


# Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine (2021)

## DETAILS

380 pages | 6 x 9 | PAPERBACK
ISBN 978-0-309-26945-2 | DOI 10.17226/26350

## CONTRIBUTORS

Gillian J. Buckley and Guy H. Palmer, Editors; Committee on the Long-Term Health and Economic Effects of Antimicrobial Resistance in the United States; Board on Population Health and Public Health Practice; Health and Medicine Division; National Academies of Sciences, Engineering, and Medicine

## SUGGESTED CITATION

National Academies of Sciences, Engineering, and Medicine 2021. *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26350.

# COMBATING ANTIMICROBIAL RESISTANCE AND PROTECTING THE MIRACLE OF MODERN MEDICINE

Gillian J. Buckley and Guy H. Palmer, *Editors*

Committee on the Long-Term Health and Economic Effects of Antimicrobial Resistance in the United States

Board on Population Health and Public Health Practice

Health and Medicine Division

A Consensus Study Report of
*The National Academies of*
SCIENCES • ENGINEERING • MEDICINE

THE NATIONAL ACADEMIES PRESS
*Washington, DC*
**www.nap.edu**

***PREPUBLICATION COPY: UNCORRECTED PROOFS***

**THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001**

This project has been funded in whole or in part with federal funds from the Applicable Institute/Center, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN263201800029I. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-XXXXX-X
International Standard Book Number-10: 0-309-XXXXX-X
Digital Object Identifier: https://doi.org/10.17226/26350
Library of Congress Catalog Number: XXXXXXXXXX

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.



Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. 2021. *Combating antimicrobial resistance and protecting the miracle of modern medicine*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26350.

***PREPUBLICATION COPY: UNCORRECTED PROOFS***

*The National Academies of*
SCIENCES • ENGINEERING • MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the National Academies of Sciences, Engineering, and Medicine at **www.nationalacademies.org**.

***PREPUBLICATION COPY: UNCORRECTED PROOFS***

*The National Academies of*
SCIENCES • ENGINEERING • MEDICINE

**Consensus Study Reports** published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process, and it represents the position of the National Academies on the statement of task.

**Proceedings** published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

***PREPUBLICATION COPY: UNCORRECTED PROOFS***

## COMMITTEE ON THE LONG-TERM HEALTH AND ECONOMIC EFFECTS OF ANTIMICROBIAL RESISTANCE IN THE UNITED STATES[1]

**GUY H. PALMER** (*Chair*), Regents Professor of Pathology and Infectious Diseases, The Jan and Jack Creighton Endowed Chair, Paul G. Allen School for Global Health, Washington State University; Senior Director of Global Health, Washington State University System
**MICHAEL BAYM,** Assistant Professor, Biomedical Informatics, Harvard University
**CÉSAR DE LA FUENTE,** Presidential Assistant Professor, Perelman School of Medicine, School of Engineering and Applied Science, University of Pennsylvania
**JENNIFER DIEN BARD,** Director, Clinical Microbiology and Virology Laboratory, Associate Professor of Pathology (Clinical Scholar), Keck School of Medicine, University of Southern California
**MARTA GOMEZ-CHIARRI,** Professor, Department of Fisheries, Animal, and Veterinary Sciences, College of the Environment and Life Sciences, The University of Rhode Island
**GUILLAUME LHERMIE,** Associate Professor, Animal Health Economics and Veterinary Public Health, College of Veterinary Medicine; Director, Simpson Centre for Agricultural and Food Innovation and Education, The School of Public Policy, University of Calgary, Canada
**PREETI MALANI,** Chief Health Officer, University of Michigan, Professor of Medicine, Division of Infectious Diseases, University of Michigan School of Medicine
**ELEFTHERIOS MYLONAKIS,** Charles C.J. Carpenter, MD, Professor of Infectious Diseases, Professor of Medicine, Assistant Dean of Medicine, Professor of Molecular Microbiology and Immunology, Warren Alpert Medical School of Brown University; Director, Rhode Island Hospital and The Miriam Hospital
**IRUKA N. OKEKE,** Professor, Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan
**EMMANUEL OKELLO,** Assistant Specialist in Cooperative Extension, Population Health, and Reproduction, School of Veterinary Medicine, University of California, Davis
**AYLIN SERTKAYA,** Vice President and Senior Economist, Eastern Research Group
**MICHELLE SOUPIR,** Associate Chair for Research and Extension, Equity Advisor, College of Engineering; Professor, Department of Agriculture and Biosystems Engineering, Iowa State University
**ANDY STERGACHIS,** Professor of Pharmacy and Global Health, Adjunct Professor of Health Metrics Sciences, Epidemiology, and Health Systems and Population Health; Associate Dean of Pharmacy; Director, Global Medicines Program & Biomedical Regulatory Affairs Program, University of Washington Schools of Pharmacy and Public Health
**MARY E. WILSON,** Clinical Professor of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco; Adjunct Professor, Global Health and Population, Harvard T.H. Chan School of Public Health
**QIJING ZHANG,** Clarence Hartley Covault Distinguished Professor, Associate Dean for Research and Graduate Studies, Veterinary Microbiology and Preventive Medicine, College of Veterinary Medicine, Iowa State University

*Study Staff*

[1] See Appendix B, Disclosure of Unavoidable Conflict of Interest.

**GILLIAN J. BUCKLEY,** Study Director
**KARA LANEY,** Senior Program Officer
**ROBERTA WEDGE**, Senior Program Officer (*from May 2021*)
**AASHAKA SHINDE,** Research Associate (*from October 2020*)
**LEILA MEYMAND,** Senior Program Assistant (*from October 2020*)
**MISRAK DABI,** Finance Business Partner
**ROSE MARIE MARTINEZ,** Senior Director, Board on Population Health and Public Health Practice
**JULIE PAVLIN,** Senior Director, Board on Global Health
**ROBIN SCHOEN,** Director, Board on Agriculture and Natural Resources

# Reviewers

This Consensus Study Report was reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the National Academies of Sciences, Engineering, and Medicine in making each published report as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

We thank the following individuals for their review of this report:

**RITU BANERJEE**, Vanderbilt University Medical College
**MARLENE BELFORT**, University at Albany, State University of New York
**KAREN C. CARROLL**, Johns Hopkins University School of Medicine
**REBECCA GARABED**, The Ohio State University
**YRJÖ GRÖHN**, Cornell University
**KENT KESTER**, Sanofi
**MARK L. LAWRENCE**, Mississippi State University
**MAUREEN LICHTVELD**, University of Pittsburgh
**MARK G. PAPICH**, North Carolina State University
**TIMOTHY M. PERSONS**, United States Government Accountability Office
**AMY PRUDEN**, Virginia Polytechnic Institute and State University
**TARA VIJAYAN**, University of California, Los Angeles

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations of this report nor did they see the final draft before its release. The review of this report was overseen by **JIM E. RIVIERE**, North Carolina State University, and **ELLEN WRIGHT CLAYTON**, Vanderbilt University. They were responsible for making certain that an independent examination of this report was carried out in accordance with the standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the authoring committee and the National Academies.

# Acknowledgments

This report is a product of the cooperation and contributions of many people. The committee and staff are grateful for the support of the National Academies of Sciences, Engineering, and Medicine's Health and Medicine Division (HMD) staff who contributed to producing this report. The committee and staff thank Tina Seliber, Lauren Shern, Leslie Sim, and Taryn Young in the HMD Executive Office; Anne Marie Houppert, Christopher Lao-Scott, Rebecca Morgan, in the National Academies Research Center; Sadaf Faraz, Devona Overton, Esther Pak, and Marguerite Romatelli in the Office of the Chief Communications Officer; Stephanie Miceli in the Office of News and Public Information; Julie Eubank in the Office of Congressional and Government Affairs; and Mandy Enriquez, Dempsey Price, Alejandro Velazquez, and in the Office of Conference Management. We extend particular thanks to Roberta Wedge for joining the project and providing invaluable analysis and Rebekah Hutton for her work on the cover design.

The committee's work was enhanced by the systematic analysis of Kristine Moore and Anje Mehr whose commissioned paper informed this report. We also thank Yunxin Joy Jiao for graciously sharing her graphic designs for reprint in Chapter 1.

The committee thanks all the speakers and moderators who participated in committee meetings, as well as others who provided information, input, and assistance. They include the following: Frank Møller Aarestrup, Mark Albrecht, Neena Anadaraman, Anand Balachandran, Manica Balasegaram, Helen Boucher, Susan Bright, Felipe C. Cabello, Angela Caliendo, Amanda Cash, Clare Chandler, Ryan Cirz, Michael Craig, Chris Crnich, Peter Panduro Damborg, Gautam Dantas, Mary Denigan-Macauley, Lynn Filpi, William Flynn, Heather Fowler, Jay Garland, Cyril Gay, Claire Gordon, Luca Guardabassi, Tim Jinks, Bill Keleher, Wes Kim, Jane Knisely, Kevin Krause, Ramanan Laxminarayan, Brian Lubbers, John Lynch, Marc Mendelson, Mark Miller, Chris Murray, Kevin Outterson, Mark Papich, Timothy Persons, Carmem L. Pessoa-Silva, Jessica Petrillo, Tom Pilcher, John Rex, Jennifer Schneider, Anand Shah, Gunnar Skov Simonsen, Brad Spellberg, Padmini Srikantiah, Bruce Stewart-Brown, Fred C. Tenover, Paige Waterman, Craig Wilson, Barbara Zimmer. To Dr. Christopher Murray, Institute for Health Metrics and Evaluation, University of Washington, and the Global Research

on Antimicrobial Resistance team, we extend particular thanks for sharing key findings from their *Lancet* paper in review.

Finally, we have special thanks to the National Institute of Allergy and Infectious Diseases of the National Institutes of Health for generously funding this project.

# Preface

I was in the lobby of the Fred Hutchinson Cancer Research Center in Seattle, waiting to meet with a colleague, when a wall display of the timeline of successful hematopoietic bone marrow transplants caught my attention. The timeline, in the form of a spiral, starts slowly in the 1970s—successes were few and failures many as scientists strove to understand the basic immunology underlying transplantation and clinicians to establish the optimal procedures and patient care. The successes slowly and then suddenly accelerate, providing life-saving transplants where previously no hope existed. Today, bone marrow transplants are performed in hospitals worldwide. Indeed, it is paradoxical that one of the highest accolades for the incredible achievements in modern medicine over recent decades is that we can take them for granted. The same is true for numerous medical procedures: organ transplants, joint replacements, improved cancer treatment, even safe childbirth. All of us know someone whose lives have been touched by these advances. Underlying this remarkable progress is the reliance on effective antibiotics to prevent and treat infections in patients at their most vulnerable moments. Addressing the challenges of the emergence and spread of resistant microbes; improving laboratory diagnostics and surveillance; and catalyzing the development of new classes of medicines is highly complex, cutting across scientific disciplines, medical specialties, institutions, and agencies. However, the goal is clear: preserve the medical advances of the past and allow continued progress, all afforded by and dependent on the availability of effective antibiotics.

Given the complexity of antibiotic resistance and the inherent multidisciplinary and interdisciplinary approaches required to address resistance, and to ensure a robust pipeline of effective medicines, the committee brought together expertise from across human, animal, and environmental health sectors. The committee has endeavored to examine the full range of initiatives and programs incorporated into the National Strategy and Action Plan for Combating

Antibiotic-Resistant Bacteria and the progress in meeting the goals of the plan. The responsiveness of the multiple U.S. government agencies engaged in carrying out the plan was deeply appreciated as was the evaluation conducted by the Center for Infectious Disease Research and Policy at the University of Minnesota. Equally, given the need for global solutions to a challenge that knows no borders, the committee benefited from the multiple international organizations engaged in preserving antibiotic effectiveness and appreciates their willingness to share their expertise and perspectives. The committee was respectful of prior reports on antibiotic resistance and endeavored to assess their recommendations in the context of the committee's statement of task. On behalf of the committee, I want to express my appreciation for the openness of these organizations and agencies and their efforts in working to ensure access to effective antibiotics.

A study of this magnitude requires a tremendous commitment from the committee members. All have sacrificed evenings, weekends, and holidays—without financial compensation—in this commitment and in their desire to bring the best possible science to bear on a challenging issue. Their commitment was all the more impressive as the study took place during the COVID-19 pandemic. Several of our committee members had front-line clinical care responsibilities, others increased commitments in laboratory testing, surveillance, and modeling—all were impacted by the pandemic by increased responsibilities at work and at home. Despite these increased responsibilities and the ability to only meet and work together virtually, the committee, individually and collectively, brought their expertise, experience, and knowledge to the task. I cannot thank them enough.

On behalf of the committee, I would like to express our thanks and appreciation to the National Academies leadership and staff: Rose Marie Martinez, Senior Director of the Board on Population Health and Public Health Practice; Kara Laney, Senior Program Officer; Roberta Wedge, Senior Program Officer; Aashaka Shinde, Research Associate; and Leila Meymand, Senior Program Assistant. A special thank you and deep appreciation to the Study Director, Gillian Buckley, who provided exceptional leadership throughout the study. Without her leadership and the work of the staff in planning, organization, and editing, this report would not have been possible.

The evolutionary basis of antimicrobial resistance dictates that there will be no magic bullets or simple solutions. Ensuring that modern medicine can continue to rely on effective antibiotics will require continual innovation and process improvement. Minimizing the need for antibiotics through preventive health care and improved sanitation, housing, and access to clean water is achievable as is ensuring that the right antibiotic is available and given at the appropriate dose for the appropriate duration. Achieving those goals is fundamental to meeting the National Academy of Medicine's vision of "a healthier future for everyone."

Guy H. Palmer, *Chair*
Committee on the Long-Term Health and Economic Effects
of Antimicrobial Resistance in the United States

# Contents

# Acronyms and Abbreviations

| | |
|---|---|
| 3GC | third-generation cephalosporin |
| AACTING | Network on quantification of veterinary Antimicrobial usage at herd level and Analysis Communication and benchmarking to improve responsible usage |
| ABSSSI | acute bacterial skin and skin structure infections |
| ACTIV | Accelerating COVID-19 Therapeutic Interventions and Vaccines |
| AIDS | acquired immunodeficiency syndrome |
| AMR | antimicrobial resistance |
| AMU | antimicrobial use |
| AR | antibiotic resistance |
| ARG | Argentina |
| ARLG | Antibacterial Resistance Leadership Group |
| ARLN | Antibiotic Resistance Laboratory Network |
| ASPR | HHS Office of the Assistant Secretary for Preparedness and Response |
| AUS | Australia |
| AUT | Austria |
| AVMA | American Veterinary Medical Association |
| AWaRe | WHO's Access, Watch, Reserve classification of antibiotics |
| BARDA | Biomedical Advanced Research and Development Authority |
| BGR | Republic of Bulgaria |
| BL | beta-lactam |
| BLI | beta-lactamase inhibitor |
| BSI | bloodstream infection |
| *C. auris* | *Candida auris* |
| *C. difficile* | *Clostridioides difficile* |
| CABP | community-acquired bacterial pneumonia |
| CARB | National Action Plan for Combating Antibiotic-Resistant Bacteria |
| CARB-X | Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator |
| CDC | Centers for Disease Control and Prevention |
| CDI | *Clostridioides difficile* infection |
| CHE | Switzerland |
| CHL | Chile |
| CI | confidence interval |
| cIAI | complicated intra-abdominal infection |
| CLIA | Clinical Laboratory Improvement Amendments of 1988 |
| CLSI | Clinical and Laboratory Standards Institute |

| | |
|---|---|
| CLSI-VAST | veterinary antimicrobial susceptibility testing |
| CMS | Centers for Medicare & Medicaid Services |
| CO-ADD | Community for Open Antimicrobial Drug Discovery |
| COVID-19 | coronavirus disease, 2019 |
| CR | carbapenem-resistant |
| CRAB | carbapenem-resistant *Acinetobacter baumannii* |
| CRE | carbapenem-resistant *Enterobacterales* |
| cUTI | complicated urinary tract infection |
| CYP | Cyprus |
| CZE | Czech Republic |
| DALY | disability-adjusted life year |
| DARPA | Defense Advanced Research Projects Agency |
| DFUI | diabetic foot ulcer infections |
| DISARM Act | Developing an Innovative Strategy for Antimicrobial-Resistant Microorganisms Act |
| DNA | deoxyribonucleic acid |
| DNDi | Drugs for Neglected Diseases Initiative |
| ECU | Ecuador |
| EMA | European Medicine Agency |
| EPA | U.S. Environmental Protection Agency |
| EQS | Environmental Quality Standard |
| ESBL | extended-spectrum beta-lactamase |
| ESP | Spain |
| EST | Estonia |
| EUCAST | European Committee on Antimicrobial Susceptibility Testing |
| FAO | Food and Agriculture Organization of the United Nations |
| FDA | U.S. Food and Drug Administration |
| GAIN Act | Generating Antibiotic Incentives Now Act |
| GARDP | Global Antibiotic Research and Development Partnership |
| GBR | United Kingdom |
| GCI | gonococcal infection |
| GCOA | Global Coalition on Aging |
| GDP | gross domestic product |
| GHA | Ghana |
| GLASS | Global Antimicrobial Resistance and Use Surveillance System |
| GLASS-EAR | Emerging Antimicrobial Resistance Reporting |
| GN | gram-negative |
| GRC | Greece |
| HABP/VABP | Hospital-associated bacterial pneumonia/ventilator-associated bacterial pneumonia |
| HHS | U.S. Department of Health and Human Services |

| | |
|---|---|
| Hib | *Haemophilus influenzae* type b |
| HIC | high-income country |
| HIV | human immunodeficiency virus |
| HRV | Croatia |
| HUN | Hungary |
| hVISA | heterogeneous vancomycin-intermediate *Staphylococcus aureus* |
| ICU | intensive care unit |
| IDSA | Infectious Diseases Society of America |
| IHME | Institute for Health Metrics and Evaluation |
| IMF | International Monetary Fund |
| IMI | imipenem-hydrolyzing β-lactamases |
| IMP | imipenemase metallo-β-lactamase |
| IND | India |
| IPPS | inpatient prospective payment system |
| ISL | Iceland |
| ITA | Italy |
| KPC | *Klebsiella pneumoniae* carbapenemases |
| LIMS | Laboratory Information Management System |
| LMIC | low- and middle-income country |
| LTU | Lithuania |
| LUX | Luxembourg |
| LVA | Latvia |
| MDR | multidrug-resistant |
| MDR G- | multidrug-resistant Gram negative bacteria |
| MIC | minimal inhibitory concentration |
| MKD | Republic of North Macedonia |
| MLST | multilocus sequence |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| NAHMS | National Animal Health Monitoring System |
| NARMS | National Antimicrobial Resistance Monitoring System |
| NCATS | National Center for Advancing Translational Sciences |
| NCBI | National Center for Biotechnology Information |
| NDARO | National Database of Antibiotic Resistant Organisms |
| NDM | New Delhi metallo-β-lactamase |
| NGO | nongovernmental organization |
| NIAID | National Institute of Allergy and Infectious Diseases |
| NIDDK | National Institute of Diabetes and Digestive and Kidney Diseases |
| NIH | National Institutes of Health |
| NITAG | National Immunization Technical Advisory Group |
| NLM | National Library of Medicine |
| NOR | Norway |

| | |
|---|---|
| NZL | New Zealand |
| OECD | Organisation for Economic Co-operation and Development |
| OIE | World Organisation for Animal Health (formerly Office International des Epizooties) |
| OXA-48 | Oxacillinase-48 |
| PACCARB | Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria |
| PCAST | President's Council of Advisors on Science and Technology |
| PCORI | Patient-Centered Outcomes Research Institute |
| PCR | polymerase chain reaction |
| PCV | pneumococcal conjugate vaccine |
| PEPFAR | U.S. President's Emergency Plan for AIDS Relief |
| POCIS | polar organic chemical integrative sampler |
| POL | Poland |
| PPE | personal protective equipment |
| QIDP | qualified infectious disease product |
| qPCR | quantitative polymerase chain reaction |
| R&D | research and development |
| rCDI | recurrent *Clostridioides difficile* infection |
| REVAMP Act | Re-Valuing Anti-Microbial Products Act |
| RNA | ribonucleic acid |
| ROM | Romania |
| rUTI | recurrent urinary tract infection |
| *S. pneumonia* | *Streptococcus pneumonia* |
| SAB | *Staphylococcus aureus* bacteremia |
| SfAM | Society for Applied Microbiology |
| SRB | Serbia |
| SVK | Slovakia |
| SVN | Slovenia |
| SWE | Sweden |
| TCV | typhoid conjugate vaccine |
| THA | Thailand |
| TUR | Turkey |
| UN | United Nations |
| U.S. | United States |
| USAID | U.S. Agency for International Development |
| USD | United States dollars |
| USDA | U.S. Department of Agriculture |
| UTI | urinary tract infection |
| UW | University of Washington |

| | |
|---|---|
| UW tele-ASP | University of Washington Tele-Antimicrobial Stewardship Program |
| VA | Department of Veterans Affairs |
| VEN | Venezuela |
| VetCAST | EUCAST subcommittee for Veterinary Antimicrobial Susceptibility Testing |
| VIM | Verona integron-encoded metallo-β-lactamases |
| VNM | Vietnam |
| VRE | vancomycin-resistant *Enterococci* |
| WASH | water, sanitation, and hygiene |
| WFD | Water Framework Directive |
| WHO | World Health Organization |
| WWTP | wastewater treatment plant |
| ZAF | South Africa |

# Summary[1]

The COVID-19 pandemic has forced society to confront human vulnerability to microbial pathogens (including viruses, bacteria, parasites, and fungi) in a way that has not been necessary in much of the world for a century. Before the mass production of penicillin in the 1940s, deaths from bacterial infections were common, elevating the risk not only of common illnesses such as pneumonia, but also that associated with surgery and other lifesaving procedures and even life events such as childbirth. The extent to which antimicrobial medicines changed these risks, though hard to overstate, is easily taken for granted. As these medicines have been used, sometimes overused, microbes' resistance to them has grown, threatening to undermine almost a century of health gains.

Microbes are constantly responding to selective pressures, including the pressures from antimicrobial medicines. One response is a classic, Darwinian evolution wherein beneficial traits are passed from one generation to another. Microbes can also pass genes to unrelated organisms through proximity or by way of mobile genetic elements. Such horizontal gene transfer allows traits to pass quickly within microbial communities.

