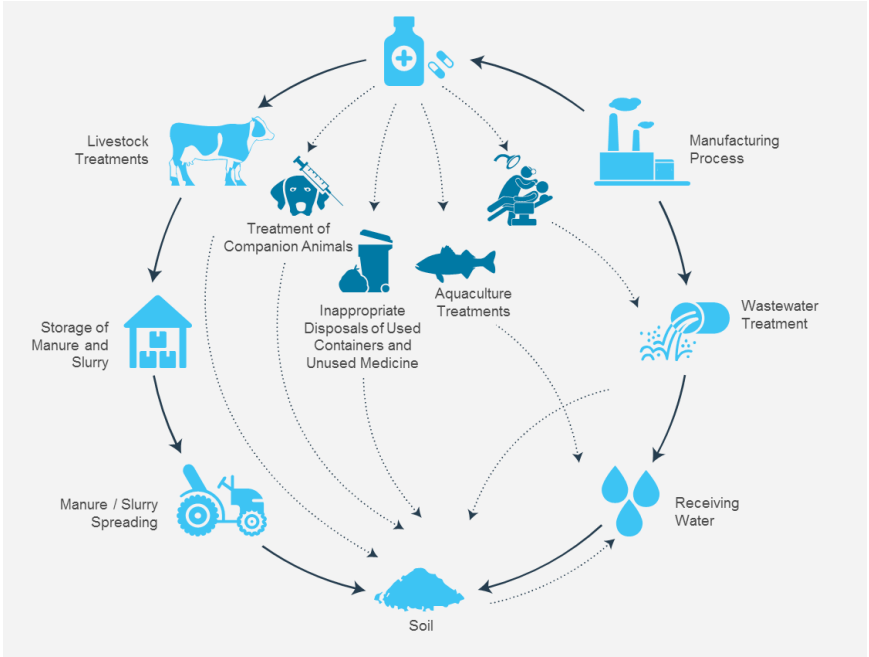


FIGURE 3-5 Manufacturing as one of many potential sources of antimicrobials in the environment.
SOURCES: Brooks presentation, June 20, 2017; adapted from Boxall, 2004.

two main types of manufacturing waste streams.[12] Solid waste generated by the manufacturing process, such as sewage sludge, must be managed to prevent soil and ground water contamination. Wastewater from manufacturing plants requires effective controls to minimize the concentration of active pharmaceutical ingredients in the receiving water. To ensure the effectiveness of those controls, he indicated, research is needed to measure wastewater concentrations, to establish "safe" discharge concentrations, and to better understand the role of other coselective agents such as metals, biocides, and cleaning agents.

Road Map to Reduce Environmental Impact of Antibiotic Production

Leading companies and industry organizations have publicly committed to address the risk of antimicrobial resistance by releasing the Declaration on Antimicrobial Resistance at the World Economic Forum in Davos, Switzerland, in January 2016,[13] with signatories including more than 80 biopharmaceutical companies. It calls on key stakeholders to take collective action to address antimicrobial resistance, including governments to commit to allocating the funds needed to create a sustainable and predictable market for new antibiotics and diagnostics while also implementing the measures needed to safeguard the effectiveness of antibiotics. The signatory companies commit to reducing the development of antimicrobial resistance, including "measures to reduce environmental pollution from antibiotics."

Because that is the only specific language related to environmental pollution in the declaration, he said, a group of 13 leading companies signed an industry road map in September 2016. The document further details their practical commitments to implement measures to reduce the environmental impact of antibiotic production. Brooks explained the road map includes other commitments to promote research and development through new collaborations and incentives; to improve access to antibiotics, diagnostics, and vaccines; and to ensure antibiotics are only used by people who need them. For the environmental piece, the road map signatories commit to the following:

- Reviewing (individually) their own manufacturing and supply chains to assess good practices in controlling releases of antibiotics into the environment;

[12] He noted that there are also less direct sources; for example, if a manufacturing plant has contamination around it, then storm water runoff could contain antibiotic material.

[13] Full text of the Declaration on Antimicrobial Resistance is available at www.ifpma.org/wp-content/uploads/2016/01/Industry_Declaration_on_Combating_Antimicrobial_Resistance_Jan2017.pdf (accessed July 30, 2017).

- Establishing a common framework for managing antibiotic discharge by 2018;
- Working with stakeholders to develop a practical mechanism to transparently demonstrate that their supply chains meet the standards in the framework;
- Working with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce the environmental impact of manufacturing discharges by 2020; and
- Supporting calls for the establishment of a high-level coordinating mechanism to provide global leadership, mobilize resources, set goals, and measure progress toward them.

Brooks reported that the Antimicrobial Resistance Industry Alliance Environmental Working Group is currently in the process of developing the environmental framework, establishing science-driven standards and risk-based targets for discharge concentrations, influencing other companies through outreach efforts to take appropriate action, and sharing best practices and environmental assessment programs with one another. The process is supported by collaboration with relevant experts and stakeholders, he said, and progress will be transparently reported. However, he emphasized that widespread promulgation of these standards and practices in the industry—among both innovators and generic manufacturers—beyond the 13 signatories will be critical to reduce the overall manufacturing contribution to antibiotics in the environment.

DISCUSSION

Duchin asked if traditional toxicologists have been engaged to help address challenges in risk assessment. Durso replied that the toxicological framework is being widely adopted in the environmental realm, with antibiotic-resistant bacteria and antibiotic resistance genes classified as contaminants. There may also be room for incorporating a conceptual framework from infectious disease modeling to inform thinking about environmental resistance, she added. Duchin suggested the food production industry could follow the pharmaceutical industry's lead in creating a road map to monitor antimicrobial drug resistance, as it already monitors for bacteria considered dangerous to the food supply. Price agreed that a regulatory infrastructure should be established, given the existence of potentially untreatable bacteria in the food supply that are not classic food-borne pathogens but that can transmit resistance and cause disease (such as *mcr-1*).

George Poste, chief scientist of the Complex Adaptive Systems Initiative at Arizona State University-SkySong, asked about new categories of tech-

nologies that could be deployed in compound destruction and elimination. Brooks replied that there are a variety of technologies in use, constrained by cost and practicality. Many biologic wastewater treatment plants use a "zero liquid discharge" system to evaporate liquid discharge through multistage evaporators; other technologies include dose analysis and tertiary carbon treatment. He explained that the industry traditionally looks at more typical ecotoxicological end points to assess the safety of discharge from plants, but surrogate resistance-based end points are an area of ongoing research. Brooks predicted that a wider network of publicly owned wastewater treatment plants will be necessary, especially in large cities, to handle other nonmanufacturing sources of resistance, such as excreted metabolized antibiotics.

Gerald Keusch, associate director of the National Emerging Infectious Diseases Laboratory at Boston University, added that clinicians rarely consider the excretion of a drug from a patient. He suggested initiating medical educational programs about excreted active metabolites and the disposal of unused antibiotics. Price added that a perfect system for the amplification of resistance arises in resource-limited settings, where water systems contain antibiotic manufacturing effluents, people drink untreated water, and human waste is untreated. But with the advent of globalization, he warned, this is not a localized problem. Even countries with excellent antibiotic stewardship practices have travelers bringing home drug-resistant bacteria. "We need education to amplify the message of the value of these drugs, but we also need these physical interventions to prevent this amplification and dissemination," according to Price.

A webcast participant asked if, from a One Health perspective, there is any evidence that the accumulation of antibiotics in soils and water systems is modifying natural microbial diversity and associated ecosystem functions. Price replied that he is more concerned about decreasing diversity by the inhibition of bacteria by antibiotics. Topp noted active research in the area suggests that antibiotic exposure in aquatic and terrestrial systems is having some impact, but it is not yet clear whether those changes are within normal operating ranges. Durso added that at least one study supported by the USDA Agricultural Research Service is specifically addressing the effect of antibiotics on the functioning of nitrogen cycling in soil.

4

Applying Social and Behavioral Sciences to Combating Antimicrobial Resistance

In session II of the workshop, speakers and discussants explored possibilities for applying social and behavioral sciences to address antimicrobial resistance. The first half of the session, moderated by Franck Berthe, senior livestock specialist in the Agriculture Global Practice of the World Bank, focused on reducing the use of antimicrobials and on strategies for achieving desired behavior change through stewardship programs, incentives, and policy for the responsible use of antimicrobials. Helen Boucher, professor of medicine and director of the infectious diseases fellowship program at Tufts Medical Center, discussed effective guidance for reducing antimicrobials use in health care. David Sjeklocha, operations manager of animal health and welfare at Cattle Empire, surveyed guidelines for antimicrobial usage in the beef industry, and Randall Singer, professor of epidemiology at the University of Minnesota, explored the changing paradigm of antimicrobial use in veterinary medicine. Bruce Stewart-Brown, senior vice president of food safety, quality, and live operations at Perdue Farms, provided retailer and consumer perspectives on eliminating antibiotic use in the broiler industry. Mary Wilson of the University of California, San Francisco, moderated the second half of the session, which focused on reducing the need for antibiotics by exploring ways to achieve desired behavior change through prevention measures and education. The concept of bacterial stewardship in production animal agriculture and companion animal medicine was presented by H. Morgan Scott, professor of veterinary pathobiology at Texas A&M University. Jeffrey Linder, professor of medicine and chief of general internal medicine and geriatrics at the Northwestern University Feinberg School of Medicine, discussed strategies

for leveraging behavioral interventions to achieve appropriate antibiotic prescribing practices. Andrew Maccabe, chief executive officer of the Association of American Veterinary Medical Colleges (AAVMC), surveyed the role of academic veterinary medicine in combating antimicrobial resistance. Darrell Kirch, president and chief executive officer of the Association of American Medical Colleges, concluded the session by reflecting on the changing paradigm of medical education and its impact on the next generation of health professionals.

REDUCING ANTIMICROBIAL USE: STEWARDSHIP PROGRAMS, INCENTIVES, AND POLICY

Effective Guidance for Reducing the Use of Antimicrobials in Health Care

Boucher focused on effective guidance for reducing antimicrobial use in health care settings. She began by defining antimicrobial stewardship as involving

> the optimal selection, dose, and duration of an antibiotic resulting in the cure or prevention of infection with minimal unintended consequences to the patient including emergence of resistance, adverse drug events, and cost.[1]

The goals of antimicrobial stewardship, said Boucher, are patient focused: improving care and health care outcomes. Decreasing antibiotic resistance is also a goal, she said, although there is debate over how to measure and report resistance. Progress is being made, she said, but more research is needed about how to most effectively approach antibiotic stewardship, how to influence prescriber behavior, and how to prevent the spread of antibiotic resistance in acute care, long-term care, and ambulatory settings. Boucher highlighted some promising regulatory developments in the United States, such as the Joint Commission's new antimicrobial stewardship standard applicable in all health care settings (Joint Commission, 2016). The Centers for Medicare & Medicaid Services (CMS) has proposed a rule for stewardship in long-term care,[2] she said, and organizations such

[1] The definition is from collaborative guidelines created by the Infectious Diseases Society of America (IDSA) and the Society for Health Care Epidemiology of America (SHEA), updated in 2016 (Barlam et al., 2016).

[2] For more information on the proposed rule by CMS, see www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-06-13.html (accessed July 30, 2017).

as the Leapfrog Group[3] and others monitor antimicrobial stewardship practices in health care settings.

Boucher directs the infectious diseases fellowship program at Tufts Medical Center, which started an antimicrobial stewardship program nearly 15 years ago. She said that the program's patient-focused approach is focused on ensuring appropriate empirical therapy via antimicrobial choice, dosage, route, and duration. Prescribers are educated on the importance of prudent antimicrobial prescribing to reduce medication errors and costs, as well as switching from intravenous (IV) to oral treatment when possible, she added. Formulary restriction, preauthorization protocols, and a system of prospective auditing are also in place. The program's aim is better outcomes for patients, including better survival rates, fewer adverse drug events, shorter hospital stays, lower rates of resistance, and reduced "collateral damage" of antibiotics, such as *Clostridium difficile* infections.

Effects of Improved Antibiotic Stewardship

Boucher remarked that for many diseases, involving infectious disease professionals early on leads to lower costs and better outcomes for patients. According to a nationwide survey on antimicrobial stewardship program characteristics, Boucher said, institutions with formal antimicrobial stewardship programs are more likely to have antibiograms,[4] infectious disease consultation services, fellowship programs, and higher admissions (Doron et al., 2013; see Box 4-1 for more about the survey). Current IDSA and SHEA guidelines report that comprehensive stewardship programs have consistently saved inpatient health care institutions between $200,000 to $900,000 per year by decreasing antimicrobial use, she said (Doron and Davidson, 2011). At Tufts Medical Center, she added, savings in drug costs alone are estimated at $400,000 annually and at more than $5.6 million since the program's inception. Published studies confirm the economic benefits of stewardship program interventions, she noted. Restricting cephalexin in a municipal hospital decreased costs for that antibiotic by nearly 30 percent (Seligman, 1981). Implementing a full-service antimicrobial management team at an academic medical center generated savings in use costs of $3 million over 3 years (Standiford et al., 2012). In another hospital, IV to oral conversion of fluoroquinolones saved $4 million over 4 years (Jones et al., 2012).

[3] The Leapfrog Group is a nonprofit watchdog organization for health care consumers that scores hospitals based on their commitment to antimicrobial stewardship principles. For more information, see www.leapfroggroup.org/ratings-reports/antibiotic-stewardship (accessed July 30, 2017).

[4] An antibiogram is a periodic summary of antimicrobial susceptibility testing results of a specific microorganism to certain antimicrobial drugs.

BOX 4-1
Results from a Nationwide Survey of Antimicrobial Stewardship Programs

Boucher reported that a nationwide survey on antimicrobial stewardship program characteristics—mainly among pharmacy directors and infectious disease pharmacists—found that 51 percent of respondents reported that their institutions had a formal stewardship program (Doron et al., 2013). Of respondents who reported that their institutions did not have a program, 63 percent were considering implementing one but faced staffing and funding barriers. Respondents from institutions with programs reported a range of strategies and techniques for stewardship. Education strategies for all levels of health care providers include newsletters, grand rounds, and conferences. The most common stewardship technique was switching from intravenous to an oral antibiotic delivery (reported by 85.3 percent of respondents), which Boucher called a low-hanging fruit of antibiotic stewardship. Other reported strategies include developing guidelines and clinical pathways (81.5 percent), dose optimization (70.7 percent), streamlining and deescalation (62.5 percent), closed formularies (59.8 percent), and adopting standard antimicrobial order forms (41.8 percent). Restriction methods for a variety of antibiotics, antifungals, and antivirals include the "back end" approach of total restriction (52.5 percent), automatic stop orders (45.9 percent), and requiring an infectious disease consultation (44.3 percent).

SOURCES: Boucher presentation, June 20, 2017; Doron et al., 2013.

Recent studies demonstrate that antibiotic stewardship interventions can have other types of effects, she said, such as decreasing infection and colonization of *Clostridium difficile* and antibiotic-resistant bacteria (Baur et al., 2017). Another study reported that among hospitalized patients who receive 1 or more days of antibiotic treatment, 20 percent develop an adverse drug event linked to that antibiotic and 20 percent of those events are attributable to antibiotics prescribed for conditions for which they are not indicated (Tamma et al., 2017). Therefore, every 10 days of antibiotic treatment conferred a 3 percent additional risk of an adverse event, Boucher said.

Core Elements of Hospital Antibiotic Stewardship Programs

Boucher summarized guidance from the U.S. Centers for Disease Control and Prevention (CDC) regarding core elements of hospital antibiotic stewardship programs, which she urged all programs to implement (CDC, 2014). The guidance includes

- Establishing leadership commitment—from the C-suite in the hospital or health care system down to the physician's office—to ensure that the necessary human, financial, and information technology resources are dedicated.
- Ensuring accountability through a single leader who is responsible for program outcomes; an infectious-disease trained physician is in a uniquely qualified position to be an effective leader.
- Providing drug expertise, ideally through a pharmacist leader trained in infectious disease, who is responsible for working to improve antibiotic use.
- Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (e.g., an "antibiotic time out" after 48 hours).
- Tracking and monitoring patterns of prescriptions and resistance using, for example, the antibiotic use module from the National Healthcare Safety Network of CDC.
- Reporting information on antibiotic use and resistance on a regular basis to doctors, nurses, and relevant staff.
- Educating clinicians about antibiotic resistance and optimal prescribing.

The One Health Approach to Antibiotic Stewardship

The first report from the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB, 2016) advocated a One Health approach for stewardship, said Boucher. It recommends implementing efforts to promote adoption of antibiotic stewardship in curricula by faculty in colleges of human and veterinary medicine. It aims to promote a culture of stewardship as an integral part of continuing education and clinical practice, she said. Ensuring an adequate stewardship workforce of trained infectious disease physicians and pharmacists is important, according to Boucher, as is collaboration between CMS (which develops all the quality improvement tools and metrics), CDC, and state and local infection prevention programs. She highlighted the need to examine and improve good stewardship practices in outpatient settings.

Guidelines for Antimicrobial Usage in the Beef Industry

Programs Addressing Antimicrobial Use in the Beef Industry

Sjeklocha explained that programs addressing antimicrobial use have been in place since the mid-1980s in the beef industry. For example, the Beef Quality Assurance (BQA) began as a food safety and residue avoidance

program, then transitioned into a meat quality program that now incorporates animal stewardship and antimicrobial stewardship. He said that BQA requires participants to demonstrate a veterinarian client–patient relationship and to provide written treatment plans and disease descriptions. BQA also offers periodic reports on injection site lesions, he said, which has attracted many more producers to buy into that program. Although BQA guidelines have been widely adopted in the industry, he said, BQA lacks "teeth" because it is voluntary and producer driven.

Progressive Beef, a comprehensive third-party audit, is a commercial program that puts more teeth into BQA program guidelines, according to Sjeklocha. Participants pay a fee and must have a veterinarian client–patient relationship and documented prescriptions, treatment schedule, treatment records, and observed withdrawal times. He suggested that this may open up more upscale beef markets for producers who are part of the program, such as higher-end restaurants.

The Veterinary Feed Directive (VFD), effective January 1, 2017, is a law set out by the U.S. Food and Drug Administration (FDA) aimed at reducing antibiotic use, said Sjeklocha. However, it has not been well received by producers, he said. The VFD does track sales data, but Sjeklocha was unsure of its value because there is not enough verifiable data to use as a benchmark base. For example, knowing the amount of antibiotics sold does not capture the effect on animal health and welfare, he said.[5]

Gaining Producer Buy-In to Antimicrobial Use Guidelines

Beef producers can be reluctant to buy into guidelines, Sjeklocha explained, for both economic and cultural reasons. Beef producers typically value their independence very highly, and many resent being forced to commit to guidelines of any kind, he said; many producers also feel like they are being unfairly cast as scapegoats for the entire problem of antimicrobial resistance. Sjeklocha explained that the BQA guidelines have been the most widely adopted because producers' participation is voluntary rather than required. He further noted that younger producers are more likely to accept new concepts, while older, more seasoned producers may feel encroached upon when asked to try new practices. He explained that most producers manage disease on their own with basic diagnostic skills and past experience, with some veterinary input and guidance. New technologies are plentiful, including disease diagnostics, new stethoscopes, high-frequency electronic identification tags, rapid blood tests, and pedometers, but they

[5] If a cow herd is severely reduced in number because of drought, said Sjeklocha, then the remaining cows may be under nutritional stress, causing the amount of antibiotics sold to increase despite the smaller number of cattle.

BOX 4-2
Calf Preconditioning

Sjeklocha used the practice of calf preconditioning to illustrate why it can be difficult to gain producer buy-in to antimicrobial stewardship programs and practices. Preconditioning of calves is used primarily to implement preventive measures—such as vaccination and stress reduction—for improving animal health and reducing the need for antimicrobial treatment. However, he said that convincing producers to precondition, even in a high market, is an ongoing struggle. Lack of vertical integration in beef production presents unique challenges, Sjeklocha explained. Ranch-raised calves are typically sold to feed yards after they are vaccinated and weaned, he said, and producers can be reluctant to expend the effort for a full preconditioning program because the return on investment is small. Weight gain is the only benefit the producer accrues from preconditioning, he said, and it is not a premium at the market. Ranchers with small herds under 100 head constitute 93 percent of the market, he explained, and most raise cattle as secondary income so they cannot afford the facilities to hold and wean calves. Preconditioning is also stressful and increases the risk of cattle dying: "Every day you own them is another day they can die, so producers want to get them off their place [and] let them be someone else's problem." Even when the prices of feeder cattle increase, Sjeklocha said, producers are less likely to precondition due to the increased demand for calves, and feed yards will buy them whether or not they are preconditioned. However, he noted that many producers who do not precondition their calves still follow Beef Quality Assurance guidelines.

SOURCE: Sjeklocha presentation, June 20, 2017.

need further development and research, he said. They can also be expensive to adopt, he warned, and may be less feasible for smaller farms than larger farms that can spread their use over more production units.

To obtain buy-in, producers must have a return on their investment while also maintaining a level of independence, said Sjeklocha. He used the practice of calf preconditioning to illustrate why it can be difficult to gain producer buy-in to antimicrobial stewardship programs and practices (see Box 4-2). Creating an economically sustainable market will require incentivizing producers, he said, to help in convincing them to accept guidance and restrictions. The sales price for preconditioned calves is inconsistent, so weight gain is the primary financial driver for preconditioning. Even value-added programs such as antibiotic-free and other upscale markets are still considered to be niche markets that producers are reluctant to commit to, he said. While specialty and niche markets can provide some incentive, he said, they are also inconsistent. Niche markets also require producers to

sign contracts to commit to the program, he said, even though the practice may have a negative effect on animal welfare. Many producers are leery of organic, natural, and antibiotic-free markets because the return on investment is inconsistent, said Sjeklocha. When he was told that he would be surprised by how many consumers want antibiotic-free beef or organic beef, his reply was:

> You'd be surprised how many consumers say they want antibiotic-free beef or organic beef, but they get into the grocery store and they have sticker shock, and they say, "I'm going do my good deed and buy it this one time, and then I'm back to the stuff that's a little cheaper."

He emphasized that producers must receive a premium to bring them to these niche markets, and he predicted that ultimately, the majority of producers will provide what consumers want, even if those are niche markets, but only if the return on investment makes it worth their time and effort.

Changing Paradigm of Antimicrobial Use in Veterinary Medicine

Antimicrobial use practices in animal agriculture are changing rapidly, said Singer, due in part to FDA policy changes that Sjeklocha discussed earlier, but also to consumer and customer demands. The actual on-the-farm practices need to be linked to antimicrobial resistance, Singer said, to help veterinarians and production companies understand the effects of antimicrobial use on resistance as they are being asked to rapidly change their production systems. Singer said that improved antimicrobial stewardship and reductions in antimicrobial use are important, but not the end goal, which is to reduce antimicrobial resistance. He suggested that efforts should focus on evaluating changes in antimicrobial resistance as a function of change in antimicrobial use.

On-farm antimicrobial use can be quantified in two ways, said Singer. A bottom-up approach balances samples with antibiotic use data for a relatively small number of farms, he said, and a top-down approach captures industry-wide estimates of on-farm usage. Singer emphasized that the terms *no-antibiotics-ever* (NAE) and *antibiotic-free* do not mean that a company never uses antibiotics in any of its animals. NAE labeling means that antibiotics were not used in meat being sold under that label, he explained, and meat treated with antibiotics is marketed elsewhere. "It is really hard to raise 100 percent of your animals without them ever getting sick and needing treatment," he said, but warned that there is no single best approach to maintaining animal health and welfare.

Regulatory Changes on Antimicrobial Use in Veterinary Medicine

Singer discussed the implications of the 2017 FDA policy changes on growth promotion. In 2012, FDA published Guidance for Industry #209, describing the overall policy change regarding the use of antimicrobials in animal agriculture. Singer explained that it specifically limited the use of medically important drugs in food-producing animals to those that are considered necessary for ensuring animal health and that include veterinary oversight or consultation. Guidance for Industry #213 followed in 2013 and was fully enacted in January 2017, he said, providing more detail on implementing those key principles. It defines the seven classes of medically important antimicrobials that are illegal to use for growth promotion or feed efficiency, and it is illegal to use them without the authorization of a licensed veterinarian.[6] It also stipulates that manufacturers voluntarily remove claims relating to production uses (growth promotion and feed efficiency) off the label, he said, or take them off the market. He emphasized that veterinarian use of those antimicrobials is not voluntary; it brings remaining therapeutic uses under veterinary oversight by changing the marketing status from over-the-counter to veterinary feed directive status or prescription status. This veterinary oversight component constitutes stewardship in action, said Singer. The VFD regulation sets requirements related to the distribution and use of VFD drugs, he said, and represents a critical step for facilitating the transition to veterinary oversight.

Field Investigation of Antimicrobial Use and Resistance

Singer described a recently completed study funded by the U.S. Department of Agriculture (USDA) and the National Institute of Food and Agriculture that used a bottom-up approach.[7] It was designed to quantify the effect of antimicrobials used for preventing necrotic enteritis in broiler meat chickens on antimicrobial resistance in the broiler environment. Necrotic enteritis is a serious disease problem (related to clostridial overgrowth) in broiler chicken production, he said, especially as companies change how they use antibiotics. Antimicrobials approved for disease prevention are typically given in feed, said Singer, but the effect on resistance of applying them for an extended duration is yet unknown. A pen trial was conducted over three successive flocks raised on the same litter (a common practice

[6] Other antimicrobials deemed not medically important are still allowed for use in growth promotion and feed efficiency.

[7] Further information about the study can be found at portal.nifa.usda.gov/web/crisprojectpages/1005062-systems-approach-to-identifying-targeted-interventions-for-minimizing-antibiotic-resistance-in-the-poultry-production-system.html (accessed July 30, 2017).

in the industry),[8] to determine if antibiotics metabolites being excreted by the birds was building up in that litter over time. He explained that weekly composite litter samples were collected from each pen and cultured for *Salmonella* and *Escherichia coli*. The researchers also performed DNA extraction to perform microbiome and metagenomic analysis, as well as quantitative polymerase chain reaction analysis on 48 genes to search for selection pressure. Antimicrobial metabolites in the litter were measured to assess accumulation as a function of feeding these antibiotics to the birds, he said.

Early analysis revealed that the genes do not have a clear pattern of gene amplification under the selection of the antibiotic, according to Singer. For example, the *tetA* gene, associated with resistance to tetracycline, is very noisy when analyzed over time across the treatment groups. Singer emphasized more agricultural studies are needed to better understand the effect of antibiotic use under a variety of different conditions. However, pen trials are too limited in scope because they do not necessarily represent all the diversity found on farms and are restricted to the litter used in the pens.

Broiler Meat On-Farm Antimicrobial Resistance Surveillance Program

Singer also runs an on-farm antimicrobial resistance surveillance and monitoring program in the poultry sector, initially funded by FDA as a pilot. It aims to collect on-farm samples and antimicrobial use data from broiler meat farms throughout the United States. It was restructured in 2016 to make it more longitudinal, with every flock cycle sampled for *Salmonella* and *Campylobacter* and DNA banked from litter from each sample. Participation is voluntary and anonymous, with current enrollment between 50 and 75 percent of annual production. More than 350 sampling efforts have been carried out on 118 farms followed over time.