The genetic adaptability of microbes contributes to the emergence of resistance, compelling careful attention to human actions that aggravate the problem. Efforts to mitigate the emergence and spread of resistant pathogens are complicated by the fact that antimicrobial resistance is notoriously difficult to measure. Although most obvious in human health, resistance emerges in animal health and in the environment. Marshalling response to such a problem requires cooperation at many levels. In the United States, the 2014 *National Strategy for Combating Antibiotic-Resistant Bacteria* (hereafter, the national strategy) sets out a plan for government work to mitigate the emergence and spread of antimicrobial resistance. Direction on the implementation of this strategy is provided in 5-year national action plans, the first for the period from 2015 to 2020, the second covering 2020 to 2025.

In 2019, Congress directed the National Institute of Allergy and Infectious Diseases (NIAID) to support a consensus committee study under the auspices of the National Academies of Sciences, Engineering, and Medicine to examine progress against the national strategy. NIAID staff, in collaboration with their counterparts at other government agencies implementing the national action plans, developed a charge for this committee. This charge includes questions on managing effective surveillance for infections related to antimicrobial resistance, measuring the health and economic consequences of antimicrobial resistance, interventions in animal health, and the incentives for developing new medical products to prevent and treat resistant infections.

[1] References are not included in the Summary. For the full list of the works cited view the body of the report.

## THE SCOPE OF THE PROBLEM

Use of antimicrobial medicines in both human and animal health drives antimicrobial resistance. Clinicians may prescribe antimicrobial medicines empirically, based on their best judgement of a patient's presentation, but without precise diagnostic information on the organism causing the infection. Empiric treatment often involves broad-spectrum drugs active against a range of pathogens. Such drug use creates selective pressure that encourages resistance and leaves patients vulnerable to other illnesses.

Antimicrobial treatment in both humans and animals ideally uses the most narrow, focused agent for the shortest effective duration. Narrowing antimicrobial treatment can be challenging in animal agriculture, where the distinction between prophylactic and therapeutic treatment is not always clear. Infections can spread quickly through a flock or herd, so when one animal is diagnosed with an infection, prophylactic treatment of others in the group may control spread. Mass medication of mostly healthy animals accounts for 90 percent of veterinary antimicrobial use in some places.

Adequate biosecurity measures, good husbandry, and other practices used in modern animal production systems can greatly reduce—sometimes eliminate—the need for antimicrobials in animal agriculture. Vaccines and other preventive tools are important alternatives to antimicrobials, but there is a shortage of efficacious and affordable vaccines for animals.

Antimicrobial resistance is a global health problem, or, more accurately, a web of related problems. The relationships between different nodes on this web are always changing making it difficult to predict how actions in one setting will affect outcomes in others, a feature of the problem sometimes described as the adaptive challenge. Adaptive challenge makes it difficult to predict where and in what pathogen–drug combinations resistance will emerge.

The mutual dependence of human and animal health and the health of the environment is central to the One Health approach. A One Health analysis is well suited to the problem of antimicrobial resistance as it requires an interdisciplinary, multisectoral collaboration. It includes attention to the often-neglected environmental dimension of resistance, especially important in light of climate change, which will almost certainly aggravate the problem

## THE HEALTH AND ECONOMIC BURDEN OF RESISTANCE

In response to the charge to examine the long-term health and economic effects of antimicrobial resistance, the committee reviewed a cross-section of recent literature. First was the Centers for Disease Control and Prevention's (CDC's) *Antibiotic Resistant Threats in the United States 2019*, which drew on population surveillance and research from electronic medical records to estimate that every year 2.8 million resistant infections in the United States cause 35,900 deaths, with *Clostridioides difficile* infection killing another 12,800 people. The CDC report also attempted to put some economic parameters on the problem, estimating the direct costs of treating six, common, multidrug-resistant pathogens at $4.6 billion a year, with *C. difficile* adding another $1 billion and drug-resistant gonorrhea adding another $133.4 million.

The Organisation for Economic Co-operation and Development (OECD) Health Committee, in collaboration with the European Centre for Disease Prevention and Control, has also given considerable attention to estimating the future health and economic burden of antimicrobial-resistant infections. Their reports estimate that the United States and Europe

together account for about 60,000 deaths a year from resistant infections, with 1.75 million years of healthy life lost every year across 33 of the OECD countries. The same infections could cost the health systems of these countries about $3.5 billion a year.

There are challenges in measuring morbidity and mortality associated with resistant infections. Most outcomes research is limited to readily observable, short-term clinical outcomes (e.g., deaths, number of days hospitalized). The downstream consequences of resistant pathogens are harder to predict. Without effective alternatives and enhanced infection control, removal of antimicrobials from animal agriculture could increase animal disease burden and mortality, leading to compromised animal welfare and productivity losses, with potential downstream effects on food security and livelihoods.

Better estimates of the burden of antimicrobial resistance in humans and animals depend on better microbiological data and more clarity on the appropriate design of epidemiological research. There are also challenges related to the complex adaptive nature of the problem. The same resistant infection can have drastically different consequences in humans and animals, depending on whether it is acquired in hospital or outside of it, in a high-income country or a low-income one.

## STRENGTHENING SURVEILLANCE

Surveillance systems are critically important for understanding the burden of antimicrobial resistance, detecting the emergence and spread of resistant pathogens, targeting interventions, and measuring their effectiveness.

In an effort to improve global surveillance for antimicrobial resistance, the World Health Organization developed the Global Antimicrobial Resistance and Use Surveillance System (GLASS), which provides information technology, standards, and tools for the surveillance of priority bacterial infections in humans. Private industry, academic researchers, and various disease-specific programs also collect information about resistance and are useful sources of complementary data to inform estimates of the burden of the antimicrobial resistance.

One commonly used tool to monitor resistance patterns is the antibiogram, a profile of phenotypic susceptibility test results drawn from aggregate data. Antibiograms are useful for monitoring trends in resistance to different drugs and are invaluable in both clinical medicine and surveillance. At the same time, since antibiograms do not give information into the mechanisms of resistance, they cannot be used to predict resistance patterns.

The National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) at the National Institutes of Health (NIH), has made public considerable information about resistance genes, genome sequences, antimicrobial susceptibility data, and bacterial genomes. The committee commends NCBI for this work. At the same time, valuable information about phenotypic antimicrobial susceptibility is generated in clinical laboratories all over the world. Collected and aggregated, this data could give valuable insight into trends in antimicrobial resistance.

**Recommendation 4-1: The National Library of Medicine (NLM) should establish an open-source, unified antimicrobial resistance database that integrates raw phenotypic data from national and international efforts. This database should support automatic importation from hospitals, laboratories,**

**and surveillance networks and linking to genotypic data when available. NLM should engage the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, and other relevant stakeholders to determine the necessary data elements and confidentiality procedures.**

An automated data ingestion pipeline could take disparate formats of collected antimicrobial resistance data and, either by a simple set of translation rules or potentially using more advanced machine learning techniques, automatically format and deposit the data in a consistent fashion. Once an initial pipeline from the laboratory information system is established, data deposition from these devices could be almost fully automated. A standard data deposition form could also help new laboratories or regional laboratories that currently do not generate their own standardized antibiograms by providing a default template, contributing to standardized reporting across the United States and internationally.

Increasing the environmental isolates collected by surveillance networks and stored in the proposed NLM database would contribute to a more holistic understanding of antimicrobial resistance. However, environmental monitoring of resistance is still limited. The challenge for environmental monitoring is to determine what factors amplify resistance genes in the environment and what factors encourage their transmission, possibly threatening public health.

Some insight into the source of the resistance genes, resistant pathogens, or antimicrobial residues in the environment could come from analyzing the places contaminants enter water. Wastewater treatment plants are one such place, equipped to contain and remove water contaminants but not to eliminate resistance traits or drug residues. Treatment plants typically discharge directly to aquatic environments, making them an important bridge between human-made contamination and the natural environment.

**Recommendation 4-2: The Environmental Protection Agency should provide guidance and funding to states for testing point source discharge at wastewater treatment plants for antimicrobial resistance traits and integrating these data with other surveillance networks.**

## STEWARDSHIP AND INFECTION PREVENTION

Efforts to improve antimicrobial stewardship in human medicine often turn first to hospitals, as infections can spread quickly in hospitals and pose a serious threat to patients. Almost 90 percent of hospitals in the United States have programs that incorporate all seven of the CDC's core elements of antimicrobial stewardship, up from only about 40 percent in 2014. Such rapid progress is heartening, but there are still many practice settings where the need for antimicrobial stewardship is pronounced. Nursing homes, dialysis centers, and long-term acute care hospitals all see considerable misuse and overuse of antimicrobials among patients who are, by definition, immunocompromised or infirm.

**Recommendation 5-1: The Centers for Medicare & Medicaid Services should require nursing homes, long-term acute care hospitals, and dialysis centers to have antimicrobial stewardship programs and include that information on**

**the Care Compare website. These programs should, at a minimum, designate key staff, a system for preauthorization of restricted antimicrobials, and a process for regular review of all antimicrobial prescriptions.**

Tailored antimicrobial stewardship programs may need to make use of telemedicine when infectious disease consultations are needed. Some modernization of record keeping may also be helpful in settings that do not routinely use electronic medical records, which could be used for preauthorization for restricted antimicrobials and to discourage treatment of asymptomatic infections. Including antimicrobial stewardship in the quality measures on the Care Compare website, a public clearinghouse for quality indicators, could help raise its prominence with facility administrators as well as with consumers and their families.

Many of the basic principles of antimicrobial stewardship are the same in human and animal medicine, but the practice differs considerably. Veterinarians often work in relatively small practices; they also dispense medicines directly from their clinics, making the roles of both administrators and pharmacists, crucial in human stewardship programs, far less relevant. Partly for these reasons there is a greater emphasis on veterinarians' individual responsibility to serve as stewards of antimicrobial medicines.

The ability to track antimicrobial use is a key part of any stewardship program, but the United States does not have a strong system to track antimicrobial use in animals. The Food and Drug Administration (FDA) could promote better antimicrobial stewardship by investing in strategies to advance the use of electronic prescriptions and to encourage the sharing of prescription information currently held in proprietary hands.

**Recommendation 5-2: The Food and Drug Administration's Center for Veterinary Medicine should establish a process and clear metrics to facilitate better tracking of antimicrobial consumption in animals. This information would support the design and implementation of stewardship programs.**

Challenges in using diagnostic tests can stand in the way of good stewardship. There are logistical barriers to testing animals, especially large animals, and a testing expense that the animal owner usually pays out of pocket. A lack of susceptibility test breakpoints specific to the species tested is another barrier.

The ability to develop new susceptibility test breakpoints depends on collecting and creating pharmacokinetic and pharmacodynamic data for different drugs in different species and on convening experts to review and interpret these data. Despite agreement that more animal-specific breakpoints are needed, the time and expense of building the evidence needed to inform breakpoint analysis stand in the way. Therefore, development of needed breakpoints has not kept pace with the demand for them, especially in light of increasing emphasis on antimicrobial stewardship in veterinary medicine.

**Recommendation 5-3: The Food and Drug Administration's Center for Veterinary Medicine should convene an advisory committee to coordinate development of antimicrobial susceptibility test breakpoints in animals and identify priority animal, drug, and pathogen combinations. When necessary,**

**the Center for Veterinary Medicine would fund the research needed to develop the priority breakpoints.**

Choosing priorities for breakpoint development from among the many combinations of pathogen, drug, and animal species of interest should be done in a more deliberate way, with more open communication among clinicians, diagnostics laboratories, standards organizations, and academic researchers. Attention from the FDA could help make veterinary susceptibility testing less ad hoc, but after setting out the priority bug, drug, and species combinations there will still be a need for pharmacokinetic and pharmacodynamic data to establish the needed breakpoints. By designating funding for this research, the agency could remove another major barrier to better antimicrobial stewardship in animals.

Appropriate diagnostic testing could reduce inappropriate antimicrobial use in human medicine as well. But the value of diagnostics, especially in terms of changes in patient outcomes such as morbidity and length of hospital stay, or financial outcomes such as cost of treatment or repeated office visits, are not usually readily apparent. Evidence of this value could inform clinical guidelines that emphasize diagnostic testing and are a step toward reimbursing the full value of the tests.

**Recommendation 5-4: The Department of Health and Human Services agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Centers for Medicare & Medicaid Services, and the Patient-Centered Outcomes Research Institute should support outcomes research in diagnostic testing to drive an iterative process of guidelines development and to influence reimbursement for diagnostic testing.**

Evidence establishing the value of diagnostics will be challenging to generate. It will depend on enrollment of patients at multiple clinical sites, as the inferences made from aggregate, multisite data are more generalizable and better able to detect small but meaningful differences.

Vaccines have the potential to reduce the need for antimicrobials and control the spread of antimicrobial resistance. Despite a plausible reason to suspect that vaccination could reduce antimicrobial use and control the emergence and spread of resistant bacteria, the relationship is not well studied. Incorporating questions about antimicrobial use or resistance into ongoing vaccine trials could yield valuable information on this question with relatively little additional effort or expense.

**Recommendation 5-5: The National Institutes of Health and the Centers for Disease Control and Prevention should provide supplemental research funding to track antimicrobial use and antimicrobial resistance in immunization trials and large cohort studies to measure the indirect benefits vaccines provide and to provide evidence to enhance vaccine deployment as a tool to mitigate antimicrobial resistance.**

Better quality evidence, ideally from randomized, controlled trials could clarify the relationship between vaccine use, antimicrobial consumption, and the emergence of resistance and the multiple, often complex relationships among them. Better clarity on the full public health value of immunization could help inform wider vaccine uptake, especially in low- and middle-income countries.

## BRINGING NEW PRODUCTS TO MARKET AND ENSURING THEIR REACH

Treating resistant infections depends on new antimicrobials, and the challenges of bringing these drugs to market is at the center of much public discourse. At the same time, new antimicrobials are not the only innovative products needed. Society would benefit from an integrated investment across different product types, some preventive and some therapeutic, for human and animal medicine.

The medicines needed to treat resistant infections are complicated to develop and have a relatively small market both in terms of duration of use, usually only a few days, and need. Although there are over 2.8 million resistant infections every year in the United States, infections with any one resistant pathogen are relatively rare. When new antimicrobials are brought to market, good stewardship requires that older drugs be used first, even if there were no difference in price. There is, therefore, a mismatch in society's need for new antimicrobials and industry's willingness to invest in them. The government invests in drug development to help fill this gap, offering different programs working at different places on the development pipeline.

Push incentives work early in this pipeline, aiming to reduce the cost of research and development by spreading those costs among many interested parties. Early grant funding is a push incentive as are various government programs that make information about resistant organisms more available to researchers. Other push incentives fund preclinical and early clinical trials. The NIH and the Biomedical Advanced Research and Development Authority (BARDA) provide considerable support for preclinical and clinical trials, both directly and through the public–private partnership Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). In general, these and other push incentives have direct benefits to the drug developers and broad, indirect benefits to society. Preclinical and early clinical research is also the riskiest stage of drug development and may therefore be the most appropriate place for public spending.

Pull incentives, on the other hand, reward successful drug development. The 2012 Generating Antibiotic Incentives Now (GAIN) Act, for example, provides additional years of market exclusivity to new drugs designated as "qualified infectious disease products" and revisions to the amount CMS will reimburse hospitals for new antimicrobials.

On the whole, the package of push and pull incentives in place appears to have improved the number of products in the antimicrobial drug pipeline by about 10 percent between 2014 and 2019. Over this time, the FDA approved 20 new antimicrobial drugs, 12 of them under priority regulatory review afforded as qualified infectious disease products. While this is a promising development, most of these products and the others in the pipeline do not appear to be meaningfully different from existing medicines. Only 6 of the 50 antibacterials currently in the pipeline meet even one criteria for being innovative. Most of the antimicrobials approved recently offer little to no added clinical value over existing treatments.

Market entry rewards between $500 million and $2 billion are often suggested as an incentive to develop an innovative antimicrobial that, for logistical and public health reasons,

will not likely sell well. These estimates appear to be based on the assumption that large pharmaceutical companies will not enter the market for profitability below $50 to $500 million, expectations based on blockbuster drug sales. But average peak-year drug sales have decreased by 50 percent since 2010. Given such trends, it may be more prudent to benchmark reward payments to market averages, thereby reducing the likelihood of over incentivizing and inciting rent seeking.

Market entry rewards require significant investment of taxpayer dollars. Before funding any market entry reward, the government needs to be clear that it is rewarding a truly novel and useful antimicrobial.

**Recommendation: 6-1: A Department of Health and Human Services (HHS) interagency committee should establish well-targeted, objective criteria to identify novel antimicrobials with high potential for filling a critical, unmet need. HHS should then support trials to establish the additional clinical benefit and optimal use of these drugs.**

The proposed committee would serve as an arbiter on what constitutes an unmet need. This strategy would also provide public funding for the trials that establish clinical value, a major incentive for drug developers as such trials are costly to run.

### Challenges Related to Diagnostic Testing

When clinical microbiology laboratories cannot test the susceptibility of a pathogen to a new antimicrobial, clinicians may not feel comfortable prescribing it, seriously limiting the use of the new medicine. There are multiple barriers to susceptibility testing for new antimicrobials. Integrating a new antimicrobial on automated testing systems is one of these barriers, as most hospitals in the United States use only automated methods for susceptibility testing.

Adding a new antimicrobial to an automated susceptibility test plate means removing another drug and forfeiting the associated diagnostic information. Balancing the need for a new test that will be used infrequently against older ones that may be used more is a difficult question for the device companies. The companies must also regularly re-evaluate the time needed to bring a new test through regulatory review against obligations to support changes for drugs already in wide use.

As antimicrobial resistance continues to emerge, breakpoint changes will only be needed more frequently. Every investment in keeping automated testing devices up to date is an investment in keeping clinical practice more responsive to antimicrobial resistance and protecting public health.

**Recommendation 6-2: To reduce regulatory hurdles in bringing automated susceptibility tests to market, the Food and Drug Administration should coordinate the review of new antimicrobials with the review of their automated susceptibility tests and work with the Clinical Laboratories Standards Institute to issue and update breakpoints for microbe–drug combinations.**

Ideally, automated susceptibility testing devices would include new antimicrobials upon market entry and revised breakpoints for older drugs as they are approved. For logistical reasons the processes work sequentially, with the device application beginning after the new drug approval. Through cooperative work, the FDA and the manufacturers could likely find less restrictive, faster methods for validation studies. Congress could also defray the expense of bringing new automated tests to market with tax credits against clinical trial expenses.

**Recommendation 6-3: Congress should make automated susceptibility test manufacturers eligible for tax incentives to bring new automated susceptibility tests to market.**

There are also some antimicrobials that simply will not be suitable candidates for inclusion on automated test devices. For such drugs, manual testing will be necessary, and such testing is difficult for many laboratories. The CDC Antibiotic Resistance Laboratory Network (ARLN) can bridge this gap by providing testing through public health laboratories. There is room to improve on this valuable service by expanding the network's capacity.

**Recommendation 6-4: The Centers for Disease Control and Prevention (CDC) should expand the capacity of the Antibiotic Resistance Laboratory Network by offering expedited, expanded susceptibility testing of all broad-spectrum antibiotics via certain CLIA–certified laboratories.[2] The CDC should also promote this service to clinical laboratories.**

A One Health approach to product development takes a broad view of the need for new therapeutic and preventative products. Such a model is helpful in guiding countries' support for products intended for animal agriculture, aquaculture, and the environment. The international product development partnerships put in place for COVID-19 have transferrable elements especially relevant to product development for other infectious threats. This is the ideal framework upon which to build a coordinated product development partnership for antimicrobial resistance, with coordinated action on the human, animal, and environmental fronts.

**Recommendation 6-5: The Department of Health and Human Services should establish a public–private partnership similar to ACTIV for antimicrobial resistance, bringing together the Biomedical Advanced Research and Development Authority, the National Institutes of Health, the U.S. Department of Agriculture, the Environmental Protection Agency, and the Department of Defense and interested academic, industry, and nonprofit organizations. The partnership would have working groups on diagnostics, alternatives to antibiotics, and prevention, with a goal of supporting a diversified and balanced portfolio of tools to reduce antimicrobial resistance using a One Health approach.**

[2] The Clinical Laboratory Improvement Amendments (CLIA) regulate testing and are required for laboratories handling human samples.

The program envisioned would streamline the U.S. government's national investment on antimicrobial resistance. This model can help avoid duplication of effort both within the United States and internationally.

There is also a need to balance investments in antimicrobial resistance across new medicines, diagnostics, and preventive products. Some products have considerable market potential that the private sector will recognize; not all product development needs the same level of government investment. Determining the right balance of investments across product types is challenging and would benefit from explicit public discussion of the sort a prominent public–private partnership could engender.

## THE NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Action against antimicrobial resistance requires coordinated efforts across many branches of government. This collaboration is emphasized in the *National Action Plan for Combating Antibiotic-Resistant Bacteria 2015–2020* (hereafter, the 2015 action plan) which provided agencies with a road map to meet the goals set out in the national strategy.

In an effort to understand agencies progress against the goals, the committee commissioned an analysis from the Center for Infectious Disease Research and Policy (CIDRAP). This analysis, which relied on review of published progress reports and agency self-reports, found that 93 percent of the 230 assigned milestones were completed, the vast majority on time, and without serious duplication of effort. This is not entirely consistent with a 2019 evaluation from the Government Accountability Office (GAO) that indicated agencies faced understandable difficulties with overlapping responsibilities, and technical challenges in implementing the action plan.

A reliance on process outcomes makes it easier to claim successes, but such process milestones will not necessarily translate into meaningful improvements in antimicrobial use or the spread of resistant pathogens. Both the 2015 national action plan and its more recent iteration for 2020 to 2025 have open-ended targets for which the responsible agency is not always clear. It is difficult to establish accountability in such cases.

The committee supports the systematic tracking of activities and outcomes related to the milestones and goals presented in the 2020 action plan. Independent assessment of these goals and reporting of their related expenditures would facilitate a process of adaptive management and course correction when necessary. It would also help experts in the United States and abroad understand the best and most effective strategies to combat antimicrobial resistance.

**Recommendation 7-1: Congress should direct the Government Accountability Office (GAO) to conduct biennial evaluations of federal agencies' progress toward meeting the goals of the 2020–2025 *National Action Plan for Combating Antibiotic-Resistant Bacteria* to ensure objective assessment of agencies' activities. Congress and the GAO should consider ways to use their evaluations to direct course corrections when necessary.**

Congress can facilitate course corrections on complex government programs by designating the program as high risk. Adding federal action against antimicrobial resistance to the GAO High Risk List might bring welcome attention to the topic, especially in the face of uncertainty regarding how the COVID-19 pandemic will influence antimicrobial resistance.