Singer described a sample report generated from the data of a single company's four farms over five different flocks; *Salmonella* was present in all but one farm on one visit. Isolates were also serotyped to demonstrate the common resistance patterns of streptomycin-sulfadiazine-tetracycline, and quantitative data were collected on how antibiotics were used (in this case, no treatments were given). While it may seem that there is matched use data to resistance patterns for *Salmonella*, he said, data from a different complex that used no antibiotics during the entire year had *Salmonella*

[8] The birds were raised for 35 days in each flock cycle, with a 7-day downtime between the flocks. Six of the seven treatment groups were given narasin, a nonmedically important ionophore that is a growth-promotion, feed-efficiency compound—plus one of five antibiotics to prevent necrotic enteritis (a bacitracin, a bambermycin, two oxytetracycline groups, and a virginiamycin). The seventh group received no narasin and no antibiotic.

present in all houses at every visit and the same resistance patterns of streptomycin-sulfadiazine-tetracycline. In Singer's opinion, *Salmonella* and its resistances do not track with antibiotic use. He also expressed concern about labeling salmonellas as multidrug resistant, because streptomycin, sulfadiazine, and tetracycline are not typically used to treat an invasive case of salmonellosis. The focus should be on the resistances in *Salmonella* that are related to the problem of treatment failure, argued Singer.

National Industrywide On-Farm Antimicrobial Use Data Collection Effort

Singer discussed an industry-wide effort to collect on-farm antimicrobial use data throughout the United States. He noted that each commodity group—layer hen, turkey, broiler meat, swine, beef, and dairy—is now actively initiating these efforts. The poultry effort began in 2014 with support from FDA and U.S. Poultry & Egg Association cooperative agreements, he said. The survey is designed to capture on-farm usage data on indication, route, dose, and duration,[9] and it is organized by how the antibiotic is used (in the hatchery, for growth promotion, for disease prevention, and for treatment and control). Broiler meat surveys are based on 6-month periods, he said, and data from 2013 and beyond are requested in order to capture trends prior to the 2017 FDA policy changes.

Consumer and Retailer Perspectives in the Poultry Industry

In 2002, Perdue Farms realized that the public health implications of antibiotic use in animals would be a matter of ongoing debate for years to come, said Stewart-Brown, and predicted that regulatory efforts would be forthcoming at the local, state, and national levels. Furthermore, consumer concerns about antibiotic use—specifically, that it was being used to cover up bad husbandry practices—also began to increase significantly, he said. To address these issues, Perdue Farms began a 15-year process of reducing with the goal of eventually eliminating the use of antibiotics in raising their chickens.

Antibiotic Use in the Poultry Industry

The chicken industry has traditionally used antibiotics in four different ways, explained Stewart-Brown. The first way is the use of antibiotics for

[9] A survey instrument was designed collaboratively with USDA's Animal and Plant Health Inspection Service (APHIS) and survey responses coded and analyzed as a composite of the industry; participation is voluntary and confidential. APHIS also serves an auditing role.

growth promotion in the chicken feed; however, using medically important antibiotics in feeds for growth promotion is no longer permitted by producers in the United States. Second, in the hatchery, antibiotics are generally mixed with a vaccine and injected directly into eggs at 18 days of embryonation, but some farms inject it into day-old chicks. The third is feed application of ionophores, which are animal-only antibiotics, and the fourth is treatment of sick or soon-to-be sick animals that are in the same house with sick birds.

Stewart-Brown differentiated between four categories of programs used by chicken producers, noting that consumers may not clearly understand the distinctions. In the industry "all in" category, human-use-approved—also called shared-use—antibiotics are used in hatcheries and in feed for growth promotion or disease prevention; this category also uses ionophores as well as shared-use antibiotics for treatment, control, and targeted prevention in sick flocks. In the gray area ("no human") category, only ionophores are used. He noted that there are not many choices for treating sick flocks that are not shared-use products, but if shared-use products are required, the flocks are taken out from the remaining two programs—organic and NAE[10]—where no antibiotics are used at all.

Raising Chickens Without Antibiotics

Perdue Farms now has extensive experience in the organic market, Stewart-Brown said, with 1 million organic chickens among the 13 million they process each week. He related some of their experiences in the process of eliminating all uses of antibiotics in organic chicken production.

Eliminating hatchery use Through a process of gradual transition beginning in 2002, said Stewart-Brown, Perdue eliminated hatchery antibiotic use in 2014. He explained that to eliminate the use of hatchery antibiotics, breeders require cleaner eggs. In a breeder farm, chicken houses have three levels. The females generally stay on the upper level, coming down to the bottom level to mate with males and then lay their eggs in nests in the middle level, he said. At night, a bar is lowered in the nest level that prevents the females from spending the night in the nest and dirtying the nests. Dirty nests contaminate the eggs, and if the farm is not using hatchery antibiotics, then the eggs must be cleaned as they travel down the conveyer belt and out of the nest level. To avoid spreading contamination from manure from using the same wet rag to clean all the eggs, he said, their breeders now use disposable baby wipes. Another development, said Stewart-Brown, build-

[10] This program was formerly known as *antibiotic-free*, but this caused confusion about whether it refers to the meat or to the production of chickens.

ing separate rooms in the hatchery to mix vaccines under a laminar-flow chemistry hood; this avoids contaminating the vaccines by mixing them in the hatchery area.

Eliminating use of antibiotics for growth promotion and use of any shared-use antibiotics Eliminating the antibiotic use for growth promotion and the use of human-approved antibiotics of any kind in chicken feed was a quicker process, Stewart-Brown said, which was completed by 2007. Chickens were provided with a regimen of probiotics and prebiotics and a vegetable-only diet, he said. It is much harder to run a no-antibiotics-ever program and still use animal by-products in feed, he noted, because any feed items that might be prone to causing gut irritation threaten the long-term success for reducing and eliminating antibiotics.

Since 2010, Perdue has adopted an aggressive approach to vaccination relative to the industry average, said Stewart-Brown. Vaccinating a hen protects the egg yolk as well as provides some protection to the chick, he explained, and low-reaction vaccines are used in the hatchery to prevent the need for antibiotics. When chickens become sick, the entire house is treated with the best possible antibiotic under veterinary supervision, he said, and outcomes are measured. When a house repeatedly needs treatment, the cause is identified and addressed, he added.

Success of the no-antibiotics-ever program at Perdue Farms Stewart-Brown reported that since 2009, the percentage of flocks treated with antibiotics has ranged between 1.1 percent to 5.4 percent per year, with 3.2 percent treated in 2017. The percentage of birds per week starting in the NAE program increased from 20 percent in 2013 to 100 percent in March 2017, he said. The success of the NAE program illustrates that antibiotics are not needed to raise chickens, Stewart-Brown emphasized. He advised that in order to accomplish this across the broader spectrum of animal agriculture, changes in animal care need to be implemented. Perdue Farms is currently rolling out organic animal husbandry rules to their nonorganic flocks, he said. He concluded by encouraging a focus on engaging farmers: "Those are the ones that are raising the animals, they've got to buy in . . . you've got to spend a lot of time with farmers."

DISCUSSION

Peter Daszak, president of EcoHealth Alliance, asked if coccidia ever recur when ionophores are removed in establishing NAE programs. Stewart-Brown explained in those situations, there are two options for coccidiosis control in chickens—either a vaccine or a nonantibiotic product, such as nicarbazin—although the latter is not suitable for organic programs.

Daszak asked if Perdue Farms has surveyed the public about why they do not want antibiotics in their chickens. Stewart-Brown said that reasons cited include public health implications (although they might not be well understood by the public), environmental effects, and, according to many consumers, the poultry industry is being selfish and not doing the right thing by using antibiotics to raise animals.

David Relman, professor of medicine at Stanford University, asked about the potential for manipulating gut microbial communities through means other than antibiotics. Stewart-Brown noted that migrating chickens around different parts of the chicken house (during brooding, for example) can be very difficult on the birds. He said that keeping the chickens on feed while they migrate is an example of a management practice that helps to maintain microbial balance in the chickens' guts. Relman asked if there are good data that the chickens' difficulty during migration is a result of a disturbance in the gut microbial ecosystem, but Stewart-Brown did not know of any. Singer said that ongoing studies are examining what makes a gut healthy and the effect of practices that try to alter the gut microbiome to make an animal healthier. Sjeklocha noted that adding yeast to the diet of cattle, to deal with the frequent problem of liver abscesses, has lowered the abscess formation rate and reduced reliance on tylosin and antibiotics, the traditional treatments.

Lonnie King, professor and dean emeritus of The Ohio State University College of Veterinary Medicine, asked Boucher about the core element of leadership in stewardship programs. According to Boucher, the leadership component of stewardship cannot be overemphasized because leaders are responsible for negotiating for high-level support, running the programs, and influencing people not to use antibiotics. As stewardship becomes more sophisticated, she said, IDSA and SHEA have put initiatives in place to help develop and train the next generation of leaders. George Poste, chief scientist of the Complex Adaptive Systems Initiative at Arizona State University-SkySong, asked Boucher about pressures to discharge patients prematurely because of concerns about hospital-acquired infections. Boucher said such pressure has never been worse, from her perspective, but has actually increased the value of her institution's stewardship program because it can be leveraged as an opportunity to, for example, send patients home with an oral rather than IV antibiotic or with no antibiotic at all.

ACHIEVING DESIRED BEHAVIOR CHANGE THROUGH PREVENTION MEASURES AND EDUCATION

Strategies to Enhance Antimicrobial Prescribing Practices Food and Companion Animal Veterinarians

Scott opened his presentation by comparing and contrasting between antimicrobial stewardship for humans and animals. He stated that the definition of antibiotic stewardship from the perspective of human clinical medicine, as presented earlier by Boucher, may be relatively aspirational and challenging to translate to production animal medicine from the veterinary perspective.

In an ideal clinical setting, Scott explained, a physician treating a patient with streptococcal pneumonia would test the bacteria and follow all relevant stewardship guidance to choose the correct antibiotic. However, if individual patients hospitalized in the same ward are receiving different antibiotics, he said, then the potential unintended effect on the nontarget bacteria is a major concern, because most patients carry bacteria as part of their natural microbiome. Scott observed:

> We use the term *antibiotic stewardship*, but if you were talking about stewardship of other natural resources like forests, you wouldn't talk about chainsaw stewardship. You would actually refer to the trees . . . we are actually talking about bacterial stewardship and, in particular, populations of bacteria that are under our care.

Scott said that *Enterococcus* normally makes up a very small fraction of the total bacteria in a person's microbiome, but in human hospital intensive care units (ICUs), antibiotic use can expand those fractions of *Enterococcus* in the patients. The same effect occurs in animals in veterinary ICU units, Scott said. The top three uses of antibiotics in companion animal veterinary practice are for dermatologic, urinary, and respiratory infections, he reported. It can be difficult to get an animal to ingest a pill, said Scott, so long-duration antibiotics have been developed to treat common conditions like chronic skin infections. He said that some of those antibiotics—such as third-generation cephalosporins—can have dramatic effects on the gut microflora in animals.

To address the problem of resistance, said Scott, animal referral hospitals have developed stewardship policies, like Texas A&M University's Drugs of Last Resort Policy, and an ongoing CDC-funded project is examining use and resistance in referral veterinary hospitals. He noted that WHO's 2012 revision of its List of Critically Important Antimicrobials (WHO, 2012) recommended that when a new class of human drug comes on the market, it should be considered critically important from the outset

unless strong evidence suggests otherwise. It also recommends that existing drugs such as carbapenems, linezolid, and daptomycin (not currently used in food production) should not be used in small animals, plants, or aquaculture in the future. This raises the question of how to prevent small-animal practitioners from using those products in an extra-label manner, Scott said, or at least how to ensure that the products are used according to good stewardship principles.

Applying Social Psychology to Antimicrobial Prescribing Practices

To frame antimicrobial prescribing and use in a theoretical context, Scott applied the theory of planned behavior (TPB) from social psychology to intensive production animal agriculture, noting that the TPB model has already been applied to physician prescribing behavior and patient compliance. The basic TPB framework (Ajzen, 1991) describes that intentions, the most important determinant of behavior, is determined by three constructs: attitude ("is the behavior good to do?"); subjective norms ("what do other salient actors expect me to do, and do I care what they think?"); and perceived behavioral controls ("how easy or difficult is the behavior for me to do?"). Perceived behavioral controls can motivate reflexive-type behavior that is not necessarily mediated by intentions, said Scott. Subjective norms can be difficult to analyze, he said, because they are qualitative and span a complex social network of potential influences on decision making.

To explore changes in antibiotic use in intensive production agriculture, Scott's team expanded the TPB framework to include the factors: "trust or confidence in others," "behavioral beliefs and belief importance," and "moral norms and salient obligations to others." They surveyed feedlot operators and veterinarians, Scott reported, and almost all respondents overwhelmingly agreed with the statement, "I have a moral duty to treat acutely ill feeder cattle with antimicrobials." When respondents were asked if they had a moral duty to use subtherapeutic antimicrobials to promote growth, the majority of feedlot operators felt they had an obligation to others (for example, to contribute to the financial stability of the business), but the majority of veterinarians did not report having any such moral duty. For Scott, exploring this type of subjective disagreement among stakeholders provides the opportunity to design interventions more effectively to drive improvements in antibiotic stewardship.

Motivating Antibiotic Stewardship in Production Agriculture

Scott explained that target bacterial pathogens such as pneumonia and bovine respiratory disease complex are the most common reason for

antibiotic use in cattle feedlots. Pneumonia, for example, can be caused by different bacterial strains (or combinations of strains) that have normal commensals in the upper respiratory tract, he said. However, stress can lead to a pneumonia outbreak in the animals through the epidemiologic triad of host, agent, and environment. Treatment with antibiotics can drive resistance in those bacteria and motivate changes in prescribing and use, said Scott, but his primary concern is the unintended consequences of antibiotic use on gut bacteria and on *Salmonella* and *Escherichia coli*. He said that antibiotic stewardship can be difficult to motivate among producers because it really has no bottom-line economic impact, short of consumer demand. The debate around using antibiotics to treat individual sick cattle versus therapeutic use of antibiotics in groups of animals to control disease (metaphylaxis) or prevent disease (prophylaxis), he noted, is echoed in similar debates around prudent use in human clinical medicine. Scott suggested broadening the focus of stewardship to "what leaves a farm," both in terms of animals going to slaughter and in terms of preventing the release of resistance determinants from the farm and into the environment at higher than background levels. Scott cited an experiment that applied behavioral science to try to change farmers' use of antibiotics in dairy farms in the Netherlands (Speksnijder et al., 2017). The intervention was a program called structural animal health planning, which involves veterinary nutritionists exploring ways to reduce antibiotic use with cohorts of farmers. After three years, the use of antibiotics among the group that received the structural animal health intervention was shown to have declined over the entire study period.

Leveraging Social and Behavioral Interventions to Achieve Appropriate Antibiotic Prescribing Practices in Health Care

Linder opened by arguing that improved diagnostics will not resolve the problem of inappropriate antibiotic use in human health. Stewardship has traditionally been an inpatient-focused activity, he said, even though 60 percent of antibiotic use in humans occurs in the outpatient setting (CDC, 2017). In the United States, he reported, there are 34 million hospitalizations each year, but there are 130 million emergency department visits and 1 billion ambulatory visits—with an antibiotic prescribed at 12 percent of those visits (National Center for Health Statistics, 2016). He reported that acute respiratory infection, which includes ear infections, pharyngitis, sinusitis, acute bronchitis, pneumonia, the flu, and nonspecific upper respiratory tract infections, accounts for 10 percent of all annual ambulatory visits in the United States and 44 percent of all the antibiotics prescribed in ambulatory settings. About half of those antibiotic prescriptions are inappropriate, he said, such as the prescription of an antibiotic for a nonspecific

upper respiratory tract infection or acute bronchitis (The Pew Charitable Trusts, 2016). He warned that these practices are causing huge problems in terms of rising costs, increases in antibiotic-resistant bacteria, more frequent adverse drug events, and changing the microbiome. He warned that "many of these antibiotics are given to people who have viral illnesses and the antibiotic has no chance of helping them and a very real chance of hurting them."

Education is important but not sufficient to address this problem, Linder said. Despite the amount of clinician education provided over the past 20 years, the antibiotic prescribing rate for some infections has not changed much at all, he reported. Four decades of randomized controlled trials have demonstrated that antibiotics do not work for acute bronchitis, he said, yet the antibiotic prescribing rate for acute bronchitis among adults in the United States remains just shy of 80 percent (Barnett and Linder, 2014). For adults with sore throat, the appropriate antibiotic prescribing rate is about 20 percent, but 60 percent of adults with a sore throat are prescribed an antibiotic in the United States (Barnett and Linder, 2014). He reported that for ambulatory visits, there are 506 antibiotic prescriptions per 1,000 people in the United States; at least 30 percent of overall antibiotic prescribing is unnecessary and half of the antibiotics prescribed for acute respiratory infections are unnecessary (Fleming-Dutra et al., 2016). When other types of prescribing are included, such as prescribing over telephone, retail clinics, and at the Veterans Affairs facilities, Linder said, the antibiotic prescribing rate in the United States jumps to 833 per 1,000 people (Hicks et al., 2013).

Linder argued that the focus should be shifted from diagnostics to increasing clinicians' knowledge about what is happening with a patient. CDC's Etiology of Pneumonia in the Community study included 2,259 adults hospitalized for pneumonia, who were intensively investigated for pathogens; the etiology was not identified in 62 percent of cases (Jain et al., 2015). Even with improved technology, he said, testing a patient who presents with a respiratory infection will not provide a single answer.

Behavioral Science of Prescribing

Prior interventions to prevent inappropriate prescribing to outpatients have had limited success, Linder reported. The implicit model holds that clinicians are reflective, rational, and deliberate, but attempts to educate and remind them about appropriate prescribing practices at the time of care have continued to fail. Linder argued that "doctoring" needs to be reconstrued as an emotional, social activity carried out by people who are subject to a range of biases and other social factors that drive prescribing behavior. He suggested supplanting the implicit model with a behavioral

model under which clinicians make fast, automatic decisions influenced by emotional and social factors as well as a range of cognitive biases.

The factors that drive antibiotic prescribing are immediate and emotionally salient, Linder explained. In an outpatient setting, he said, the social and emotional factors that promote inappropriate prescribing practices often outweigh the factors that promote appropriate prescribing. For example, a clinician may believe that a patient wants antibiotics and have the perception that it is easier and quicker just to prescribe them, he said. Alternatively, a clinician may prescribe antibiotics out of ingrained habit or prescribe them "just to be safe" out of concern for potential serious complications. The factors that deter antibiotic prescribing are more remote and less emotionally salient, explained Linder. These include the risk of adverse reactions or drug interactions, the need for stewardship, the desire to deter low-value care, and a preference for following guidelines. The effect of nonclinical factors on antibiotic prescribing behavior has been borne out by evidence, Linder said. An analysis of antibiotic prescribing over the course of the day—stratified by diagnoses for which antibiotics were sometimes indicated or antibiotics were never indicated—found a 5 percent absolute increase in antibiotic prescribing at the end of the day versus the beginning of the day with a small drop during lunch (Linder et al., 2014). He noted that this effect was replicated by athenahealth, in a study that found the antibiotic prescribing rate for acute respiratory infections increased over the course of the day as the number of appointments accrued (see Figure 4-1).

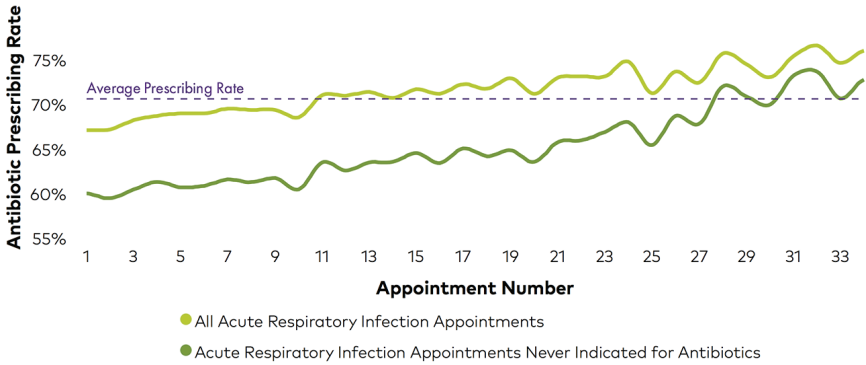


FIGURE 4-1 Antibiotic prescriptions over the course of a day.
SOURCES: Linder presentation, June 20, 2017; athenahealth, 2016. Image courtesy of athenahealth research.

Social and Behavioral Interventions to Reduce Inappropriate Antibiotic Prescribing in Primary Care

To illustrate the application of behavioral science concepts toward decreasing inappropriate antibiotic prescribing in primary care, Linder reviewed some results from the Behavioral Economics to improve treatment of Acute Respiratory Infection (BEARI) trial (Meeker et al., 2016). Interventions using clinical decision support and health information technology often yield disappointing results, he said. Electronic health records (EHRs) with clinical decision support have been touted as a solution to problems of medical safety, cost, and quality, he said, but they often fail to achieve expected improvements because they implicitly assume that clinicians follow a standard economic and behavioral model. The aim of the BEARI project was to evaluate three behavioral interventions in three different health systems using three different electronic health records, he said.

The three interventions Linder explained that they looked at an 18-month baseline period and an 18-month intervention period. The first type of behavioral intervention—suggested alternatives—is similar to traditional reminder-based clinical decision support. When clinicians seek to prescribe certain types of antibiotics through the EHR system for certain acute respiratory infections, the system triggers a pop-up reminder that antibiotics are not generally indicated for nonspecific upper respiratory infections, he said, and it suggests several nonantibiotic alternatives before the clinician can proceed with the prescription. The second intervention—accountable justification—builds on suggested alternatives with an element of social motivation. Linder explained that an attempted antibiotic prescription in the EHR system triggers advice that an antibiotic is not indicated for likely viral diagnosis, and requires the clinician to input a reason for prescribing the antibiotic. If no justification for prescribing antibiotics is given, he said, there is an implicit understanding that clinician's colleagues will see that in the EHR system. Linder noted that the first two interventions can be combined easily. The third intervention—peer comparison—involves a different form of social motivation, he explained. Everyone receives a monthly email that stratifies clinicians into top performers with the lowest inappropriate antibiotic prescribing rate, and non-top-performers (all others). Linder explained that this simple, emotionally laden message tends to "pull in the tails on the bell curve": bad performers do a bit better and good performers may backslide slightly. But keying interventions on top performers, he said, can shift the whole mean toward top performance.

Outcomes and implications of the interventions Linder reported that over 18 months, nearly 250 clinicians enrolled in the BEARI trial from 47

primary care practices. The study's primary outcome was the antibiotic prescribing rate for nonantibiotic-appropriate diagnoses. He reported that during the 18-month baseline period prior to the intervention, the antibiotic prescribing rate decreased for the control group and that being enrolled in the trial itself had the largest absolute decrease in antibiotic prescription of any intervention, which he attributed to the participants' knowing that their prescribing was being watched. The antibiotic prescribing rate for the control group continued to decrease during the 18-month intervention period. The antibiotic prescribing rate decreased for the suggested alternative group through both the baseline and intervention periods, but the change was not statistically significantly different from the control group by the end of the study. The accountable justification intervention group had a statistically significantly lower prescribing rate by the end, with a relative 7 percent drop.[11] Linder reported an even bigger drop in the peer comparison intervention group, which started off lower and then dropped down to a 4 percent inappropriate antibiotic prescribing rate by the end of the study, for a relative decrease of 5 percent compared to the control practices. In summary, Linder noted that these studies suggest that doctors' behaviors are influenced by social factors so insights from social and behavioral sciences can facilitate the development of interventions to influence doctors' prescribing behavior for acute respiratory infections.

The Role of Academic Veterinary Medicine in Combating Antimicrobial Resistance

Maccabe described initiatives to combat antimicrobial resistance by AAVMC, an association of all veterinary medical colleges in Canada and the United States, as well as colleges of veterinary medicine worldwide, facilitating an international approach with a global footprint. The AAVMC felt that academia was not responding actively enough to the need for a One Health approach to address antimicrobial resistance, he said. To help address this gap, Maccabe explained that AAVMC partnered with the Association of Public and Land-grant Universities (APLU) to create a task force focusing on antimicrobial resistance in production medicine.[12] He said that the task force also includes the American Veterinary Medicine Association and representation from government (CDC, FDA, and USDA), and industry (Animal Health Institute, National Cattle-

[11] He explained that this estimate calculates the effect of the intervention by comparing the changes in outcomes over time between the intervention group and the control group.

[12] APLU is North America's oldest higher education association, which represents 237 public universities and 49 veterinary medical colleges accredited by AVMA Council on Education and agricultural experiment stations.

men's Beef Association, National Chicken Council, and National Pork Producers Council).

Task Force Activities to Combat Antimicrobial Resistance

The AAVMC-APLU task force was charged with proposing recommendations and activities for academic institutions related to antibiotic resistance in production agriculture, said Maccabe. The resulting AAVMC-APLU task force report, *Addressing Antibiotic Resistance*, focuses on education and research (AAVMC, 2017), but Maccabe focused on recommendations related to education specifically. A working group developed learning outcomes for competency-based training and education across six domains: healthy animals, global impact, antimicrobial stewardship, antimicrobial drugs and antimicrobial resistance, roles and relationships, and critical analysis. Individual institutions develop the rubrics and curricular materials that link to those learning outcomes, he explained. Table 4-1 shows a representative page detailing the learning outcomes related to antimicrobial stewardship for novice, intermediate, and advanced students.

TABLE 4-1 Antimicrobial Stewardship Learning Outcomes

	Developmental Level		
	Novice (4-H/FFA/Youth)	Developing (animal science undergraduate or graduate)	Advanced (veterinary medical students)
Definition	Define antimicrobial drug stewardship		
Societal resource	Recognize that there is increasing societal concern about bacterial resistance to antimicrobials and potential reduction or loss of effectiveness	Recognize that there is increasing societal concern about bacterial resistance to antimicrobials and potential reduction or loss of effectiveness. Cite examples of antimicrobial stewardship that might be helpful	Describe specific examples of resistance in pathogenic and nonpathogenic bacteria that are commonly found in a specific animal species and in important human pathogens

TABLE 4-1 Continued

	Developmental Level		
	Novice (4-H/FFA/Youth)	Developing (animal science undergraduate or graduate)	Advanced (veterinary medical students)
Definition	Define antimicrobial drug stewardship		
Common uses of antimicrobial drugs	Identify common situations in which antimicrobials are needed to address animal health and welfare and minimize suffering	Recognize that there are common situations in which antimicrobials are needed to address animal health and welfare and minimize suffering and those in which antimicrobial drugs will not make a difference	Distinguish common or important situations in which antimicrobials are needed to address animal health and welfare and minimize suffering and those in which antimicrobial drugs will not make a difference
Complexity of bacterial infections	Recognize that infectious diseases can be caused by a variety of microorganisms, and that disease risks can vary among different animals	Recognize that infectious diseases can be caused by a variety of microorganisms, and describe how disease risks can vary among different animals	Describe the epidemiology and pathogenesis of the most common and the most significant bacterial disease challenges in major domestic species of animals; describe the organism or patient factors that may effect treatment options
Need for antimicrobial drugs	Recognize that there may be a need to use antimicrobial drugs in cases of infectious disease where subsequent health and life or lives of animals are threatened	Recognize that there is a need to use antimicrobial drugs in cases of infectious disease where subsequent health and life or lives of animals are threatened, and understand that antimicrobial drugs may not be required	Explain to animal owner or manager why an antimicrobial drug is or is not recommended based on the perceived need and benefit to the animal, including differentiating an infection requiring treatment and a contaminant not requiring treatment

NOTE: 4-H = U.S. youth organization focused on personal development in "head, heart, hands, and health"; FFA = U.S. student organization, formerly the Future Farmers of America.
SOURCES: Maccabe presentation, June 20, 2017; from AAVMC, 2017.