## A ROLE FOR THE UNITED STATES IN COORDINATED GLOBAL ACTION

The effectiveness of a national strategy to combat antimicrobial resistance will depend on global investment and sustained international engagement integrated across human, animal, and environmental health. Part of the challenge of responding to antimicrobial resistance is that, while the U.S. strategy and action plan, like most countries' strategies and action plans, evoke a One Health grounding, putting it into practice is difficult. Ultimately, every implementing agency involved in the response to antimicrobial resistance has its own mandate and mission, and none of these is explicitly a One Health mission.

The integration of surveillance data from human, animal, and environmental sources will be a critical component of a global strategy against antimicrobial resistance. The largest increases in antibiotic consumption over the past 2 decades, for both humans and livestock, have occurred in low- and middle-income countries. These countries also have a high burden of infectious disease and a growing demand for animal-source foods that could contribute to increased antimicrobial use.

Serious international investment in combating antimicrobial resistance is both morally compelling and in the best interest of the United States. A national response proportionate to the size and scope of the threat would work across government agencies and in collaborative bilateral and multilateral relationships internationally. A program modelled on the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) may be best suited to this problem.

**Recommendation 8-1: Congress should expand the United States global engagement on antimicrobial resistance by (1) strengthening surveillance of resistant pathogens both by supporting existing, multilateral surveillance systems and by expanding U.S. agencies' international surveillance programs; (2) reducing need for antimicrobials by broadening agencies' work on infection prevention and antimicrobial stewardship in humans and animals; and (3) ensuring sustained leadership and critical evaluation by creating a Global Coordinator for Antimicrobial Resistance similar to the Global AIDS Coordinator.**

Any program or policy intended to combat antimicrobial resistance depends on a foundation of reliable information that surveillance networks supply, yet recent analysis has found surveillance and One Health integration to be common weak spots in countries' antimicrobial resistance action plans. The United States could help build on the GLASS framework to give more attention to animal and environmental health surveillance.

Good surveillance can, in turn, inform effective stewardship programs especially in resistance hotspots. By attacking root problems, such as crowding, contaminated water and food, lack of sanitation, and infection prevention, the U.S. government could do much to prevent the development of antimicrobial resistance abroad.

The ambitious global program envisioned in this recommendation will require coordination with an increasingly large group of stakeholders both in the United States and abroad. A designated national leader modelled on the Global AIDS Coordinator would be crucial to managing this coordination and efficient response. By supporting a truly systemic, One Health response, the recommended program may be able to drive progress on a range of health indicators, including, but not limited to, the burden of resistant infections.

# 1

# Introduction

Since the mass production of penicillin began in the 1940s, antimicrobials have drastically improved human health, preventing death from bacterial infection and lowering the risk associated with surgery and other lifesaving medical procedures (Ventola, 2015). These medicines are often credited with driving a sharp rise in life expectancy in the latter half of twentieth century (Hutchings et al., 2019; Sullivan, 2018). But almost as quickly as the first family of antibacterials was introduced, its usefulness declined. Within 6 years of the introduction of penicillin, roughly a quarter of staphylococcal infections in hospitals (where the drug was often used) were no longer susceptible to it (Chambers, 2001). Penicillin resistance continued to spread, by the 1970s being as common in community-acquired infections as in hospitals (Chambers, 2001).

The genes that cause microbes (bacteria, viruses, fungi, and parasites) to survive against the organisms that try to kill them or stop their growth (antimicrobials) are not new. Genomic analysis of permafrost soil samples has found resistance to most antimicrobials in use today existed 30,000 years ago (D'Costa et al., 2011; Perry et al., 2016). While selective pressure from modern antimicrobial medicines has undoubtedly encouraged the survival of resistant organisms (simplified in Figure 1-1), they are an ancient and persistent part of the ecosystem. As Gerry Wright, director of McMaster University Institute for Infectious Disease Research, explained, "[antimicrobials] are part of our natural world and therefore we need to be incredibly careful in how we use them. Microorganisms have figured out a way of how to get around them well before we even figured out how to use them" (McMaster University, 2011).

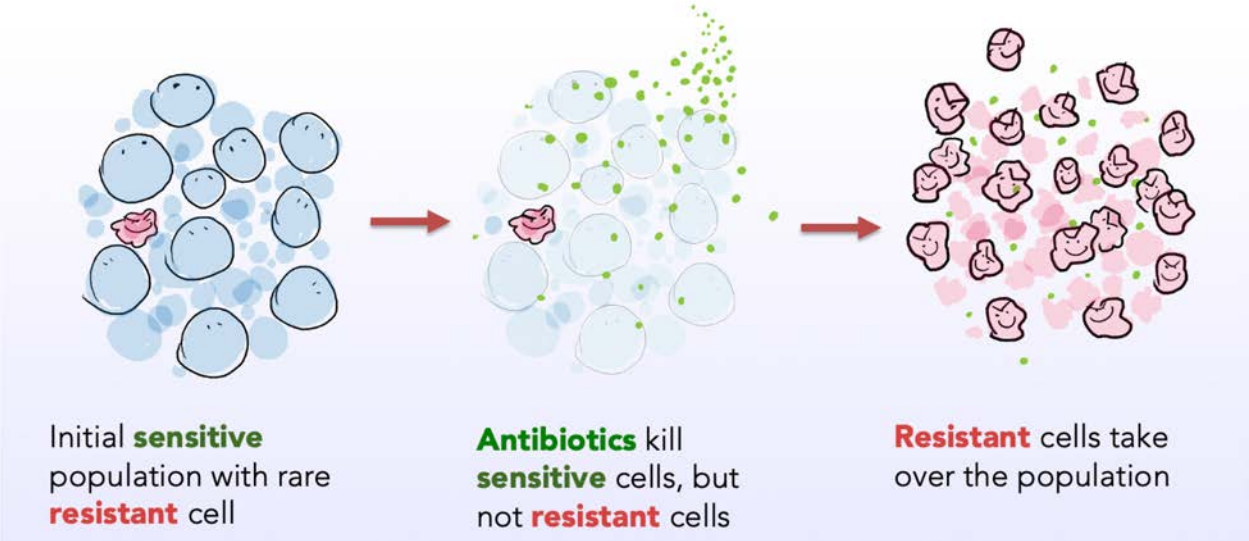



**FIGURE 1-1** Selective pressure encourages antimicrobial resistance.
SOURCE: Yunxin Joy Jiao, reprinted with permission.

Part of the challenge lies in the many ways microorganisms have for responding to selective pressures. One way is through vertical gene transmission, the classic, Darwinian evolution wherein beneficial gene mutations are passed from one generation to another. But microorganisms, especially bacteria, can pass genes to unrelated organisms, even to other species, in processes described as horizontal or lateral gene transfer (Abe et al., 2020; Keeling and Palmer, 2008). Described as, "the movement of genetic information between organisms … except for those from parent to offspring," horizontal gene transmission is thought to be the dominant means of evolution in microbes (Abe et al., 2020; Burmeister, 2015). Horizontal transmission processes, shown in Figure 1-2, can rapidly spread beneficial genes across microbial communities, ultimately accounting for much of the baseline genetic variability then acted upon by selection pressure (Hall et al., 2020).

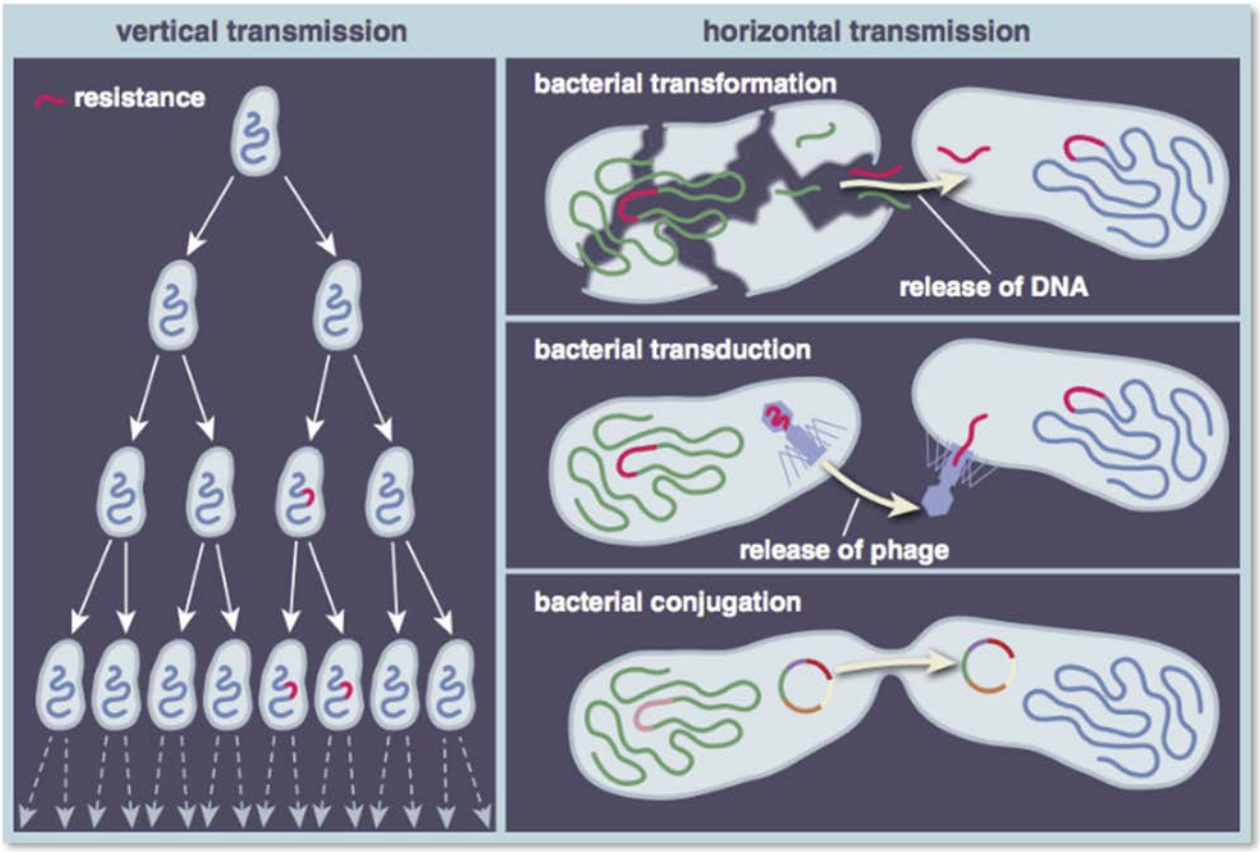



**FIGURE 1-2** Resistance genes can pass through vertical or horizontal mechanisms.
SOURCE: Sommer and Dantas, 2014.

Furthermore, microbes move easily across habitats, living in water and soil as well as in animals and humans. Because of the interconnectedness of these habitats, shown in Figure 1-3, pressures in one setting can easily affect others, creating a reservoir of resistance genes. “All the genes [in a microbial community] that directly or indirectly contribute to resistance” make up the resistome (Wright, 2010). Monitoring changes in the resistome and the concentration of different antimicrobials and resistance genes can give insight into emerging resistance patterns, a topic discussed more in Chapter 4.

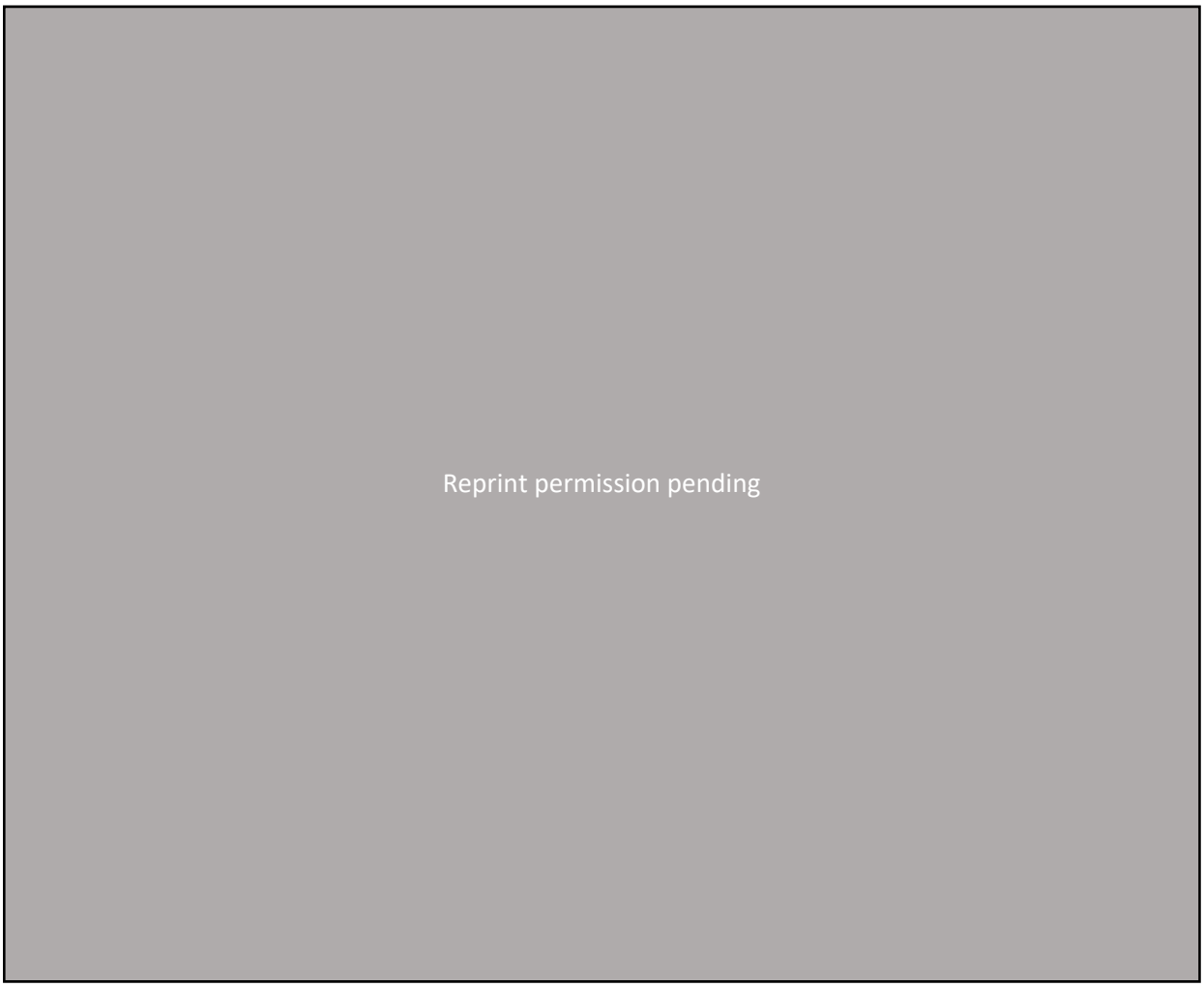



**FIGURE 1-3** Microbes and resistomes travel across habitats.
SOURCE: Adapted from Biomerieux, 2020.

Soil is an especially diverse and important reservoir of both antimicrobials and resistance genes (Bello-Lopez et al., 2019; Nesme and Simonet, 2015). Most of the antibiotics developed in the so-called golden age of drug discovery, and even until the 1990s, were developed from soil microorganisms (Nesme and Simonet, 2015). The soil resistome has changed markedly with the use of antimicrobial medicines. Research in archived soil samples from the 1940s to the early 2000s has found a dramatic increase in the genes causing resistance to all classes of antibiotics tested, with tetracycline-resistance genes alone increasing 15-fold between the 1970s and 2000s (Knapp et al., 2010).

Clinical isolates tell a similar story. Samples from the British antimicrobial reference laboratory have shown an exponential rise in resistance to carbapenems, a group of broad-spectrum antibiotics often used as the drug of last resort for resistant infections (Papp-Wallace et al., 2011; Shallcross et al., 2015) (see Figure 1-4). A 2016 report from the Organisation for Economic Co-operation and Development (OECD) found the prevalence of resistance in clinical testing to have increased in 23 of 26 OECD countries in the years between 2009 and 2014,[1] rising about 5 percentage points on average, despite largely stable rates of

[1] As indicated through an aggregate combination of six common pathogen-drug combinations.

antibiotic use (OECD, 2016). In low- and middle-income countries, where certain infections are more common, as are the crowding, poor sanitation, and limited clinical infection control that make transmission more likely, the situation is worse (Alvarez-Uria et al., 2016). By some estimates, resistant infections are 66 percentage points more common in lower-middle income countries than in rich ones (Alvarez-Uria et al., 2016).

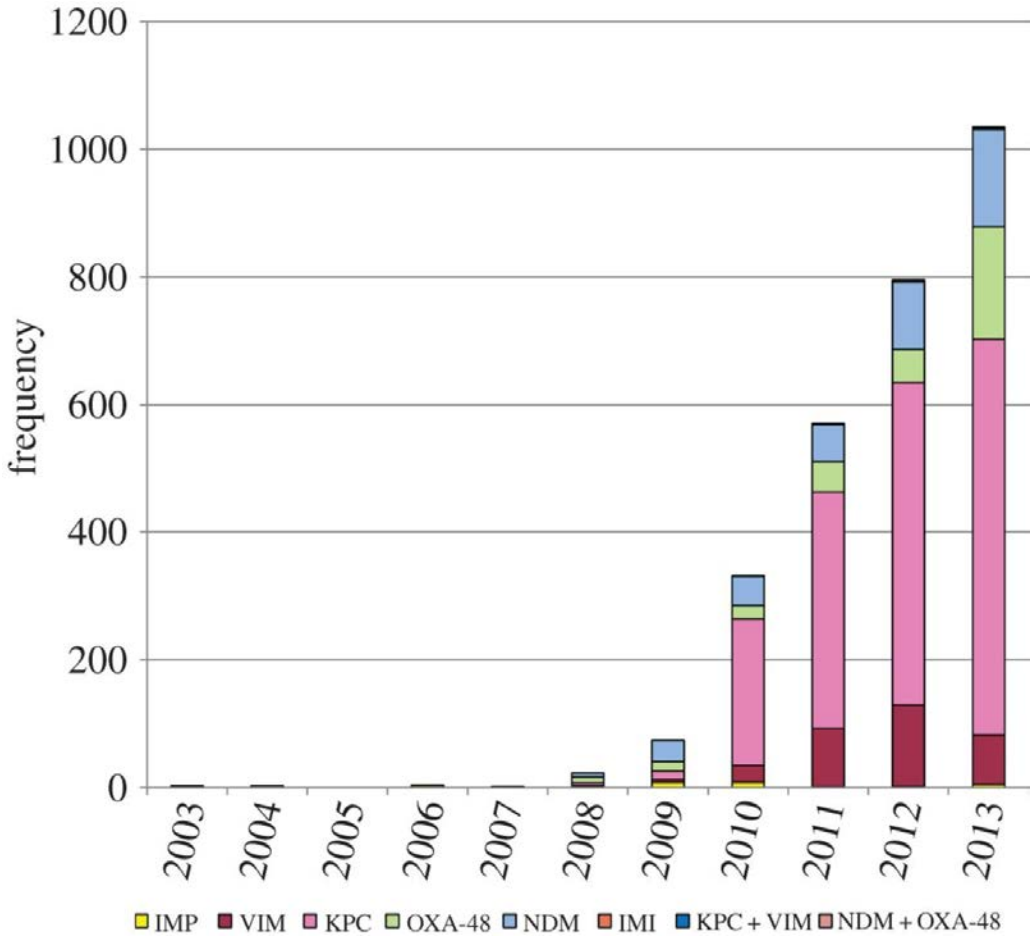



**FIGURE 1-4** Carbapenemase-producing Enterobacteriaceae confirmed by Public Health England's Antimicrobial Resistance and Healthcare Associated Infections unit, from UK laboratories.
NOTE: Resistance and Healthcare Associated Infections unit, from UK laboratories.
NOTE: IMI = imipenem-hydrolyzing beta-lactamases; IMP = imipenemase metallo-beta-lactamase; KPC = *Klebsiella pneumoniae* carbapenemases; NDM = New Delhi metallo-beta-lactamase; OXA-48 = oxacillinase-48; VIM = Verona integron-encoded metallo-beta-lactamases.
SOURCE: Shallcross et al., 2015, from Public Health England.

Later sections of this report discuss the global nature of antimicrobial resistance and the challenges of responding to a health crisis with multiple root causes that manifests itself differently in different parts of the same country, or even within the same state or county. It is challenging to marshal a national response to such a varied and disparate threat. A coordinated, strategic response is essential and something the U.S. government has set out in its *National Strategy for Combating Antibiotic Resistant Bacteria* (PCAST, 2015, 2020; The White House, 2014).

## THE CHARGE TO THE COMMITTEE

The first national action plan for antimicrobial resistance was released in 2015, the result of President Obama's executive order *Combating Antibiotic-Resistant Bacteria*, which created both an interagency task force to implement the *National Strategy for Combating Antibiotic-Resistant Bacteria* (released at the same time) and an independent presidential advisory council to make recommendations to the secretary of health on the government's implementation of the national strategy (CDC, 2020; HHS, 2021; U.S. Congress, 2014). The strategy and the national action plan that guides its implementation, drive the U.S. government's response to the problem of antimicrobial resistance (PCAST, 2015). Its five goals are shown in Box 1-1. Figure 1-5 shows the recent timeline of relevant U.S. government publications.

**BOX 1-1**
**The Goals of the *National Action Plan for Combating Antibiotic-Resistant Bacteria 2015 to 2020***

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections
2. Strengthen national One-Health surveillance efforts to combat resistance
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
5. Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development

SOURCE: Reprinted from CDC, 2020.

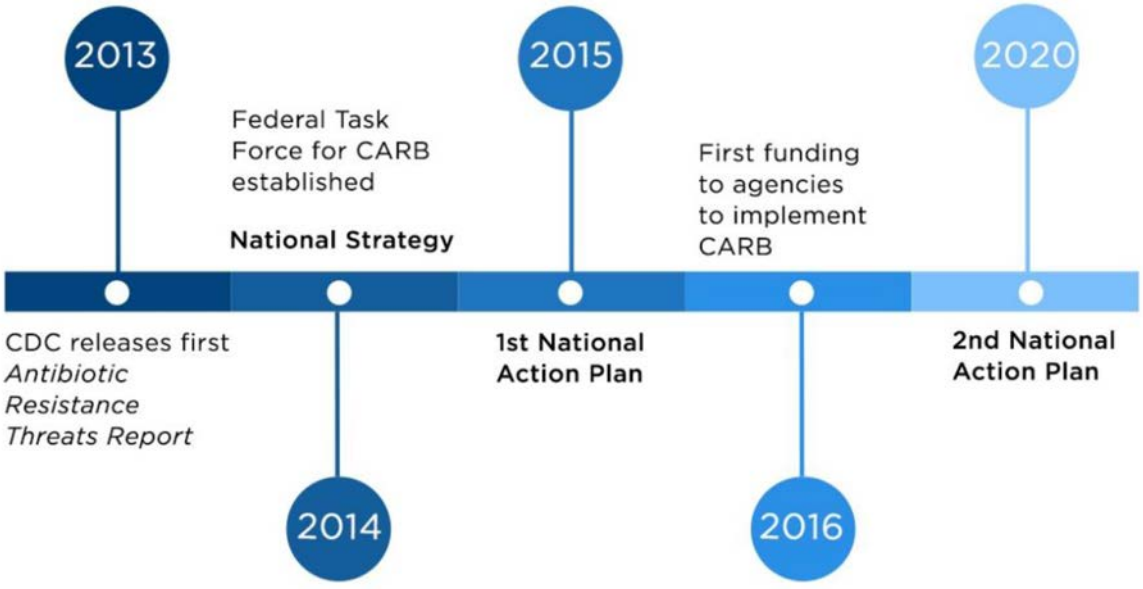



**FIGURE 1-5** The timeline of key U.S. government publications on antimicrobial resistance. SOURCE: CARB, 2020.

When the first national strategy and action plans were in their last year, but before the release of the 2020 to 2025 documents, Congress directed the National Institute of Allergy and Infectious Diseases (NIAID) to convene a consensus committee under the auspices of the National Academies of Sciences, Engineering, and Medicine (hereafter, the National Academies) to examine national progress against the goals shown in Box 1-1 (NASEM, 2020). NIAID is an important implementer of the national action plan, but it is only one of many agencies involved. With this in mind, the study sponsors requested input from their counterparts across the task force to develop the statement of task for this study, shown in Box 1-2. More information about the committee members answering this charge can be found in Appendix A.

**BOX 1-2**
**Statement of Task**

The National Academies will convene an expert committee to examine and quantify the long-term medical and economic impacts of increasing antimicrobial resistance (AMR) in the United States. The study shall examine progress made on the U.S. National Strategy and Action Plan for Combating Antibiotic-Resistant Bacteria, including domestic and international strategies employed by NIH, CDC, FDA, ASPR, USDA, and USAID.

Opportunities to add to the current body of knowledge include:

- Advising on an effective strategy to scale up global detection of resistant infections and infection prevention and control efforts—especially outside of the United States and Europe;
- Helping to assess and quantify the risk to human health from environmental sources and reservoirs of antibiotic-resistant pathogens and genes;
- Assessing any methodologies for evaluating how interventions in agriculture affect public health and how to improve them;
- Assessing any methodologies for evaluating the effects of interventions in agricultural settings on animal health and welfare and how to improve them;
- Assessing the effect of new incentives for antibiotic development (BARDA's project Bioshield, 2019 CMS IPPS) on the health of the antibiotic pipeline;
- Exploring methodological innovations to improve projections of the burden of AMR and its economic impacts, with an eye toward informing the development of incentives for antimicrobial products;
- Exploring ways to develop, benchmark, and track rigorous quantitative measures of the effect of various strategies to mitigate AMR, with a focus on relevant, timely, and actionable measures;
- Assessing the need for and advise on key diseases and antibiotics for which animal-specific antimicrobial susceptibility testing breakpoints are needed; and
- Assessing the need for and explore how to incentivize and promote cooperative relationships between industry and professional societies to prioritize test development of new diagnostics for use in veterinary settings, especially animal-side diagnostics that allow precise selection of antibiotics.

## The Committee's Approach to Its Charge

The committee met six times, each meeting via videoconferencing and spread over several days. The agendas for the public meetings are shown in Appendix C. In closed session, the committee debriefed on the material presented at public meetings and on the literature presented in this report. Committee members also had regular videoconferences to develop their conclusions and recommendations. Members of the public submitted articles and other information for the committee's review, available upon request from the National Academies' Public Records Office.

To better understand the progress various agencies involved in the *National Action Plan on Combating Antibiotic-Resistant Bacteria* made from 2015 to 2020, the committee commissioned an analysis from the Center for Infectious Disease Research and Policy at the University of Minnesota. The researchers drew on published sources and key informant interviews to evaluate agencies' work. Their analysis is presented as a supplementary web appendix available at https://www.nap.edu/catalog/26350.

At the committee's first meeting, representatives from NIAID and other task force agencies gave an overview of their work and an orientation to the task. One area where they gave the committee some leeway was in its interpretation of the term *antimicrobial resistance*. This term can refer to resistance in many kinds of microbes, including viruses and protozoa, and to multidrug-resistant strains of mycobacteria that cause tuberculosis. The committee chose to narrow the scope of this study to include antibacterials, excepting tuberculosis medicines, and antifungals. Even though many of the points in this report could be broadly applicable, resistance to antimalarials, bioterrorism agents, and to antivirals, such as those used to treat hepatitis and HIV, are outside of the scope. This is consistent with the national strategy and the priority pathogens listed in the Centers for Disease Control and Prevention's (CDC's) *Antibiotic Resistant Threats in the United States, 2019* (CDC, 2019). This strategy is also consistent with the National Strategy for Combating Antimicrobial Resistance. The 2020 to 2025 strategy does not discuss malaria or HIV programming, and mentions tuberculosis only tangentially in relation to global surveillance for resistant infections (PCAST, 2020).

In defining its scope, the committee recognizes that the emergence of resistance is a common biological process largely similar for HIV, tuberculosis, and malaria as for other resistant infections. The scope of public health programming and funding for HIV, tuberculosis, and malaria vastly outweighs the national and international resources directed to other resistant infections, however. Though the underlying mechanisms causing resistance are the same, the response to these diseases is not comparable to that for bacterial and fungal pathogens more broadly. Many of the recommendations presented in this report to counter resistance to antibiotics or antifungals are transferable to other types of resistance. The committee members determined that attention to gaps in the response to bacterial and fungal resistance broadly would allow them to make more meaningful recommendations than had they concentrated on HIV, tuberculosis, and malaria, recognizing nonetheless that the underlying mechanism of resistance to medicines is similar across infectious diseases.

The study sponsors at NIAID also gave the committee considerable leeway in interpreting the charge, "to examine and quantify" the impact of antimicrobial resistance in the United States. While this charge could be interpreted as a call for original data collection and analysis, the sponsor supported the committee's strategy to address this point with review of the recent health and economic literature on the topic, especially the major national and international publications that have driven some of the recent public dialogue. This is not a systematic review

in the style of a Cochrane review or an exhaustive analysis of every publication on the topic, however.

Part of the challenge of responding to antimicrobial resistance lies in the varied and dynamic nature of the threat. The burden of resistant pathogens differs widely from one place to another, even within different hospitals in the same county, and from one year to the next. It is difficult to predict which pathogens will emerge as serious threats and which will subside, partly because human response influences the future disease burden from any pathogen. For this reason, the committee avoided a reactive emphasis on the pathogens driving the burden of resistant infections today in favor of a broader, more adaptive strategy applicable to a range of bacteria and fungi. This is not to say that this report avoids drawing upon and citing the CDC Urgent Threats and the World Health Organization Priority Pathogens lists (CDC, 2019; WHO, 2017). Rather, in tailoring its recommendations the committee refrained from making recommendations regarding any particular pathogen in favor of those with broader applicability. In short, the committee chose a more fundamental approach to the problem, in line with the One Health view of antimicrobial resistance in humans, animals, and the environment discussed more in the next chapter. For this reason, individual infections (methicillin-resistant *Staphylococcus aureus*, for example) are not the subject of different report chapters, but the interconnectedness of resistance with other topics in health and disease are discussed throughout.

The committee approached its charge and recommendations with an effort to identify key problems and barriers to their solutions. This should not be understood as the committee's judgement on the relative merit of strategies that are not the topic of recommendations. Similarly, in making its recommendations the committee tried to strike a balance between innovation and practicality, directing the recommendations to organizations for which the suggested action would be challenging but feasible.

## The Organization of This Report

In their deliberation, committee members worked to find common threads and common gaps in response to antimicrobial resistance across sectors. Some of their recommendations are relevant only to animal health, others only to human medicine, some cut across multiple sectors. Rather than being organized by topic (agriculture, medicine, economics) the report handles these topics together and presents the committee's analysis by theme. This chapter introduces the topic and the background for this study. The next chapter discusses the scope of the problem and provides context on global action against antimicrobial resistance. Chapter 3 reviews the literature on the health and economic burden of resistance. Chapter 4 discusses surveillance and tools for strengthening it, and Chapter 5 discusses ways to prevent infection and improve stewardship. Chapter 6 turns to the market for new medical products and steps that could make this market work better for public health. Chapter 7 looks at the national action plan and the U.S. government's response from 2015 to 2020, and the last chapter suggests a role for the United States in the global response to antimicrobial resistance. These chapters contain the reasoning supporting the committee's recommendations, based on literature review and the result of its deliberations.

This report presents actions that, in the committee's judgment, have strong promise to control the problem of antimicrobial resistance. The recommendations highlight important gaps and solvable problems but do not constitute an exhaustive list of potential policy actions against antimicrobial resistance. Many of the actions recommended are within the purview of the U.S. government, a strategy the committee sees as suitable to its charge and the congressional

mandate for this study. At the same time, action against as complex and global a threat as antimicrobial resistance cannot be limited to any one country or to government action. With this in mind, the committee gave considerable attention to ways to involve international organizations, foundations, and the private sector in this work, work which, to be effective, must look internationally at least as much as domestically.

## REFERENCES


Abe, K., N. Nomura, and S. Suzuki. 2020. Biofilms: Hot spots of horizontal gene transfer (hgt) in aquatic environments, with a focus on a new hgt mechanism. *FEMS Microbiology Ecology* 96(5):fiaa031.

Alvarez-Uria, G., S. Gandra, and R. Laxminarayan. 2016. Poverty and prevalence of antimicrobial resistance in invasive isolates. *International Journal of Infectious Diseases* 52:59-61.

Bello-Lopez, J. M., O. A. Cabrero-Martinez, G. Ibanez-Cervantes, C. Hernandez-Cortez, L. I. Pelcastre-Rodriguez, L. U. Gonzalez-Avila, and G. Castro-Escarpulli. 2019. Horizontal gene transfer and its association with antibiotic resistance in the genus aeromonas spp. *Microorganisms* 7(9):363.

Biomerieux. 2020. *A global approach to human and animal health*. https://amr.biomerieux.com/en/challenges/from-farm-to-food-to-people-one-health/ (accessed July 13, 2021).

Burmeister, A. R. 2015. Horizontal gene transfer. *Evolution, Medicine, and Public Health* 2015(1):193-194.

CARB (National Action Plan for Combating Antibiotic-Resistant Bacteria). 2020. National action plan for combating antibiotic resistant bacteria. *Federal Task Force on Combating Antibiotic-Resistant Bacteria*.

CDC (Centers for Disease Control and Prevention). 2019. *Antibiotic resistance threats in the United States, 2019.* US Department of Health and Human Services, Centers for Disease Control and Prevention.

CDC. 2020. U.S. National action plan for combating antibioticresistant bacteria (national action plan). *US Department of Health and Human Services, Centers for Disease Control and Prevention*.

Chambers, H. F. 2001. The changing epidemiology of staphylococcus aureus? *Emerging Infectious Diseases* 7(2):178-182.

D'Costa, V. M., C. E. King, L. Kalan, M. Morar, W. W. Sung, C. Schwarz, D. Froese, G. Zazula, F. Calmels, R. Debruyne, et al. 2011. Antibiotic resistance is ancient. *Nature* 477(7365):457-461.

Hall, R. J., F. J. Whelan, J. O. McInerney, Y. Ou, and M. R. Domingo-Sananes. 2020. Horizontal gene transfer as a source of conflict and cooperation in prokaryotes. *Frontiers in Microbiology* 11:1569.

HHS (U.S. Department of Health and Human Services). 2021. *Presidential advisory council on combating antibiotic-resistant bacteria (PACCARB)*. https://www.hhs.gov/ash/advisory-committees/paccarb/index.html (accessed September 23, 2021).

Hutchings, M. I., A. W. Truman, and B. Wilkinson. 2019. Antibiotics: Past, present and future. *Current Opinion in Microbiology* 51:72-80.

Keeling, P. J., and J. D. Palmer. 2008. Horizontal gene transfer in eukaryotic evolution. *Nature Reviews Genetics* 9(8):605-618.

Knapp, C. W., J. Dolfing, P. A. Ehlert, and D. W. Graham. 2010. Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940. *Environmental Science & Technol*ogy 44(2):580-587.

McMaster University. 2011. *Resistance to antibiotics is ancient*. www.sciencedaily.com/releases/2011/08/110831155334.htm (accessed April 8, 2021).

NASEM (National Academies of Sciences, Engineering, and Medicine). 2020. *Further consolidated appropriations act, 2020*. https://www.nationalacademies.org/ocga/public-laws/further-consolidated-appropriations-act-2020 (accessed April 8, 2021).

Nesme, J., and P. Simonet. 2015. The soil resistome: A critical review on antibiotic resistance origins, ecology and dissemination potential in telluric bacteria. *Environmental Microbiology* 17(4):913-930.

OECD (Organisation for Economic Co-operation and Development). 2016. Antimicrobial resistance, policy insights: Organisation for Economic Co-operation and Development.

Papp-Wallace, K. M., A. Endimiani, M. A. Taracila, and R. A. Bonomo. 2011. Carbapenems: Past, present, and future. *Antimicrobial Agents and Chemotherapy* 55(11):4943-4960.

PCAST (President's Council of Advisors on Science and Technology). 2015. *National action plan for combating antibiotic-resistant bacteria.* Washington, DC: White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

PCAST. 2020. *National action plan for combating antibiotic-resistant bacteria, 2020-2025.* Washington, DC: White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

Perry, J., N. Waglechner, and G. Wright. 2016. The prehistory of antibiotic resistance. *Cold Spring Harbor Perspectives in Medicine* 6(6):a025197.

Shallcross, L. J., S. J. Howard, T. Fowler, and S. C. Davies. 2015. Tackling the threat of antimicrobial resistance: From policy to sustainable action. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 370(1670):20140082.

Sommer, M., and G. Dantas. 2014. How to fight back against antibiotic resistance. *American Scientist* 102(1).

Sullivan, T. 2018. Antibiotics are often used at the end of life, but at what cost?: Health Affairs Blog.

The White House. 2014. *National strategy for combating antibiotic resistant bacteria.* Washington DC: The White House.

U.S. Congress. 2014. *Executive order 13676 of September 18, 2014: Combating antibiotic-resistant bacteria*

Ventola, C. L. 2015. The antibiotic resistance crisis: Part 1: Causes and threats. *P T* 40(4):277-283.

WHO (World Health Organization). 2017. *WHO publishes list of bacteria for which new antibiotics are urgently needed*. https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (accessed July 13, 2021).

Wright, G. D. 2010. The antibiotic resistome. *Expert Opinion on Drug Discovery* 5(8):779-788.

# 2

# The Scope of the Problem

Responding to a complex problem like antimicrobial resistance requires some attention first to its root causes. As the previous chapter explained, microbes have many ways of surviving the agents used to fight them. Selection pressure from exposure to antimicrobials leads to the proliferation of mutations that render microbes immune to these agents. At the same time, the ability of microbes, especially bacteria, to pass genes horizontally even among different species in the same ecosystem speeds the spread of resistance traits. Mobile genetic elements, a plasmid, for example, may carry multiple different resistance genes. The selection of one resistance trait can therefore lead to the co-selection of other traits conveying resistance to other medicines (Lowy, 2009).

The concept of resistance is hard to separate from its application in medicine. Even the central concept of microbial virulence is often defined, without clear consensus, in terms of the microbes' capacity to harm its host; the innocuous or beneficial relationship between most microbes and their hosts are not as widely investigated (Casadevall and Pirofski, 2019). Even among pathogenic microbes, commensalism and colonization are more common outcomes of the relationship between microbe and host than disease (Casadevall and Pirofski, 2019). In these states, antimicrobial resistance may come at the cost of disease pathogenic potential (called pathogenicity) or may be the result of a complex relationship between antimicrobial resistance and microbial pathogenesis that allow microbes to survive in harsh conditions and niches (Dewan et al., 2018).

Mobile genetic elements that can be transferred among bacterial strains belonging to the same or different species can co-select for both resistance and pathogenicity (Cepas and Soto, 2020). Other microbial characteristics such as biofilm formation, efflux pumps, and cell wall changes can contribute to both resistance and pathogenicity (Schroeder et al., 2017). In an immune-suppressed host, these features can increase the disease potential of otherwise less virulent microbes. However, the genetic connection between antimicrobial resistance and pathogenicity, especially in the context of multispecies communities, is not well understood (Beceiro et al., 2013; Schroeder et al., 2017). It is possible that anti-virulence molecules have a role as anti-infective agents that could supply less selection pressure.

There is considerable uncertainty regarding how microbes and their hosts interact in states of health and disease. While the depth of this relationship is beyond the scope of this report, this chapter gives background on the ways human antimicrobial use encourages resistance. First, the chapter explores the ways in which human action contributes to resistance,

then it gives more context on the global nature and distribution of resistant infections. The last section discusses the dynamic and adaptive nature of the problem, explaining why it is difficult to both measure and counteract.

## HUMAN ACTION EXACERBATES RESISTANCE

Antimicrobials are used frequently in human medicine, the field for which they were developed and the one with the highest, most direct stake in their preservation. Antimicrobials are also widely used in veterinary medicine. Animal agriculture accounts for the largest total use of antimicrobials today, while aquaculture accounts for a smaller, but faster growing share of total use (Ritchie, 2017; Schar et al., 2020). Finally, antimicrobials are also used in crop agriculture on field and tree crops (Williams-Nguyen et al., 2016). Common problems across settings contribute to misuse and overuse. As the previous chapter explained, microbes can spread through water, air, and soil; through travel, including the travel of wildlife; and through environmental contamination. It can be difficult to disentangle the relative contribution of any one type of use to the global burden of resistance, though Figure 2-1 indicates the substantial evidence that the overuse and misuse of antimicrobials in both human and animal medicine drives much of the problem (Holmes et al., 2016).

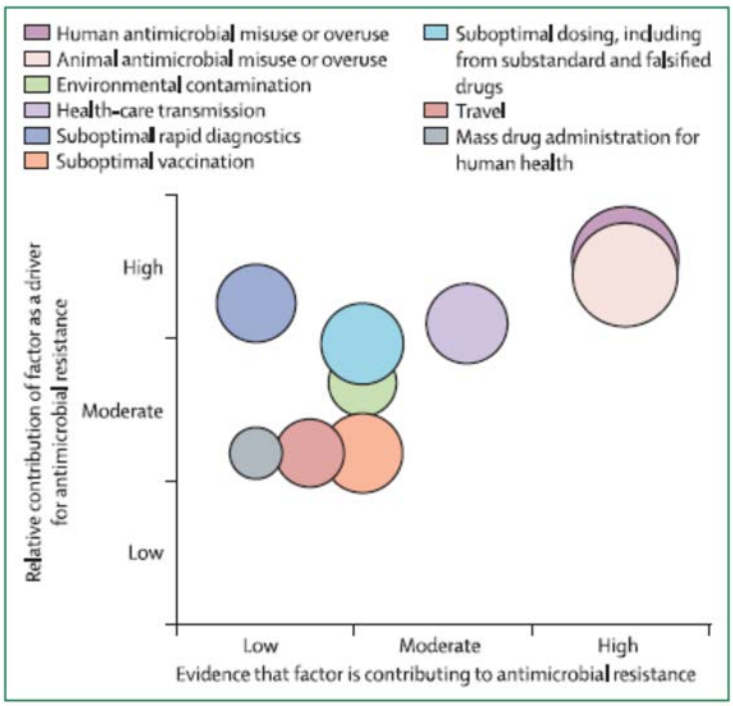



**FIGURE 2-1** A conceptual framework for the role of modifiable drivers of antimicrobial resistance. NOTES: An infographic to show the considered potential contribution of each factor as a driver for antimicrobial resistance. Associated relative contribution, supporting evidence, and potential population affected (diameter of bubble) was created from a two-round Delphi method of Holmes and colleagues, who identified factors from review of the national and international antimicrobial resistance literature. The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to identify the quality of the evidence (the study with the highest GRADE estimate was cited) supporting each driver as being contributory to the rise in antimicrobial resistance.

SOURCE: Adapted from Holmes et al., 2016.

### The Misuse and Overuse of Antimicrobials in Human Medicine

Antimicrobials are fast-acting, powerful medicines that can avert considerable suffering. For this reason, prescribers may be quick to use them, even before the precise cause of their patients' illness can be determined. An empirical diagnosis is one based on the best judgement of the clinician considering the patient's history and the clinical presentation (Leekha et al., 2011). In the absence of information suggesting otherwise, a clinician suspecting bacterial infection will usually start with a broad-spectrum drug that has action against a wide range of pathogens. Broad-spectrum treatment carries risks. It wages a somewhat indiscriminate attack on a wide swath of potential pathogens, as well as commensal bacteria, thereby disrupting the gut microbiome (see Box 2-1). By disrupting the commensal bacteria, broad-spectrum treatment can leave patients vulnerable to *Clostridioides difficile* infection (Crowther and Wilcox, 2015; Johanesen et al., 2015). Broad-spectrum treatment also supplies the selective pressure that breeds resistance. For these reasons, microbiological information about the pathogen should inform a switch to a narrow-spectrum antimicrobial whenever possible (a process called de-escalation) (Leekha et al., 2011). Clinicians may be reluctant to switch medicines when a patient seems to be responding, however. In outpatient medicine, only about 10 percent of patients are correctly de-escalated (Leekha et al., 2011). Even in hospitals, where microbiological diagnosis is easier, there can be reluctance to de-escalate (Goldstein et al., 2016). The antimicrobial stewardship programs now common in the United States have improved antibiotic de-escalation in hospitals, a topic discussed more in Chapter 5, though local norms can vary widely (Liu et al., 2016).