In another activity, Maccabe explained, the joint task force partnered with the Association for Prevention Teaching and Research, an association composed primarily of faculty from medical schools that teach preventive medicine and public health, to develop the One Health Interprofessional Education Initiative. It seeks to integrate One Health concepts into the degree programs of health profession students through the case study method of instruction, he said, and 15 peer-reviewed case studies have already been published through a competitive process that financially incentivizes faculty members to contribute.[13] The same process will be used to solicit the development of curricular materials for dissemination. Maccabe explained that the Antimicrobial Resistance Learning Site is a project that provides open-source teaching modules for instructors in veterinary medical education on antimicrobial resistance with modules in pharmacology, microbiology, public health, and species-specific medicine.[14]

According to Maccabe, the AAVMC's education and outreach efforts also involve developing key messages and communication strategies for engaging decision makers at all levels. Informational materials will be made available to producers and veterinarians (e.g., FDA VFD guidance, disease prevention strategies, and antimicrobial stewardship), to agricultural youth groups, and to the general public. Looking forward, said Maccabe, the AAVMC will continue to build its coalition of partners and stakeholders to further develop its strategic communication strategy.

The Medical Curriculum Meets Microbial Threats

Kirch considered the challenge of translating the goal of improved antibiotic stewardship into the educational process. He commended the One Health initiative for bringing together the disciplines of human, animal, and environmental health toward a common cause, but he noted that individuals within those disciplines have traditionally been educated in silos. This is one of the consequences of the traditional model of medical education that, he warned, is rapidly becoming outdated and ineffective. To illustrate, he provided three perspectives on the continuum of medical education. The aspirational model is a true seamless continuum, he said, that creates the mythic "master" clinician. It begins at the premedical stage, continues through medical or veterinary school, residency, and fellow-

[13] For example, a case study related to an antimicrobial resistance effort focuses on the interplay of methicillin-resistant *Staphylococcus aureus* (MRSA) between companion animals and humans; it discusses infection prevention measures with emphasis on the interaction that is needed between human and veterinary medical professionals in resolving recurrent household MRSA infections.

[14] Produced and operated by Michigan State University and the University of Minnesota, in cooperation with CDC.

ships, and on through practice, with continuous learning and assessment throughout the process. When Kirch became a dean, he said, this fantasy was soon dispelled. He explained that the reality is a process that involves a series of sealed and autonomously controlled compartments along the path to becoming a specialist and then subspecialist. The wide array of entities involved—in education, training, certification, program accreditation, assessment, and licensure—form an educational path that is hugely fragmented rather than integrated, said Kirch.

From Facts to Competencies in Learning and Assessment

Better coordination among the different "compartments" is not the answer, said Kirch. He highlighted what he considers to be a major paradigm shift in education. Traditionally, the acquisition of knowledge and facts has driven learning and assessment in medical education, he said, as well as in education writ large. Standardized fact-based assessment is used at various stages to assess the students' accumulation of facts. Kirch said that the problem today, however, is that the evolution of science has hugely increased the size of the available fact base, such as structural genetics, functional genetics, and now proteomics and other effector molecules. Therefore, the number of facts required per decision has also increased exponentially, he said, and now vastly exceeds human cognitive capacity.

The complexity of clinical decision making will only continue to accelerate, said Kirch, while human cognitive capacity remains static. Unlike decades ago, he said, a single clinician can no longer accumulate all the relevant knowledge required to make clinical decisions. He said, "We need to wean ourselves from the notion that our task is to fill people with facts and rather say that our task is to help people develop foundational knowledge." He conceded that facts remain important, especially those that constitute key conceptual notions. However, he said that helping health professionals develop the competencies to use those facts is more important and has become a topic of intense interest over the last decade.

Health Profession Competency Domains

Kirch cited a paper that collated more than 150 systems articulating health professional competencies from around the world (Englander et al., 2013). The authors found that virtually all of those competencies map onto eight fundamental domains:

1. medical knowledge,
2. patient care,
3. interpersonal and communication skills,

4. professionalism,
5. practice-based learning and improvement,
6. systems-based practices,
7. personal and professional development, and
8. interprofessional collaboration.

Kirch noted that the Accreditation Council for Graduate Medical Education core competencies for residency training in the United States emphasize the first six of those domains. He explained that traditional medical knowledge, together with all other competencies, amount to what are called core entrustable professional activities. He defined this as a set of activities that entering residents should be expected (entrusted) to perform on day 1 of residency without direct supervision (AAMC, 2014). He noted that this has been expanded to establish core competencies for Interprofessional Collaborative Practice,[15] spanning the domains of values and ethics for interprofessional practice, roles and responsibilities, interprofessional communication, and teamwork.

Creating a Clear Educational Pathway to Mastery

Kirch emphasized that the classroom is "flipped" and learning becomes asynchronous in the pedagogical shift from facts to competency-based learning. Traditional classrooms are being replaced by online tools for acquiring core knowledge, he said, which are coupled with smaller facilitated learning groups that focus on how the facts translate to challenges in day-to-day practice. Along the continuum of educational development, a health professional's competencies move from novice to expert level. However, he said that a barrier is the poor standard of general health literacy within the undergraduate medical curricula. Preprofessionals often lack the basic foundational knowledge and competencies, he said, that would enable them to move through progressive stages of mastery. Kirch suggested that technology-based tools have great potential to help close this gap and move pedagogy toward the competency-focused flipped classrooms, case studies, and problem-based learning.

The Path to Mastery in Addressing Antimicrobial Resistance

Practice-based learning and communication are particularly relevant to mastery in antibiotic stewardship, Kirch said. He offered a sketch of a four-step pathway to mastery in addressing antimicrobial resistance. The

[15] For more information on the core competencies for Interprofessional Collaborative Practice, see www.ipecollaborative.org/resources.html (accessed July 30, 2017).

first step is fundamental "health literacy" in the One Health framework. The second is acquiring basic science foundational concepts of prevention, epidemiology, microbiology, pharmacology, and genetics. The third, Kirch said, is the appropriate prevention and treatment of uncomplicated infections. The fourth step is to acquire the competencies to manage population health threats, complex infections, and treatment resistance in humans, the food supply, and the environment.

DISCUSSION

Wilson asked Linder if the BEARI trial followed up to see if the prescriber behavior persisted after the intervention phase. Linder said there was a significant persistent effect in the peer comparison group, but the suggested alternative group had migrated back to control practices after 12 months, while the peer comparison group had a smaller amount of backsliding.

Suerie Moon, director of research at the Global Health Centre, Graduate Institute of International and Development Studies, Geneva, asked Linder if the BEARI interventions would work as well in resource-poor, lower-technology settings. Linder noted that the peer comparison intervention was the most effective—and the lowest-tech—of the interventions tested, using email rather than the EHR system. Linder continued that in a resource-poor setting, determining with confidence that an antibiotic prescription is inappropriate would be challenging and the consequences of getting that wrong could be much deeper. He remarked, "we can only improve what we are measuring," so creating a paradigm to measure the quantity and quality of antibiotic prescribing is a needed first step. Jeffrey Duchin, health officer and chief of Communicable Disease Epidemiology and Immunization Section for Public Health for Seattle and King County, Washington, asked Linder to clarify whether the peer comparison intervention was actually the second largest effect, if the largest effect was simply from being enrolled in the study. Linder agreed that in absolute terms, the strongest effect of any intervention was just being in the trial, but he noted that participants had to actively enroll to take part. After looking at the difference between people who did and did not enroll in the trial, he found that the people who enrolled had a lower baseline antibiotic prescribing rate than those that did not. Linder said that this set the bar higher for the interventions that they tested, as well as highlighting the need to engage people who are not prescribing well and may be aware that they are not.

Gerald Keusch, associate director of the National Emerging Infectious Diseases Laboratory at Boston University, asked if it takes longer to make the decision not to prescribe an antibiotic than to make the decision to prescribe and, given the pressures on time with patients, that itself may

make a difference in the ultimate outcome. Linder replied that according to data he has analyzed, the difference is not huge. However, there are also downstream effects, he said; for example, people who get an antibiotic are much more likely to think they need one in the future and to come back again. Northern European countries have used this tendency to cut down on visits, he said, but in the United States, such visits tend to be perceived as an easy and quick way to satisfy patients and ensure that they return. This is an ongoing issue in urgent care clinics, he said.

Peter Sands, senior fellow at the Mossavar-Rahmani Center for Business and Government, Harvard Kennedy School, commented that experience in the United Kingdom with peer comparison intervention is consistent with Linder's findings. Antibiotic use data for every general practitioner (GP) in the country is measured monthly and the data are made public. Clinical commissioning groups—who buy services from GPs—receive a financial incentive from the government to manage that performance, he said, which serves as an incentive to shift behavior by naming and shaming. Linder added that the chief medical officer in England sent single letters to high-prescribing GPs, stating their practice was prescribing more antibiotics than others in their region, which resulted in a measurable decrease in antibiotics dispensed overall (Hallsworth et al., 2016). However, he reported that a study in the United States involving letters sent by CMS, which compared the most frequent prescribers of opioids to their peers, had no impact on behavior (Sacarny et al., 2016). This illustrates that the message, the data, and the messenger are all important in the way feedback is delivered, said Linder. Scott commented that there are similar examples on the veterinary side from Denmark and the Netherlands. Both countries have sufficient granularity in their capture of antimicrobial prescribing, both by veterinarians as well as at the producer level, to use annual evaluations and resetting based on standard deviations.

Kirch drew a distinction between the education of future professionals and the problem of remediating clinicians who develop prescribing patterns over many years. A practical experiment is ongoing with the Choosing Wisely campaign,[16] he said. Medical societies in the United States have developed specialty-specific consensus lists consisting of five practices that reflect overutilization or misutilization of diagnostic tests and treatments. He said that many of the lists include inappropriate antibiotic prescribing. However, he reported that although these lists are generally ignored by practitioners, they are prominent in medical school and residency curricula, reflecting the difference between imprinting and behavioral change in adults. He suggested adopting a two-pronged approach to address practitioners who have

[16] For more information on the Choosing Wisely campaign, see www.choosingwisely.org (accessed July 30, 2017).

established habits with dedicated strategies on the one hand, and to imbue stewardship as a basic concept in health education on the other.

Kumanan Rasanathan, chief of the Implementation Research and Delivery Science Unit at the United Nations Children's Fund, asked if any of the programs aimed at changing prescribing behavior have been paired with synergistic interventions aimed at demand, such as by changing expectations around antibiotic prescribing in both medical and veterinary settings. Kirch reported that the Choosing Wisely campaign also has a patient-facing side, Consumers Union, that is engaging with the issue of antibiotic overprescribing. Linder commented that intervening to prevent unnecessary patient visits is a next frontier, albeit a complicated one in terms of patient education and prescreening. He also commented that decades ago, studies showed that the greatest predictor of antibiotic prescribing was not a patient's demand for an antibiotic, or a patient's desire for an antibiotic, but the physician's perception of the patient's demand for an antibiotic. Linder carried out a study on precommitment, which asked physicians to sign a letter committing to only prescribe antibiotics when a patient needs it, which was displayed prominently in their waiting rooms (Meeker et al., 2014). They found that the intervention reduced inappropriate antibiotic prescribing by around 20 percent, he said. According to Linder, physicians are often reluctant to even bring up the topic of antibiotics with a patient out of fear that the patient will request a prescription. The precommitment letter, he said, is a simple intervention that short-circuits that thought and lets the patient know that the physician will not prescribe an antibiotic unless it is necessary: "The doctor knows the patient knows and the patient knows the doctor knows."

Lonnie King, professor and dean emeritus of The Ohio State University College of Veterinary Medicine, remarked that a change in production agriculture, especially in food animals, arose out of food safety issues when producers accepted that responsibility and accountability extended past the farm gate. He asked Scott how to extend that into the shifting paradigm of appropriate antibiotic use. Scott said that the clinical side of treating individual animals is fairly straightforward, but the appropriate use of antibiotics for prevention and control is less clear. FDA and pharmaceutical companies facilitated the shift away from growth promotion uses in feed efficiency using a cost-benefit economic model, he said, but the economic benefits around antibiotic stewardship are less tangible. Scott said that the quality assurance program and labeling that focus on residue avoidance have paved the way, but many of the costs of microbial safety have thus far been borne by the processing and slaughter industry. However, he warned that stewardship needs to move away from simply following labels and to be extended to the concept of broader antimicrobial safety in the preharvest environment.

5

Research and Development Actions for Reducing the Need for Antimicrobials

Session III of the workshop, moderated by Kent Kester, vice president and head of translational science and biomarkers at Sanofi Pasteur, focused on research and development actions aimed at reducing the need for antimicrobials. The human health perspective on effective scientific advances and promising research was provided by L. Clifford McDonald, associate director for science in the Division of Healthcare Quality Promotion at the U.S. Centers for Disease Control and Prevention (CDC). Timothy Johnson, associate professor of microbiology at the University of Minnesota, described alternatives to antibiotic use in animal health and production agriculture. Keith Klugman, director for pneumonia at the Bill & Melinda Gates Foundation (BMGF), discussed the potential for vaccination to reduce the burden of antimicrobial resistance. Ellen Jo Baron, professor emerita at Stanford University and executive director of medical affairs at Cepheid, described research and development actions in the area of diagnostics. Gregory Daniel, deputy director and clinical professor at the Duke-Margolis Center for Health Policy, explored economic strategies for accelerating research and development for new antimicrobials.

SCIENTIFIC ADVANCES AND PROMISING RESEARCH TO REDUCE THE NEED FOR ANTIMICROBIALS FROM A HUMAN AND AN ANIMAL HEALTH PERSPECTIVE

Human Health Perspective: Research on the Microbiome

"New drugs alone aren't enough to protect Americans," said McDonald. He explained that combating antimicrobial resistance will require comprehensive, aggressive action across the U.S. government and around the globe on multiple fronts to prevent the spread of infectious disease, to track the spread of resistance and disease, to improve stewardship, and to develop new drugs and diagnostics.

CDC has gained useful experience in addressing health care–associated infections (HAIs), said McDonald. Many HAIs have been prevented by mobilizing grassroots patient support, he said, to spur local governments to mandate state reporting and action. He emphasized the importance of patient-centered messaging about antibiotic-resistant infections: When messaging to the public, he said, CDC emphasizes that "you don't become resistant to antibiotics, but the bacteria in and on your body can." While many more infections are now preventable using existing technologies and better stewardship, he said, discovering how to prevent other types of HAIs and antibiotic-resistant infections will require new approaches and innovation.

CDC's Approach to Combating Antibiotic Resistance

McDonald provided an overview of CDC's approaches to combating antimicrobial resistance. Work with academic and health care partners includes 28 collaborative groups of hospitals, he said, that are devising innovative ways to protect patients and to scale up effective interventions across health systems. Eleven prevention epicenters, which are academic centers of excellence, are identifying new prevention strategies to guide clinical practice and to maximize public health impact, he said. CDC's Broad Agency Announcement is an innovative funding contract mechanism that invites applicants from academia, government, and industry to work with CDC. To date, he reported, this has generated 260 white paper submissions as well as 14 1-year studies exploring the gut–drug relationship and patients' microbiomes. CDC is also working with industry partners in several initiatives including the Antibiotic Resistance Isolate Bank, which is a collaboration activity with the U.S. Food and Drug Administration (FDA) that supports the development of new drugs and diagnostics. To further spur innovation, he said, CDC is making its sequencing data from antibiotic-resistant pathogens publicly available at the National Center for Biotechnology Information.

Antibiotic Resistance and the Microbiome

In recent years, CDC has made significant investment in research on the microbiome, said McDonald, because it considers it integral to antibiotic resistance. The microbiome is a community of organisms in and on a body: the skin, gut, oral, respiratory systems, and urogenital tract are examples. When communicating to the public, he suggested using the analogy of a forest to describe how a healthy microbiome is an ecology with microorganisms that exist in complex communities. Although a single microorganism can be isolated in the laboratory, he said,

> Antibiotic pressure on the community is like a forest fire that disrupts that microbiome and it wipes out all that normal flora. . . . It's not just about selection within a species. It's selection across species.

A healthy microbiome protects people and their communities against infection, he said, but antibiotics disrupt the microbiome by eliminating both good and bad bacteria. Resistant bacteria can take advantage of this disruption and multiply, he said, and this overgrowth can prime a person's body for infection. Once a person is colonized, the resistant bacteria can spread easily to other people. He noted that the term *antibiotic pressure* more aptly refers to pressure on the individual microbiome and collectively on the human population microbiome, the environmental microbiome, and the animal microbiome.

CDC's key premise, according to McDonald, is that an intact human microbiome is a primary host defense for preventing antibiotic-resistant outcomes of human health importance. Colonization and dominance often precede transmission, he said; dominance with a high organism load is a precedent risk factor for becoming infected with opportunists or pathobionts such as *Clostridium difficile*, *Salmonella*, *Shigella*, and *Campylobacter* as well as multidrug-resistant organisms (vancomycin-resistant *Enterococci*, carbapenem-resistant Enterobacteriaceae [CRE], and the extended spectrum beta-lactamases [ESBL]).[1]

To facilitate research on the microbiome, McDonald said, CDC is developing microbiome indices (MIs) for use in clinical medicine and public health. MIs can be used to monitor patients who are receiving antibiotics, he said, and to detect when disruption to the microbiome reaches a level that can promote antibiotic-resistant outcomes. He explained that MIs can also be used to gauge the relative risks of different antibiotics and other agents

[1] The organisms are often called *opportunists*, but McDonald suggested that the term places too much emphasis on the immune system, when the problem actually lies with the microbiome. The term *pathobiont* implies an organism that causes inflammation after the microbiome has been disrupted in some way (e.g., *Clostridium difficile*, *Salmonella*, *Campylobacter*, CRE, and ESBLs are all pro-inflammatory).

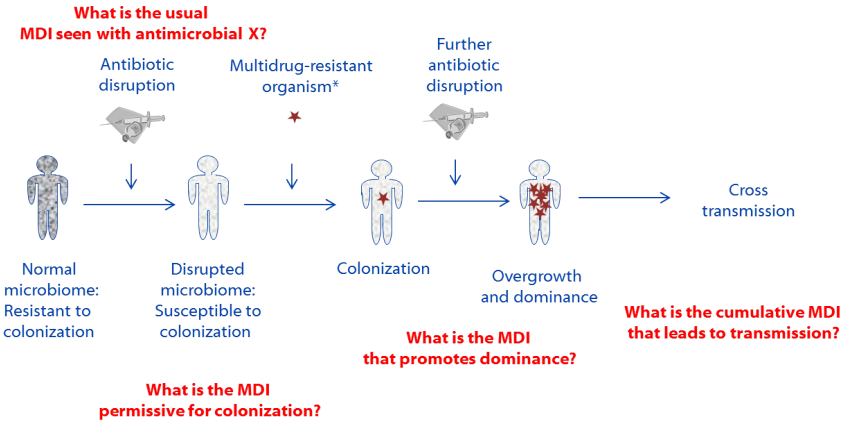


FIGURE 5-1 Conceptualizing microbiome disruption indices.
NOTE: MDI = microbiome disruption indices.

* Examples include carbapenem-resistant enterobacteriaceae, vancomycin-resistant enterococci, extended-spectrum beta-lactamase producing enterobacteriaceae. May also include transfer of genetic transfer of resistance determinants.
SOURCES: McDonald presentation, June 21, 2017; adapted from Halpin et al., 2016. Reprinted from *American Journal of Infection Control*, Vol. 4/Edition 7, Halpin et al., "Intestinal microbiome disruption in patients in a long-term acute care hospital: A case for development of microbiome disruption indices to improve infection prevention," Pages 830–836, Copyright (2016), with permission from Elsevier.

disruptive to the microbiome, and to develop microbiome protectants and restoratives, such as probiotics. The broad concept of MIs is to align the sciences around antibiotic-resistant outcomes (see Figure 5-1) by establishing which measures of microbiome disruption are the best risk markers for colonization, expansion, transmission, and infection with antibiotic-resistant organisms. MI research can be used to tailor antibiotic stewardship to the microbiome of a patient or patient population, said McDonald, as well as to develop better microbiome diagnostics and therapeutics.

Therapeutic developments of note, McDonald said, include using fecal microbiota transplantation to reduce resistant bacteria in patients with significantly disrupted microbiomes, such as people with multiple recurrent *Clostridium difficile* infections and hematopoietic stem cell transplant patients colonized with CRE (Bilinski et al., 2017). Phage therapy is also very promising for treating chronic infections involving biofilms, he said, although they are cleared quickly from the bloodstream. McDonald predicted that phage therapy will play a large role in microbiome remediation

as well as dealing with CRE hospital outbreaks that are very difficult to eradicate.

Animal Health Perspective: Alternative Approaches to Antibiotic Use

Although there is no single replacement for antibiotics in animal agriculture, Johnson said, the emergence of antibiotic alternatives on the market represents a promising development. He noted that the concept of using the self-microflora to combat pathogens has existed since 1973, when researchers discovered that feeding adult gut content from a hen to newly hatched chickens inhibits *Salmonella* colonization (Nurmi and Rantala, 1973). Today, there are dozens of alternative product choices on the market, he said, but veterinarians lack a platform or central resource to learn about how alternative products work in different situations. Johnson said that common alternative approaches to antibiotic use include prebiotics and probiotics to "seed" the gut with healthy flora, vaccinations, and products such as oregano, saponins, garlic, thyme, organic acids, cinnamaldehyde, and carvacrol (see Figure 5-2).

A prebiotic called XPC, a combination of extracted nutrients, is widely used across the animal agriculture industry, said Johnson. The product was initially geared toward improving feed efficiency, but it turned out also to help reduce the colonization of *Salmonella* in the animal's gut. According

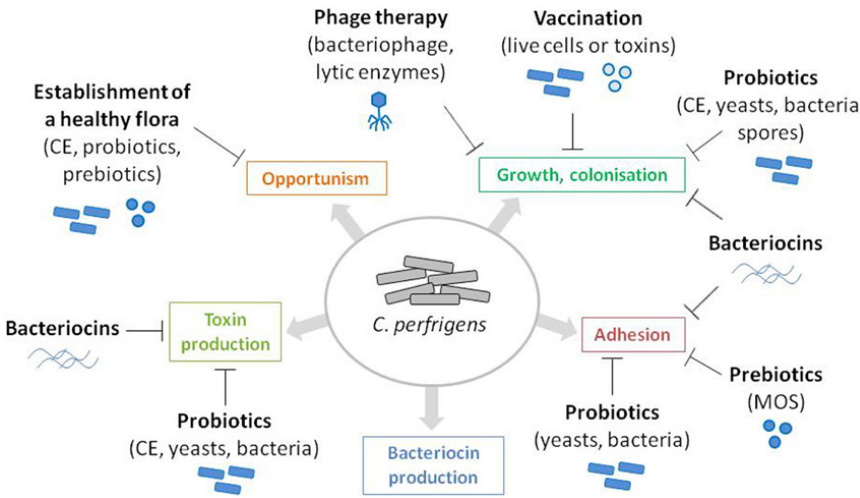


FIGURE 5-2 Common alternative approaches to antibiotic use.
NOTE: CE = competitive exclusion; MOS = mannan-oligosaccharides.
SOURCES: Johnson presentation, June 21, 2017; Caly et al., 2015.

to Johnson, studies now show that XPC makes the remaining *Salmonella* in the gut less resistant by expelling one of the genomic islands that contains multidrug resistance in that *Salmonella*. He surmised that more products may have similar potential to affect resistance, but their mechanisms are not yet understood.

Understanding the potential effect of an antibiotic alternative requires understanding the animal microbiome, said Johnson. To work toward defining the microbiome, he said, gut samples from thousands of animals have been analyzed. He reported that predictable patterns have been exposed in the succession of the microbiome over time and in tissues from different parts of the gut. This predictability, he said, has been helpful in identifying the dominant bacteria to modulate in the microbiome. However, he reported that so far, microbiome analysis by different types of alternative treatment products (versus control) have indicated that around 95 percent of those products do not have much effect on the gut microbiome.

Custom-Tailored Vaccines and Probiotics

Vaccines are widespread in animal agriculture, Johnson noted, referring to commercial subunit vaccines based on iron-receptor proteins in bacteria that have been very effective in chicken cholera and cow mastitis. But when there is no effective commercial vaccine to use against a specific disease, he said, veterinarians can make their own "autogenous" vaccine by identifying and sending the particular flock's strain to a company that will produce the vaccine directly. While this is highly effective, he added, the main challenge has been surveying the pathogen ecology to identify which strains would make the most effective vaccines. Developments in genomic technology are enabling more detailed surveillance of pathogen isolates, he continued. Phylogenetic analysis of different vaccine strains for the same bacteria will help to determine the best combination of strains to vaccinate with, he said, as well as serving as a diagnostic tool to understand the overall pathogen population in a flock.

Probiotics custom-tailored to a specific flock or herd will eventually dominate the market in animal agriculture, predicted Johnson. This involves cross-referencing a library of potential probiotic strains against a library of flock-specific pathogens, he explained, to identify the appropriate combination of probiotic pathogens. He noted that this technique is already highly effective in poultry flocks with chronic *Escherichia coli* infection. However, he added that evidence already indicates that resistance to the probiotic strains can develop over time, even if the strains are cycled.

A new area of research is taking the probiotic approach a step further to host-specific probiotics, Johnson said, such as turkey-specific products containing combinations of strains from turkeys only. He presented evi-

dence showing that when comparing controls, nonhost-specific commercial probiotics, antibiotics, and a turkey-specific probiotic, only the turkey-specific probiotic had an effect on performance and was associated with increased bacterial diversity in the turkey gut.[2] He said that this underscores the need to further explore the microbiome–host connection. He also suggested conducting mechanistic studies about how the effective products work, as well as comparing different combinations of products. Johnson warned that it is still not possible to compare the effects of alternative products in different types of animals—or even among different breeds of the same animal. He also suggested researching the effects of timing and animal stress on the effectiveness of alternative products.