**BOX 2-1**
**Antimicrobials and the Microbiome**

Antimicrobials, either through direct medical use or environmental exposures, can alter the human microbiome, the trillions of microorganisms that live in the human body, mostly in the gut. The diversity of organisms and composition of the microbiome influences the functioning of the immune system and may be related to obesity and a range of gastrointestinal diseases. Age and other factors such as gastric acidity can influence the composition of the microbiome and may underlie the increased risk of *Clostridioides difficile* infection over age 65.

A healthy and diverse microbiome can help control the spread of resistant pathogens by increasing the competition for nutrients and other resources. Because antimicrobial treatment alters microbial ecology, there is growing interest in therapeutic steps to restore the microbiome after an infectious disease, as well as therapies that work to combat resistance by moderating host immunity through the microbiome. Already research in the microbiome has identified some promising phages, viruses that attack bacteria that may be useful in treating drug-resistant infections.

Microbiome treatments may be most useful for people whose conditions make frequent exposure to broad-spectrum antimicrobials necessary, such as cancer and organ transplant patients. Tools to restore the microbiome in such cases are still in early development. The transplanting of microbes from healthy donors, as through fecal transplantation, and the use of probiotics and other nutritional tools may be able to beneficially alter the microbiome. Other research draws on animal studies, mathematical modelling, and genomic analysis to better understand what constitutes a healthy microbiome and how microbiome deficiencies might be corrected.

SOURCES: Benler et al., 2021; Buffie et al., 2015; CDC, 2018a; Shreiner et al., 2015; The Nutrition Source, 2021.

Rapid diagnostic testing could do much to change broad-spectrum empiric treatment, a topic discussed more in Chapter 6. In the absence of such tests, empiric antimicrobial therapy is part of the practice of medicine. Microbiological analysis of patient specimens is time consuming at best. Even in U.S. hospitals, there is at least a 2-day turnaround time for microbiological identification of most pathogens; susceptibility test results even longer (Tabak et al., 2018). Laboratory diagnostics are less available in low- and middle-income countries and testing kits more expensive, making empiric treatment the only practical option in many cases (Engel et al., 2016; Ombelet et al., 2019). An acknowledgement that empiric diagnosis is part of the practice of medicine is reflected in the World Health Organization (WHO) AWaRe System, which gives guidance on the empiric treatment of common infections (WHO, 2019d) (see Box 2-2).

**BOX 2-2**
**The WHO AWaRe System**

The WHO Model List of Essential Medicines is a tool used in the selection and supply of medicines for primary health care in low- and middle-income countries, updated every other year since 1977. The 2017 revision to the list introduced a system of categorizing antibiotics based on their potential for resistance to guide optimal use in cases when laboratory diagnosis is not possible. By categorizing antibiotics into access, watch, and reserve groups (AwaRe) the WHO aimed to preserve the effectiveness of powerful, new medicines.

**Access Group:** The first-choice treatments for the 25 most common infections; these 29 medicines are described as “the core set of antibiotics that should be available everywhere.”

**Watch Group:** Antibiotics with greater potential for resistance or toxicity; medicines on this list are highly valuable in human medicine and should not be used in agriculture; their use is routinely monitored to ensure consistency with WHO guidelines.

**Reserve Group:** These medicines of last resort are only used for serious or life-threatening infections when other drugs have failed or cannot be used. This category includes the newer antibiotics being held in reserve as part of international stewardship efforts.

The AWaRe system also gives useful guidance on the best treatment of 25 common infections. The information is now available in an interactive database that can be used to guide clinical decisions and public health surveillance. This database also identifies medicines to avoid at all costs, namely irrational fixed-dose combinations of broad-spectrum antibiotics for which there is no treatment guideline to support their use.

The AWaRe classification has its limits. As with any broad categorical grouping, there is an element of arbitrariness; it is not always clear which category a drug should fall into. Furthermore, the decision to use a medicine or hold it in reserve is largely influenced by the local burden of disease and local cost and availability of medicines. There are doubtless examples of watch group medicines that should be first-line treatments in certain settings.

The system is, nevertheless, an invaluable tool for antibiotic stewardship and for tracking access and use in low- and middle-income countries.

SOURCES: Sharland et al., 2018; WHO, 2019d.

Not all misuse of antimicrobials is made under such constrained circumstances, however. Claims data suggest that roughly 17 percent of antibiotic prescriptions in the United States are made in the absence of any diagnosis of infection, while another 20 to 30 percent are not associated with any clinical visit at all (Fischer et al., 2020). The Centers for Disease Control and Prevention (CDC) estimates that, despite improvement in antibiotic prescribing practices, more than 30 percent of antibiotics prescribed in outpatient medicine are inappropriate (CDC, 2011). More recent prospective research has found that more than 20 percent of antibacterials prescribed in outpatient medicine are not associated with a bacterial infection (Fischer et al., 2021).

The common use of antibacterials to treat viral respiratory tract infections accounts for considerable overuse of antimicrobials (CDC, 2011). Furthermore, the broad-spectrum agents that encourage resistance are the most commonly prescribed antibacterials in primary care (Shapiro et al., 2014). The same trends are seen in the treatment of children. National data indicate that about a third of antimicrobial prescriptions made to children in emergency department visits are not indicated (Poole et al., 2019). The overuse of broad-spectrum treatment may be especially common in children under 2 years of age (Alzahrani et al., 2018).

The clinicians responsible for this misuse are often pressured by their patients or, for pediatricians, their patients' parents (Sirota et al., 2017). They may also be acting on a sense of obligation. Faced with a seriously sick, feverish patient and uncertainty about the source of the infection, a doctor may prescribe an antibiotic even knowing that the infection is likely viral, out of a misplaced caution, or from the cumulative effect of various social pressures, or an insufficient time to explain the ambiguity in their diagnosis (Imanpour et al., 2017; Pichichero, 2002).

The risk of secondary bacterial infections may drive clinicians to prescribe prophylactic antimicrobials in some patients (Manohar et al., 2020). Prophylactic antimicrobial treatment in dentistry, for example, often uses broad-spectrum antibiotics to control the risk of wound infections after an extraction or oral surgery (Singh Gill et al., 2018). However, trial data does not support the routine use of prophylactic antimicrobials in routine dental implants or extractions in healthy patients (Singh Gill et al., 2018). Nevertheless, there is still wide variation in national practice guidelines on antimicrobial prophylaxis in dentistry and other clinical practices (Bakhsh et al., 2020).

Confusion over treatment guidelines can drive antimicrobial use in medicine as well. Long treatment regimens with antimicrobials were common historically, driven partly by a limited understanding of mechanisms of action or biomarkers of cure (Wald-Dickler and Spellberg, 2019; Wilson et al., 2019). For example, the optimal duration of antibiotic therapy even for the common infections, such as community acquired pneumonia, was not established for decades. Now, despite multiple national and international guidelines recommending a maximum of 5 to 8 days of antibacterial treatment for most patients, community-acquired pneumonia patients are treated on average for 10 days or longer (Fally et al., 2021; Lim et al., 2009; Mandell et al., 2007; Tansarli and Mylonakis; Woodhead et al., 2011). Up to 40 percent of uncomplicated cases receive antimicrobials for more than 10 days (Walsh et al., 2018; Welte et al., 2012). Such prolonged treatment puts patients at risk for a range of health problems (e.g.

allergic reactions, diarrhea, organ toxicity and extremely low white blood cell count) and even death (Keighley et al., 2019; Murphy et al., 2016; Tamma et al., 2017). Evidence also supports shorter course therapy for otitis media, skin and soft tissue infections, acute bacterial sinusitis, and uncomplicated urinary tract infection (Wilson et al., 2019). Shorter therapies for these and other infections have been shown to have similar clinical outcomes and far lower risk of adverse events, but many prescribers, especially primary care doctors, default to treatment regimens of 10 days or longer (CDC, 2019b; Lee et al., 2021).

## The Misuse and Overuse of Antimicrobials in Veterinary Medicine

Many of the same psychological factors and adherence to outdated treatment guidelines that influence doctors, dentists, and nurses to overuse antimicrobial medicines apply to veterinarians as well. One important difference however, lies in the size of their practice. The steps in treating companion animals are largely similar to those for humans: an individual, clinical evaluation followed by diagnosis then administering medicine. The process for treating food-producing animals however, can involve dosing groups of animals (Aarestrup, 2015). In swine and poultry, this treatment would be administered through feed or water, and in young calves through injection (Agriculture.com Staff, 2018; National Chicken Council, 2014; Word et al., 2020; Zangaro, 2018). Therefore a single veterinarian may routinely treat animals in herds or flocks of hundreds or thousands at a time (Cima, 2017; USDA, 2019; Widmar, 2017). Partly for this reason, the volume of antibiotics used in animal agriculture often exceeds the use in human medicine (Woolhouse et al., 2015). In some parts of the world, agricultural use exceeds human use by four times in volume (Laxminarayan et al., 2013).

Some antimicrobials are reserved for human use only, such as the isoniazid group of antibiotics used to treat tuberculosis (McEwen and Collignon, 2018). Others, ionophores for example, are toxic to humans and used only in animals (McEwen and Collignon, 2018). Most classes of antimicrobial medicines, however, are used in both human and animal medicine, including the treatment of fish, livestock, birds, honeybees, and pets (McEwen and Collignon, 2018). The limited pool of medicines can be a source of tension, some people are uncomfortable with animal use (more specifically, livestock use) of antimicrobials that are important for human health (Aarestrup, 2015; Mellon, 2013). As in human medicine, the antimicrobial treatments in animals should be judicious, with an emphasis on the shortest effective duration of treatment and lowest effective dose through the most effective route of administration (MSU, 2011). At the same time, care should be taken not to exaggerate the risk animal antimicrobial use poses to humans, and understand the need for treatments to control animal diseases that could affect food security and human health.

Determining the minimal effective dose of antimicrobials can be less straightforward in animal agriculture, however, as the line between prophylactic and therapeutic treatment is not always clear. After one animal in a flock or herd has been diagnosed, all or part of that group may be treated to control the risk of an outbreak or to treat animals already infected but not yet showing signs of illness (Farm Antibiotics, 2017). This control treatment is sometimes administered before animals are transported or brought into close or otherwise stressful conditions (MSU, 2011). European surveillance data suggest that the mass medication of mostly healthy animals, especially pigs and poultry, accounts for 90 percent of veterinary antimicrobial consumption (Baptiste and Pokludová, 2020). There is relatively little hard evidence on the effects reducing such use would have on animal health, welfare, or productivity (Aarestrup, 2015).

Such estimates do not account for the mass treatment of livestock and fish with antimicrobials to enhance growth. The mechanisms through which these medicines promote growth is unclear, but the use of subtherapeutic doses of antibiotics in feed and water was common practice by the 1950s, and highly favorable to selecting for and retaining resistant bacteria (Kirchhelle, 2018; Van et al., 2020; Wall et al., 2016; Woolhouse et al., 2015).

The extent to which antimicrobial growth promoters improve yields is unclear. Studies from the 1950s and 1960s suggest increases of 8 to 12 percent of body weight in poultry, but predate modern good agricultural practices, high-efficiency feeds, or selective breeding (Graham et al., 2007). More recent research in the United States suggests much lower gains (Graham et al., 2007). Antimicrobial growth promoters appear to confer a minimal advantage when the biosafety and preventive measures are strong, and on a background of optimal genetic potential (Laxminarayan et al., 2015; Wall et al., 2016). But in places where baseline water sanitation and husbandry measures are lacking, even a marginal offset from growth-promoting antibiotics can be a meaningful difference in yields (Laxminarayan et al., 2015). Nevertheless, because of the implications for public health, antimicrobial growth promoters have been banned in Europe since 2006 and more recently in the United States (Casewell et al., 2003; Cogliani et al., 2011; FDA, 2017; Sneeringer, 2015).

Agricultural use of antimicrobials in low- and middle-income countries is difficult to measure, but demand for animal-source foods and for antimicrobials used in their production is increasing (Nadimpalli et al., 2018; Schar et al., 2018). It is not clear that regulatory interventions to curb this use would be effective, given relatively unrestricted retail access to antimicrobials and limited capacity to enforce regulations (Schar et al., 2018; Wellcome, 2020). India, for example, has bans on using antimicrobials important for human medicine in livestock, but the majority of antimicrobials that WHO designates as "critically important for human health" can be found in poultry feeds in India (Thakur and Panda, 2017; Wellcome, 2020).

At the same time, there is good evidence the situation is improving. The World Organization for Animal Health, known by the historical acronym OIE, monitors antimicrobial use in animals; its most recent survey found that only 26 percent of 160 countries still allow the use of antimicrobial growth promoters in livestock—the lowest proportion since the organization began monitoring (OIE, 2021). Recent reports highlight decreasing antimicrobial use, especially in China (Schoenmakers, 2020; Tiseo et al., 2020b). By 2030 global antimicrobial sales are expected to rise only about 11 percent relative to a 2017 baseline (Tiseo et al., 2020b).

Aquaculture also accounts for considerable antimicrobial use, especially in the fish-farming countries in Asia (Van Boeckel et al., 2015). A recent study of small fish farms in the Mekong Delta found that 84 percent of tilapia and 69 percent of catfish farms used antibacterials, usually for three days or longer, often with different drugs tried sequentially after treatment failure—a serious risk factor for emergence of resistance (Ström et al., 2019). The amount of drugs used and the way they are deployed in some countries poses high risk, not just to human health from exposure to drug residues, but to aquatic biodiversity (Lulijwa et al., 2019). At the same time, these products are important for livelihoods and food security, especially in poor rural areas (Olaganathan, 2017). The key challenge is to support farmers in efficient animal husbandry that makes minimal use of antimicrobials.

The demand for food from animal sources is increasing in low- and middle-income countries, driven by population growth and a higher standard of living (Baltenweck et al., 2020; FAO, 2018). Even if economic growth were to stagnate, demand for meat is projected to increase 77 percent in Asia and 280 percent in Africa by 2050 (Baltenweck et al., 2020; FAO, 2018). To

respond to this demand, animal agriculture in low- and middle-income countries is shifting from small-scale farming to a more intensive, specialized farming of larger flocks or herds (Hedman et al., 2020; Lam et al., 2016). By some projections, antimicrobial use in livestock may double total antimicrobial consumption in Brazil, China, India, Russia, and South Africa by 2030 (Manyi-Loh et al., 2018; Van Boeckel et al., 2015). At the same time, a sharp decrease in antimicrobial sales in some countries, notably China, mean that global antimicrobial use is projected to rise only about 11 percent by 2030 (relative to 2017 levels) (Tiseo et al., 2020a).

There are numerous examples that good animal husbandry can significantly reduce or eliminate the need for antibiotics. In Norway for example, salmon production in the 1980s was consuming the same amounts of antibiotics by weight as human medicine (Simonsen, 2020). As Figure 2-2 shows, antimicrobial use in Norwegian salmon farming dropped off in the mid-1990s with the development of vaccines against furunculosis and vibriosis, common infectious disease of salmonids (WHO, 2015b). The vaccine, combined with a labor-saving automated delivery system, brought about a sharp reduction in the industry's reliance on antibiotics (NORM/NORM-VET, 2019). Coupled with improvements in husbandry practices and biosecurity, including the rotating and scheduled disinfecting of holding areas, vaccination has brought the Norwegian salmon industry's use of antimicrobials to negligible levels since 2013 (NORM/NORM-VET, 2019; WHO, 2015b).

A similar emphasis on prevention, combined with increasingly specialized systems and knowledgeable farmers allowed the Danish pig producers to reduce antibiotic use by 50 percent between 1992 and 2008, even as production increased by 8.7 million weaned pigs a year (Jul et al., 2019; Levy, 2014). Perdue Farms, a major U.S. poultry producer, has used similar tools (sanitation, vaccination, and re-engineering barns) to stop using antibiotics in their branded products between 2002 and 2017, with other U.S. chicken producers following suit (Bunge, 2016; Leventini, 2018).

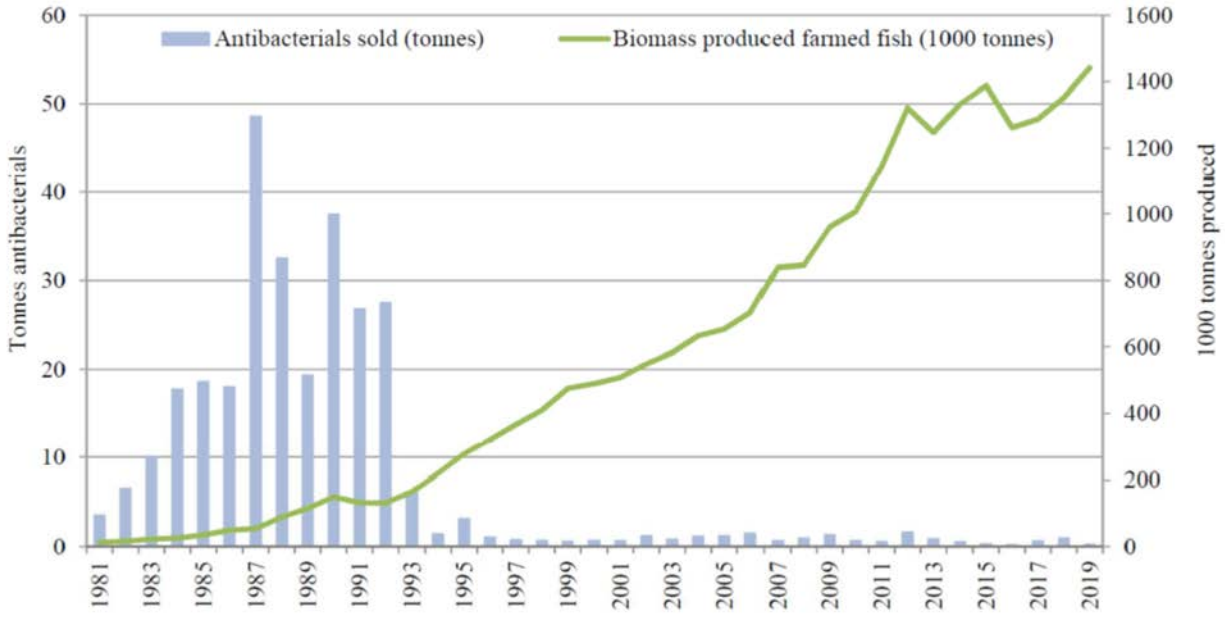



**FIGURE 2-2** Historic use of antibiotics in Norwegian aquaculture.
SOURCE: Simonsen, 2020.

Replicating these successes depends on wider access to vaccines and other preventative products and tools. But despite the demonstrated benefits of vaccination, there is still significant shortage of efficacious and economically affordable vaccines for animal agriculture, a topic discussed more in Chapters 6 and 8 (Hoelzer et al., 2018). Compared to human vaccines, the market for animal vaccines is smaller both in market size and in unit prices, translating to a lower return on investment for companies (Meeusen et al., 2007). At the same time, the range of hosts and pathogens is greater, and the ways they interact are more complicated than for human vaccine production (Hoelzer et al., 2018; Meeusen et al., 2007). While some tools, such as genetically modified live vaccines are promising, widely divergent regulatory barriers across markets present another barrier to use (Hoelzer et al., 2018).

Furthermore, raising farm animals without antimicrobials comes at a cost. Especially in parts of the world where basic water and sanitation infrastructure is lacking, antibiotics are often used as a stopgap. Labor costs are also a concern. Vaccines that can be administered without individually handling each animal in the herd or flock are desirable as the labor costs of vaccinating the group are lower. Similarly, treating groups of animals via feed or water is less labor intensive than identifying a sick animal and treating it individually (Lekagul et al., 2019). Farmers pay out of pocket for animal medicines and diagnostics. The cost of culture and susceptibility tests is difficult to justify especially when empiric treatment is relatively cheap (Norris et al., 2019). As in human medicine, there is considerable unmet need for rapid veterinary diagnostics (Buller et al., 2020). As long as animal samples have to be sent to a central lab and the test results reported back to a veterinarian, the opportunity cost alone will get in the way of more judicious use (Buller et al., 2020).

*Resistant Pathogens Overlap Human and Animal Hosts*

The extent to which antimicrobial use in farm animals threatens human health is not clear, nor is the direction of this relationship one-way (Muloi et al., 2018). Animals may acquire resistant infections from humans and vice versa; shared water sources may be an important conduit transmitting microbes between and among species (Iramiot et al., 2020). In some cases, the direction of transmission may be inferred from context. Carbapenems, for example, have never been widely used in veterinary medicine, so carbapenem resistance in animals is likely of human origin (Davies and Wales, 2019). Most examples of transmission of resistance between species are less clear, however. The majority of studies in a 2018 systematic review on the transmission of resistant *Escherichia coli* from animals to humans found overlap in resistant bacteria between humans and food animals, but only about 18 percent claimed to identify animal-to-human transfer of pathogens, and these studies often based their claims on evidence only of co-occurrence of pathogens between species (Muloi et al., 2018). In short, the complexity of potential transmission routes through which resistant bacteria may pass among and between species and the lack of detailed environmental monitoring make it difficult to establish the source of resistant bacteria or resistance genes in a population (Argudin et al., 2017).

At the same time, the cross-transmission of resistant pathogens is likely whenever humans and animals have close contact. Farmers, veterinarians, and other people who handle livestock may be at higher risk for contracting resistant pathogens from animals, especially when personal protective measures (i.e. wearing of masks, gloves, eye protection) are limited (Franceschini et al., 2019). There are also points in animal production, livestock auctions for example, which involve the comingling of different animal populations, a higher risk for

transmission of resistant pathogens within and between herds or flocks (Argudin et al., 2017; Lhermie et al., 2019a).

Food is another vehicle through which resistant bacteria may spread from animals to humans (Wall et al., 2016; Wright, 2010). Whole genome sequencing, discussed at length in Chapter 4, and other trace-back tools can help determine the source of antibiotic-resistant infections spread through food (CDC, 2019a; Wall et al., 2016; Wee et al., 2020; Wright, 2010). Such tools were used in a 2019 CDC investigation of *Salmonella enterica* that was traced from patients in 32 states to infected cattle in Mexico and a Texas slaughterhouse (Plumb et al., 2019). Cases like these can raise concern about the risks of antimicrobial resistance in livestock. At the same time, the risk of transmission of resistant pathogens through food is not necessarily higher than from human-to-human transmission. Livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA), for example, is associated with lower risk of severe disease than human MRSA subtypes (Davies and Wales, 2019). Biosecurity measures in farms can help control the spread of resistant bacteria between humans and livestock (Davies and Wales, 2019). Efforts to eliminate rodents and other wildlife that act as vectors of pathogens may also be helpful (Davies and Wales, 2019).