VACCINATION TO REDUCE THE BURDEN OF ANTIMICROBIAL RESISTANCE

Vaccines have been underresearched, argued Klugman, and they have not been sufficiently prioritized as a potential modality for reducing antimicrobial resistance in both humans and animals. Evidence demonstrates that existing vaccines designed to target antimicrobial-resistant bacterial pathogens can affect both the use of antibiotics and the burden of resistance, he said. Other types of vaccines given to humans may also affect antibiotic resistance and/or use, he said, but many lack published data on resistance. Vaccines that warrant further study, according to Klugman, include pneumococcal conjugate vaccine (PCV), *Haemophilus influenzae* type B vaccine, cholera vaccine, meningococcal vaccines, tuberculosis (TB) vaccines, and vaccines under development for typhoid and nontyphoid *Salmonella* and group B strep.[3]

Competing Selection of Vaccines and Antibiotic Use on Antimicrobial Resistance

Good data on vaccine impact on resistance comes from the PCV model, Klugman said, because PCV has reduced the burden of antibiotic-resistant pneumococcal disease globally. He reported that when given to children, PCV successfully eliminates between 10 and 13 of 98 known pneumococcal serotypes, including 90 percent of antibiotic-resistant strains. PCV also reduces resistance in adults, he said, by interrupting the transmission of

[2] For more information on Johnson's paper presented at the 2018 Midwest Poultry Federation Convention, see midwestpoultry.com/wp-content/uploads/Johnson-Tim.pdf (accessed July 30, 2017).

[3] Given that one-third of pregnant women get antibiotics for fear of group B strep to prevent transmission, a vaccine could have a huge effect on use, even though it is not particularly a resistant pathogen, Klugman said.

antibiotic-resistant vaccine-type strains. Direct evidence from large randomized trials has demonstrated that PCV can reduce resistance in the *Pneumococcus* bacteria among children in South Africa (Klugman et al., 2003), and that PCV can prevent a total of 35 antibiotic prescriptions per 100 children vaccinated in California (Fireman et al., 2003). Recent evidence from Finland shows that rolling out the PCV vaccine reduced the use of antibiotics for respiratory infections in children, as well as reducing the proportion of resistant *Pneumococcal* strains (Sihvonen et al., 2017).

Vaccines may reduce resistance, Klugman warned, but continued use drives resistance in residual strains. When PCV was introduced in the United States in 2000, incidence rates decreased both for penicillin-susceptible disease and for penicillin-nonsusceptible disease among children under 2 years of age (Kyaw et al., 2006). Resistant infection rates also decreased among unvaccinated adults older than 65 years of age through herd immunity, because the vaccine interrupts transmission in the community. However, he noted, after the initial drop in incidence, a slight uptick in resistance occurred only among children less than 2 years of age. The selection of strains resistant to trimethoprim-sulfamethoxazole and penicillin was occurring only in the children and not the adults, he added (see Figure 5-3). He explained that antibiotic use continues to select resistance in the remaining 85 to 88 serotypes that PCV does not cover (in this case, it was serotype 19A). A similar trend is occurring for another strain—serotype 15A—for which there is not yet a pneumococcal vaccine. Between 1999 and 2007, susceptibility to penicillin among isolates collected by CDC surveillance dropped from 75 percent to 15 percent (Gertz et al., 2010). He warned that if the vaccine used does not prevent the major resistant strains, while an initial effect on resistance is observed, nonvaccine strains may become increasingly antibiotic resistant.

Impact of Viral Vaccines on Antibiotic Use

Vaccines that affect viral pathogens instead of bacterial pathogens can also affect antibiotic use, said Klugman. For example, influenza vaccination can reduce antibiotic use for otitis media, the leading indication for antibiotics in children, he reported. A large multinational study on the effect of the influenza vaccine on antibiotic use in healthy children has reported a 50 percent reduction in antibiotic use among children who received the vaccine compared to controls (Dbaibo et al., 2017). Klugman suggested that the measles vaccine also has the potential to prevent both antibiotic use for pneumonia complications and the need for antibiotic prophylaxis. Future viral vaccines, such as one for respiratory syncytial virus, may also affect antibiotic resistance simply because it reduces antibiotic use and therefore the attendant selection of strains in the flora, he suggested.

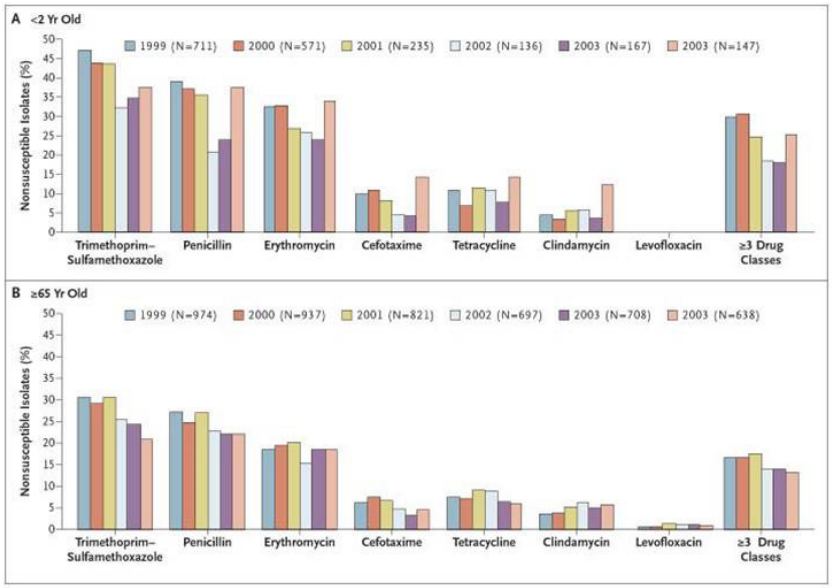


FIGURE 5-3 Effect of pneumococcal conjugate vaccine on drug-resistant pneumonia. SOURCES: Klugman presentation, June 21, 2017; Kyaw et al., 2006. From the *New England Journal of Medicine*, Kyaw et al., "Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant *Streptococcus pneumoniae*," Vol. 354, Page 1461. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Klugman also recommended that new human vaccines should be developed to combat the key current antimicrobial-resistant pathogens, known as ESKAPE pathogens, which include *Enterococcus faecalis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa*, and *Enterobacter*. These pathogens lend themselves to vaccines, which could provide short-term protection for hospitalized patients against nosocomial infection by these pathogens, as well as short-term protection against neonatal sepsis, which is increasingly becoming untreatable, particularly in developing countries, he said. Klugman suggested that alternative approaches to antibiotics such as monoclonal antibodies, which are cells that are derived from a single ancestral cell, can play a major role. Maternal immunization could also protect neonates from resistant pathogens in the first 3 months of life. Finally, Klugman offered the perspective of a human infectious disease specialist on the potential effect of the use of animal vaccines to reduce antibiotic use and resistance, citing several examples on

fish and poultry where vaccines have been an essential part of controlling antibiotic use.

RESEARCH AND DEVELOPMENT ACTIONS IN DIAGNOSTICS

To illustrate the value of investing in diagnostics, Baron described the effect that a new rapid diagnostic test (developed by Cepheid) had during the Ebola outbreak. Before the test, patients suspected of having Ebola were quarantined in a holding area for up to 8 days while waiting for results from a distant reference laboratory. When the rapid test became available, it reduced the time to an accurate diagnosis at point of care to within 2 hours. Patients not infected with Ebola were no longer at risk of exposure to other patients who were infected in the quarantine area, and health care workers—also at high risk of infection—were able to collect samples in a safer and more expeditious way. The rapid test offered increased specificity as well as the capability for ongoing monitoring by testing of semen and breast milk over the longer term.

Baron described another example of the effect of diagnostics: the Xpert MTB/RIF assay, which can detect both *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin (RIF). Xpert MTB/RIF is now used in 122 of 145 developing countries with high burdens of TB, she said. The rollout of the test has increased RIF-resistant TB case detection by over fivefold (Sachdeva et al., 2015), and the detection of multidrug-resistant TB has increased by threefold to eightfold (Albert et al., 2016). The rollout of the test has changed the worldwide diagnostic landscape of TB, she said, and it has attracted researchers and stakeholders to the TB field. However, most studies have found no difference in TB mortality after the rollout, said Baron, which demonstrates that a diagnostic test is not the only answer to these complex problems.

Potential Prioritization of Diagnostic Tests

According to Baron, certain types of diagnostic tests should be prioritized. The first are tests for conditions in which immediate patient management decisions will affect both public health and individual patient outcomes, she suggested. For example, a study from France on intrapartum group B strep polymerase chain reaction screening for pregnant women reported that the screening is cost neutral and achieves a 50 percent reduction in the probability of group B strep disease in neonates (El Helali et al., 2012). Baron argued that knowing which patients are colonized with group B strep at the time of delivery will not only decrease the use of intrapartum prophylactic antibiotics, but will also help with the infant obesity

epidemic.[4] Another example of diagnostics with both public and individual benefit concerns sexually transmitted infections, she said. One study found that using a rapid polymerase chain reaction test for chlamydia/gonorrhea in an emergency department reduced empiric treatment by 35 percent and increased notified results by 56 percent (May et al., 2016).

Baron suggested prioritizing the development of three other types of diagnostic tests. The first is any test to rapidly identify patients eligible for clinical trials of new antimicrobial agents at enrollment, such as Ebola tests for Ebola vaccine trials. The second are rapid tests that can definitively rule out bacterial infection at patient presentation, which she predicted would prevent the unnecessary use of antibiotics. The third are rapid tests to detect resistance factors directly from patient samples for screening and surveillance. She said that this type of test could inform the type of prophylaxis used for surgery, as well as helping to prevent transmission of antibiotic resistance in a hospital setting. Connectivity to enable shared knowledge of resistance factors in real time across sectors will also be critical, she said; for example, South Africa has a host information system that aggregates diagnostic test results and presents organisms, diseases, and resistance factors on a geopositioned map.

Accelerating the Development of Diagnostics

Lack of predictable profit is a barrier to the development of diagnostics, said Baron, who suggested that the Ebola diagnostic test would not have been developed by Cepheid today if the BMGF had not supported them financially. Many countries require their own clinical trials before a diagnostic can be introduced, she noted, but clinical trials are costly, lengthy, and impeded by regulatory issues. The product's final cost and market acceptability can be a barrier to scaling up and maintaining quality, she warned. Changing microbial genetics and epidemiology are huge challenges, she said, because tests must be updated and go through new clinical trials for approval.

To achieve the greatest short-term impact, she suggested several immediate steps. First, she said that target product profiles should be publicized and made very specific, so that companies do not make a product that will not be accepted in the marketplace. Her second suggestion was to create a rapid, inexpensive regulatory path to market, which may include abbreviated clinical trials up front and then extensive post-market review and surveillance to ensure it is performing as expected. To address some of those regulatory barriers, she suggested that rather than adding stringency,

[4] Baron characterized this infant obesity epidemic as a function of disturbing the microbiome of newborns who come through the birth canal in a penicillin-laden environment.

FDA should transition toward the CE marking process,[5] which is required for certain products sold within the European Economic Area and allows a company to self-register a test. Finally, Baron advised that companies have no incentive to develop diagnostics without a guaranteed market, so companies should be given prepurchase agreements or sufficient sales guarantees to offset their development costs.

ECONOMIC STRATEGIES FOR ACCELERATING RESEARCH AND DEVELOPMENT FOR NEW ANTIMICROBIALS

Very few antibiotic drugs are currently in the pipeline, said Daniel, who cited data from The Pew Charitable Trusts that show that only 41 antibiotics are in some phase of clinical testing (The Pew Charitable Trusts, 2017). This is a relatively low number compared to other therapeutic areas as he explained that only a couple of those would be expected to make it to market, and it is unlikely that any of those would have efficacy against the most concerning types of multidrug-resistant infections. Large pharmaceutical companies are moving out of the antibiotic development space, he said, because of low use, very slow uptake, and low revenues.

Economic Challenges to Antimicrobial Development

Daniel explained that appropriate antibiotic stewardship presents an economic challenge for antimicrobial development, especially in the United States. New antibiotic drugs on the market have limited use, so sales volumes and revenue are very low. Furthermore, the lack of rapid diagnostic tools leads to empiric treatment with broad-spectrum antibiotics, he said, which tends to involve low-cost generic antibiotics and contributes to inappropriate use. Daniel added that the strong and effective generic market also limits the cases in which new antibiotics are needed, thus driving down prices. He noted that reimbursement for antibiotics almost never reflects the public health benefit that the antibiotics bring to the whole of society; for example, they enable invasive medical interventions and help prevent the spread of rampant infections that are multidrug resistant. Daniel argued that new models are urgently needed to reward the development of innovative antimicrobial products, while supporting stewardship and appropriate use.

[5] "CE," which originated as an abbreviation of Conformité Européenne (meaning European Conformity), is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.

National Efforts to Combat Antimicrobial Resistance

Legislative efforts to stimulate more interest in developing antibiotics include the Generating Antibiotic Incentives Now Act of 2012, said Daniel, which effectively adds additional years of patent exclusivity. However, he explained that extending a patent does not significantly improve revenues, because appropriate stewardship limits the use of brand-new drugs on the market. Daniel said that the 21st Century Cures Act of 2016 shortened the regulatory pathway for antibiotics to enable products to reach the market sooner, but it does not affect the way that antibiotics are used or reimbursed. Daniel explained that other U.S. government efforts have included the White House National Strategy for Combating Antibiotic-Resistant Bacteria, released in 2014, which was followed by the President's Advisory Council on Combating Antibiotic-Resistant Bacteria. The latter formed in 2015 to address the concerns about low returns on investment and recommended a combination of general and targeted incentives, Daniel said. He added that CARB-X is a public–private partnership designed to provide significant research and development funding in very early stages of antibiotic development.

Push and Pull Incentives

Daniel clarified the distinction between push and pull financial incentives. Push incentives are provided during clinical development to help stimulate research and development through the basic research, preclinical, and clinical trial phases. He said that these may include grant funding, public–private partnerships, and tax credits, for example. Pull incentives, he explained, are provided during the approval process and the post-market period and include add-on payments, market exclusivity, and delinking reimbursement from use to encourage sustainable, appropriate use. Daniel explained that in the United States, where there has been more activity on the push side without effective pull incentives, "it's like running into a brick wall." Few companies will enter the market without significant pull incentives, he warned.

Global efforts and expertise have converged on a fundamental principle of delinking revenues for antibiotics from the volume of use, said Daniel, to ensure return on investment regardless of how often the antibiotic is used. Market entry reward is a pull incentive that is an example of removing the "link" between development costs and revenues by paying for vital antibiotic drugs with public funds, he said. It provides substantial additional revenues to reflect public health value quickly after approval and removes the need for volume sales, explained Daniel, which helps the developer recoup investments (see Figure 5-4). Once an eligible antibiotic gets to market, the

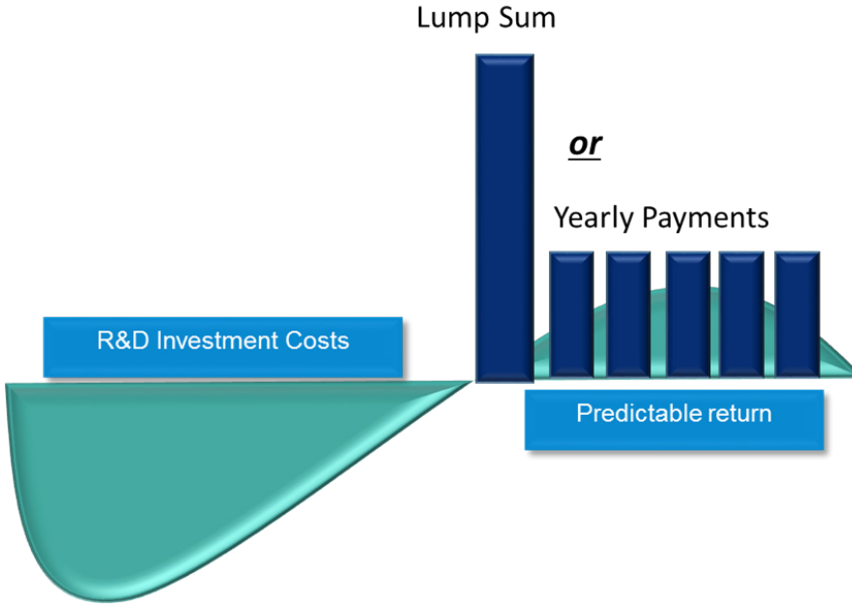


FIGURE 5-4 Market entry reward model.
SOURCES: Daniel presentation, June 21, 2017; adapted from Drive-AB, 2016.

company either gets a lump sum or gets some yearly payment over 5 or 6 years that, in aggregate, results in a positive net present value, which he estimated at between $1 and $2 billion.

Duke-Margolis Approach to Reinvigorating the Antimicrobial Pipeline

Daniel explained that the Duke-Margolis Center for Health Policy has analyzed economic pull incentives to outline a path for feasible implementation of economic incentives in the U.S. health care system. The project generated eight core principles for antimicrobial economic incentives:

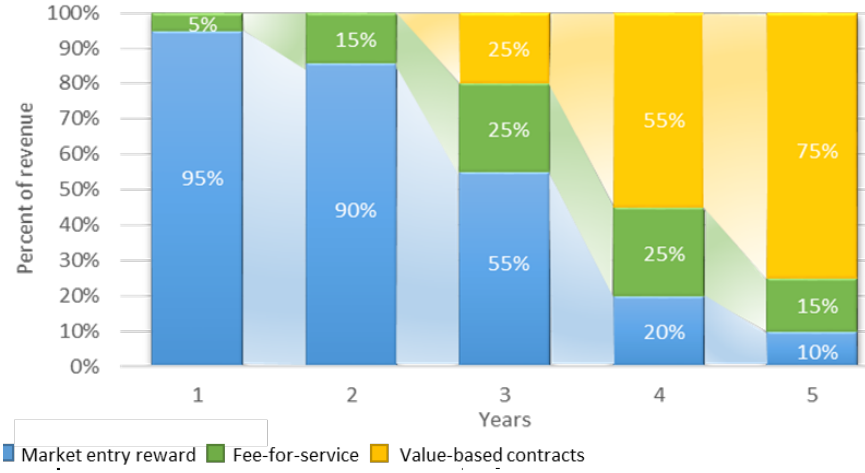
1. Form part of a comprehensive strategy to provide pull incentives in combination with other push incentives.
2. Promote and reward innovation.
3. Promote stewardship so antibiotics are sustainable over generations.
4. Promote access.
5. Provide public funding leveraged by private payments.

6. Provide developers with rapid access to funds upon market entry.
7. Be sustainable and dependable over the entire drug development cycle.
8. Support and align with broader shifts in payment models toward value and quality and away from volume and intensity.

Priority Antimicrobial Value and Entry Award Proposal

Daniel cautioned that the traditional volume-based, fee-for-service payment scheme for drugs does not support high-value, appropriate use of antibiotics. He noted that the U.S. health care system is transitioning away from this model to place more emphasis on value and quality in care delivery, which creates new opportunities for how antibacterial drugs are reimbursed. To capitalize on this opportunity, the Duke-Margolis Center for Health Policy has developed the Priority Antimicrobial Value and Entry (PAVE) Award proposal, which combines market entry reward with a shift to value-based reimbursement for antimicrobials to incentivize innovation. In the proposal, he explained, market entry reward payments phase down over time and continued eligibility for payment requires adherence to a set of conditions: reliable availability of the drug; continued sensitivity of priority organisms; tracking and reporting appropriate prescribing; data collection for post-market studies, if needed; and shifting to alternative payment models that are not volume based. He explained that the PAVE Award model resolves the current conflict between the drivers of return on investment and strong stewardship programs by leveraging private financing to reinforce the "volume to value" shift.

Figure 5-5 describes how the PAVE Award would be phased in, said Daniel. The top figure represents the first 5 years a drug is on the market, he explained. The publicly funded market entry reward (blue) starts off very high as the source of most of the company's revenue, he said, but it phases down drastically in subsequent years and is contingent on the company demonstrating that it is increasing its revenue with alternative payment models from the private side. By year 5, he added, the company is expected to have 75 to 80 percent of its revenue coming from the value-based payments, with full delinkage in year 6. He added that all of the revenue going back to that company is borne by the private sector and is dependent on population sizes that are covered by these payers—not dependent on how often patients are using the drug—so the company has a strong incentive to maintain a healthy supply chain.



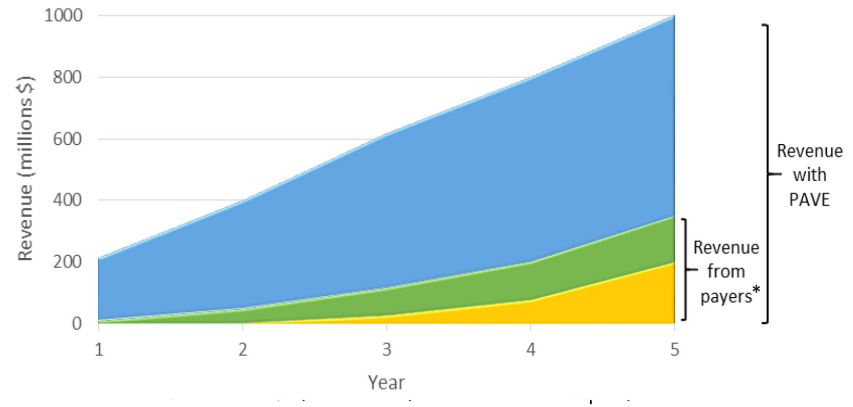


FIGURE 5-5 Phased-in approach to the Priority Antimicrobial Value and Entry (PAVE) Award.

Top: The distribution of the company's revenue includes a high percentage from the publicly funded market entry reward at the start but decreases subsequently over the 5 years a drug is on the market.

Bottom: The cumulative revenue for new antimicrobials would increase with PAVE, but the level of revenue from payers is the same as under the current fee-for-service model.

* Level of revenue from payers is the same under current fee-for-service model and new PAVE model.

SOURCES: Daniel presentation, June 21, 2017; Duke-Margolis Center for Health Policy, 2017. Reprinted with permission from Duke University, Copyright (2017).

DISCUSSION

Jeffrey Duchin, health officer and chief of Communicable Disease Epidemiology and Immunization Section for Public Health in Seattle and King County, Washington, asked about the relationship between the mechanism of action of the pneumococcal vaccine and the mechanism of action of resistance, as well as the implications of using vaccines against antimicrobial drug-resistant pathogens in the future. Klugman replied that the ecology of resistance is located within the nasopharynx; the duration of time that invasive strains spend in the nasopharynx correlates with their exposure to antibiotics and their likelihood of acquiring resistance genes. He added that there are now strains that are less adapted to the nasopharynx and because there is less competition, they can colonize and acquire resistance. Fortunately, he said, those strains appear to be less invasive than the original strains, but there is also an increasing population of individuals who are able to get invasive pneumococcal disease because of immune issues, such as diabetes. However, he noted that in the United States today, there is generally much less antibiotic use, fewer antibiotic-resistant strains, and the total number of infections is far below baseline. On the other hand, in the United Kingdom, he reported, the number of nonvaccine strains is expanding rapidly and acquiring resistance, particularly in adults, for reasons that are unclear. David Relman, professor of medicine at Stanford University, asked what it takes to preempt or displace a resistant organism from one of those ecological niches. Klugman replied that the low-hanging fruit is to develop a vaccine that protects against invasive disease, but the ultimate goal would be to interrupt transmission. He added that the notions are complementary within the context of changing the complex environment of the microbiome through multiple strategies.

Caroline Harwood, professor of microbiology at University of Washington, asked McDonald to elaborate about phage therapy and in what setting it would be most effective. McDonald responded that there is natural resistance, although "cocktails" against a variety of strains in biofilm applications seem most promising, both environmentally and for patients. He noted that strains will need to be shifted, because the strains that transmit the best are the ones that tend to pick up the most resistance. The aim is to target the ones that transmit the best or are most virulent, he explained. He suggested that this may lead to targeting against colonization in cases where it is known that something less virulent and less resistant will take its place (which is true with *Streptococcus pneumococcus*). The worry had been that something like methicillin-resistant *Staphylococcus aureus* might occupy the niche in the nasopharynx after the decolonization, he continued, but that does not seem to be the case. He suggested that in the future, vaccines, tools like phage, and the microbiome will work in tandem to eliminate the most

virulent and resistant strains. He said there is also potential to manipulate phage to render antibiotic-resistant strains ecologically disadvantaged.

Emily Erbelding, deputy director of the Division of AIDS at the National Institutes of Health, asked Baron if specimen repositories would be useful for diagnostic companies to help in getting tests cleared for additional indications, such as gonorrhea and chlamydia from the oropharynx and the rectum. Baron responded that access to more clinical samples would be extremely helpful for manufacturing approval testing. She explained that they currently create artificial matrices to simulate clinical samples, because acquiring the number of real samples needed from commercial providers is cost prohibitive. Jesse Goodman, professor of medicine and infectious diseases at Georgetown University, suggested that a promising target is the tremendous need for new drugs for gonorrhea.

Rima Khabbaz, deputy director for infectious diseases at CDC, asked about incentives for modalities other than new antibiotics, such as vaccines, diagnostics, phages, and manipulating the microbiome. Daniel said that incentives are definitely needed, but the delinkage model will not necessarily work for modalities like diagnostics. He explained that the fundamental challenge with antibiotics is the need to use less of them, whereas the use of diagnostics needs to be increased. As the health care system shifts toward value and outcomes for patients, he said, it will incentivize development of diagnostics and vaccines given their fundamental effect on quality for patients. Daniel suggested focusing on the unique economic consequences and post-market issues that drive the use of those products.

McDonald wondered whether there is potential for pharmaceutical companies to branch out beyond drug development and adopt an integrated approach to managing the overall health of animals or the health of humans, such as by acquiring diagnostic technology expertise, information technology expertise, and other proprietary knowledge. Daniel agreed that the combination of antibiotics, vaccines, and diagnostics makes sense. He cited Medtronic as an example of a company that is shifting from being a medical device manufacturer to a services provider and is currently operating surgical suites in hospitals to provide end-to-end care for patients. Daniel noted that the regulatory approach with companion diagnostics is starting to address this, but a challenge is that the diagnostic itself is literally tied to a particular drug. Baron added that commercial companies are working on companion diagnostics with drug manufacturers or vaccine manufacturers (for example, on the Ebola vaccine). However, she cautioned that having a coproduct limits the use and does not provide much financial incentive. Baron warned that because policies have not changed to keep up with technology, billions of dollars are being wasted in the United States alone. For example, she said, rapid TB tests can pull TB-negative patients

out of airborne isolation faster, but jurisdictions still follow very old rules that require three negative smears to pull patients out of airborne isolation.