The potential contribution of antimicrobial use in animals to the development of resistance is of concern largely because of the volume of antimicrobials involved, which is in turn a reflection of the number and size of livestock animals relative to humans. For this reason, antimicrobial use in livestock is usually expressed relative to the target animal biomass, which accounts for the number of animals and a standard weight at time of exposure (Brault et al., 2019).

But most people, especially in the United States, do not have anything close to the level of contact with animals as veterinarians or agricultural workers do. In contrast, many people share their homes with pets, for which there are no restrictions on the use of medically important antimicrobials (Morley et al., 2005; Odoi et al., 2021). A recent CDC investigation of an extensively drug-resistant *Campylobacter jejuni* outbreak, for example, found molecular or epidemiological links to pet store puppies in 97 percent of cases (Francois Watkins et al., 2021).

The potential emergence of resistant pathogens in companion animals and the transmission of these pathogens to humans is not an area that is well studied, however (Joosten et al., 2020). Efforts to better monitor antimicrobial use in veterinary medicine, discussed in Chapter 5, will be essential to better understanding this relationship. Ultimately a shared environment between humans and animals is central to any understanding of antimicrobial resistance.

### The Use of Antimicrobials in Crop Agriculture

A full analysis of antimicrobial use, especially the environmental risk it poses to humans and animals, also considers the use of antimicrobials to combat some bacterial and fungal diseases of plants. There is some uncertainty regarding such use. Recent research from the WHO and the Food and Agriculture Organization of the United Nations (FAO) found that only 14 of 154 countries surveyed have a system to monitor antimicrobial use in crops (FAO and WHO, 2019).

Antibacterials are a relatively expensive way to control plant diseases, so application is limited to high-value fruit and vegetable crops and ornamental plants (McManus et al., 2002; Stockwell and Duffy, 2012). In the United States, crop agriculture accounts for only about 0.12 percent of agricultural use of antibacterials (Stockwell and Duffy, 2012). Experts estimate that

globally crops account for between 0.26 and 0.50 percent of antibacterial use in agriculture (Taylor and Reeder, 2020).

The most widespread use of antibacterials on U.S. crops is to control fire blight, a disease caused by the gram-negative bacterium *Erwinia amylovora*, in apples and pears (Taylor and Reeder, 2020). Antibacterials can also be used on vegetable crops, especially in Latin America, and to control rice diseases in Asia (Taylor and Reeder, 2020). More recently, EPA authorized oxytetracycline and streptomycin for use against huanglongbing, a bacterial disease of citrus trees more commonly referred to as citrus greening (EPA, 2016, 2018, 2021b).

Unlike antibacterials, antifungals are relatively widely used in crop agriculture. Fungi are common causes of infections in plants, and fungicides have been used in agriculture for more than 150 years (Fisher et al., 2018). Antifungals can be important tools for food security. FAO data suggest that crop losses from fungal infections alone would be enough food for 500 million people (Almeida et al., 2019).

The azoles are a class of antifungal medicines used on crops and in humans and animals (Fisher et al., 2018). Although fungicide use data are not widely available for most countries, azoles account for almost a quarter of global fungicide sales (ECDC, 2013). Use of a specific group of azoles, the triazoles, has become widespread in the last 30 years, with a noticeable increase in the last 15 years (Toda et al., 2021). In the United States, triazole application increased by over 400 percent between 2006 and 2016, driven largely by its use in wheat (Toda et al., 2021).

Increasing use of triazole contributes to selective pressure on the *Aspergillus* spp. which can cause aspergillosis, a severe and often fatal fungal infection in humans (Toda et al., 2021). Triazoles are one of only two or three classes of antifungal medicines able to treat aspergillosis (Toda et al., 2021). Work by the International Society for Human and Animal Mycology and the European Confederation of Medical Mycology indicates that triazole-resistant aspergillosis has been increasing since 2007 and that most clinical isolates showing resistance contain mutations associated with environmental exposures (Resendiz Sharpe et al., 2018).

Azole use has been linked to the emergence of drug resistant *Candida auris*; climate change is also thought be a contributing factor (Arora et al., 2021; Casadevall et al., 2019). Climate change may be selecting fungal pathogens with ability to survive at higher temperatures and in varied hosts (Casadevall et al., 2019). *C. auris*, for example, can survive in harsh conditions, in wet or dry environments, and at varied temperature and salinity (Arora et al., 2021). Drug-susceptible strains of *C. auris* have been recovered in ecosystems relatively untouched by humans, but its drug-resistant strains may have emerged in response to contact with soil and plants (Arora et al., 2021). Fungi are also easily spread by high winds and flood waters (Nnadi and Carter, 2021). Given the influence of the environment on the emergence of both resistance and infectious disease, some consideration for how resistance moves through the environment is important.

## Antimicrobial Resistance in the Environment

All antimicrobial use, be it in human or veterinary medicine, in terrestrial animals, aquaculture, or crop agriculture selects for resistance genes. Human and animal waste both contain antimicrobial residues and resistance genes, as does the runoff from pharmaceutical factories. Research from various manufacturing sites has found high concentrations of antimicrobials downstream of factory wastewater (Bielen et al., 2017; Hogerzeil et al., 2020; Kristiansson et al., 2011; Li et al., 2008). Nevertheless, the evidence indicating the extent to

which resistant organisms and resistance genes from environmental sources pass to humans is lean (Chatterjee et al., 2018). The movement of resistant bacteria from water or soil to humans or other animals, while plausible, is something few studies have investigated with sufficient rigor to allow causal inferences to be drawn (Chatterjee et al., 2018).

To complicate the matter, antimicrobials are not the only chemicals in the environment that select for resistance. Metals such as copper are used in agriculture as biocides, and can co-select for resistance,[1] as can disinfectants, surfactants, and chemical solvents (Holmes et al., 2016; Singer et al., 2016a). The concentration of resistance genes in the environment is dynamic and influenced by the concentration of the antimicrobial they protect against, as well as such factors as temperature and microbial ecology. The many pathways through which resistance genes and antimicrobial residues enter the environment raises concerns about the safety of the wider ecosystem (Singer et al., 2016a).

As Figure 2-3 shows, water is a particularly important potential vehicle for spreading antimicrobial residues and resistance genes. The substances enter the water from human and animal waste, as well as industrial and agricultural runoff (Holmes et al., 2016; Singer et al., 2016a). Antimicrobial-polluted water can be used to irrigate crops or water animals; it can also be consumed directly by humans (Wall et al., 2016). Research on *bla*$^{NDM-1}$, the gene that encodes metallo-beta-lactamase 1 (NDM-1), an enzyme that conveys resistance to carbapenems and other antimicrobials, has been found in surface and tap water samples in New Delhi (Lubick, 2011; Walsh et al., 2011).

Water can bring microbes, residues, and resistance genes into contact with varied microbial ecosystems. Research in Chinese estuaries has found the concentrations of antimicrobial residues and resistance genes in water to be driven by human activity in the area, including veterinary and human medical uses and pharmaceutical manufacturing (Zhu et al., 2017). Other research in the United States has found a correlation between human activity, especially animal agriculture, and the concentration of resistance genes in rivers (Pruden et al., 2012).

Hospital wastewater is an even more concentrated source of medicine residue and resistant bacteria (Aga et al., 2018). Research from Sweden, where antimicrobial consumption per capita is low, has shown hospital wastewater to have sufficient antibacterial activity to kill all susceptible bacteria in a sample, leaving only the drug-resistant organisms (Kraupner et al., 2021). In South Africa, *Pseudomonas aeruginosa* isolates recovered from hospital wastewater showed virulence and resistance traits that could translate into serious infection in a host (Mapipa et al., 2021). As the hospital effluent enters the wastewater treatment, however, antimicrobial byproducts appear to be diluted and less activity can be measured (Kraupner et al., 2021).

[1] Co-selection can occur when one resistance gene encourages the selection of others, regardless of any competitive advantage conferred; it can also be the result of one resistance trait offering protection against multiple toxic chemicals (Singer et al., 2016a).

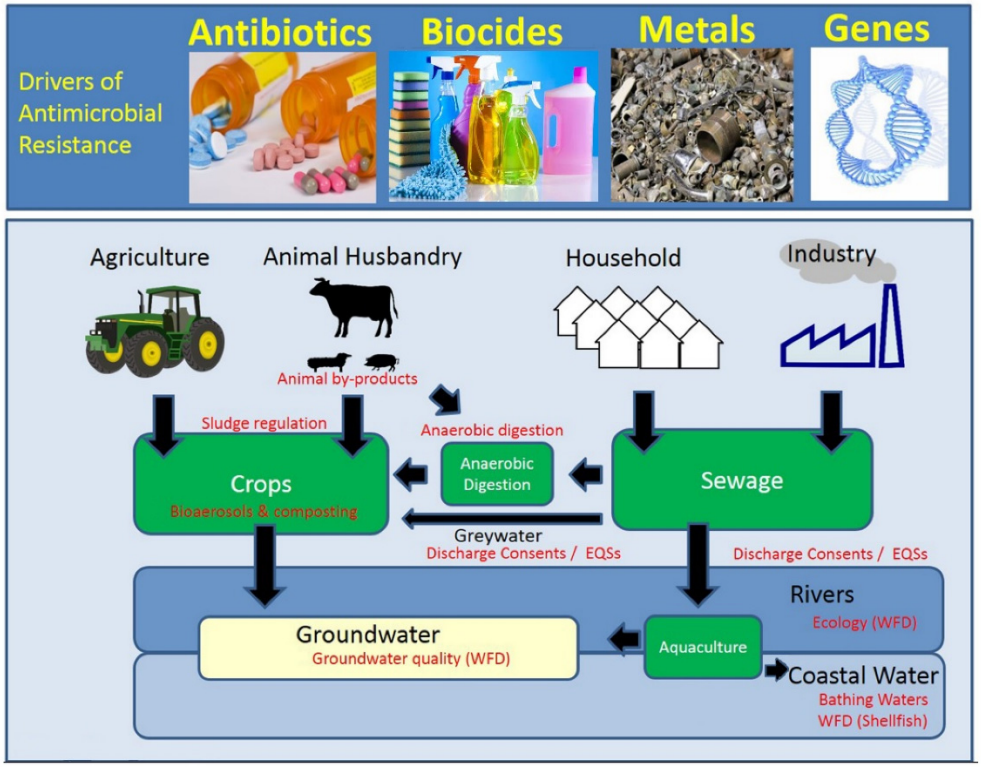



**FIGURE 2-3** Drivers of antimicrobial resistance in the environment.
SOURCE: Adapted from Singer et al., 2016a.

Treated wastewater is typically discharged to surface waters, but it can also be reused in agriculture, industry, or for drinking, or to replenish groundwater supplies (EPA, 2021a). Resistance genes can remain in wastewater after treatment, raising concerns about its use in irrigation and the potential to introduce resistance traits into the environment (Fahrenfeld et al., 2013).

Wastewater treatment is also an important point of contact for treating raw sewage. After treatment, the remaining nutrient-rich material, called biosolids, can be used as fertilizer. This practice is at least a theoretical risk for the introduction of human antimicrobial residues to soil and crops (Williams-Nguyen et al., 2016). Some research suggests that mobile genetic elements associated with resistance persist in the biosolids and in the environment after their use (Law et al., 2021). Other studies have found that the application of biosolids do not have an effect on the concentration of resistance genes in soil or increase phenotypic resistance (Rahube et al., 2014; Rutgersson et al., 2020). The even more common practice of using animal manures for fertilizer may be higher risk, however. While methods such as composting can decrease the concentration of resistance genes by an order of magnitude, methods for processing manure vary widely (Checcucci et al., 2020; Szogi et al., 2015). Less can be said about trace antimicrobials, which can remain unmetabolized in an animals' gut (Elmund et al., 1971; Halling-Sorensen et al., 1998). These compounds are then excreted, some of them retaining their antimicrobial activity. Concentrations of antibiotic resistance genes in manures are considerably higher than in sewage biosolids (Munir and Xagoraraki, 2011). But on the whole, the relationship between resistance genes and drug metabolites in manure and risk for antimicrobial resistance in humans or animals

is not clear, and information about antibiotic half-lives in manure is not usually available (Williams-Nguyen et al., 2016).

Furthermore, even the limited research on environmental reservoirs of antimicrobial resistance is mostly from high-income countries. In developing countries, the risk factors for all kinds of water and environmental contamination are higher. Wastewater is generally discharged partially or wholly untreated into rivers and other water sources (WHO, 2019b). Less than a third of the world's population uses sanitation connected to formal wastewater treatment (WHO, 2019b). About a billion people use a basic pit latrine; open defecation is common practice for another 673 million (WHO, 2019b).

Poor sanitation is itself a cause of infectious disease; it also brings resistant bacteria and antimicrobial by-products into contact with the environment, including untreated surface and groundwater. The WHO estimates that 2 billion people worldwide drink water contaminated with feces, 144 million drink directly from surface water (WHO, 2019a). Only about 40 percent of people in low- and middle-income countries have trash collection, and even that is not necessarily removed to engineered landfills or industrial incinerators (Vikesland et al., 2019). This brings people into closer contact with trash, including trash from hospitals and clinics containing antimicrobials (Vikesland et al., 2019). For all these reasons, soil and water concentrations of antimicrobials appear to be higher in low- and middle-income countries (Vikesland et al., 2019; Williams-Nguyen et al., 2016). At the same time, a higher burden of antimicrobial resistance and greater antimicrobial use are common in these parts of the world, making it difficult to estimate the relative contribution of the environmental reservoir to the overall burden of resistance or even to separate cause from effect in this circular problem.

## ANTIMICROBIAL RESISTANCE IS A GLOBAL PROBLEM

At the root of the problem of antimicrobial resistance are disparities among countries, disparities in wealth, living conditions, health systems, and access to medicines. As the previous chapter discussed, the parts of the world that have the highest burden of drug-resistant infections have, not coincidentally, the most serious problems with crowding and infection control that allow infectious diseases to spread quickly among humans and livestock. In 2018, a modest majority (55 percent) of the world's people lived in cities; by 2030 this share is projected to grow to close to 70 percent (UN, 2018). Increasing urbanization puts a strain on health systems, partly because of the increasing demand for good quality, free primary health care and also through the increasing crowding and slum conditions that drive infectious disease (Elsey et al., 2019; Shawar and Crane, 2017).

Partly for these reasons, the WHO included antimicrobial resistance on its 2020 list of urgent health challenges for the decade, carrying over from its previous year's list of top global health threats (WHO, 2019c, 2020d). In introducing the urgent challenges, the WHO Director General emphasized how most of them are interlinked (WHO, 2020d). This is especially true of antimicrobial resistance, a problem that contributes to and is aggravated by other health challenges. The proliferation of substandard medicines,[2] for example, means that patients can be exposed to subtherapeutic doses of antimicrobials, providing the selective pressure that encourages resistance (Ayukekbong et al., 2017). Problems with the drug supply and

[2] Defined by the WHO as, "authorized medicines that fail to meet either their quality standards or specifications, or both" (WHO, 2018c).

procurement of essential medicines can mean that many patients use the wrong antimicrobial, the wrong dose, or the wrong length of treatment (Loosli et al., 2021). Poor availability of human and animal health services create a void where patients turn to less regulated providers, introducing considerable confusion into diagnosis and treatment, including the diagnosis and treatment of infections (Loosli et al., 2021).

Drug-resistant infections are hard to treat and carry an elevated risk of serious illness or death (WHO, 2020a). They are more often resistant to the inexpensive, off-patent drugs in the WHO Access Group. The medicines needed to fight them are newer and more expensive, putting a strain on health budgets among payers in high-income countries and putting them out of reach of many patients in low- and middle-income ones (Alvarez-Uria et al., 2016; WHO, 2020a). To complicate the problem, microbes are famously difficult to confine. Recent research indicates that international travel, including the travel of livestock, wildlife, birds, and fish, is an important spreader of antimicrobial resistance (D'Souza et al., 2021; Frost et al., 2019).

Increasingly, policy attention to antimicrobial resistance recognizes the global nature of the problem (Podolsky, 2018). In 2011, Britain's Chief Medical Officer, Sally Davies, released an influential report comparing antimicrobial resistance to climate change both in the size of the threat, described as a "ticking time bomb … for the world," and in its costs, which will be considerably higher in the future if mitigating steps are delayed (Davies, 2013). The International Monetary Fund (IMF) echoed the parallels with climate change in 2014, naming antimicrobial resistance one of the four global health threats of the twenty-first century (Jonas et al., 2014). The IMF analysis presented it as a problem of the commons, growing to our shared, global detriment because, "no single patient, physician, hospital, insurer, or pharmaceutical company has an incentive to reduce antibiotic use" (Jonas et al., 2014). On the contrary, antimicrobial consumption is often in best interest of the individual user (Laxminarayan, 2016). Unlike most commons problems however, the shared resource that overuse destroys is not the supply, but the effectiveness of these medicines (Laxminarayan, 2016).

### Antimicrobial Resistance and the Changing Global Burden of Disease

With the effectiveness of antimicrobial medicines at risk, some experts caution that mortality from infectious disease could return to levels not seen since the nineteenth century (Podolsky, 2018; Shallcross et al., 2015). The specifics of this claim are debatable; as the 2014 IMF report observed, "antibiotics are not a substitute for good public health policy, vaccinations, clean water, and proper sanitation. The infectious disease mortality rates in low- and lower-middle-income countries today vastly exceed those in high-income countries before antibiotics were introduced in 1941" (Jonas et al., 2014). Still, the underlying premise that untreatable infections would have ramifications across the health system, changing the risk calculations underlying routine procedures, is undeniable.

The irony of the problem is that the same factors that drive the high burden of infectious disease, including poor sanitation, lack of primary care, and limited access to medicines, in turn encourage the emergence of resistant pathogens. The prevalence of multidrug resistant organisms, especially *E. coli* and *Klebsiella* spp., in gut bacteria that can spread partly through contaminated food and water, decreases with rising gross national income (Alvarez-Uria et al., 2016) (see Figure 2-4). The medicines that treat these pathogens are expensive and often unavailable in low- and middle-income countries, while treating the resistant infection with an ineffective antimicrobial provides selective pressure that encourages the spread of resistant pathogens (Alvarez-Uria et al., 2016).

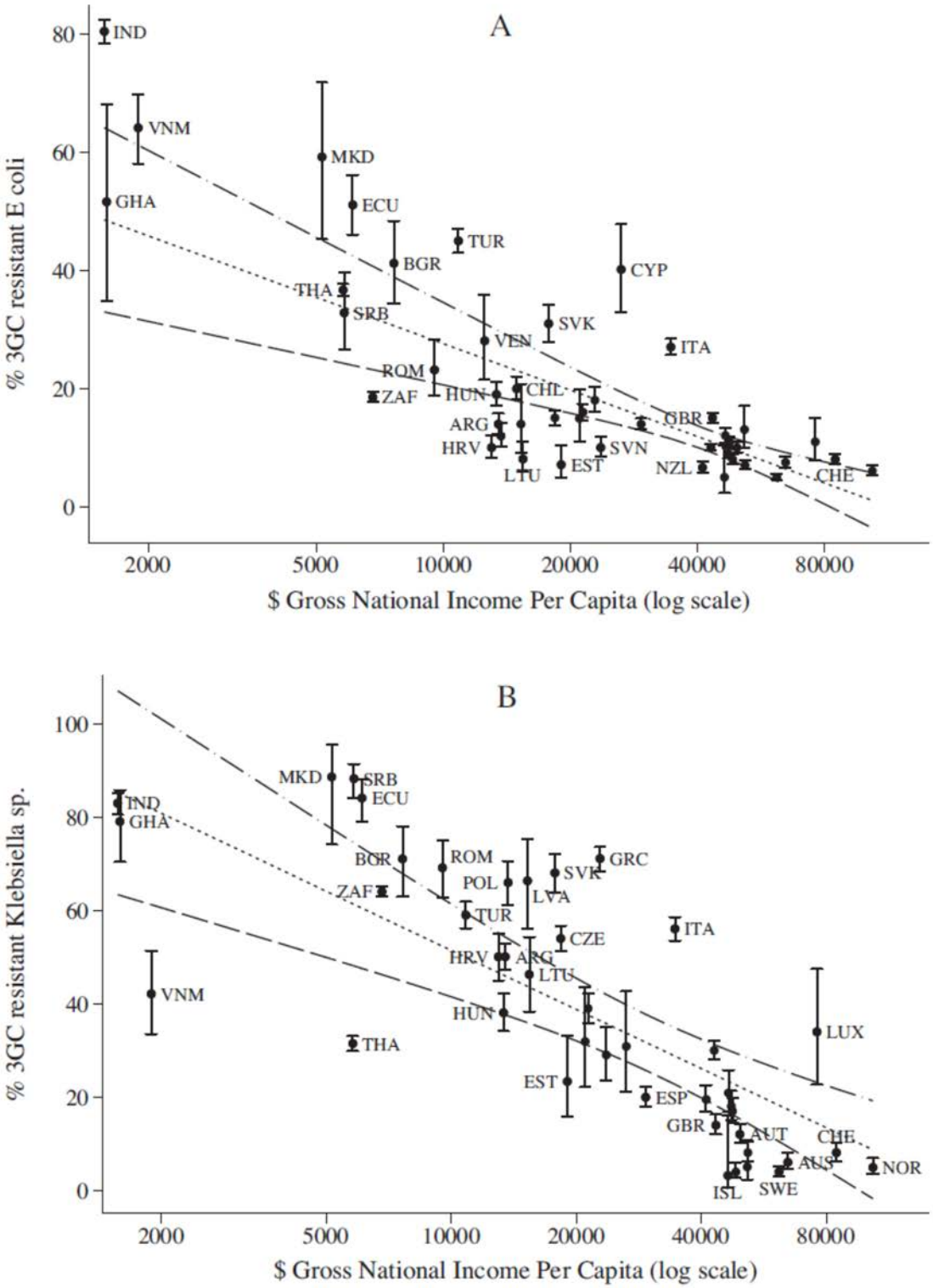



**FIGURE 2-4** Prevalence of third-generation cephalosporin-resistant (3GCR) *E. coli*3 (A) and *Klebsiella* spp. (B) against gross national income per capita, predicted values with 95% confidence intervals. SOURCE: Alvarez-Uria et al., 2016.

An epidemiological transition in low- and middle-income countries has increased their relative burden of noncommunicable diseases, especially cardiovascular disease, cancer, respiratory diseases, and diabetes (Ritchie and Roser, 2018; WHO, 2018b). The increasing global burden of chronic diseases could, ironically, lead to greater demand for effective anti-infective medicines. Conditions such as cancer and diabetes weaken the immune system, increasing susceptibility to infection. Some surgery and cancer treatments require prophylactic antibacterials, which carry their own risks and trade-offs relating to development of resistance (Liss and Cornely, 2016; WHO, 2018a). The consequences of resistance for cancer and surgical treatments are also serious. By recent estimates 39 to 51 percent of surgical site infections in the United States are resistant to standard prophylactic antibiotics, as are about a quarter of infections after cancer chemotherapy (Teillant et al., 2015). Further reductions in the efficacy of prophylactic antibiotics, even a relatively modest decrease of 10 percent, could cause an additional 2,100 deaths a year in the United States alone (Teillant et al., 2015).

Such figures are especially troubling in light of recent attention to the unmet global need for surgery. Around 60 percent of the world's surgeries happen in high-income countries, home to less than 20 percent of population, while the third of the world living in the poorest countries account for only 6 percent of surgeries (Weiser et al., 2016). This disparity has tangible consequences. By 2015 estimates, almost a third of the global burden of disease has a surgical component, including the almost two-thirds of cancer patients who will need surgery and the roughly 15 percent of pregnant women who will need surgery to deliver safely (Meara et al., 2015; Shrime et al., 2015). The *Lancet* Commission on Global Surgery concluded that an additional 143 million surgeries a year are needed in low- and middle-income countries (Meara et al., 2015).

A worldwide increase in surgery will carry an increasing risk of surgical site infections, a common form of hospital-acquired infection. Already infections at the surgical incision contribute to 4 million postoperative deaths a year (Allegranzi et al., 2011; Nepogodiev et al., 2019). In the United States, 2 to 4 percent of surgical patients may develop these infections (PSNet, 2019). Less can be said about the roughly 122 million surgeries that happen annually in low- and middle-income countries, though evidence indicates rates of surgical site infections to be much higher, affecting roughly 17 percent of surgical patients (Bhangu et al., 2018; Rickard et al., 2020; Stanley, 2020). The limited culture data available indicate that postoperative infections in low- and middle-income countries are also more likely to be drug resistant. Analysis of data from 66 countries found over 35 percent of surgical site infections in the least developed countries to be drug resistant (Allegranzi et al., 2011). Studies from teaching hospitals in Ghana and Egypt have found the majority of surgical site infections to be resistant to multiple drugs (Bediako-Bowan et al., 2020; Elsayed Sabal et al., 2017).

Chronic disease patients also have more contact with the health system and more hospital stays. Resistant pathogens are common in hospitals and can spread easily, surviving in sink drains and on surfaces, occasionally spreading through the hospital staff or contact with medical equipment (CDC, 2019c). In the United States, non-susceptible pathogens, meaning those pathogens either resistant or not entirely susceptible to treatment, are most commonly acquired from contact with catheters, central lines, and ventilators (Weiner-Lastinger et al., 2020). CDC data on infections acquired in hospitals from devices indicate that almost half of *Staphylococcus aureus* are not susceptible to methicillin and over 80 percent of *Enterococcus faecium* are not susceptible to vancomycin (Weiner-Lastinger et al., 2020). Resistant pathogens are at least three times higher in hospitals in low- and middle-income countries than in United States, and

infections associated with hospital devices are up to 13 times higher (Allegranzi et al., 2011; WHO, 2015a).

### The Risk Resistant Pathogens Pose to Children

Increasing resistance has consequences for everyone, described in more detail in Chapter 3. Resistant pathogens pose some of their most serious threats to children. The combination of immature immune systems and frequent, repeated exposure to viruses and bacteria makes children more vulnerable to infections (WHO, 2020c). Despite marked declines over the past 30 years, infectious diseases are still among the leading causes of death for children under 5 worldwide, including over 800,000 deaths from pneumonia and over 500,000 from diarrhea (Dadonaite, 2019; WHO, 2020b). Sepsis, a life-threatening and dysregulated response to infection, is especially dangerous to children as their symptoms may be hard to recognize and their deterioration rapid (Plunkett and Tong, 2015; Singer et al., 2016b). Children under age 5 account for almost half of the world's roughly 49 million sepsis cases a year and about a quarter of all sepsis deaths (Rudd et al., 2020).

Neonatal infections are often caused by drug-resistant pathogens (Folgori et al., 2017; Laxminarayan et al., 2016). Roughly 214,000 neonates die from resistant, septic infections every year (Laxminarayan et al., 2016) (see Figure 2-5). Of particular concern for newborns are the gram-negative infections that are difficult to treat for reasons described in Box 2-3 (Folgori et al., 2017). Enterobacterales, the order of gram-negative bacteria that includes pathogens such as *Escherichia coli* and *Klebsiella* spp., are adept at sharing genes and developing resistance, and are a major threat to neonates (CDC, 2019d; Folgori et al., 2017; Partridge, 2015). Enterobacterales-producing extended-spectrum beta-lactamase (ESBL), an enzyme that conveys resistance to the beta-lactam family of antibiotics, are increasingly common in neonates, both in hospitals and in the community (Folgori et al., 2017; Stapleton et al., 2016). Studies in Asia, South America, and the Middle East have found ESBL-producing bacteria in a majority of neonatal sepsis patients (Folgori et al., 2017). More recent research in seven low- and middle income countries indicates ampicillin-gentamicin is no longer an effective treatment for neonatal sepsis because of high rates of resistance (Thomson et al., 2021).[3]

[3] Bangladesh, India, Pakistan, Ethiopia, Nigeria, Rwanda, and South Africa.

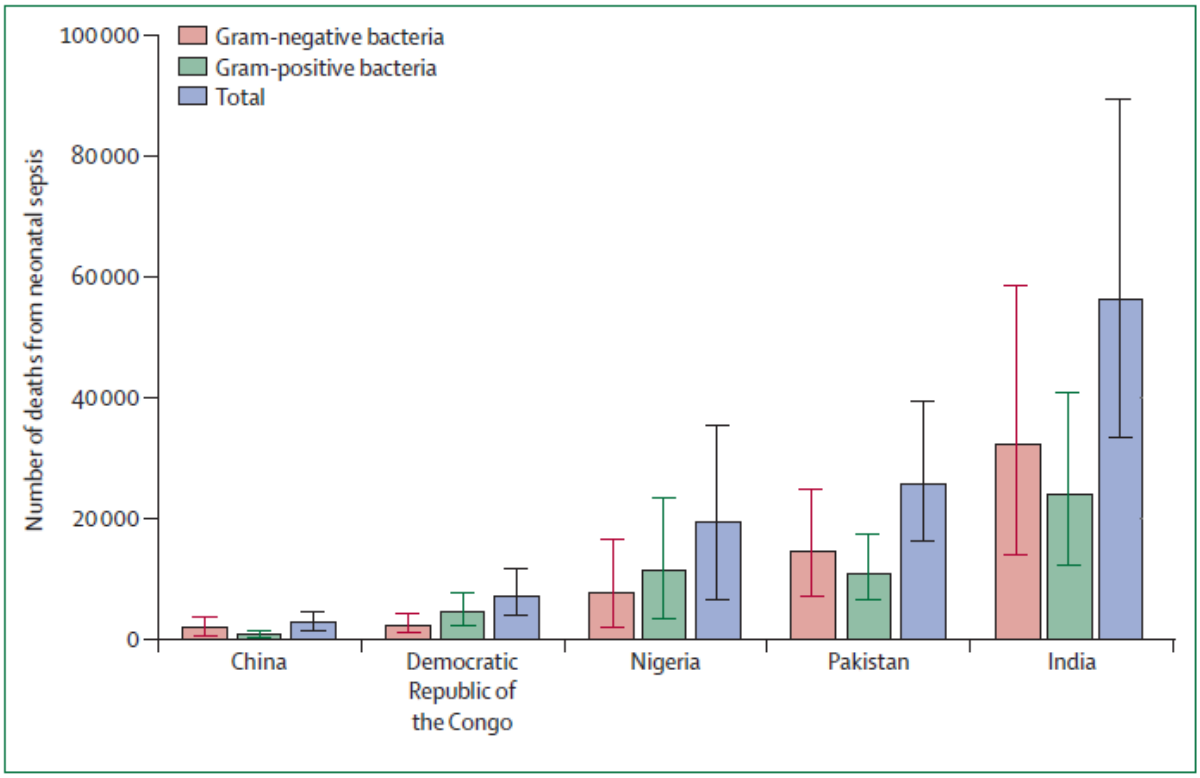


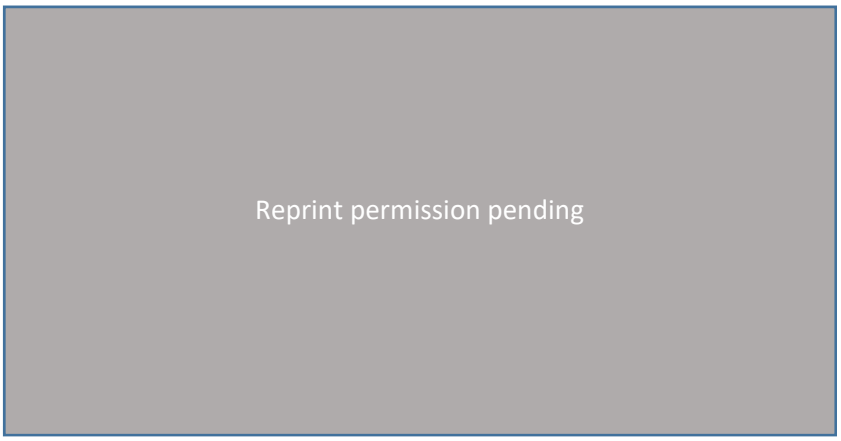

**FIGURE 2-5** Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries, estimates with maximum and minimum values from Latin Hypercube Sampling. SOURCE: Laxminarayan et al., 2016.

**BOX 2-3**
**The Challenge of Treating Gram-Negative Bacteria**

The description of bacteria as gram negative or gram positive refers to the results of a laboratory staining test called the Gram stain. Differences in the structure of the bacterial cell wall cause bacteria either to retain a crystal violet dye (gram positive) or be decolorized and retain a pink color upon treatment with a counterstain (gram negative). Although not all bacteria fall clearly into one of these two groups, Gram stain is traditionally the first step in identifying a bacterial pathogen. Four of the six most problematic, multidrug resistant pathogens found in hospitals (*Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) are gram-negative bacteria.

As the figure below shows, gram-negative bacteria have less permeable cell walls than gram-positive ones. Gram-negative bacteria have an envelope made up of three layers: a phospholipid outer membrane, a rigid, peptidoglycan cell wall, and an inner phospholipid membrane. The outer membrane of gram-negative bacteria provides crucial protection and acts as a selective barrier that can restrict access of certain antibiotics into the cell, providing intrinsic resistance to antibiotics that target processes within the cell. Gram-negative bacteria can also produce enzymes that can degrade the antibiotic or modify its shape to inactivate it (e.g., beta-lactamases inactivate the beta-lactam antibiotics).

The cell envelopes of gram-negative bacteria also contain efflux pumps, structures that remove toxins, including antibiotics, from the bacteria. By removing antibacterial agents from the cell, drug efflux raises the concentrations of these agents in their vicinity, thereby reducing the growth of commensal bacteria, and triggering a shift in the composition of the bacterial community, with more resistant bacteria dominating in only a few generations.




SOURCE: Mahadevia, 2017.

SOURCES: Breijyeh et al., 2020; Bush and Bradford, 2020; Delcour, 2009; Ramirez et al., 2014; Soto, 2013; Wen et al., 2018.

Prompt treatment with effective antimicrobials could avert hundreds of thousands of child deaths every year. Pneumonia deaths alone could be reduced 75 percent, meaning over 400,000 deaths averted among children under 5 every year (Laxminarayan et al., 2016). Yet access to these medicines is uneven. Survey data from health posts, hospitals, and dispensaries in 20 low- and middle-income countries indicate even Access Group antibiotics are available less than half the time, most of that driven by fairly reliable stocks of only three drugs: co-trimoxazole, amoxicillin, and metronidazole (Knowles et al., 2020) (see Figure 2-6).

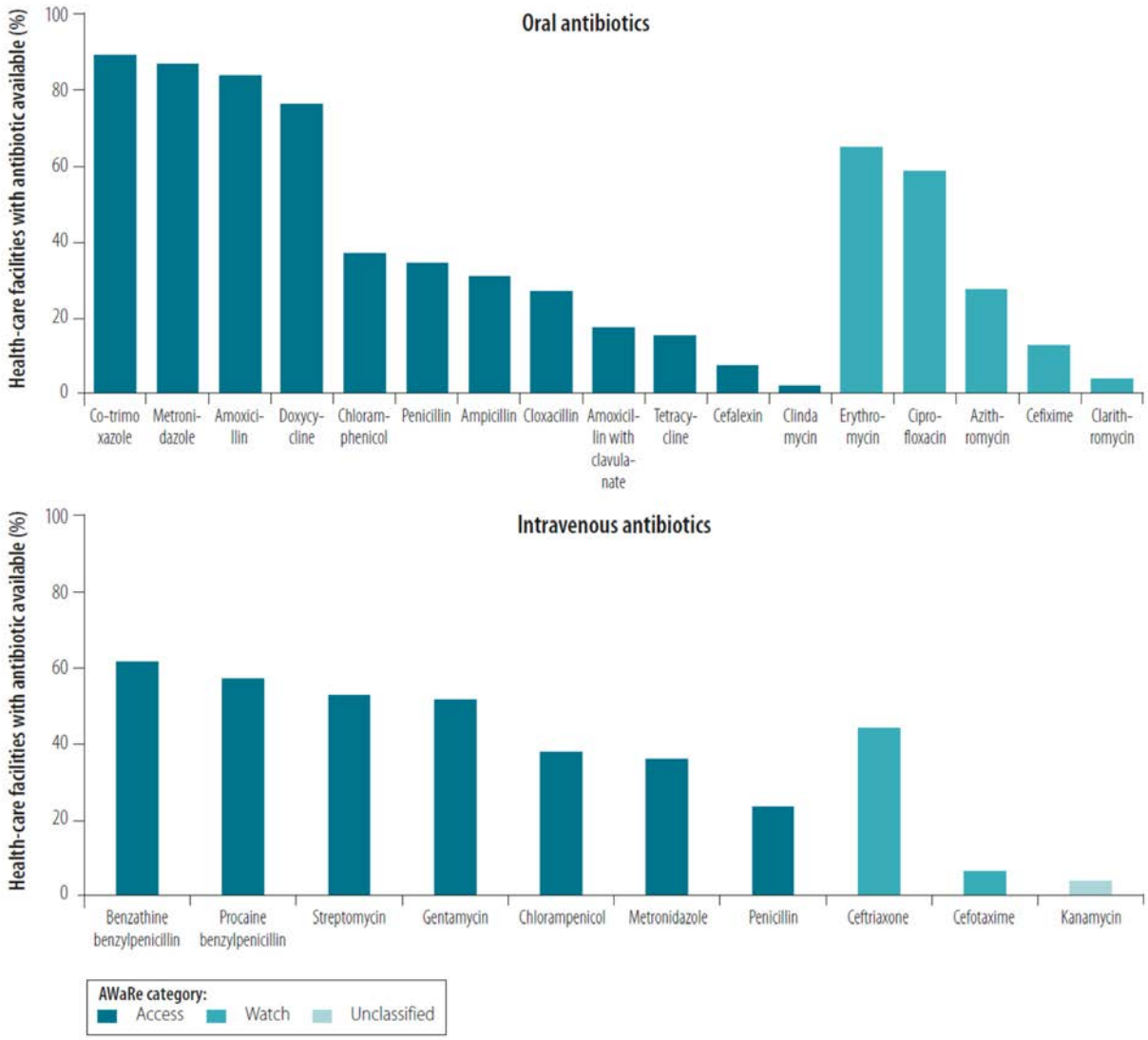



**FIGURE 2-6** Antibiotic availability at health facilities, survey data from 20 low- and middle-income countries, 2014–2017.
SOURCE: Knowles et al., 2020.

## ANTIMICROBIAL RESISTANCE IS A COMPLEX ADAPTIVE PROBLEM

Antimicrobial resistance is complex. It is a health and, less obviously, an environmental problem. It affects everyone, both today and in the future in a, “shared, interdependent

vulnerability … that will have a substantial impact on all aspects of our lives" (Littman et al., 2020). A global health response will be central to any mitigation strategy, but it is difficult to find transferable strategies from other global health problems, as antimicrobial resistance is not the result of any one pathogen or casual process, but a complex web of related problems, sometimes related only loosely (Hoffman et al., 2020). The dynamic relationships among different nodes on this web mean that action in one setting can reverberate in another in ways that are not direct or linear. This feature of the problem is sometimes described as an *adaptive challenge* (Hinchliffe et al., 2018; Pham, 2017). Because of the adaptive challenge, it is difficult to predict how resistance will emerge, despite wide agreement that global changes will influence both antimicrobial use and resistance (Lambraki et al., 2021).

The inappropriate or irrational use of antimicrobials in human medicine is often the first feature of this complex adaptive problem to attract policy attention. Antimicrobial use in farming, especially animal agriculture and aquaculture, is another common point of discussion, though the ramifications for the price of food and livelihoods of farmers are less well studied (FAO, 2017; Hinchliffe et al., 2018). But there is relatively little known about the economic and ecological impact of antimicrobials that leach into the environment through water and soil contamination. Box 2-4 gives an example of how disruptions to the microbiome in a species of ecological importance may have serious downstream ramifications, even among species not generally referenced in discussions of antimicrobial resistance.

**BOX 2-4**
**The Ecosystem Value of the Oyster Microbiome**

Ecosystem services is a way of describing the benefits, both direct and indirect, humans draw from their interactions with the ecosystem. These services can be tangible (e.g., wood, food) or intangible (e.g., recreation, spiritual experiences). They can be basic, underlying processes that sustain systems such as nutrient cycling and photosynthesis, or the benefits humans accrue from the processes that make the environment clean, sustainable, and resilient. The ability of oysters to remove nitrogen from coastal waters is an example of the last type of ecosystem service.

Shellfish, especially oysters, are a keystone or foundational species in coastal ecosystems, meaning that they influence the environment in ways that allow other species in the ecosystem to survive. With the exception of their harvest for food, most of the services oysters provide do not have an obvious dollar value. Attempts to quantify the value of the ecosystem services oysters provide have to consider a range of factors including their filtering sediment and plankton, allowing light to penetrate further into the water, aiding the growth of aquatic plants, and the influence of oysters and their reefs in protecting other fish species. Such analyses have put the value of ecosystems services oysters provides between $55,000 and $99,000 per hectare per year.

One of the valuable ecosystem services oysters provide is denitrification, the process of converting dangerous waste into a harmless gas. Denitrification by oysters is bacterially mediated, meaning that the microbiome in oysters' gut and shell drive the process. Antimicrobial residuals and other pollutants in wastewater and agricultural runoff disrupt these microbiomes. A decrease in colonization with beneficial bacteria and a rise in the concentrations of pathogenic bacteria poses a threat not just to oysters, but to the entire ecosystem they support and the humans who consume them. No economic analysis to date has looked at these distal, but potentially devastating, consequences.

SOURCES: Arfken et al., 2017; Britt et al., 2020; Grabowski et al., 2012; NWF, 2021; Schug et al., 2009.

As the concentration of antimicrobials in water and soil increases, so does the likelihood of encountering resistant microbes. Horizontal gene transmission, working against a background of increasing selection pressure and microbial diversity, increases the chances of a microbe acquiring resistance (Knapp et al., 2010). In this regard, susceptibility of pathogens to antimicrobial medicines, most of them descendants of soil bacteria, is a natural resource. The erosion of this resource is to some degree inevitable, but its rate is not. The challenge remains to preserve susceptible microbial communities that benefit the ecosystem (Jørgensen et al., 2018). The introduction of new medical products, both to avoid unnecessary use and replace ineffective medicines, will be central to any response strategy. So will a better understanding of the interrelatedness of resistance in human, animal, and environmental reservoirs (Jørgensen et al., 2018).

An emphasis on new medicines and a multisectoral response to antimicrobial resistance was a feature of the O'Neill report, a 2-year expert review of rising antimicrobial drug resistance and policy recommendations to mitigate it (Review on Review on AMR). The final report, published in 2016, set out seven steps to reduce demand for antimicrobials, thereby prolonging

the useful life of the medicines available today, and two further steps to increase the supply of new antimicrobials (Review on Review on AMR).

The O'Neill report encouraged global interest in the problem of antimicrobial resistance (Collier and O'Neill, 2018; SfAM, 2018). Its call for the attention of the United Nations (UN) and the G7 and G20 forums resulted in antimicrobial product development partnerships such as the Global Antibiotic Research and Development Partnerships and CARB-X (officially, the Combating Antibiotic Resistance Biopharmaceutical Accelerator) discussed in Chapter 6, and the UN High-Level Meeting on Antimicrobial Resistance (Evans, 2017; UN, 2016a). At this meeting the UN General Assembly called for wide support for national action plans for antimicrobial resistance and for coordinated action at the global, regional, and national levels (UN, 2016b). At the same time, progress against most of the O'Neill commission's recommendations has been partial at best (Collier and O'Neill, 2018). As with other complex adaptive problems, change can be slow and progress difficult to measure.

## ONE HEALTH IS A COMPLEX ADAPTIVE RESPONSE

Response to the global health problem of antimicrobial resistance needs to consider the relationships among human, animal, and plant health, and the role of the environment as a source and conduit of resistance. This mutual dependence is central to the One Health approach, a way of working on health problems at the interface of human, animal, and environmental health (CDC, 2018b). The One Health movement has its roots in recognition of the intermeshed vulnerabilities of animals and humans (McEwen and Collignon, 2018). One Health adds attention to the environment, acknowledging the equal importance of the environmental health and natural resources to human and animal health problems (McEwen and Collignon, 2018).