Kumanan Rasanathan, chief of the Implementation Research and Delivery Science Unit at the United Nations Children's Fund, asked about evidence comparing vaccinations in low-income countries with poor access to higher-income countries with good access. Klugman replied that PCV appears to interrupt transmission, so it is well suited to developing countries with poor access and coverage. The percentage of coverage required to interrupt transmission is likely to be between 50 and 70 percent, he estimated, so even in areas without access, half of the community will be covered. Klugman argued that vaccine prevention should be introduced before antibiotics:

> If a kid has three or four episodes of life-threatening pneumonia in the first year of life and doesn't get antibiotics for all three of them, that's it. [However], if they get vaccines very early on, it could have saved their lives.

He added that vaccination programs are vertical systems that are easier to establish in-country than programs to increase antibiotic exposure. Rasanathan followed up by asking if the effect on antimicrobial resistance has been incorporated into the investment case for vaccines. Not currently, replied Klugman, because investment decisions are being related to the disease burden and mortality prevention, but the BMGF intends to add the effect on antimicrobial resistance to make the value proposition for vaccines even more attractive.

Rasanathan asked Baron whether advance market commitments for diagnostics should be delinked in emergency situations of immediate need or if there should be other mechanisms in place. Baron responded that the current system both is and is not working. For example, there is an emergency use authorization quick route through FDA for a crisis-situation drug or diagnostic, for very specific utilizations during that emergency, which goes away after a certain number of years. But that in itself is not a sufficient incentive to develop a diagnostic because after the emergency authorization ends, Baron explained, the diagnostic must go through the normal regulatory process. Goodman cautioned that if the approval process is too lax, it could affect public health as well as the industry, because it disincentivizes the quality players to make good products. He considers the diagnostic approval process in the United States to be relatively well balanced. Goodman continued by observing that the transition to value-based health care could offer opportunities around drug pricing, as it has happened in oncology where you pay sufficiently for a drug that you only use when you truly need it. The pricing of the drug can serve as an important disincentive to inappropriate use of antibiotics.

6

Strengthening Partnerships and International Cooperation

Session IV of the workshop, moderated by Peter Sands, senior fellow at the Mossavar-Rahmani Center for Business and Government, Harvard Kennedy School, focused on strengthening partnerships and international cooperation to combat antimicrobial resistance. The session opened with a presentation about the experience in Kenya implementing the World Health Organization's (WHO's) global action plan on antimicrobial resistance at the country level, provided by Evelyn Wesangula, national focal point on antimicrobial resistance in the Ministry of Health in Kenya. Robert Newman, vice president and global head of the tuberculosis (TB) program at Johnson & Johnson Global Public Health described experiences in developing and deploying bedaquiline, a novel anti-TB drug, to illustrate the importance of partnerships in driving global action. Angela Siemens, vice president of food safety, quality, and regulatory at Cargill Protein Group, provided a food industry perspective on improving the safety of the global food supply chain. Kathy Talkington, director of the Antibiotic Resistance Project at The Pew Charitable Trusts, described her organization's work to convene experts across sectors to collaborate on solving specific problems related to antimicrobial resistance. John Rex, chief strategy officer at CARB-X, concluded the session with an overview of existing partnerships worldwide that are working to address various facets of the problem.

IMPLEMENTATION OF THE WORLD HEALTH ORGANIZATION'S GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE AT THE COUNTRY LEVEL

Wesangula provided a country-level perspective on the experience of Kenya adapting the WHO's global action plan on antimicrobial resistance into its own national action plan (WHO, 2015b). She hoped that sharing the Kenyan experience would assist other countries just beginning this process. She reported that about half of deaths among Kenya's population of 48 million are due to infectious diseases, so the use of antimicrobials remains critical. To optimize the use of antibiotics in both human and animal health, Wesangula underscored the need to develop new antibiotics and improved rapid diagnostic techniques.

Process of Policy Formulation

In Kenya, formal policy development on antimicrobial resistance began in 2009, Wesangula said, after a growing body of evidence showed rising resistance trends caused by overuse of antimicrobial agents both in humans and animals. However, the evidence being accrued was not coupled with government action to develop and implement policy action, she said. Thus, an expert working group was convened by the Kenya Medical Research Institute with support from the Center for Disease Dynamics, Economics and Policy, which was followed by the formation of a Joint Taskforce between the Ministry of Health and the Ministry of Agriculture, Livestock, and Fisheries in 2010. In 2011, the *Situation Analysis and Recommendations on Antibiotic Use in Kenya* report was released (GARP-Kenya Working Group, 2011). By the time the global resolution to combat antimicrobial resistance was endorsed by the World Health Assembly in 2014, she explained, not much progress had been made in Kenya at the national government level to implement the strategies recommended by the situation analysis because of a new constitution in 2010, which mandated a transition from a centralized system of governance to a devolved system of governance. However, momentum in addressing antimicrobial resistance began gathering within the next year, Wesangula said, in the wake of further global and national initiatives aligned with the multisectoral One Health approach. Spurred by the 2005 International Health Regulations (IHR), which includes a core capacity requirement for national progress reports about antimicrobial resistance tracking, she said, the Kenyan Infection Prevention and Control Strategic Plan (2014–2017) recommended establishing a national integrated surveillance system and advisory committee for antimicrobial resistance. In 2015, the Global Health Security Agenda (GHSA) prompted increased governmental effort toward addressing antimicrobial resistance, said Wesangula.

Developing Kenya's National Action Plan

"The big job for us was breaking down the global action plan [to our national policy and action plan], knowing that the challenge is global, but really the solutions to antimicrobial resistance must be localized as much as possible because countries are different," reflected Wesangula. Throughout 2016, consultative workshops engaged diverse stakeholders to build synergy toward a coherent, country-specific, country-owned national action plan. She reported that relevant constitutional and sector-specific policies were reviewed to find ways to leverage antimicrobial resistance, and Kenya's existing commitments to international policies on resistance were also considered. She added that national and international stakeholders were involved throughout the progress (e.g., the Food and Agriculture Organization of the United Nations [FAO], the World Organisation for Animal Health [OIE], WHO, and the U.S. Centers for Disease Control and Prevention [CDC]). Wesangula reported that process was completed in May 2017 with the release of the National Policy on Prevention and Containment of Antimicrobial Resistance (Government of Kenya, 2017).

Achievements, Successes, and Barriers Encountered

Wesangula surveyed the Kenyan national effort's achievements and barriers encountered to date. An active multisectoral national advisory committee continues to lead the process in accordance with the One Health approach. A new integrated national surveillance strategy was developed concurrently with the national action plan, she said, which is being implemented in four pilot sites in the country. She added that Kenya has enrolled in WHO's Global Antimicrobial Surveillance System (GLASS) and a national communication strategy is helping to communicate the risk of antimicrobial resistance, with support from a dedicated media network, in ways that are clear and appropriately pitched for the public.

The biggest barrier in engaging the highest level of policy making, according to Wesangula, has been lack of awareness, largely because of insufficient data on the economic cost of antimicrobial resistance. "Our policy makers want to see numbers," she said. "What would it cost if we did not act? What can we save if we have interventions in place?" In the advisory committee, disproportional representation from the human medical sector has also been a barrier, she said. Funding has posed another big challenge, she added, and has been heavily reliant on partnerships and collaborations that require complex coordination.

Wesangula used surveillance-related challenges to illustrate some of the ways they have surmounted barriers. To build a surveillance system upon poor infrastructure and virtually no data, she said, they partnered with

and leveraged the infrastructure of established academic, private-sector, and World Bank–supported laboratories to enhance capacity to accurately detect and report antimicrobial resistance. To bolster workforce capacity, they created onsite and online mentorship programs as well as a field epidemiology training program. She added that upgrading information technology and databases has improved problems with reporting and data management. To improve quality, she said, they established a national calibration center and a system to accredit laboratories.

Wesangula concluded by reviewing lessons learned from the process of implementing the national plan in Kenya. She said that multisectoral platforms work best from inception, if possible, and that it is important to identify and clearly define the burden of antimicrobial resistance in order to engage policy makers. Government leadership and political commitment are critical for pushing the resistance agenda, she continued, and implementers should be involved throughout the process. For instance, medical students work to engage the community during Antimicrobial Resistance Awareness Week, she said. Planning needs to be realistic, she warned, because it can take years to garner meaningful stakeholder engagement. Finally, she advised that the process should be driven by persistence, patience, collaborative relationships, and trust building.

IMMEDIATE STRATEGIES TO DEVELOP OR REFINE PARTNERSHIPS

Partnerships in the Age of Bedaquiline: Successes, Challenges, and the Beginning of the End of Tuberculosis

Newman explained that the pipeline for new TB drugs has been virtually empty since 1965, despite the enormous and growing burden of multidrug-resistant TB (MDR-TB) worldwide. According to WHO data, there are nearly 600,000 incident cases of MDR-TB per year, of which less than one-quarter are treated and only half of those treated are cured (WHO, 2016). Janssen Pharmaceuticals (the pharmaceutical company of Johnson & Johnson) developed bedaquiline with a novel mechanism of action called an adenosine triphosphate synthase inhibitor, which was approved by the U.S. Food and Drug Administration (FDA) in 2013. Around 30 percent of adult patients with MDR-TB and extensively drug-resistant TB (XDR-TB)[1]

[1] According to WHO, MDR-TB involves resistance to the two most effective anti-TB drugs: isoniazid and rifampicin. XDR-TB involves resistance to those two drugs, as well as to any fluoroquinolones and to at least one of the three injectable second-line drugs (amikacin, capreomycin, or kanamycin).

are eligible for bedaquiline as part of combination therapy, he said, which amounts to around 37,000 patients worldwide.

Bedaquiline at the Core of Collaboration

Newman explained that making bedaquiline available to each patient who needs it—the ultimate goal—is stymied by constrained funding, weak health care delivery systems, limited diagnostic capacity, poor prescribing and adherence practices, patient populations with limited resources, and inadequate standards of care. But at the core of the many challenges faced in the TB sphere, he argued, is complacency and lack of urgency. He suggested that by enabling an improved standard of care, bedaquiline is driving collaborative efforts around TB by galvanizing a renewed sense of optimism that addressing drug-resistant TB is not a hopeless endeavor. The many partners involved in the rollout of bedaquiline, he said, include the U.S. Agency for International Development (USAID), PATH, the International Union Against Tuberculosis and Lung Disease, the Global Drug Facility (GDF), the Bill & Melinda Gates Foundation, the TB Alliance, Pharmstandard, and the Stop TB Partnership. On the regulatory side, he reported that as of May 2017 bedaquiline had been registered in countries that cover 70 percent of the high-burden countries for MDR-TB, and the process is ongoing in other high-burden countries. Newman observed:

> It takes an enormous amount of partnership to help governments change TB programs that haven't seen a new drug in a long time, and to actually build a system of stewardship around bedaquiline so that we're sure it reaches the patients who need it, but we don't foster the development of resistance for a drug that we desperately need.

Collaboration in High-Burden Countries

Newman surveyed the collaborations under way to deploy bedaquiline in three high-burden countries. He commended South Africa as a leader in engaging partners and sustaining investments. He added that the bedaquiline rollout included the introduction of routine audiometry, which revealed that ototoxicity, which refers to damage to the inner ear, is a major problem in existing regimens that had not been identified before. Most importantly, Newman emphasized, the drug is saving lives: treatment outcomes in XDR-TB patients (and pre-XDR-TB patients)[2] taking bedaquiline are now over-

[2] Pre-XDR TB is defined as *in vitro* resistance of the patient's isolate to (1) isoniazid, (2) rifampin, and (3) either a fluoroquinolone or at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin). See www.who.int/selection_medicines/committees/expert/20/applications/Bedaquiline_Janssen.pdf (accessed August 28, 2017).

taking outcomes for MDR-TB patients who are not taking bedaquiline. As part of its goal to eliminate TB, India is planning to scale up bedaquiline administration to 156 sites in 2017, he said; given its huge population and incredibly complex health system, this effort is dependent on an extensive network of partnerships. Bedaquiline is set to launch commercially in China in 2019, reported Newman, and the country is laying the groundwork through a controlled access program driven by national and international partners. Newman said that the 4-year bedaquiline donation program—a partnership with USAID, GDF, and other partners—has a commitment to fund up to 30,000 treatments in more than 100 low- and middle-income countries meeting Global Fund eligibility criteria who agree to appropriate use per WHO guidance.[3]

Innovation for Tuberculosis Therapeutics

As of May 2017, Newman estimated that bedaquiline had been received by more than 19,000 patients in over 80 countries, but he warned that progress against TB needs to be accelerated by reducing the lag between innovation and uptake. The incidence of TB is currently decreasing at an unacceptably low rate of 1.5 percent per year, he reported. Eliminating the global burden of TB—a disease that has been curable since 1946—will remain aspirational without accelerated discovery, development, and deployment of new tools and technologies, said Newman (see Figure 6-1).

Newman warned that therapeutic innovations for TB are urgently needed because current treatment regimens are very long (bedaquiline is part of a 24-month course), often involve injectables, and are associated with many adverse effects. He suggested that innovation needs to be directed toward all-oral, shorter-course, fixed-dose combination regimens with low toxicity, with more far-reaching goals of a vaccine and of a pan-TB regimen for both drug-sensitive and drug-resistant TB. The broader problem of TB infection—sometimes referred to as "latent TB"—also looms large, he cautioned. An estimated 2 billion people worldwide are infected with TB, Newman said, and around 10 percent of those people will go on to develop the active disease. "Turning off the tap" by treating TB infection in people before they progress to active disease is a critical aim, he argued. Although Johnson & Johnson has new tools under development with bedaquiline as a foundation in terms of shorter regimens, new platforms, and novel targets,

[3] During the discussion, Newman clarified that the name *donation program* is somewhat of a misnomer; the term *accelerated access program* is more apt, because its aim is to remove the issue of price to improve drug availability, but it also incorporates country-level policy changes, capacity building, and collecting safety data to further inform international-level policy.

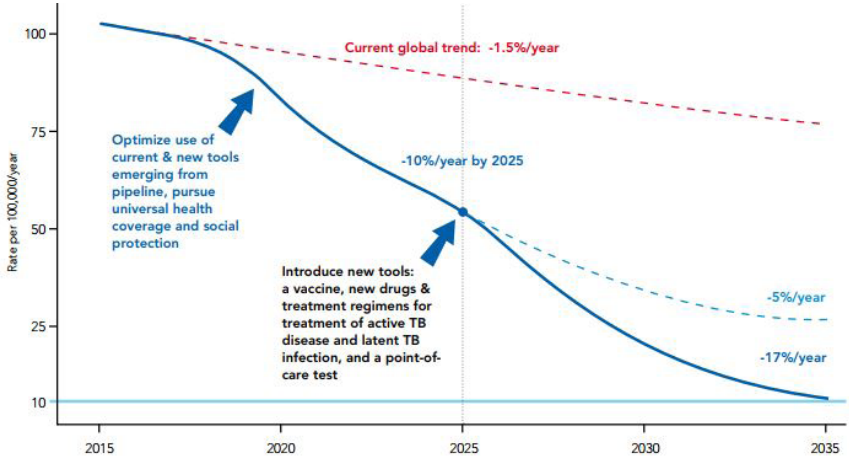


FIGURE 6-1 Projected effect of new tools on the global incidence rate of tuberculosis (TB).
SOURCES: Newman presentation, June 21, 2017; WHO, 2015a. Reprinted from *The End TB Strategy*, "Actions to Impact," page 11, Copyright (2015).

Newman said, the current market for TB drugs lacks the necessary pull incentives to drive the innovation so urgently needed.

Bedaquiline as an Accelerator for Innovation

Incentivizing further innovation will require demonstrating the readiness to capitalize on emerging innovations, Newman said, and to deploy them to affected people as quickly as possible. Expanding the impact of new technology, however, he added, requires having the appropriate infrastructure in place for stewardship, controlled distribution, and surveillance. Health system capacity is a huge barrier in rolling out new interventions, he said. Newman predicted that progress toward strengthening infrastructure and capacity during the bedaquiline rollout may ultimately help to unlock the broader transformational potential that addressing drug-resistant TB could have on the global impact of antimicrobial resistance. For example, he suggested that it could aid in creating a blueprint for addressing antimicrobial resistance in developing countries. See Box 6-1 for other ways that Newman suggested the bedaquiline experience might inform the development of new tools and improve the ecosystem of antimicrobial resistance.

BOX 6-1
Lessons from Bedaquiline for Addressing Antimicrobial Resistance

Informed by the experience of deploying bedaquiline, Newman offered a set of additional tools for fostering a healthy antimicrobial resistance ecosystem:

- Build on existing structures and concepts.
- Create a networked solution that involves academia, governments, and industry.
- Introduce risk-sharing mechanisms for drug development.
- Provide market entry awards or incentives for innovators.
- Devise equitable procurement mechanisms to ensure the sustainability of funding and manufacturing.
- Establish a structure for stewardship and postapproval support.

Newman also suggested several ways that the creation and rollout of new tools could gain from the experience of developing and deploying bedaquiline. The first is to leverage the bedaquiline registry and other infrastructure for faster clinical evaluation. Secondly, he encouraged building faster regulatory approval pathways in key markets and finding ways to share costs of postapproval commitments. Newman also suggested improving forecasting for low-volume manufacturing by using the rollout of bedaquiline to help improve predictions. Finally, he suggested taking advantage of existing market access strategies and appropriate use programs for faster rollout.

SOURCE: Newman presentation, June 21, 2017.

Integrating Food Safety, Animal Health, and Plant Health to Improve the Integrity of the Food Supply Chain

Siemens provided a perspective from Cargill on the value of partnerships and international cooperation in the food industry. Cargill is among the largest private companies in the world, operating in 70 countries across multiple sectors in the global food supply chain. Cargill has been working for many years on ensuring food safety and applying safety standards globally. She noted that many of the issues regarding systems, partnerships, and knowledge sharing being discussed in the workshop are also pursuant to food safety. Siemens provided an overview of several organizations that are working to disseminate best practices in food safety across the world in a competitive, market-driven industry.

The Global Food Safety Initiative and SSAFE

The Global Food Safety Initiative (GFSI) is a voluntary initiative of the global food industry to enhance food safety practices and consumer confidence, explained Siemens. Established in 2000, GFSI addresses critical issues affecting supply chains and enhances food safety by facilitating the sharing of expertise and best practices among food professionals, she said. It also benchmarks food safety management schemes to increase consumer confidence and reduce costs for both producers and consumers, she added. Through GFSI, she explained, major retailers agree to require manufacturers entering their food supply chains to meet established minimum verified standards for food safety. Ten food safety verification schemes are currently recognized, with more than 85,000 certificates issued to suppliers worldwide, she reported, with suppliers benefiting from streamlining their processes and gaining new business. She suggested that the voluntary verification piece through third-party audit in the private sector may be applicable to antimicrobial stewardship programs outside the auspices of the regulatory realm. Through an annual global summit, she continued, GFSI facilitates dialogue about food safety regulations between private sector and the government—especially in countries that have not yet focused on food safety—about whether these global standards may be appropriate for regulatory environments. Facilitation between governments has made strides against the problem of nonharmonized regulations in the food security space, she said. To avoid excluding resource-constrained smaller food and animal suppliers from the market, Siemens explained, GFSI has adopted a "go-to-market" system. Suppliers can continue to sell into the marketplace while they are supported in working toward their full certification. Suppliers typically enjoy the correlate benefits of improvements in the production management process that a food safety management system generally entails, she added.

In the context of setting up such a global private-sector organization, Siemens recommended setting a specific and focused vision. For GFSI, for example, it is only about standard setting. Specifically, she said that the objective is to improve food safety by delivering equivalence and convergence between effective food safety management systems:

> When I talk to someone in China and they receive a certificate, I know what the standard is by which they received that certificate and I can have confidence in the product they are sending me.

She emphasized that GFSI does not set policy for retailers or manufacturers, undertake training, or accredit or certify suppliers directly. Siemens explained that other organizations, such as SSAFE (Safe Supply of Affordable Food Everywhere), carry out training that GFSI does not undertake.

Initially, SSAFE was established to support training through public–private partnerships to contain the spread of high-path avian influenza, she said. It is now working on facilitating food safety education and training in developing countries. SSAFE is currently rolling out a global food safety training framework for dairy farming that can be used in cooperation with GFSI, Siemens reported.

Competition and Precompetition in Animal Agriculture

In the context of animal agriculture relative to antibiotics, Siemens said, it is important to consider the competitive versus precompetitive aspect. She expressed concern about how to ensure that there are precompetitive discussions to collaborate and innovate when antibiotics represent a competitive advantage, particularly in the United States. Recent research demonstrates that consumer interest in reduced use of antibiotics is increasing, she reported, and some companies are indicating that they are willing to meet this market demand. However, she said that there is still a gap between consumers who profess that antibiotic-free meat is important to them and those who actually purchase antibiotic-free meat. She suggested that attracting those consumers to purchase antibiotic-free meat, and bringing more of that product to market, is a market opportunity. She observed, "a company, especially in the U.S. in the competitive set, is going to look for that differentiated competitive position; they're going to have improved performance and long-term growth." However, Siemens noted that this is challenging the industry because food safety was declared a noncompetitive item in 2001 by the meat industry. But to solve this overall problem, she said, there needs to be precompetitive discussions—despite marketplace competition—about stewardship, best practice sharing, and aligning metrics in the animal agriculture sector.

The Pew Charitable Trusts' Role in Strengthening Partnerships in the Fight Against Antibiotic Resistance

The Pew Charitable Trusts is engaged in the issue of antibiotic resistance, said Talkington, in the areas of stewardship, animal agriculture, and drug innovation. One of Pew's primary strategies, she said, is to serve as a convener by bringing the right people to the table from multiple sectors to collaborate by aligning interests to affect change against the unique challenge of antibiotic resistance. She emphasized the value of partnerships in addressing this complex problem of antimicrobial resistance, and in her opinion, partnerships are particularly important given the urgency of the situation. She cautioned that the window of the opportunity in terms of interest in antibiotic resistance will not necessarily last, so harnessing the

current enthusiasm is critical to moving the issue forward. Partnerships also help to avoid the duplication of efforts, Talkington said, and to ensure the optimal use of partners' respective skills and expertise. She presented some of Pew's work in the antimicrobial resistance sphere.

Preserving Antibiotics for Patients Who Need Them

Talkington described Pew's work on the issue of preserving antibiotics for those patients who really need them, part of which translates into reducing the inappropriate use of antibiotics. The U.S. action plan sets forth the target of reducing antibiotic use in the outpatient setting by 50 percent by 2020 (PACCARB, 2016), and Pew has worked to make that goal actionable in partnership with CDC, she said, by convening a group of frontline implementers—including primary care physicians, emergency care doctors, and other participants in the outpatient arena—to explore methodologies for applying existing information.

Reducing the Need for Antibiotics in Animal Stewardship

The issue of antibiotics in animal agriculture is complicated, Talkington said, with a wide variety of players coming to the table with different challenges and goals in mind. Government, international organizations, the private sector, and pharmaceutical companies are all involved, she said. To find common ground between such a diverse set of partners, a meeting was convened in 2016 by OIE and the U.S. Department of Agriculture to examine alternatives and potential research priorities for reducing the need for antibiotics in animal agriculture; she reported that the area seems very promising. An additional benefit of channeling such diverse voices in a uniform way, she said, is the opportunity to use that common voice to advocate for additional resources in order to fund the research needed to study potential alternatives.

Spurring Innovation Through Data

Data are also a powerful tool for spurring development and innovation, Talkington said. Given that no registered classes of antibiotics have been discovered since 1984, she said, the antibiotics being used today are based on 30-year-old research. This is a problem and a failing of the current system, she said, but the solutions are complex. Pew initially focused on the scientific challenges for discovery of antibiotics, convening a diverse group of experts to identify next steps, and that chief among them is the need to share data and information, she said. She reported that currently, there is no available mechanism for facilitating the large amount of pub-

licly available data in research (e.g., from failed studies or former manufacturers). She said they are preparing to launch a new program called the Shared Platform for Antibiotic Research and Knowledge. As a first step, it will collect publicly available data targeted toward gram-negative bacteria issues, Talkington said, which will be curated by experts seeking to identify specific questions or patterns so that data can be made readily available to the research community.

THE ROLE OF PARTNERSHIPS IN ADDRESSING ANTIMICROBIAL RESISTANCE

Rex spoke from the perspective of an infectious disease doctor with extensive academic and industrial experience in developing new drugs and diagnostics. He began by reflecting on the term *antimicrobial resistance*, suggesting that it confuses the layperson because it suggests that somehow the person becomes resistant to an antibiotic, so if a person does not take that specific antibiotic, then they cannot be resistant. The term drug-resistant infection (DRI) more often conveys the right message, he said (Mendelson et al., 2017).

Rex identified three informal levels of increasing complexity in partnership. The simplest level is sharing information and methods. The next level involves adding on the joint setting of priorities and scale, he said, which can enable partnerships to become competitive at the international level. The most complex level, he continued, involves adding on the component of risk sharing and intent to create public goods with market potential or knowledge. Rex aligned his informal model to WHO's global action plan to survey the current partnership landscape.

Sharing Information and Methods

Relative to WHO's global action plan, Rex explained, the first level of partnership—sharing information and methods—involves awareness and understanding of DRI. This includes improving awareness of DRI, reducing the incidence of infection, developing an economic case, and optimizing use of antibiotics, he said. Partnerships focusing on awareness at this level tend to be easily replicated, he added, and include the Euro AMR Barometer,[4] along with CDC's Get Smart About Antibiotics.[5] In partnerships focusing on reducing the incidence of both susceptible and resistant infections, he noted that action is local ("one hospital at a time") but experience can

[4] For more information, see ec.europa.eu/health/amr/antimicrobial-resistance_en (accessed July 31, 2017).

[5] For more information, see www.cdc.gov/getsmart/index.html (accessed July 31, 2017).

be shared and transferred. Sharing information about optimizing the use of antibiotics is straightforward, he said, through national and regional guidelines for human use of antibiotics, for example, and through sharing methods to reduce and eliminate animal use. Partnerships in the realm of sharing scientific knowledge are CARB-X, a public–private partnership that funds preclinical research, and the Global Antibiotic Research and Development Partnership (GARDP), a program that seeks to deliver data and products addressing specific gaps.

It is exceedingly difficult, Rex warned, to make an economic case for sustainable investment in new medicines, diagnostics, and vaccines:

> Anyone who sets out today to develop a new antibiotic is engaging in a 30-year exercise that is almost guaranteed to destroy $50 million in terms of net present value.

An economic tension arises because the greatest value of antibiotics is their nonuse, he said, likening them to the fire extinguishers of medicine: "If you don't have a fire extinguisher on hand, the building goes down; there is no opportunity to build a fire station at the time that you observe the fire." However, he noted some ongoing global conversations about innovative approaches. DRIVE-AB, an Innovative Medicines Initiative (IMI) project in the European Union, is a 3-year, multistakeholder effort to create novel business models, he said. The Duke-Margolis antimicrobial payment reform project, which Gregory Daniel, deputy director and clinical professor at the Duke-Margolis Center for Health Policy, discussed earlier in the day (see Chapter 5), is an FDA-funded project on delinking use from profit, Rex noted, and the United Kingdom's Review on Antimicrobial Resistance produces reports and convenes workshops in the area.

Joint Priorities and Scale

At the level of partnership with joint priorities, Rex continued, optimizing the use of antibiotics involves strengthening knowledge through surveillance. He provided several examples of those types of research and development networks. GARDP is analyzing the use of antibiotics in neonatal sepsis and sexually transmitted infections in several networks. The European Union's Joint Programming Initiative on Antimicrobial Resistance is obtaining national-level money to fund projects across Europe, he said. The Wellcome Trust is developing a collaborative clinical trials network to help deliver the registration data required to get new drugs approved (McDonnell et al., 2016). Rex also provided examples of partnerships with joint priorities at a global scale that are strengthening knowledge through surveillance: the UK Fleming Fund, a £256 million government investment

Bacteria	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	Serious (VRE)	Yes
Staphylococcu	High	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter p	High		
Campylobacter	High	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R	High	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	Urgent (drug-R)	
Streptococcus pneumoniae, penicillin-NS	Medium	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R	Medium		
Shigella spp., fluoroquinolone-R	Medium	Serious	
Clostridium difficile		Urgent	
Candida spp. fluconazole-R		Serious (Flu-R)	
M. tuberculosis		Serious (drug-R)	
Group A *Streptococcus*		Concerning (erythro-R)	
Group B *Streptococcus*		Concerning (clinda-R)	

Priority Pathogen Lists: There are now three and they help create global alignment

FIGURE 6-2 Global alignment of priority pathogen lists to discern which drugs are most needed.
NOTE: -R = -resistant; CDC = U.S. Centers for Disease Control and Prevention; ESBL = extended-spectrum beta-lactamases; ESKAPE = *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* pathogens; MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococcus*; VRSA = vancomycin-resistant *Staphylococcus aureus*; WHO = World Health Organization.
SOURCES: Rex presentation, June 21, 2017; from CDC, 2013b; WHO, 2017b.

in improving laboratory capacity for diagnosis and surveillance of antimicrobial resistance; and WHO's GLASS. CDC's National Antimicrobial Resistance Monitoring System (NARMS) (see Chapter 2) is doing the same thing at very large national scale, he noted. Rex said that the three priority pathogen lists are in good alignment (ESKAPE[6] as well as lists from both WHO and CDC), which is in effect setting joint global priorities about the drugs that are most needed (see Figure 6-2).

[6] ESKAPE pathogens include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter*.

Risk, Knowledge, and Market Goods

Partnerships at the highest level of complexity create knowledge and goods, both public and private, Rex explained. Because of the scale, the synergies that flow from any such partnership can have extraordinary impact, he added. He cited three examples of such partnerships. Rex explained that the IMI is a €2 billion program that is a collaboration funded by the European Commission with in-kind funding from the pharmaceutical industry in Europe to create multicompany, multiacademic group projects (designed to be precompetitive). One such program is the New Drugs for Bad Bugs program, which is the biggest part of IMI and has spawned seven projects on collaborative drug discovery, drug development, and economics and stewardship, according to Rex.

Rex's organization, CARB-X, is a pooled funding mechanism with $455.5 million committed by the U.S. government and the Wellcome Trust so far. Its goal is to accelerate preclinical research and development on antimicrobial therapeutics, diagnostics, and preventatives through phase I, he explained, with plans to fund 50 preclinical projects over the next 5 years. It is a public–private partnership that also leverages capital from private partners, he said. Rex explained that CARB-X was designed with a set of portfolio priorities. He said that new direct-acting therapies for gram-negative bacterial infections are the highest priority, followed by rapid diagnostics and diagnostics that predict susceptibility. He predicted that at least one novel mechanism agent supported by CARB-X will be registered in the next 10 years.[7]

The way that antibiotics are purchased must change, argued Rex, because in economic terms, antibiotics are a positive externality. He explained: "You benefit from it even if you don't personally use it, but I can't charge you for the fact that you benefit from it." Positive externalities are classically dealt with in economics by government-level subsidies such as market entry awards, he added. Such incentives have not yet been implemented, he continued, and will require global coordination through shared target product profiles to assist drug developers, as well as some global allocation of financial obligation.

DISCUSSION

Suerie Moon, director of research at the Global Health Centre, Graduate Institute of International and Development Studies, Geneva, noted that in aspects of the global politics of antimicrobial resistance, there are ten-

[7] Rex reported that the first 11 awardees cover three novel class candidate small molecules, four nontraditional products, seven new antibacterial targets, and one point-of-care diagnostic for nosocomial pneumonia.

sions at play between the need to reduce antibiotic use in animal agriculture and the commercial or economic interests in developing those industries. She asked Wesangula whether such tensions arose in Kenya during the development of the national strategy. Wesangula replied that such tensions have not yet arisen because they consulted with the agriculture and livestock industry throughout the process, building trust and explaining the importance of appropriate antibiotic use. However, she noted that the real test will come when the required standards for antibiotic use are implemented. Dennis Carroll, director of Global Health Security and Development Unit, USAID, asked Wesangula about potential increases in antibiotic misuse across sub-Saharan Africa, given the data predicting that economic and demographic changes occurring within the region will dramatically increase livestock production. He asked about any policies and regulations to deal with food security and antibiotic stewardship in animal agriculture. Wesangula noted that Kenya's current health reforms are creating new institutions within the government—such as the independent Kenya Food and Drugs Authority—that may help to navigate these complicated issues, as well as addressing problems with enforcing compliance to regulations governing human and animal health, including antibiotic use.

Kumanan Rasanathan, chief of the Implementation Research and Delivery Science Unit at the United Nations Children's Fund, asked about the extent of political buy-in in Kenya across sectors at the ministerial level and, given the government's recent decentralization, the county level. Wesangula replied that after year-long engagement efforts, the Minister for Health and the Minister for Agriculture, Livestock, and Fisheries clearly understand the issues and are committed to pushing the antimicrobial resistance agenda at the country level. In terms of decentralization, she noted that the county level governs the actual implementation of the standards set at the national level. To facilitate relationships between the national and county levels, she said, they have developed intergovernmental mechanisms and engaged hundreds of representatives across sectors at the grassroots county level. She was optimistic that this engagement will ease the implementation process. Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization, remarked that he considers the GHSA—a nonbinding multicountry initiative—to be a catalytic initiative to help the IHR, which is a binding legal treaty. Wesangula noted that in Kenya, the GHSA was a strong catalyst for the government's response to antimicrobial resistance, even though it is nonbinding.

Espinal asked Newman if the pharmaceutical industry is working to develop new tools for addressing the problem of latent TB, which he considers to be a critical public health issue. Newman agreed that stemming the tide of the TB epidemic will not be possible without addressing latent TB infection; he noted that there are different possible approaches. One

strategy is to develop ways to predict which people are likely to progress to active TB and treat those people, he said. Another strategy is to develop a simple diagnostic test to detect TB infection and then to treat all infected people with a new safe, well-tolerated, and simple regimen, said Newman, such as a super long-acting injectable. He said that long-acting delivery systems are under development for other diseases, and they may be applicable to TB. Moon asked Newman to elaborate on any lessons about stewardship gleaned from the bedaquiline experience that might be broadly applicable to antimicrobial resistance. Newman commented on the need to strike a "balance between trying to make sure that you're being good stewards of a new molecule but, also not doing that to the point of impeding access to the people who need it." Capitalizing on new molecules is important, he said, but shorter-term efforts should focus on building capacity in national TB programs to responsibly deliver imminent new regimens with existing drugs, such as bedaquiline, delaminid, or pretomanid. He said that new diagnostic and drug sensitivity tests for TB would be transformative against the epidemic.

In the context of CARB-X's strategy of early investment in preclinical research and development and interest in market entry rewards, Moon asked Rex about the possibility of putting provisions into those early-stage grants to ensure that any of those future drugs adhere to certain public health principles, such as sustainable use and equitable access. Rex replied this will be fundamental in affecting the needed change in the antibiotic development process, and CARB-X is building such provisions into its contracts, starting with principles and a subsequent road map espoused by the Davos Declaration, which is a collective action agreement among more than 100 entities in the pharmaceutical, biotechnology, and diagnostics industries to guide the development and stewardship of new antimicrobial products (see Chapter 3). An important component of the Davos Declaration, said Rex, is that it requires country engagement after the industry develops the new drugs. He warned:

> We have, for too long, used antibiotics as a cheap band aid for bad infrastructure. It has been cheaper to treat the diarrhea than to provide the adequate infrastructure to provide clean food, clean water, and appropriate sewage, than to provide the vaccines. Antibiotics have been too easy in that (a) it's a pill that you put in somebody's mouth and, (b) it has been cheap. And it has been viewed as a cheap substitute for doing the hard stuff.

Lonnie King, professor and dean emeritus at The Ohio State University College of Veterinary Medicine, asked Rex about the potential for transferring knowledge related to antibiotics that were developed, but ultimately not approved, to animal health and to vaccine development. Rex replied that the notion of a "graveyard" of pharmaceutical failures is largely

mythical; therapeutics are discarded because they did not work then and will not work now. In terms of animal antimicrobials, he said that efforts are better spent keeping the pressure on new development. As for vaccines, Rex explained that the animal immune system is quite different from the human immune system and translational failures between the two have been more the rule than the exception. He did note that GARDP has an ongoing project, the Antibiotic Memory Recovery Initiative, which tries to gather knowledge from the older generation of antibiotic researchers that might be relevant for the new generation of researchers.

King asked Siemens about the incentives that were used to create great interest in certification and about any suggestions applicable to a similar certification program for an animal health stewardship program. Siemens responded that in the food safety space, interest in certification was driven by competition and market access; a milestone occurred when seven major retailers signed on to require certification (a process that took place over several years). In the last 10 years, she said, interest has been further accelerated by issues with global food safety and consumer confidence about the integrity of the supply. The go-to-market program is also crucial, she said, in enabling food supply security in resource-constrained settings. She advised implementing some form of verified stewardship program to ensure judicious use but also to integrate animal welfare and some appropriate use of antibiotics. In Cargill's animal nutrition business, she said, they are seeking alternatives to broad-spectrum antibiotics, but they are not as consistently effective. Reducing use in animal populations can have unintended consequences, she warned. Siemens referred to emerging evidence that withdrawing antibiotics changes the microbial profile of the animals, for example, causing elevated rates of subclinical *Salmonella* among chicken flocks. She emphasized the need to leverage the precompetitive space in animal agriculture to address these types of dynamics.

7

Moving from Knowledge to Action—Participants' Perspectives

Session V of the workshop focused on moving from knowledge to action in combating antimicrobial resistance. The session was moderated by James Hughes, professor of medicine and public health at Emory University Rollins School of Public Health. During this session, workshop organizers asked forum members, speakers, and attendees to break into four groups, each focusing on a specific theme: surveillance; stewardship, infection prevention, and behavior modification; basic and applied research and development; and global policy and coordination. Each group was given 1 hour to discuss and explore the top three immediate or short-term actions that could result in the biggest impacts that are feasible and cost-effective against antimicrobial resistance. A member of the Forum on Microbial Threats or speaker of the workshop was assigned to moderate each of the four breakout groups. The moderator for the breakout group on surveillance (Group 1) was Jeffrey Duchin, health officer and chief, Communicable Disease Epidemiology and Immunization Section for Public Health, Seattle and King County, Washington. For the breakout group on stewardship, infection prevention, and behavior modification (Group 2), the moderator was John Rex, chief strategy officer at CARB-X. Emily Erbelding, deputy director of the Division of AIDS at the National Institutes of Health, was the moderator for the breakout group on basic and applied research and development (Group 3). For the breakout group on global policy and coordination (Group 4), the moderator was Suerie Moon, director of research at the Global Health Centre, Graduate Institute of International and Development Studies, Geneva. All speakers and attendees were invited to join the breakout group of their choice. This

chapter summarizes some of the suggested actions that emerged from the breakout groups and reflections on possible next steps by some workshop participants during the final synthesis discussion of the workshop. The ideas that each group came up with should not be construed as collective conclusions or recommendations, and do not necessarily represent the views of all workshop participants, the Forum members, or the National Academies.

SUGGESTED ACTIONS TO IMPROVE SURVEILLANCE

Duchin reported for the breakout group on surveillance. The first suggested action, he said, was to optimize data acquisition from existing sources, including

- Antibiotic prescribing patterns,
- Antibiograms from clinical health care facilities and the U.S. Department of Defense,
- Information from clinical laboratories including isolate repositories,
- Information from health care systems on outcomes in patients with antimicrobial drug-resistant infections,
- Information on antimicrobial drug usage both in humans and animals,
- Information from citizen science related to environmental sampling, and
- Data from veterinary diagnostic laboratories (e.g., state diagnostic laboratories for animals, veterinary laboratories, and data from the U.S. Food and Drug Administration).

Duchin suggested that the data acquired could be incorporated into a central data repository in a standardized format for analysis and interpretation, perhaps accompanied by guidelines for interpretation.

According to Duchin, the breakout group's second suggested action was to improve the standardization of surveillance systems by adopting the recommendations of the World Health Organization (WHO) Advisory Group on Integrated Surveillance for Antimicrobial Resistance. This includes organisms to surveil (and the order of priority), laboratory methods, data quality issues, and methods for sampling and culture. The group's third suggested action, said Duchin, was to improve and standardize environmental surveillance. This could include locations for obtaining surveillance isolates, surveillance methods, and data collection protocols to accompany guidance. Duchin said that the sampling of farm animals could be more extensive if environmental sampling were a precompetitive process among producers.

Guidance from the Genomic Standards Consortium[1] could be included as part of the standardization process around environmental sampling, he said. Finally, Duchin commented on the issue of culture-independent diagnostic testing and molecular methods, emphasizing the need for guidance about how these methods should be used and interpreted, as well as their implications for various aspects of surveillance and response.

SUGGESTED ACTIONS TO IMPROVE STEWARDSHIP, INFECTION PREVENTION, AND BEHAVIOR MODIFICATION

Reporting for the breakout group on stewardship, infection prevention, and behavior modification, Rex explained that the discussion was divided into human and veterinary domains. A suggested action applicable to both domains, he said, is the need for more vaccines; this entails everything from funding basic development science to establishing priority vaccine targets. Another suggested action for both domains, Rex said, is building workforce capacity by training health care providers and leadership, as well as establishing standardized curricula that include stewardship and infection prevention.

A suggested action specific to the human domain, said Rex, concerns measuring and reporting data on antimicrobial usage, such as usage by tonnage by a territory and usage by health care providers. Referring to the previous day's presentation by Jeffrey Linder, Rex noted the simple act of measuring—and telling people you are measuring—coupled with minimal feedback can have an effect on behavior. Rex said that the group highlighted a gap around stewardship and incentive principles for all of the domains of veterinary medicine. Some structure exists for food animals in terms of guidance and incentives, he said, but not for companion animals and aquaculture. He suggested working on how to structure stewardship and incentives for the latter space.

SUGGESTED ACTIONS TO IMPROVE BASIC AND APPLIED RESEARCH AND DEVELOPMENT

Erbelding reported for the breakout group on basic and applied research and development. The group's suggested action was to prioritize an ecologic systems biology approach to validate biosignatures, she said. This approach would include measurements from water systems, antibiotic use, and food, among other relevant entities in the ecosystem, and would enable description of the microbiome and of factors that correlate with the resistome, she added. A description of the entire ecosystem would

[1] For more information, see gensc.org/mixs (accessed July 31, 2017).

also enable the identification of the biosignatures of resistance in each compartment, said Erbelding, which could be validated by experimentally perturbing the system in a positive or negative way. Having established this approach and validated the biosignatures, Erbelding said, specific interventions could be tested. For example, it would enable comparisons between various animal food production practices to measure the persistence of effect on the resistome over time. Validated biosignatures could also be used for modeling new approaches in other ecosystems, such as animal management methods, she said.

SUGGESTED ACTIONS TO IMPROVE GLOBAL POLICY AND COORDINATION

Reporting for the breakout group on affecting global policy and coordination, Moon explained that the group began by looking at the world of antimicrobial resistance. She described it as "a world of about 10,000 pieces that may or may not fit together into a puzzle." However, she noted, there may be better ways to frame the issue because of natural overlap of these activities with such things as global health security and universal health coverage. The group discussed the importance of bearing in mind the global political context, Moon said. She predicted that the appetite for big, multilateral solutions may be diminishing, but that we fortunately have a number of broad multilateral plans already in place.

Much of the group's discussion focused on the activities needed at the transnational level (either at the regional or global levels), but there were no suggestions for further agreements or declarations on this issue, Moon reported. The first suggested activity, Moon said, concerns convening the global community of practice around antimicrobial resistance, with stakeholders from all sectors sharing knowledge and identifying gaps. She said that in particular, it would be very useful to strategically convene smaller groups that could form a transnational network of exchange for sharing and strategizing about concrete, day-to-day practices among private-sector actors, prescribers, stewardship policy makers, and scientific researchers, for example. The second suggested activity is a more concerted coordination of efforts in areas of need, she said. This might include global coordination of economic incentives provided for research and development in health technologies, she continued, as well as the regulatory and policy frameworks within which it occurs. She said that similar global coordination is needed among funders that are building health care capacity at the country level. In terms of the economic actors in agriculture, aquaculture, and other sectors, there is also a need for incentives and frameworks for regulation and policy. She highlighted the importance of "small tweaks or levers of trade policies or trade incentives that can, in fact, change the

behavior of actors without having to resort to necessarily global level plans or strategies." Finally, the third suggested activity, Moon reported, is the development of monitoring and accountability efforts outside of the existing United Nations (UN) system that may be required to ensure that this global complex system to fight against antimicrobial resistance continues to evolve in a forward direction in line with the global goals, strategies, and action plans that are already in place.

SYNTHESIS AND GENERAL DISCUSSION

After the moderators reported some suggested actions that emerged from the breakout groups, several workshop participants reflected on potential next steps that could be taken moving forward to counter the threat of antimicrobial resistance. The discussion began with the topic of funding as well as refining and leveraging the message of antimicrobial resistance. David Relman, professor of medicine at Stanford University, noted that the funding system is currently fragmented and not well aligned with the One Health view, and as a result, much of this work suggested by the four breakout groups might be difficult to fund with the existing defined portfolios and disparate priorities of individual institutions. He asked about new types of funding systems or organizational principles that could bring together separate institutions to collaborate on identifying the resources needed to carry out the work proposed. Keiji Fukuda, director and clinical professor at the University of Hong Kong School of Public Health, observed that it is very difficult to create new systems to package together funding and partners at the international level, which may pose a barrier to Relman's suggestion. Fukuda suggested that there is more potential for success at the country level to leverage antimicrobial resistance as a rallying cry, but the concept of antimicrobial resistance will need to be clarified as a unified concept—with a consistent description—to sustain attention on the issue. He suggested reshaping the concept:

> So that we think of antimicrobial drugs in the same way that we think about clean water. . . . We use as much as we need, but we don't waste it. It's like food. You eat as much as you need, and you don't waste it. It's a concept that people can understand.

Rex suggested that putting antimicrobials in a framework underlined by the notion of security—secure food, secure water, secure antibiotics supply—may help unify the concept.

Jesse Goodman, professor of medicine and infectious diseases at Georgetown University, agreed about the importance of messaging to sustain action against resistance. He noted that ongoing revolutions in science—

from the microbiome to vaccinology to metabolomics—offer new potential to stimulate and sustain interest; similar scientific revolutions have changed the perception of antibiotics in animal agriculture in just a few years, he said. As an attention-getting tactic, Goodman suggested focusing on the threat that untreatable infections pose to basic health system functions that affect everyone in society.

Kumanan Rasanathan, chief of the Implementation Research and Delivery Science Unit at the United Nations Children's Fund, reflected that strengthening the antimicrobial ecosystem does need that type of unifying banner, but that it needs to be coupled with efforts to penetrate into existing agendas that already have ongoing community action. He used climate change as an example, noting that it has moved forward, not necessarily because people identified with the climate change movement under a unified banner, but because of people acting in their own spheres of interest (e.g., transport planners want to reduce congestion because it is often a key deliverable for them). He suggested inserting surveillance of antibiotic use and outcomes into the huge existing quality improvement agenda to strengthen health systems, particularly in low- and middle-income countries, which already calls for better data systems to improve health systems' performance. That said, Rasanathan noted, there are specifics that need to remain under the antimicrobial resistance agenda because they cannot be carried out elsewhere.

Sally Davies, chief medical officer for England in the United Kingdom Department of Health, noted that because a report produced by the Interagency Coordination Group on Antimicrobial Resistance is due to the UN Secretary General for the UN General Assembly session in 2018 (see Chapter 2), now is the time to shape the desired changes, targets, structures and so forth for the immediate and longer term. Low-hanging fruit, she suggested, is inserting antimicrobial resistance into all policies (universal health care, tuberculosis, and malaria, for example). Davies expressed concern about a potential schism that could arise if—as some people have suggested—a new UN body or global fund is created for antimicrobial resistance. She noted that this would be a mistake:

> We need to see antimicrobial resistance as an underpinning issue that impacts the whole health system and food chain, and we have got to strengthen health systems. But if we are not careful, we will find those who are about the subject starting to have a battle about what the future's structures are, whether there is enough money—and there isn't enough money—and where we need a special fund . . . rather than staying together, which we are at the moment, to help people lead better lives and have safer food.

Lonnie King, professor and dean emeritus at The Ohio State University College of Veterinary Medicine, noted a positive shift in the sphere of

antimicrobial resistance toward establishing shared interests. He suggested that despite a common misconception, establishing shared interests does not require compromising if it is mutually agreed that those interests will achieve the best outcome for everyone involved. He said the public represents part of that shared interest, and thus the public should be involved in this effort.

Davies also highlighted the need to engage civil society and create a public face for antimicrobial resistance. Rima Khabbaz, deputy director for infectious diseases at the U.S. Centers for Disease Control and Prevention, similarly suggested promoting its public face:

> People have to see antimicrobial resistance as a problem, their problem. . . . The change that we have seen in public safety and what people are saying—[that] it is not acceptable to go to a health care setting to get treated and come up with an adverse event—has changed things. I think with antimicrobial resistance, we need the same—people saying "No, it is not okay; I need the antibiotics protected."

Goodman agreed that the problem of antimicrobial resistance is so complex and important that both the payoffs and the solutions need to be synergistic across the human, animal, and environment sectors. Similarly, incentivizing product development will require both public–private and government partnerships, he said. To add to the discussion on product development, George Poste, chief scientist of the Complex Adaptive Systems Initiative at Arizona State University-SkySong, commended Rex's presentation (see Chapter 5) for its pragmatic description of the fragility of the research and development process. He expressed concern that certain predictions—for example, that 10 new antibiotics will be developed by 2020—are not at all feasible. Poste suggested that for the situation to improve, pragmatic policies will need to be developed by drug development experts in direct collaboration with the pharmaceutical industry.

On the topic of data, Peter Daszak, president of EcoHealth Alliance, observed that for gains to be achieved against the problem of resistance, surveillance data will need to be collected in countries other than the United States, where antimicrobials are freely available and unregulated. To better understand the actual level of risk and find solutions, Daszak suggested the pharmaceutical industry should be persuaded to open up their sales and surveillance data. Davies noted that efforts to promote the fight against resistance on the global stage are hampered by the lack of a WHO *International Classification of Diseases* code for people who have severe morbidity or mortality from antimicrobial resistance, which is a requisite step for standardizing data. Finally, Rasanathan added that while data to inform hard science on usage and behavior are needed, so are data on

policy implications, economic markets impact, and relative impact modeling around different regulatory choices.

King concluded the workshop by reiterating the importance of shaping the concept of antimicrobial resistance, both for unifying efforts and for inflecting the progress that has already been made to galvanize momentum toward future actions that are measurable and impactful. He hoped that the workshop would help stimulate even more action moving forward and achieve big wins in the immediate term.

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Appendix A

Statement of Task

An ad hoc committee under the auspices of the National Academies of Sciences, Engineering, and Medicine will plan a 2-day public workshop that will examine the key areas in human, animal, and environmental health that contribute to the emergence and spread of antimicrobial resistance. Through a One Health approach, this workshop will discuss gaps in these areas and present the complexities of bridging the different sectors and disciplines to address this global threat. A key focus of the workshop will be to explore immediate and short-term actions and research needs that will have the greatest impact on reducing antimicrobial resistance. This workshop will feature invited presentations and discussions on topics including

- The implications and effect on human health of the movement of resistance genes across different ecosystems;
- The antimicrobial resistance burden in humans attributed to human health care practices, the use of antimicrobials in livestock, and the effect of environmental sources;
- The expected effect of the implementation of U.S. Food and Drug Administration Guidances #209 and #213, and changes to the existing veterinary feed directive that were rolled out in January 2017 and the exploration of key measures determining the future success of these actions;
- The role and effectiveness of stewardship programs in reducing and preventing antimicrobial resistance through changes in the use, prescription, sales, regulation, and manufacturing of antimicrobials;

- The importance of data availability and data sharing to monitor and evaluate the implementation and progress strategies, to maintain the effectiveness of existing drugs, to develop new drugs and diagnostics, and to implement disease prevention strategies, including vaccine use and the adoption of alternatives to antibiotics to better understand the clinical value and patient outcomes; and
- The need for collaboration and coordination mechanisms across the One Health domains for prevention, control, and research and development of new antimicrobials, other therapeutics, diagnostics, and disease prevention strategies to combat antimicrobial resistance.

Workshop speakers will discuss the key elements that may be prioritized for achieving the greatest impact in the short term, and immediate research that could be conducted in the next few years. Workshop speakers and discussants will contribute perspectives from government, academia, private, and nonprofit sectors. The committee will plan and organize the workshop, select and invite speakers and discussants, and moderate the discussions. A proceedings of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines. The designated rapporteur will not be a member of the committee, and no committee members will be consulted in the development of the workshop proceedings.

Appendix B

Workshop Agenda

TUESDAY, JUNE 20, 2017

9:00 am ET — Opening Remarks
Victor Dzau, National Academy of Medicine

The Global Momentum for Antimicrobial Resistance—Moving from Knowledge to Action
Keiji Fukuda, University of Hong Kong

Devising and Prioritizing a Strategy for Immediate Action and Implementation to Combat Antimicrobial Resistance
Dame Sally Davies, UK Department of Health

Workshop Overview and Goals
Lonnie King, Workshop Chair

Session I: Key Gaps and Needs in Our Understanding of the Microbial and Genetic Movements Across the One Health Domains

PART A: Strengthening the Knowledge and Evidence Base
Rima Khabbaz, *Moderator*

10:00 am — 20 Years of the National Antimicrobial Resistance Monitoring System (NARMS): What Have We Learned So Far, and What Is Next?
Patrick McDermott, U.S. Food and Drug Administration

Quality and Gaps in Surveillance Across the One Health Domains: Critical and Immediate Actions
Paula J. F. Cray, North Carolina State University

Global Perspectives and Challenges for Antimicrobial Resistance Surveillance in the Environment
James M. Tiedje, Michigan State University

11:10 am Break

PART B: The Impact of Antimicrobials in the Environment—The Neglected Link
Jeffrey Silverstein, *Moderator*

11:20 am The Interface and Pathways of Gene Transfer Across the One Health Domains
Lance Price, The George Washington University

Environmental Compartments of Antimicrobial Resistance and Antibiotic Metabolites
Ed Topp, Agriculture and Agri-Food Canada

Management Options for Reducing the Transfer of Antimicrobials to the Environment and Ameliorating the Risk
Lisa Durso, U.S. Department of Agriculture

Pharmaceutical Industry to Reduce Environmental Impact from Production of Antimicrobials: What Can Be Done?
Stephen Brooks, Pfizer Inc.

12:45 pm Lunch Break

Session II: Social and Behavioral Sciences and Antimicrobial Resistance—Modifying Behavior and Choices

PART A: Reducing the Use—Achieving Desired Behavior Change Through Stewardship Programs, Incentives, and Policy for Responsible Use of Antimicrobials
Franck Berthe, *Moderator*

1:30 pm Pathways to Effective Guidance for Reducing the Use of Antimicrobials in Health Care Settings
Helen W. Boucher, Tufts Medical Center

Animal Health and Welfare Programs and Guidelines for Antimicrobial Usage—The Gap Between Knowledge and Practice Behavior
David Sjeklocha, Cattle Empire, LLC

The Changing Paradigm of Antimicrobial Use in Veterinary Medicine—Implications of the FDA Guidance on Growth Promotion and Changes to the Veterinary Feed Directive
Randall Singer, University of Minnesota

Consumer and Retailers Perspectives in the Food Industry—The New Social Value of Food
Bruce Stewart-Brown, Perdue Farms, Inc.

3:00 pm Break

PART B: Reducing the Need—Achieving Desired Behavior Change Through Prevention Measures and Education
Mary Wilson, *Moderator*

3:15 pm Enhancing Practitioner Knowledge and Adoption of Infection Prevention and Control Measures for Both Food and Companion Animal Veterinarians
H. Morgan Scott, Texas A&M University

Leveraging Behavioral Interventions to Achieve Appropriate Antibiotics Prescribing Practices in Health Care Settings
Jeffrey A. Linder, Northwestern University Feinberg School of Medicine

Educating the Next Generation of Health Professionals—How Will Opportunities for Interprofessional Education and Learning Make a Difference?
Andrew T. Maccabe, Association of American Veterinary Medical Colleges
Darrell G. Kirch, Association of American Medical Colleges

4:50 pm Wrap-Up
Lonnie King, Workshop Chair

5:00 pm Adjourn

5:05 pm Reception

WEDNESDAY, JUNE 21, 2017

8:30 am ET Welcome
Lonnie King, Workshop Chair

Session III: Reducing the Need for Antimicrobials—Critical Research and Development Actions
Kent Kester, *Moderator*

8:35 am Effective Scientific Advances and Promising Research to Reduce the Need for Antimicrobials

Human Health Perspective
L. Clifford McDonald, U.S. Centers for Disease Control and Prevention

Animal Health Perspective
Tim Johnson, University of Minnesota

Vaccination to Reduce Antimicrobial Resistance Burden—How Should We Use Existing Vaccines? What Vaccines Might We Seek to Develop?
Keith Klugman, Bill & Melinda Gates Foundation

The Value of Diagnostic Tools to Combat Antimicrobial Resistance—What Type of Tools Should Be Prioritized?
Ellen Jo Baron, Stanford University Medical Center; Cepheid

Critical Incentive Strategies for Accelerating R&D to Fight Against Antimicrobial Resistance
Gregory Daniel, Duke-Margolis Center for Health Policy

Session IV: Strengthening Partnerships and International Cooperation
Peter Sands, *Moderator*

10:45 am Implementation of the Global Action Plan on Antimicrobial Resistance at the Country Level—To What Extent Is the Integration with the IHR Core Capacity Building Efforts Possible?
Evelyn Wesangula, Ministry of Health, Kenya

Immediate Strategies to Develop or Redefine Partnerships

Partnerships in the Age of Bedaquiline: Successes, Challenges, and the Beginning of the End of Tuberculosis
Robert Newman, Johnson & Johnson

Integrating Food Safety, Animal Health, and Plant Health to Improve the Integrity of the Food Supply Chains
Angela Siemens, Cargill Protein Group

Regulatory and Policy Frameworks
Kathy Talkington, The Pew Charitable Trusts

Partnerships to Combat Antimicrobial Resistance
John Rex, CARB-X

12:45 pm Lunch Break

Session V: Moving Knowledge to Action—Devising and Prioritizing a Strategy for Immediate Action and Implementation

1:30 pm Introduction to Session
James Hughes, Emory University

1:40 pm Group Discussion: Focus on the Most Impactful, Feasible, and Immediate Actions Across the One Health Domains

Purpose to address the critical question: What are the top three immediate or short-term actions within each of these themes that could result in the biggest impact that is feasible and cost-effective?

Group 1: Surveillance
Jeffrey Duchin, *Moderator*

Group 2: Stewardship, Infection Prevention, and Behavior Modification
John Rex, *Moderator*

Group 3: Current Basic and Applied Research and Development
Emily Erbelding, *Moderator*

Group 4: Global Policy and Coordination
Suerie Moon, *Moderator*

2:30 pm Synthesis and General Discussion
James Hughes, Emory University

3:20 pm Closing Remarks
Lonnie King, Workshop Chair
David Relman, Forum Chair

3:30 pm Adjourn

Appendix C

Biographical Sketches of Workshop Speakers and Moderators

Ellen Jo Baron, Ph.D., was the director of the clinical microbiology/virology laboratories at Stanford University Medical Center for 15 years before joining Cepheid, a molecular diagnostics manufacturer in 2009, where she is now executive director of medical affairs. She has been a board-certified clinical microbiology laboratory director for more than 30 years. Her basic microbiology flowchart system is in use in laboratories throughout the world. She was bacteriology editor for the American Society for Microbiology (ASM) *Manual of Clinical Microbiology* for four editions and also edited the Infectious Diseases Society of America and ASM "Guideline on Infectious Diseases Diagnostic Testing." She has written or edited more than 30 books and chapters and more than 100 journal articles about infectious diseases diagnostics. She received the Stanford Medicine Lifetime Achievement Award, as well as the ASM bioMérieux Sonnenwirth Award for Leadership in Clinical Microbiology, ASM Alice Evans Award for serving as a role model for women in microbiology, and ASM Founders Distinguished Service Award in 2012. She has been an invited speaker throughout the world at more than 300 conferences and symposia. She is the co-founder of the Diagnostic Microbiology Development Program, a nongovernmental organization that does laboratory capacity building in the developing world, with major activities in Cambodia.

Franck Berthe, D.V.M., Ph.D., is a senior livestock specialist in the Agriculture Global Practice of the World Bank and coordinator of the Livestock Global Alliance since March 2016. The Alliance brings together the Food and Agriculture Organization of the United Nations, the International Fund

for Agriculture Development, the International Research Institute on Livestock (ILRI/CGIAR), the World Organisation for Animal Health (OIE), and the World Bank, five global public institutions committed for safer, fairer, and more sustainable livestock. Dr. Berthe was previously head of the Animal and Plant Health Unit at the European Food Safety Authority based in Parma, Italy. His core activity was to assess animal and plant production systems and practices with respect to primary production, ecosystems, and public health. Dr. Berthe's job was to provide scientific advice to the EU risk managers and decision makers on a wide range of risks at the human–animal–ecosystem interface. Prior to coming to Italy in 2007, Dr. Berthe was associate professor at the Atlantic Veterinary College (UPEI) and Canada research chair in aquatic health sciences, exploring host pathogens relations in their environment. From 1994 to 2004, Dr. Berthe has led active research in aquatic animal health at the French institute for the exploitation of the sea (IFREMER) in France and overseas territories. Dr. Berthe is vice president of the Biological Standards Commission of OIE. He has served on OIE specialized commissions since 1996. A native of France, Dr. Berthe received a doctorate of veterinary medicine and a Ph.D. degree in molecular parasitology. He has a diploma in bacteriology from the Pasteur Institute.

Helen W. Boucher, M.D., FACP, FIDSA, is the director of the Infectious Diseases Fellowship Program at Tufts Medical Center and professor of medicine at the Tufts University School of Medicine. Dr. Boucher's clinical interests include infections in immunocompromised patients and *S. aureus* infections. Her research interests focus on *S. aureus* and the development of new anti-infective agents. She is the author or co-author of numerous abstracts, chapters, and peer-reviewed articles, which have been published in such journals as the *New England Journal of Medicine*, *Antimicrobial Agents and Chemotherapy*, *Clinical Infectious Diseases*, and the *Annals of Internal Medicine*; she is associate editor of *Antimicrobial Agents and Chemotherapy.* She has been included in "Best Doctors in America" since 2009. In 2011, Dr. Boucher was elected fellow and member of the Board of Directors of the Infectious Diseases Society of America (IDSA). In 2012, she was elected to the American Board of Internal Medicine Infectious Disease Exam Writing Committee and in 2014, to the American Board of Internal Medicine Infectious Diseases Subspecialty Board. In 2015, she was appointed to the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, and elected treasurer of IDSA. She was awarded the IDSA Society Citation Award in October 2015. Dr. Boucher serves on the Board of Trustees of the Physicians of Tufts Medical Center and the College of the Holy Cross.

Stephen Brooks, B.Sc., joined Pfizer Inc. as a discovery chemist in the United Kingdom in 1982. He moved into health and safety in 1989 and

has held positions of increasing responsibilities in the company's Environment, Health, and Safety (EHS) organization in the European Union, United Kingdom, and the United States. Mr. Brooks has led Pfizer's Global EHS organization since 2007 when he also assumed responsibility for Business Resiliency, Environmental Sustainability, and Quality Audit (cGMP) for the company. Mr. Brooks and his leadership team are responsible for developing strategy, policies, and standards, and for driving continuous improvement in the management of relevant risk across all Pfizer divisions and locations. Mr. Brooks is also responsible for monitoring and where appropriate, seeking to influence the external environment on EHS matters of importance to the company, as well as the biopharmaceutical industry. In this capacity, Mr. Brooks is a committee member of relevant trade associations and other external organizations. He holds an honors degree in chemistry from Bath University, UK, is a chartered safety practitioner (UK), and is a professional member of the American Society of Safety Engineers.

Paula J. F. Cray, Ph.D., is a professor and head of the Department of Population Health and Pathobiology at the College of Veterinary Medicine, North Carolina State University-Raleigh (2014 to present). Prior, she was a microbiologist and research leader for the U.S. Department of Agriculture's Agricultural Research Service (USDA-ARS) for 24 years. From 1997 to 2012, she served as the director of the animal arm of the National Antimicrobial Resistance Monitoring System (NARMS) and the director of USDA VetNet (PulseNet equivalent) from 2003 to 2014. Dr. Cray served on numerous World Health Organization (WHO) expert working groups and continues service as a member of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance, which includes serving as a lead mentor for developing countries implementing WHO surveillance programs. Currently, she is leading an expansion of global research efforts in the department that involves Africa, China, and India. Dr. Cray's current research continues to focus on the global ecology and impact of antimicrobial resistance from a One Health perspective. She holds a bachelor of science degree from The Pennsylvania State University, a master of science degree from North Dakota State University (bacteriology), a master in administrative sciences from Johns Hopkins University (administration), and a Ph.D. from the University of Nebraska Medical School. She has received numerous national and international awards, published more than 195 peer-reviewed papers, and given more than 210 invited presentations and interviews.

Gregory W. Daniel, Ph.D., M.P.H., R.Ph., is the deputy director of the Duke-Robert J. Margolis, M.D., Center for Health Policy and a clinical professor in Duke's Fuqua School of Business. Dr. Daniel directs the Wash-

ington, DC-based office of the center and leads the center's pharmaceutical and medical device policy portfolio, which includes developing policy and data strategies for improving development and access to innovative pharmaceutical and medical device technologies. This includes post-market evidence development to support increased value, improving regulatory science and drug development tools, optimizing biomedical innovation, and supporting drug and device value-based payment reform. Dr. Daniel is also adjunct associate professor in the Division of Pharmaceutical Outcomes and Policy at the University of North Carolina Eshelman School of Pharmacy. Previously, he was the managing director for evidence development and biomedical innovation in the Center for Health Policy, a fellow in economic studies at the Brookings Institution, and vice president of government and academic research at HealthCore (an Anthem, Inc., company). In addition to health and pharmaceutical policy, Dr. Daniel's research expertise includes real-world evidence development using electronic health data in the areas of health outcomes and pharmacoeconomics, comparative effectiveness, and drug safety and pharmacoepidemiology. Dr. Daniel received a Ph.D. in pharmaceutical economics, policy, and outcomes from the University of Arizona, as well as an M.P.H., M.S., and B.S. in Pharmacy, all from The Ohio State University.

Sally Davies, FRS, FMedSci, is the chief medical officer for England and chief medical advisor to the UK government. She advises on medical matters with particular responsibilities for public health providing leadership to public health directors. She founded the National Institute for Health Research and was the Department of Health's chief scientific advisor and research and development lead. Professor Davies is a member of several prominent international advisory committees and sat on the World Health Organization (WHO) Executive Board. Her 2013 Annual Report highlighted the increasing threat from antimicrobial resistance (AMR) and called for global action to address this. She continues to advocate globally on AMR. She chaired the World Innovation Summit for Heath 2013 AMR forum and chairs the WHO AMR Strategic and Technical Advisory Group. She raised public awareness of AMR through a Penguin book and a TED talk. Professor Davies is a fellow of The Royal Society and a member of the U.S. National Academy of Medicine.

Jeffrey S. Duchin, M.D., is a health officer and the chief of the Communicable Disease Epidemiology and Immunization Section for Public Health in Seattle and King County, Washington, and professor of medicine, Division of Infectious Diseases and adjunct professor in the School of Public Health at the University of Washington. Dr. Duchin trained in internal medicine at Thomas Jefferson University Hospital. He completed a fellowship in general

internal medicine and emergency medicine at the Hospital of the University of Pennsylvania and infectious disease subspecialty training at the University of Washington. After several years on the faculty at the University of Pennsylvania, he joined the U.S. Centers for Disease Control and Prevention's (CDC's) Epidemic Intelligence Service program where he was assigned to the National Center for Infectious Diseases, and CDC's Preventive Medicine Residency program. He worked for CDC as a medical epidemiologist in the Divisions of Tuberculosis Elimination and HIV/AIDS Special Studies Branch before assuming his current position. Dr. Duchin is a member of CDC's Board of Scientific Counselors, Office of Infectious Diseases, and past member of the Advisory Committee on Immunization Practices. He is a fellow of the Infectious Diseases Society of America (IDSA) and has chaired IDSA's Public Health Committee and the Bioemergencies Task Force. Dr. Duchin serves on the Editorial Board and Technical Advisory Group for Communicable Disease Alert and Response to Mass Gatherings for the World Health Organization and previously served as a member of the U.S. Department of Health and Human Services 2004 Tiger Team, consulting with the government of Greece on health preparations for the 2004 Olympics, in Athens, Greece. Dr. Duchin's peer-reviewed publications and research interests focus on communicable diseases of public health significance, and he has authored textbook chapters on outbreak investigations, bioterrorism, and the epidemiology of HIV/AIDS.

Lisa Durso, Ph.D., is a microbiologist working for the U.S. Department of Agriculture's Agricultural Research Service (USDA-ARS), in Lincoln, Nebraska. She began her career in state and federal public health, including 1 year spent as an Emerging Infectious Disease Training fellow at the Foodborne and Diarrheal Disease Branch of the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, and employment in the Rabies and Arbovirus unit of the Texas Department of Health and molecular diagnostics at the Iowa State Hygienic Laboratory. Following her Ph.D. in food safety microbiology, Dr. Durso worked as a postdoctoral researcher in the Animal Health unit of the USDA Meat Animal Research Center where her work focused on the microbial ecology of *E. coli* O157:H7 in beef cattle. Her current assignment in Lincoln focuses on environmental components of microbes in manure, including pathogens, fecal indicators, and antibiotic-resistant bacteria, as well as contributions of manure microbial communities to soil health and nutrient cycling.

Victor J. Dzau, M.D., is the president of the National Academy of Medicine. In addition, he serves as chair of the Health and Medicine Division Committee of the National Academies of Sciences, Engineering, and Medicine. He is chancellor emeritus and James B. Duke Professor of Medicine

at Duke University and the past president and chief executive officer of the Duke University Health System. Previously, Dr. Dzau was the Hersey Professor of Theory and Practice of Medicine and chairman of medicine at Harvard Medical School's Brigham and Women's Hospital, as well as chairman of the Department of Medicine at Stanford University. Dr. Dzau has made a significant impact on medicine through his seminal research in cardiovascular medicine and genetics, his pioneering of the discipline of vascular medicine, and his leadership in health care innovation. His important work on the renin angiotensin system (RAS) paved the way for the contemporary understanding of RAS in cardiovascular disease and the development of RAS inhibitors as widely used, lifesaving drugs. Dr. Dzau also pioneered gene therapy for vascular disease, and his recent work on stem cell paracrine mechanisms and the use of microRNA in direct reprogramming provides novel insight into stem cell biology and regenerative medicine. As one of the world's preeminent academic health leaders, Dr. Dzau advises governments, corporations, and universities worldwide. He has been a member of the Council of the IOM and the Advisory Committee to the director of the National Institutes of Health (NIH), as well as chair of the NIH Cardiovascular Disease Advisory Committee and the Association of Academic Health Centers. He served on the Governing Board of the Duke-National University of Singapore Graduate Medical School and the Board of Health Governors of the World Economic Forum and chaired its Global Agenda Council on Personalized and Precision Medicine. He also served as the senior health policy advisor to Her Highness Sheikha Moza (chair of the Qatar Foundation). Currently, he is a member of the Board of Directors of the Singapore Health System; the Expert Board of the Imperial College Health Partners, UK; and the International Advisory Board of the Biomedical Science Council of Singapore. In 2011, he led a partnership among Duke University, the World Economic Forum, and McKinsey, and he founded the International Partnership for Innovative Healthcare Delivery and currently chairs its Board of Directors.

Emily Erbelding, M.D., M.P.H., is the director of the Division of Microbiology and Infectious Diseases (DMID) at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). She is responsible for the strategic and scientific vision for DMID's complex national and international research program. DMID supports basic, preclinical, and clinical investigations into the causes, diagnosis, treatment, and prevention of a broad range of pathogens, including those related to biodefense and emerging infectious diseases. Prior to joining DMID in 2017, Dr. Erbelding served as deputy director of the Division of AIDS at NIAID, spent 14 years on the faculty of the Johns Hopkins University School of Medicine, in the Division of Infectious Diseases, and was

the director of Clinical Services for the Baltimore City Health Department STD (sexually transmitted disease)/HIV program. Dr. Erbelding received her bachelor's and master's degrees from Cornell University and her medical degree from Indiana University School of Medicine. She completed her residency in internal medicine at Northwestern University Medical Center and earned a Master of Public Health degree from the Johns Hopkins Bloomberg School of Public Health. Since 2011, Dr. Erbelding has served as an attending physician for a weekly half-day infectious disease clinic at the Veterans Affairs Medical Center in Washington, DC. She is certified by the American Board of Internal Medicine as a Diplomate of Infectious Disease.

Keiji Fukuda, M.D., M.P.H., is the director and a clinical professor at the University of Hong Kong School of Public Health. He previously worked at the World Health Organization (WHO) in several capacities including assistant director-general (ADG) and special representative of the director-general for antimicrobial resistance; ADG for the Health Security and Environment Cluster; and director of the Global Influenza Programme. Before that, he worked at the U.S. Centers for Disease Control and Prevention (CDC) as the Epidemiology Section chief, Influenza Branch, and as a medical epidemiologist in the Viral Exanthems and Herpesvirus Branch, National Center for Infectious Diseases. Dr. Fukuda has been a global public health leader in many areas, including health security; emerging infectious diseases, including seasonal, avian and pandemic influenza, severe acute respiratory syndrome, Middle East respiratory syndrome, and Ebola; antimicrobial resistance; development of the Pandemic Influenza Preparedness Framework; implementation of the International Health Regulations; food safety; and chronic fatigue syndrome. He has considerable experience in epidemiological research and field investigations, media communications, and international diplomatic negotiations, including those held to establish a historic heads of state-level meeting on antimicrobial resistance at the United Nations in 2016. He has a B.A. in biology, an M.D., an M.P.H., was trained in the Epidemic Intelligence Service at CDC, and is certified in internal medicine by the American Board of Internal Medicine.

James M. Hughes, M.D., is a professor of medicine and public health, with joint appointments in the School of Medicine (infectious diseases) and the Rollins School of Public Health (global health), at Emory University and the co-director of the Emory Antibiotic Resistance Center. Prior to joining Emory in June 2005, Dr. Hughes worked at the U.S. Centers for Disease Control and Prevention (CDC), serving as director of the National Center for Infectious Diseases (NCID) and as a rear admiral and an assistant surgeon general in the U.S. Public Health Service. He first joined CDC as a member of the Epidemic Intelligence Service in 1973. He served as director

of CDC's Hospital Infections Program from 1983 to 1988, as NCID deputy director from 1988 to 1992, and as NCID director from 1992 to 2005. Dr. Hughes received his B.A and M.D. from Stanford University and completed his postgraduate training and board certification in internal medicine (University of Washington), infectious diseases (University of Virginia), and preventive medicine (CDC). He is a member of the National Academy of Medicine and a fellow of the Infectious Diseases Society of America (IDSA), the American Society of Tropical Medicine and Hygiene, the American Academy of Microbiology, and the American Association for the Advancement of Science. He has served on the Forum on Microbial Threats since 1996 and as vice chair of the Forum since 2009. He served on the Board of Directors of IDSA from 2004 to 2007 and as IDSA President from 2010 to 2011. He is currently a member of the Board of Directors of the American Academy of Microbiology, the One Health Commission, and the EcoHealth Alliance. Among his honors and awards are the Distinguished and Meritorious Service Medals and the Surgeon General's Exemplary Service Award from the U.S. Public Health Service, the Secretary's Open Forum Distinguished Public Service Award from the U.S. Department of State, the CDC Lifetime Scientific Achievement Award, the Gen–Probe Joseph Award from the American Society for Microbiology for "exemplary leadership and service in the field of public health," the Jonathan M. Mann Lectureship Award from the Council of State and Territorial Epidemiologists, the Bailey K. Ashford Memorial Lecturer at the University of Puerto Rico School of Medicine, and membership in the Emory Millipub Club. Dr. Hughes has published more than 110 research articles, 10 reviews, 15 editorials, and 45 book chapters. He has co-edited 10 books on emerging infectious diseases.

Timothy Johnson, Ph.D., is an associate professor of microbiology at the University of Minnesota. He received his Ph.D. in molecular pathogenesis from North Dakota State University in 2004, followed by postdoctoral studies at Iowa State University College of Veterinary Medicine. Dr. Johnson joined the University of Minnesota Department of Veterinary and Biomedical Sciences in 2007. He has since developed an internationally recognized research and outreach program focused on the genetic mechanisms enabling the spread of antibiotic resistance in Enterobacteriaceae. In tandem, his work focuses on the identification of antibiotic alternatives that manipulate the animal microbiome allowing for enhanced growth and reduced disease. He also currently serves as director of research and development at the Mid-Central Research and Outreach Center's Poultry Research Laboratory in Willmar, Minnesota.

Kent E. Kester, M.D., is currently the vice president and head of Translational Science and Biomarkers at Sanofi Pasteur. During a 24-year career

in the U.S. Army, he worked extensively in clinical vaccine development and led multiple research platforms at the Walter Reed Army Institute of Research, the U.S. Department of Defense's largest and most diverse biomedical research laboratory—an institution he later led as its commander/director. His final military assignment was as the associate dean for clinical research in the School of Medicine at the Uniformed Services University of the Health Sciences (USUHS). Dr. Kester holds an undergraduate degree from Bucknell University and an M.D. from Jefferson Medical College. He completed his internship and residency in internal medicine at the University of Maryland and a fellowship in infectious diseases at the Walter Reed Army Medical Center. A malaria vaccine researcher with more than 70 scientific manuscripts and book chapters, Dr. Kester has played a major role in the development of the malaria vaccine candidate known as RTS,S. Currently a member of the U.S. Government Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, he previously chaired the Steering Committee of the National Institute of Allergy and Infectious Diseases (NIAID)-USUHS Infectious Disease Clinical Research Program, and has served as a member of the U.S. Food and Drug Administration's Vaccines and Related Biologics Products Advisory Committee, the NIAID Advisory Council, and the U.S. Centers for Disease Control and Prevention's Office of Infectious Diseases Board of Scientific Counselors. Board certified in both internal medicine and infectious diseases, he holds faculty appointments at USUHS and the University of Maryland. He is a fellow of the American College of Physicians, the Infectious Diseases Society of America, and the American Society of Tropical Medicine and Hygiene.

Rima F. Khabbaz, M.D., is the deputy director for infectious diseases and director of the Office of Infectious Diseases at the U.S. Centers for Disease Control and Prevention (CDC). Prior to her current position, she served as the director of CDC's National Center for Preparedness, Detection, and Control of Infectious Diseases and held other leadership positions across the agency's infectious disease national centers. She is a graduate of the American University of Beirut, Lebanon, where she obtained both her bachelor's degree in science and her medical doctorate degree. She trained in internal medicine and completed a fellowship in infectious diseases at the University of Maryland, Baltimore. She joined CDC in 1980 as an Epidemic Intelligence Service officer, working in the Hospital Infections Program. During her CDC career, she has made major contributions to advance infectious disease prevention, including leadership in defining the epidemiology of non-HIV retroviruses (HTLV-I and II) in the United States and developing guidance for counseling HTLV-infected persons, establishing national surveillance for hantavirus pulmonary syndrome following the 1993 U.S. outbreak, and developing CDC's blood safety and food safety programs

related to viral diseases. She has also played key roles in CDC's responses to outbreaks of new and/or reemerging viral infections, including Nipah, Ebola, West Nile, severe acute respiratory syndrome, and monkey pox, as well as the 2001 anthrax attacks. She is a fellow of the Infectious Diseases Society of America (IDSA) and member of the American Epidemiologic Society, the American Society for Microbiology, the Council of State and Territorial Epidemiologists, and the American Society for Tropical Medicine and Hygiene. She served on IDSA's Annual Meeting Scientific Program Committee and currently serves on the society's Public Health Committee. In addition to her CDC position, she serves as adjunct professor of medicine (infectious diseases) at Emory University. She is a graduate of the National Preparedness Leadership Initiative at Harvard University and of the Public Health Leadership Institute at the University of North Carolina.

Lonnie King, D.V.M., M.S., M.P.A., is the professor and dean emeritus of the College of Veterinary Medicine at The Ohio State University (OSU). In addition to leading this college, Dr. King is also a professor of preventive medicine and holds the Ruth Stanton Endowed Chair in Veterinary Medicine. He also serves as the executive dean for the seven health science colleges at OSU. Before becoming dean at OSU, he was the director of the new National Center for Zoonotic, Vector-Borne, and Enteric Diseases (NCZVED) at the U.S. Centers for Disease Control and Prevention (CDC). In this new position, Dr. King leads the center's activities for surveillance, diagnostics, disease investigations, epidemiology, research, public education, policy development, and disease prevention and control programs. NCZVED also focuses on waterborne, foodborne, vector-borne, and zoonotic diseases of public health concern, which include most of the CDC's select and bioterrorism agents, neglected tropical diseases, and emerging zoonoses. Before serving as director, he was the first chief of the agency's Office of Strategy and Innovation. Dr. King was in private veterinary practice for 7 years in Dayton, Ohio, and Atlanta, Georgia. As a native of Wooster, Ohio, Dr. King received his bachelor of science and doctor of veterinary medicine degrees from OSU in 1966 and 1970, respectively. He earned his master of science degree in epidemiology from the University of Minnesota and received his master of public administration degree from American University in Washington, DC, in 1991. Dr. King is a board-certified member of the American College of Veterinary Preventive Medicine and has completed the senior executive fellowship program at Harvard University. He served as president of the Association of American Veterinary Medical Colleges from 1999 to 2000 and was the vice chair for the National Commission on Veterinary Economic Issues from 2000 to 2004.

Darrell G. Kirch, M.D., is the president and chief executive officer of the Association of American Medical Colleges (AAMC), which represents the nation's medical schools, teaching hospitals, and academic medical societies. A distinguished physician, educator, and medical scientist, Dr. Kirch speaks and publishes widely on the need for transformation in the nation's health care system and how academic medicine can lead change across medical education, biomedical research, and patient care. Prior to becoming AAMC president in 2006, Dr. Kirch served as the dean and academic health system leader of two institutions, the Medical College of Georgia and the Penn State Milton S. Hershey Medical Center. He has co-chaired the Liaison Committee on Medical Education, the accrediting body for U.S. medical schools, and chaired the Washington Higher Education Secretariat. Dr. Kirch also is a member of the National Academy of Medicine. A psychiatrist and clinical neuroscientist by training, Dr. Kirch began his career at the National Institute of Mental Health, becoming the acting scientific director in 1993, and receiving the Outstanding Service Medal of the U.S. Public Health Service. A native of Denver, he earned his B.A. and M.D. degrees from the University of Colorado.

Keith Klugman, Ph.D., leads the Bill & Melinda Gates Foundation's work to improve the development and delivery of pneumonia vaccines and expand the use of antibiotic treatments and diagnostic tools. Dr. Klugman is a leading expert on antibiotic resistance in pneumonia pathogens and helped develop the pneumococcal vaccine that is part of the immunization regimen for children born in the United States, which is also being rolled out globally. Dr. Klugman previously served as a professor of global health and professor of epidemiology in the Rollins School of Public Health at Emory University and professor of medicine in the Division of Infectious Diseases at the Emory School of Medicine. He serves as an honorary professor in the Respiratory and Meningeal Pathogens Research Unit at the University of the Witwatersrand in South Africa and is a member of the National Academy of Medicine.

Jeffrey A. Linder, M.D., M.P.H., FACP, is a general internist and primary care clinician-investigator. Dr. Linder is the chief of the Division of General Internal Medicine and Geriatrics and the Michael A. Gertz Professor of Medicine at the Northwestern University Feinberg School of Medicine. His research focuses on the care of ambulatory patients with acute respiratory infections—the number one symptomatic reason for seeking medical care in the United States—and the appropriate use of antibiotics in ambulatory care. Dr. Linder has expertise in electronic health records and clinical decision support, as well as using behavioral science and social psychology

to understand and change behavior. Dr. Linder serves on the Outpatient Antibiotic Use Target-Setting Workgroup, which was convened by the U.S. Centers for Disease Control and Prevention and The Pew Charitable Trusts; the Antibiotic Stewardship Research Workshop Planning Committee of the Society for Healthcare Epidemiology of America; and is a standing member of the Agency for Healthcare Research and Quality's Healthcare Safety and Quality Improvement Study Section. Dr. Linder received his medical degree from Northwestern University Feinberg School of Medicine and a Master of Public Health degree from the Harvard T.H. Chan School of Public Health.

Andrew T. Maccabe, D.V.M., M.P.H., J.D., is the chief executive officer of the Association of American Veterinary Medical Colleges (AAVMC). He received his bachelor of science and doctor of veterinary medicine degrees from The Ohio State University in 1981 and 1985, respectively and began his professional career in a mixed animal practice with primary emphasis on dairy herd health. In 1988, he was commissioned as a public health officer in the U.S. Air Force where he managed the preventive medicine activities of several Air Force installations and directed programs in occupational health, communicable disease control, and health promotion. Dr. Maccabe completed his master of public health degree at Harvard University in 1995. That same year he became chief of the Health Risk Assessment Branch of the U.S. Air Force where he directed the health risk assessment program for environmental restoration activities throughout the Air Force. Dr. Maccabe completed his juris doctor degree, magna cum laude, at the University of Arizona in 2002 and subsequently became the associate executive director at the Association of American Veterinary Medical Colleges where he led programs to advance veterinary medical education. In 2007, he was appointed as U.S. Centers for Disease Control and Prevention's Liaison to the Food and Drug Administration, where he coordinated policies and programs between the two agencies before returning to AAVMC in 2012 as the chief executive officer.

Patrick McDermott, Ph.D., is the director of the National Antimicrobial Resistance Monitoring System (NARMS) at the U.S. Food and Drug Administration (FDA). NARMS was established in 1996 and is a One Health interagency effort among FDA, the U.S. Department of Agriculture (USDA), and the U.S. Centers for Disease Control and Prevention (CDC) that tracks antibiotic resistance in food-borne bacteria. He is past director of the Division of Animal and Food Microbiology and past deputy director of the Office of Research in the Office of Research at FDA's Center for Veterinary Medicine. Dr. McDermott is a founding member of the World Health Organization (WHO) Advisory Group on Integrated Surveillance of Antimicrobial Resistance and serves on the steering Committee of the

WHO Global Foodborne Infections Network. He represents FDA on the Transatlantic Task Force on Antimicrobial Resistance and the National Science and Technology Subcommittee on Food and Agriculture, devising a pathway for sustainable agriculture in the United States. Dr. McDermott is the 2016 recipient of the Francis Kelsey Award for Excellence and Courage in Protecting the Public Health. He is a microbiologist by training who has studied antimicrobial resistance for 25 years.

L. Clifford McDonald, M.D., is an internationally recognized expert on the epidemiology and prevention of health care–associated infections and antibiotic resistance, with particular expertise in the epidemiology, diagnosis, and prevention of *Clostridium difficile* infections. He is the author or co-author of more than 150 peer-reviewed publications and book chapters on these subjects. Dr. McDonald is currently the associate director for science in the Division of Healthcare Quality Promotion at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Dr. McDonald graduated from the Northwestern University Medical School, completed his internal medicine residency at Michigan State University, and an infectious diseases fellowship at the University of South Alabama, following which he completed a fellowship in medical microbiology at Duke University. Past positions have included associate investigator at the National Health Research Institutes in Taiwan, where he assisted in the development of an island-wide antibiotic resistance monitoring program, and assistant professor in the Division of Infectious Diseases at the University of Louisville, where he served as health care epidemiologist. Dr. McDonald is a former officer in CDC's Epidemic Intelligence Service and former chief of the Prevention and Response Branch, as well as former senior advisor for science and integrity in the Division of Healthcare Quality Promotion at CDC.

Suerie Moon, Ph.D., M.P.A., is the director of research at the Global Health Centre, Graduate Institute of International and Development Studies, Geneva, Switzerland, and adjunct lecturer on global health at the Harvard T.H. Chan School of Public Health. She has served on a number of advisory bodies, including most recently the World Health Organization Fair Pricing Forum Advisory Group, Expert Advisory Group to the United Nations Secretary-General's High-Level Panel on Access to Medicines, and Proposal Review Committee of UNITAID. Prior to joining the Graduate Institute, she was study director of the Harvard-London School of Hygiene & Tropical Medicine Independent Panel on the Global Response to Ebola, and co-founded and led the Forum on Global Governance for Health, a focal point at Harvard University for research, debate, and strategic convening on issues at the intersection of global governance and health. Her research and teaching focus on global governance, the political economy of global

health (focusing on innovation and access to medicines; outbreak preparedness and response; trade, investment, and intellectual property rules; and development assistance for health), the evolution of international regimes, and innovative policies for addressing global problems. She received a B.A. from Yale, an M.P.A. from Princeton, and a Ph.D. from the Harvard Kennedy School of Government.

Robert D. Newman, M.D., M.P.H., is the global head of TB Programs within the Global Public Health group at Johnson & Johnson, where he leads a team focused on accelerating the company's ongoing efforts toward ending tuberculosis (TB). From 2015 to 2017, Dr. Newman was the Cambodia country director for the U.S. Centers for Disease Control and Prevention (CDC), overseeing activities related to HIV/AIDS, TB, malaria, health security, outbreak response, health systems strengthening, and capacity building. From 2014 to 2015, Dr. Newman served as managing director for Policy and Performance at Gavi, the Vaccine Alliance, in Geneva, Switzerland. In that role, he oversaw organizational strategy setting, performance metrics, market shaping, policy development, business planning, monitoring and evaluation, and risk management. From 2009 to 2014, he was the director of the Global Malaria Program at the World Health Organization in Geneva. From 2000 to 2009, Dr. Newman served in the U.S. Public Health Service, and was assigned to the Malaria Branch at CDC, where he led the CDC team for the U.S. President's Malaria Initiative from 2006 to 2009. He has also spent time in the field in South America and Africa, first studying *Cryptosporidium* in a favela in Brazil in the early 1990s, and then as country coordinator of Health Alliance International in Mozambique in the late 1990s supporting the government in its efforts to improve maternal and child health. He received his B.A. in English literature from Williams College, his M.D. from Johns Hopkins University, and his M.P.H. from the University of Washington. Dr. Newman is a board-certified pediatrician; he completed his residency in pediatrics at the University of Washington's Seattle Children's Hospital in 1996, and stayed on to complete a National Research Service Award fellowship in general pediatrics in 1998. He has published more than 65 peer-reviewed articles on infectious diseases.

Lance Price, Ph.D., is a professor at The George Washington University's Milken Institute School of Public Health in Washington, DC. He is also the founding director of the Antibiotic Resistance Action Center. Dr. Price works at the interface between science and policy to address the growing crisis of antibiotic resistance. In the laboratory, Dr. Price uses cutting-edge molecular approaches to trace the origins of antibiotic-resistant bacteria and develop strategies to block their transmission. In the policy arena,

Dr. Price works with nongovernmental organizations and policy makers to develop science-based policies to curb antibiotic abuse in food-animal production. Dr. Price's works have been covered in media outlets around the world. Dr. Price has a bachelor's and master's degree from the Department of Biology at Northern Arizona University and a Ph.D. from the Johns Hopkins Bloomberg School of Public Health.

David A. Relman, M.D., is the Thomas C. and Joan M. Merigan Professor in the Departments of Medicine and of Microbiology and Immunology at Stanford University, and chief of infectious diseases at the Veterans Affairs Palo Alto Health Care System in Palo Alto, California. He is also co-director of the Center for International Security and Cooperation and senior fellow at the Freeman Spogli Institute for International Studies at Stanford University. Dr. Relman was an early pioneer in the application of molecular methods for studying the human indigenous microbiota. Most recently, his work has focused on human microbial community assembly, and community stability and resilience in the face of disturbance. Previous work included the development of molecular methods for identifying novel microbial pathogens and the subsequent identification of several historically important microbial disease agents, as well as molecular mechanisms of bacterial pathogenesis. One of his papers was selected as "1 of the 50 most important publications of the past century" by the American Society for Microbiology. Dr. Relman received an S.B. (biology) from the Massachusetts Institute of Technology, an M.D. from Harvard Medical School, and joined the faculty at Stanford in 1994. He is currently a member of the Board of Scientific Counselors for the National Center for Biotechnology Information at the National Institutes of Health (NIH). Besides serving on the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats, he is a member of the Committee on Science, Technology and Law, and a member of the Intelligence Community Studies Board, both at the National Academies, and advises several U.S. government agencies on current and future microbial threats. He previously served as vice chair of the National Academies committee that reviewed the science performed as part of the Federal Bureau of Investigation's inquiry of the 2001 anthrax letters, as a member of the National Science Advisory Board on Biosecurity (2005 to 2014), and as president of the Infectious Diseases Society of America (2012 to 2013). He received an NIH Pioneer Award in 2006, an NIH Transformative Research Award in 2011, and was elected a member of the National Academy of Medicine in 2011.

John H. Rex, M.D., is a physician and drug developer with 30 years of development and policy experience focused on antimicrobial agents. His experience includes moving compounds from early preclinical development

through all development phases in the context of academic positions, vice president-level roles at AstraZeneca, board-level roles in biotech companies, and operating partner role with a venture capital group. He also is currently a voting member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

Peter A. Sands, M.P.A., is a senior fellow at the Mossavar-Rahmani Center for Business and Government at Harvard Kennedy School, where he is working on a range of research projects in financial markets and regulation, financial technology, and global health. He is chair of the International Working Group on Financing Preparedness and Response Commission, which is supported by the World Bank and the Wellcome Foundation, and he also chaired the International Commission on a Global Health Risk Framework for the Future under the auspices of the National Academy of Medicine. Mr. Sands has published several papers on global health issues in journals such as the *New England Journal of Medicine* and *The Lancet*. He is also the lead nonexecutive director of the Department of Health in the United Kingdom. Mr. Sands is a board member or advisor to several startups in the financial technology and medical technology arenas, such as Noble Markets (United States) and Cera (United Kingdom). Mr. Sands was group chief executive of Standard Chartered PLC from November 2006 to June 2015. He joined the board of Standard Chartered PLC as group finance director in May 2002, responsible for Finance, Strategy, Risk, and Technology and Operations. Prior to this, he was director and senior partner at worldwide consultants McKinsey & Co. Before joining McKinsey, Mr. Sands worked for the UK Foreign and Commonwealth Office. He has served on various boards and commissions, including as a director of the World Economic Forum and co-chairman of Davos; governor of the UK National Institute for Economic and Social Research; member of the International Advisory Board of the Monetary Authority of Singapore; member of the Browne Commission on Higher Education Funding in the United Kingdom; member of the China People's Association for Friendship with Foreign People's Global CEO Council, co-chair of the UK-India CEO Forum; board director of the Institute of International Finance; chairman of the International Monetary Conference; member of the International Advisory Board of Lingnan University, China; and trustee of the Camden Roundhouse, London. Mr. Sands graduated from Brasenose College, Oxford University, with a First Class degree in Politics, Philosophy, and Economics. He also received a Master in Public Administration from Harvard University, where he was a Harkness Fellow.

H. Morgan Scott, D.V.M., Ph.D., is a graduate veterinarian holding a Ph.D. in epidemiology and postdoctoral training in public health. In addition to

private veterinary practice, he has worked in both government (food safety surveillance) and academic settings. He is currently professor of epidemiology in the Department of Veterinary Pathobiology at Texas A&M University. He was recruited there in 2014 as part of the Texas A&M University System Chancellor's Research Initiative and the University President's Initiative on One Health and Infectious Diseases. He relocated from Kansas State University, where he previously held the E.J. Frick Professorship in veterinary medicine. Much of his research emphasis has been on studying factors affecting antimicrobial resistance among commensal and pathogenic enteric bacteria in food animal production systems, with a program spanning the realm from the molecular to the sociological. In particular, he is interested in applying both epidemiological and ecological approaches to quantify the emergence, propagation, dissemination, and persistence of resistant enteric bacterial strains in integrated populations of animals, their food products, and humans. Using this knowledge, he hopes to identify opportunities to prevent and intervene against resistance among enteric pathogens in animal agriculture, preferably by developing readily adoptable and cost-effective management practices suited to modern animal and food production systems.

Angela Siemens, Ph.D., is the vice president of food safety, quality, and regulatory for Cargill in Wichita, Kansas. She is responsible for food safety issues and quality management systems and processes in approximately 40 beef, turkey, egg, case-ready, and processing facilities in North America. She also oversees the food safety issues of meat co-packers and meat and ingredient suppliers. Dr. Siemens served as Beef Industry Food Safety Council chairman in 2014 to 2015. Prior to her tenure at Cargill, she worked as vice president of food safety and technical services for Smithfield Packing Company in Smithfield, Virginia. She also worked at the Oscar Mayer Foods Division of Kraft Foods in Madison, Wisconsin, and Beatrice Cheese. She served 1 year as a Congressional Science Fellow to the U.S. House of Representatives Committee on Agriculture in Washington, DC. The *National Provisioner* named her as 1 of "25 Future Icons." Dr. Siemens received a Ph.D. in meat science and an M.S. in animal science from the University of Missouri, Columbia, and a B.S. in animal science from Purdue University, West Lafayette, Indiana. She received the 2010 Purdue University College of Agriculture Distinguished Alumni award.

Jeffrey Silverstein, Ph.D., is the deputy administrator for animal production and protection with the Office of National Programs at the U.S. Department of Agriculture's Agricultural Research Service (USDA-ARS). He started in this position in October 2016. In his 20-year career with ARS, Dr. Silverstein has held a variety of positions, as research geneticist and

administrator including both National Program and Area Office capacities. He earned a B.A. in biology and East Asian studies from Colgate University and after a stint working on an oyster farm, he began graduate studies in aquaculture at the University of Washington. He received his Ph.D. in fisheries genetics in 1993. He completed a postdoctoral fellowship at the Japanese National Research Institute for Aquaculture (Mie, Japan) and returned to the United States as a research faculty at University of Washington in the fish physiology program. He joined USDA-ARS in 1997 as a research geneticist, and his research focused on physiology and selective breeding of finfish, particularly for improved growth, feed efficiency, use of alternative feeds, and disease resistance. In 2011, he worked with the U.S. Agency for International Development on research aspects of the Feed the Future Initiative with the Bureau for Food Security and the Science and Technology group in the Policy, Planning, and Learning Division. In 2013, he served as the acting director for the Office of the Chief Scientist for USDA. He is the author and co-author of more than 85 scientific and technical research publications and has delivered more than 50 invited lectures on animal genetics and genomics in the United States and internationally.

Randall Singer, D.V.M., M.P.V.M., Ph.D., is a professor of epidemiology at the University of Minnesota. He has a dual appointment in the Department of Veterinary and Biomedical Sciences, College of Veterinary Medicine, and the Division of Epidemiology, School of Public Health. Prior to joining the faculty at Minnesota, he was an assistant professor of epidemiology at the University of Illinois at Urbana-Champaign. He received his D.V.M. and M.P.V.M. in 1995 and his Ph.D. in Epidemiology in 1999, all from the University of California, Davis. Dr. Singer has developed an internationally recognized research and educational program focused on predicting the emergence, spread, and persistence of infectious diseases. In 2000, he was awarded the Presidential Early Career Award for Scientists and Engineers by President Clinton for his work on antibiotic resistance. Since that time, he has devoted most of his research program to understand the emergence, spread, and persistence of antimicrobial resistance. In 2005, he was selected as a McKnight Land-Grant Professor at the University of Minnesota, a distinguished group of junior faculty within the university, for his work on this topic. Between 2006 and 2010 he served on the U.S. Delegation to the CODEX Task Force on Antimicrobial Resistance. He has spoken twice to the U.S. House of Representatives on this topic and currently serves as a voting member of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria.

David Sjeklocha, D.V.M., is a 1994 graduate of the Kansas State University College of Veterinary Medicine. His entire career has been focused on

helping to produce ethically raised, safe, wholesome beef. Dr. Sjeklocha spent 10 years in mixed animal practice in Kansas and Nebraska. As his practice evolved, he eventually specialized in cattle feed yard veterinary consultation, with a focus on animal welfare and managing cattle health to reduce antimicrobial use. In 2011, he joined Cattle Empire, LLC, a large, family-owned cattle feeding company in southwest Kansas as Operations Manager of Animal Health and Welfare. In this position, he has been able to oversee the development and implementation of cutting-edge efforts to improve animal welfare and animal health management. He firmly beliefs that "use of an antimicrobial is an indication that there has been a breakdown in management."

Bruce Stewart-Brown, D.V.M., is the senior vice president of live production, food safety, and quality for Perdue Farms, based at the company's corporate office in Salisbury, Maryland. He is responsible for the food safety and quality programs in all the fresh and cook plants. Mr. Stewart-Brown is also responsible for the company's chicken live operations, which include parent breeding operations, hatcheries, feed mills, and grow-out management.

Kathy Talkington, M.P.Aff., directs The Pew Charitable Trusts' work on antibiotics, which seeks to address the growing threat of antibiotic resistance by spurring the innovation of new antibiotics and ensuring the appropriate use of antibiotics in both human health care settings and in food animals. Before joining Pew, Ms. Talkington managed the immunization and infectious disease programs at the Association of State and Territorial Health Offices, where she developed policies on hospital-acquired infections, antimicrobial resistance, and issues related to immunization. Previously, she led strategic initiatives and programs on a wide range of health care issues for numerous nonprofit advocacy organizations and also state and federal policy makers. Ms. Talkington has a bachelor's degree from the University of Virginia and a master's degree in public affairs from The University of Texas at Austin.

James M. Tiedje, Ph.D., is a university distinguished professor of microbiology and molecular genetics and of plant, soil, and microbial sciences, and is director of the Center for Microbial Ecology at Michigan State University. His research focuses on microbial ecology, physiology, and diversity, especially regarding the nitrogen cycle, biodegradation of environmental pollutants, and more recently on the use of genomics and metagenomics to understand speciation, community structure, and functions, including antibiotic resistances. He has served as editor-in-chief of *Applied and Environmental Microbiology* and editor of *Microbial and Molecular Biology Reviews*. He has more than 500 referenced publications. He served on the

National Academies of Sciences, Engineering, and Medicine's Board on Life Sciences; the U.S. Environmental Protection Agency's Science Advisory Panel; and the U.S. Department of Energy's Biological and Environmental Research Advisory Committee. He was president of the American Society for Microbiology and the International Society of Microbial Ecology. He shared the 1992 Finley Prize from the United Nations Educational, Scientific and Cultural Organization for research contributions in microbiology of international significance and was awarded an Einstein Professorship in 2010 by the Chinese Academy of Sciences. He is a fellow of the American Association for the Advancement of Science, the American Academy of Microbiology, the Soil Science Society of America, the Ecological Society of America, and a member of the U.S. National Academy of Sciences.

Ed Topp, Ph.D., is a native of Montreal and received his Ph.D. from the Department of Microbiology at the University of Minnesota in 1988. Since then, he has toiled as a research scientist with Agriculture and Agri-Food Canada (AAFC) and has adjunct appointments in the Department of Biology at the University of Western Ontario in London, and the Department of Soil and Water Science at the University of Florida. Dr. Topp's research concerns the interface between agriculture and human and environmental health and has generated more than 250 co-authored publications. In the past decade he has notably led several national studies concerning the fate and management in agro-ecosystems of pathogenic and antibiotic-resistant bacteria carried in animal and human (biosolids) waste. He recently received the AAFC Gold Harvest Award for career achievement and the Canadian Public Service Award for Excellence for research contributions. Dr. Topp is past president (2011) of the Canadian Society of Microbiologists, and over the past several years he has organized a number of international workshops and conference sessions concerning antibiotic resistance, agriculture, and the environment.

Evelyn Wesangula, M.Sc., B.Pharm., is a pharmacist with postgraduate training in tropical and infectious diseases. She currently heads the Antimicrobial Resistance (AMR) Program at the Ministry of Health of the Government of Kenya. Dr. Wesangula has been the coordinator for the Global Antibiotic Resistance Partnership-Kenya (GARP-Kenya) working group for the past 4 years. Through the coordination of GARP, she initiated a platform for information sharing on antimicrobial resistance within the Ministry of Health through the National Infection Prevention and Control Committee, while coordinating the Global AMR week in 2013 and 2014, and advocated for the establishment of the National AMR program and the appointment of the multisectoral members of the National Antimicrobial Stewardship Advisory Committee. Over the past 10 years, Dr. Wesangula

has worked within the public sector and gained an in-depth knowledge on the working of pharmaceutical systems in relation to public health. She has gained competencies in developing and implementing training curricula for different target groups for diseases of public health priority. She has also gained skills in editing scientific papers and report writing and in conducting operational research. As the focal person for AMR, Dr. Wesangula coordinated the establishment of the AMR program at the Ministry of Health in collaboration with the Ministry of Agriculture Livestock and Fisheries and recently led the process of implementation of the Global Action Plan on Antimicrobial Resistance in Kenya resulting in the development of a National Policy and Action Plan for AMR.

Mary E. Wilson, M.D., is an adjunct professor of global health and population at the Harvard T.H. Chan School of Public Health and clinical professor of epidemiology and biostatistics in the School of Medicine at the University of California, San Francisco. Her academic interests include the ecology of infections and emergence of microbial threats, travel medicine, tuberculosis, and vaccines. She received her M.D. from the University of Wisconsin and completed an internal medicine residency and infectious disease fellowship at the Beth Israel Hospital in Boston. She was chief of infectious diseases at Mount Auburn Hospital, a Harvard-affiliated community teaching hospital in Cambridge, Massachusetts, for more than 20 years. She is a fellow in the Infectious Diseases Society of America, the American College of Physicians, and the American Society of Tropical Medicine and Hygiene. She has served on the Advisory Committee on Immunization Practices of the U.S. Centers for Disease Control and Prevention, the Academic Advisory Committee for the National Institute of Public Health in Mexico, and on five committees for the National Academies of Sciences, Engineering, and Medicine. She has worked in Haiti at the Albert Schweitzer Hospital and led the Harvard-Brazil Collaborative Course on Infectious Diseases, taught in Brazil. In 1996 she was a resident scholar at the Bellagio Study Center, Italy, and in 2002 she was a fellow at the Center for Advanced Study in the Behavioral Sciences in Stanford, California. She was a member of the Pew National Commission on Industrial Farm Animal Production, whose report, *Putting Meat on the Table: Industrial Farm Animal Production in America*, was released in the spring of 2008. She serves as a special advisor to the GeoSentinel Surveillance Network, a global network. She serves on several editorial boards and is an associate editor for *NEJM Journal Watch Infectious Diseases*. She is the author of *A World Guide to Infections: Diseases, Distribution, Diagnosis* (Oxford University Press, New York, 1991); senior editor, with Richard Levins and Andrew Spielman, of *Disease in Evolution: Global Changes and Emergence of Infectious Diseases* (New York Academy of Sciences, 1994); and editor

of the volume *New and Emerging Infectious Diseases* (Medical Clinics of North America) published in 2008. She served on the Board of Trustees for icddr,b (International Centre for Diarrheal Disease Research, Bangladesh) from 2009 through 2015 and is a member of the FXB-USA Board and the Alliance for the Prudent Use of Antibiotics Board of Directors.