The environmental component of antimicrobial resistance includes not only the watershed and soil management of drug residues and resistance genes, but the likelihood that climate change will aggravate the problem. Historical data strongly suggest a relationship between an increasing burden of antibiotic resistance and an increasing average temperature (MacFadden et al., 2018). The mechanism driving this relationship is not clear, but may be related to increasing horizontal gene transfer (including transfer of resistance genes) at higher temperatures (Burnham, 2021). Higher temperatures are also a key predictor of bacterial growth rates and are therefore thought to drive an increased bacterial carriage in both humans and animals (Burnham, 2021). Research on resistant isolates collected in Europe over 16 years found ambient temperature to be the most important contributor to the emergence of resistance (McGough et al., 2020). Average minimum temperature and population density are associated with an increasing percentage of resistance among common pathogens (MacFadden et al., 2018). While rising temperature and water levels have a role in encouraging resistance, it is also likely that more complicated social factors related to climate change are driving antimicrobial pollution in the environment. As the climate warms, for example, the atmosphere retains more water, causing more severe storms and flooding. Floods in turn, displace people, increasing crowding and infections, and bring more humans and livestock into contact with contaminated sewage (Burnham, 2021). Ripple effects of climate change will aggravate the crowding and sanitation problems that cause diseases such as tuberculosis, cholera, and dengue (McMichael et al., 2003; Murray et al., 2020). Increasing temperatures and rainfall will influence the survival, breeding, and biting rates of mosquitoes and other arthropod vectors of disease (Franklinos et al., 2019; McMichael et al., 2003). All of these changes will cause a great demand for effective

antimicrobial medicines, medicines that are themselves in jeopardy, partly for the same root reasons.

Antimicrobial resistance is a textbook One Health problem (Mackenzie and Jeggo, 2019; Robinson et al., 2016). Because of the rapid spread of microbes internationally it has also been described as a "One World" problem (Mackenzie and Jeggo, 2019; Robinson et al., 2016). It is a priority item in the World Bank's *One Health Operational Framework* (Berthe et al., 2018). Most national and international strategy documents for action against antimicrobial resistance, including the U.S. government's national strategy and action plans for combating antibiotic-resistant bacteria, emphasize the importance of an integrated, cross-sector, One Health response (CARB, 2020; PCAST, 2015; White and Hughes, 2019).

Nevertheless, the capacity to put One Health principles into practice tends to lag the realization of their importance (Mackenzie and Jeggo, 2019; Queenan et al., 2017; Sinclair, 2019). It can be difficult to bring experts from different agencies or disciplines together, especially when there are competing needs and trade-offs to be made among the different sectors (Lhermie et al., 2019b; Robinson et al., 2016). At the same time, without joint ownership and shared intellectual effort that One Health affords, some perspectives will be pushed to the margin (Waltner-Toews, 2017). A One Health response may be complicated, but is an unavoidable reflection of the complexity of the problem.

One Health gives a style of analysis well suited to complex and adaptive systems. The nature of the collaboration recognizes the interrelationships between humans, animals, and the environment (Complex adaptive systems, 2010). Though sometimes cumbersome, such collaboration can help ensure communication among all stakeholders (Waltner-Toews, 2017).

## REFERENCES

Aarestrup, F. M. 2015. The livestock reservoir for antimicrobial resistance: A personal view on changing patterns of risks, effects of interventions and the way forward. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 370(1670):20140085.

Aga, D., J. Davies, S. Gandra, B. Kasprzyk-Hordern, J. Larsson, J. McLain, A. Singer, J. Snape, H. Slijkhuis, and A. Sweetman. 2018. Initiatives for addressing antimicrobial resistance in the environment: Current situation and challenges: Wellcome; The U.S. Centers for Disease Control and Prevention; The UK Science and Innovation Network.

Agriculture.com Staff. 2018. *Feeding medicated chicken feeds*. https://www.agriculture.com/livestock/poultry/feed/medicated-chicken-feeds_292-ar13577 (accessed September 10, 2021).

Allegranzi, B., S. Bagheri Nejad, C. Combescure, W. Graafmans, H. Attar, L. Donaldson, and D. Pittet. 2011. Burden of endemic health-care-associated infection in developing countries: Systematic review and meta-analysis. *Lancet* 377(9761):228-241.

Almeida, F., M. L. Rodrigues, and C. Coelho. 2019. The still underestimated problem of fungal diseases worldwide. *Frontiers in Microbiology* 10:214.

Alvarez-Uria, G., S. Gandra, and R. Laxminarayan. 2016. Poverty and prevalence of antimicrobial resistance in invasive isolates. *International Journal of Infectious Diseases* 52:59-61.

Alzahrani, M. S., M. K. Maneno, M. N. Daftary, L. Wingate, and E. B. Ettienne. 2018. Factors associated with prescribing broad-spectrum antibiotics for children with upper respiratory tract infections in ambulatory care settings. *Clinical Medicine Insights: Pediatrics* 12:1179556518784300.

Arfken, A., B. Song, J. S. Bowman, and M. Piehler. 2017. Denitrification potential of the eastern oyster microbiome using a 16s rrna gene based metabolic inference approach. *PloS One* 12(9):e0185071.

Argudin, M. A., A. Deplano, A. Meghraoui, M. Dodemont, A. Heinrichs, O. Denis, C. Nonhoff, and S. Roisin. 2017. Bacteria from animals as a pool of antimicrobial resistance genes. *Antibiotics (Basel)* 6(2):12.

Arora, P., P. Singh, Y. Wang, A. Yadav, K. Pawar, A. Singh, G. Padmavati, J. Xu, and A. Chowdhary. 2021. Environmental isolation of candida auris from the coastal wetlands of andaman islands, india. *mBio* 12(2):e03181-03120.

Ayukekbong, J. A., M. Ntemgwa, and A. N. Atabe. 2017. The threat of antimicrobial resistance in developing countries: Causes and control strategies. *Antimicrobial Resistance & Infection Control* 6(1):47.

Bakhsh, A. A., H. Shabeeh, F. Mannocci, and S. A. Niazi. 2020. A review of guidelines for antibiotic prophylaxis before invasive dental treatments. *Applied Sciences* 11(1).

Baltenweck, I., D. Enahoro, A. Frija, and S. Tarawali. 2020. Why is production of animal source foods important for economic development in africa and asia? *Animal Frontiers* 10(4):22-29.

Baptiste, K. E., and L. Pokludová. 2020. Mass medications: Prophylaxis and metaphylaxis, cascade and off-label use, treatment guidelines and antimicrobial stewardship. In *Antimicrobials in livestock 1: Regulation, science, practice*: Springer. Pp. 167-193.

Beceiro, A., M. Tomas, and G. Bou. 2013. Antimicrobial resistance and virulence: A successful or deleterious association in the bacterial world? *Clinical Microbiology Reviews* 26(2):185-230.

Bediako-Bowan, A. A. A., J. A. L. Kurtzhals, K. Molbak, A. K. Labi, E. Owusu, and M. J. Newman. 2020. High rates of multi-drug resistant gram-negative organisms associated with surgical site infections in a teaching hospital in ghana. *BMC Infectious Diseases* 20(1):890.

Benler, S., N. Yutin, D. Antipov, M. Rayko, S. Shmakov, A. B. Gussow, P. Pevzner, and E. V. Koonin. 2021. Thousands of previously unknown phages discovered in whole-community human gut metagenomes. *Microbiome* 9(1):78.

Berthe, F. C. J., T. Bouley, W. B. Karesh, I. C. Legall, C. C. Machalaba, C. A. Plante, and R. M. Seifman. 2018. *One health: Operational framework for strengthening human, animal, and environmental public health systems at their interface.* The World Bank.

Bhangu, A., A. O. Ademuyiwa, M. L. Aguilera, P. Alexander, S. W. Al-Saqqa, G. Borda-Luque, A. Costas-Chavarri, T. M. Drake, F. Ntirenganya, J. E. Fitzgerald, S. J. Fergusson, J. Glasbey, J. C. A. Ingabire, L. Ismaïl, H. K. Salem, A. T. T. Kojo, M. C. Lapitan, R. Lilford, A. L. Mihaljevic, D. Morton, A. Z. Mutabazi, D. Nepogodiev, A. O. Adisa, R. Ots, F. Pata, T. Pinkney, T. Poškus, A. U. Qureshi, A. Ramos-De la Medina, S. Rayne, et al. 2018. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: A prospective, international, multicentre cohort study. *The Lancet Infectious Diseases* 18(5):516-525.

Bielen, A., A. Simatovic, J. Kosic-Vuksic, I. Senta, M. Ahel, S. Babic, T. Jurina, J. J. Gonzalez Plaza, M. Milakovic, and N. Udikovic-Kolic. 2017. Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. *Water Research* 126:79-87.

Brault, S. A., S. J. Hannon, S. P. Gow, S. J. G. Otto, C. W. Booker, and P. S. Morley. 2019. Calculation of antimicrobial use indicators in beef feedlots-effects of choice of metric and standardized values. *Frontiers in Veterinary Science* 6(330):330.

Breijyeh, Z., B. Jubeh, and R. Karaman. 2020. Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. *Molecules* 25(6):1340.

Britt, A., M. Bernini, B. McSweeney, S. Dalapati, S. Duchin, K. Cavanna, N. Santos, G. Donovan, K. O'Byrne, S. Noyes, M. Romero, K. N. T. Poonacha, and T. Scully. 2020. The effects of atrazine on the microbiome of the eastern oyster: Crassostrea virginica. *Scientific Reports* 10(1):11088.

Buffie, C. G., V. Bucci, R. R. Stein, P. T. McKenney, L. Ling, A. Gobourne, D. No, H. Liu, M. Kinnebrew, A. Viale, E. Littmann, M. R. van den Brink, R. R. Jenq, Y. Taur, C. Sander, J. R. Cross, N. C. Toussaint, J. B. Xavier, and E. G. Pamer. 2015. Precision microbiome reconstitution restores bile acid mediated resistance to clostridium difficile. *Nature* 517(7533):205-208.

Buller, H., K. Adam, A. Bard, A. Bruce, S. Hinchliffe, L. Morgans, G. Rees, and K. K. Reyher. 2020. Veterinary diagnostic practice and the use of rapid tests in antimicrobial stewardship on uk livestock farms. *Frontiers in Veterinary Science* 7:765.

Bunge, J. 2016. *Perdue farms eliminated antibiotics from chicken supply*. https://www.wsj.com/articles/perdue-farms-eliminated-all-antibiotics-from-its-chicken-supply-1475775456 (accessed April 27, 2021).

Burnham, J. P. 2021. Climate change and antibiotic resistance: A deadly combination. *Therapeutic Advances in Infectious Disease* 8:2049936121991374.

Bush, K., and P. A. Bradford. 2020. Epidemiology of beta-lactamase-producing pathogens. *Clinical Microbiology Reviews* 33(2):e00047-00019.

CARB (National Action Plan for Combating Antibiotic-Resistant Bacteria). 2020. National action plan for combating antibiotic resistant bacteria. *Federal Task Force on Combating Antibiotic-Resistant Bacteria*.

Casadevall, A., D. P. Kontoyiannis, and V. Robert. 2019. On the emergence of candida auris: Climate change, azoles, swamps, and birds. *mBio* 10(4):e01397-01319.

Casadevall, A., and L. A. Pirofski. 2019. Benefits and costs of animal virulence for microbes. *mBio* 10(3).

Casewell, M., C. Friis, E. Marco, P. McMullin, and I. Phillips. 2003. The european ban on growth-promoting antibiotics and emerging consequences for human and animal health. *Journal of Antimicrobial Chemotherapy* 52(2):159-161.

CDC (Centers for Disease Control and Prevention). 2011. Office-related antibiotic prescribing for persons aged≤ 14 years--united states, 1993-1994 to 2007-2008. *Morbidity and Mortality Weekly Report* 60(34):1153-1156.

CDC. 2018a. *The AMR challenge*. https://www.cdc.gov/drugresistance/intl-activities/amr-challenge.html (accessed June 30, 2021).

CDC. 2018b. *One health*. https://www.cdc.gov/onehealth/basics/index.html (accessed April 28, 2021).

CDC. 2019a. *Antibiotic resistance and narms surveillance*. https://www.cdc.gov/narms/faq.html (accessed November 21, 2021).

CDC. 2019b. *Antibiotic use in the united states, 2018 update: Progress and opportunities.* Atlanta, GA.

CDC. 2019c. *Healthcare-associated infections, antibiotic resistant germs in hospitals*. https://www.cdc.gov/hai/patientsafety/ar-hospitals.html (accessed April 8, 2021).

CDC. 2019d. *Healthcare-associated infections, ESBL-producing enterobacterales* https://www.cdc.gov/hai/organisms/ESBL.html (accessed April 8, 2021).

Cepas, V., and S. M. Soto. 2020. Relationship between virulence and resistance among gram-negative bacteria. *Antibiotics (Basel)* 9(10).

Chatterjee, A., M. Modarai, N. R. Naylor, S. E. Boyd, R. Atun, J. Barlow, A. H. Holmes, A. Johnson, and J. V. Robotham. 2018. Quantifying drivers of antibiotic resistance in humans: A systematic review. *Lancet Infectious Diseases* 18(12):e368-e378.

Checcucci, A., P. Trevisi, D. Luise, M. Modesto, S. Blasioli, I. Braschi, and P. Mattarelli. 2020. Exploring the animal waste resistome: The spread of antimicrobial resistance genes through the use of livestock manure. *Frontiers in Microbiology* 11(1416):1416.

Cima, G. 2017. *Herd sizes, trade risk pig health: Swine veterinarians preparing for emergence of more diseases*. https://www.avma.org/javma-news/2017-05-01/herd-sizes-trade-risk-pig-health (accessed April 22, 2021).

Cogliani, C., H. Goossens, and C. Greko. 2011. Restricting antimicrobial use in food animals: Lessons from europe. *Microbe* 6(6):274.

Collier, P., and L. J. O'Neill. 2018. Two years on: An update on achievement towards the recommendations of the antimicrobial resistance report. *Journal of Applied Microbiology* 125(2):308-312.

Complex adaptive systems. 2010. *The Health Foundation*.

Crowther, G. S., and M. H. Wilcox. 2015. Antibiotic therapy and clostridium difficile infection–primum non nocere–first do no harm. *Infection and drug resistance* 8:333.

Dadonaite, B. 2019. *Pneumonia — no child should die from a disease we can prevent*. https://ourworldindata.org/child-deaths-from-pneumonia (accessed April 8, 2021).

Davies, R., and A. Wales. 2019. Antimicrobial resistance on farms: A review including biosecurity and the potential role of disinfectants in resistance selection. *Comprehensive Reviews in Food Science and Food Safety* 18(3):753-774.

Davies, S. C. 2013. *Annual report of the Chief Medical Officer, volume two, 2011, infections and the rise of antimicrobial resistance.* London: Department of Health.

Delcour, A. H. 2009. Outer membrane permeability and antibiotic resistance. *Biochimica et Biophysica Acta* 1794(5):808-816.

Dewan, K. K., A. L. Skarlupka, I. Rivera, L. E. Cuff, M. C. Gestal, D. L. Taylor-Mulneix, S. Wagner, V. E. Ryman, C. Rodriguez, I. Hamidou Soumana, B. R. Levin, and E. T. Harvill. 2018. Development of macrolide resistance in bordetella bronchiseptica is associated with the loss of virulence. *Journal of Antimicrobial Chemotherapy* 73(10):2797-2805.

D'Souza, A. W., M. Boolchandani, S. Patel, G. Galazzo, J. M. van Hattem, M. S. Arcilla, D. C. Melles, M. D. de Jong, C. Schultsz, C. Consortium, G. Dantas, and J. Penders. 2021. Destination shapes antibiotic resistance gene acquisitions, abundance increases, and diversity changes in dutch travelers. *Genome Medicine* 13(1):79.

ECDC (European Centre for Disease Prevention and Control). 2013. *Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in aspergillus species.* Stockholm, Sweden: ECDC.

Elmund, G. K., S. M. Morrison, D. W. Grant, and S. M. Nevins. 1971. Role of excreted chlortetracycline in modifying the decomposition process in feedlot waste. *Bulletin of Environmental Contamination and Toxicology* 6(2):129-132.

Elsayed Sabal, M., W. Zahran, A. Zein-Eldeen, and S. Hamam. 2017. Surgical site infections: Problem of multidrug-resistant bacteria. *Menoufia Medical Journal* 30(4):1005-1013.

Elsey, H., I. Agyepong, R. Huque, Z. Quayyem, S. Baral, B. Ebenso, C. Kharel, R. A. Shawon, O. Onwujekwe, B. Uzochukwu, J. Nonvignon, G. C. Aryeetey, S. Kane, T. Ensor, and T. Mirzoev. 2019. Rethinking health systems in the context of urbanisation: Challenges from four rapidly urbanising low-income and middle-income countries. *BMJ Global Health* 4(3):e001501.

Engel, N., K. Wachter, M. Pai, J. Gallarda, C. Boehme, I. Celentano, and R. Weintraub. 2016. Addressing the challenges of diagnostics demand and supply: Insights from an online global health discussion platform. *BMJ Global Health* 1(4):e000132.

EPA (U.S. Environmental Protection Agency). 2016. Pesticide emergency exemptions; agency decisions and state and federal agency crisis declarations.

EPA. 2018. *Polymers; exemptions from the requirement of a tolerance.* https://www.govinfo.gov/content/pkg/FR-2018-12-04/pdf/2018-26343.pdf (acccessed September 24, 2021).

EPA. 2021a. *Basic information about water reuse*. https://www.epa.gov/waterreuse/basic-information-about-water-reuse (accessed September 23, 2021).

EPA. 2021b. *Streptomycin; pesticide tolerances.* https://www.govinfo.gov/content/pkg/FR-2021-02-09/pdf/2021-02511.pdf (accessed September 24, 2021).

Evans, L. 2017. *G20 Health Ministers' declaration on AMR*. https://noharm-europe.org/articles/news/europe/g20-health-ministers-declaration-amr (accessed April 8, 2021).

Fahrenfeld, N., Y. Ma, M. O'Brien, and A. Pruden. 2013. Reclaimed water as a reservoir of antibiotic resistance genes: Distribution system and irrigation implications. *Frontiers in Microbiology* 4:130.

Fally, M., E. Diernaes, S. Israelsen, B. Tarp, T. Benfield, L. Kolte, and P. Ravn. 2021. The impact of a stewardship program on antibiotic administration in community-acquired pneumonia: Results from an observational before-after study. *International Journal of Infectious Diseases* 103:208-213.

FAO (Food and Agriculture Organization of the United Nations). 2017. Antimicrobial resistance in food and argiculture. *Food and Agriculture Organization of the United Nations*.

FAO. 2018. *The future of food and agriculture 2018: Alternative pathways to 2050*: Food and Agriculture Organization of the United Nations.

FAO and WHO (World Health Organization). 2019. *Joint FAO/WHO expert meeting in collaboration with OIE on foodborne antimicrobial resistance: Role of the environment, crops and biocides - meeting report.* Rome.

Farm Antibiotics. 2017. *How are antibiotics used? What are prophylaxis (prevention), metaphylaxis (control), and therapeutic (curative) treatments?* https://www.farmantibiotics.org/ufaqs/antibiotics-used-prophylaxis-prevention-metaphylaxis-control-therapeutic-curative-treatments/ (accessed October 12, 2021).

FDA (U.S. Food and Drug Administration). 2017. FDA announces implementation of GFI# 213, outlines continuing efforts to address antimicrobial resistance.

Fischer, M. A., M. Mahesri, J. Lii, and J. A. Linder. 2020. Non-infection-related and non-visit-based antibiotic prescribing is common among medicaid patients. *Health Affairs* 39(2):280-288.

Fischer, M. A., M. Mahesri, J. Lii, and J. A. Linder. 2021. Non-visit-based and non-infection-related antibiotic use in the us: A cohort study of privately insured patients during 2016-2018. *Open Forum Infectious Diseases* 8(9):ofab412.

Fisher, M. C., N. J. Hawkins, D. Sanglard, and S. J. Gurr. 2018. Worldwide emergence of resistance to antifungal drugs challenges human health and food security. *Science* 360(6390):739-742.

Folgori, L., J. Bielicki, P. T. Heath, and M. Sharland. 2017. Antimicrobial-resistant gram-negative infections in neonates: Burden of disease and challenges in treatment. *Current Opinion in Infectious Diseases* 30(3):281-288.

Franceschini, G., M. Bottino, I. Millet, E. Martello, F. Zaltron, A. R. Favretto, N. Vonesch, P. Tomao, and A. Mannelli. 2019. Assessment of the exposure of turkey farmers to antimicrobial resistance associated with working practices. *Journal of Veterinary Science* 6(1):13.

Francois Watkins, L. K., M. E. Laughlin, L. A. Joseph, J. C. Chen, M. Nichols, C. Basler, R. Breazu, C. Bennett, L. Koski, M. P. Montgomery, M. J. Hughes, S. Robertson, C. G. Lane, A. J. Singh, D. Stanek, E. Salehi, E. Brandt, G. McGillivary, J. Mowery, J. DeMent, R. D. Aubert, A. L. Geissler, S. de Fijter, I. T. Williams, and C. R. Friedman. 2021. Ongoing outbreak of extensively drug-resistant campylobacter jejuni infections associated with us pet store puppies, 2016-2020. *JAMA Network Open* 4(9):e2125203.

Franklinos, L. H. V., K. E. Jones, D. W. Redding, and I. Abubakar. 2019. The effect of global change on mosquito-borne disease. *Lancet Infectious Diseases* 19(9):e302-e312.

Frost, I., T. P. Van Boeckel, J. Pires, J. Craig, and R. Laxminarayan. 2019. Global geographic trends in antimicrobial resistance: The role of international travel. *Journal of Travel Medicine* 26(8).

Goldstein, E. J., D. A. Goff, W. Reeve, S. Naumovski, E. Epson, J. Zenilman, K. S. Kaye, and T. M. File, Jr. 2016. Approaches to modifying the behavior of clinicians who are noncompliant with antimicrobial stewardship program guidelines. *Clinical Infectious Diseases* 63(4):532-538.

Grabowski, J. H., R. D. Brumbaugh, R. F. Conrad, A. G. Keeler, J. J. Opaluch, C. H. Peterson, M. F. Piehler, S. P. Powers, and A. R. Smyth. 2012. Economic valuation of ecosystem services provided by oyster reefs. *Bioscience* 62(10):900-909.

Graham, J. P., J. J. Boland, and E. Silbergeld. 2007. Growth promoting antibiotics in food animal production: An economic analysis. *Public Health Reports* 122(1):79-87.

Halling-Sorensen, B., S. Nors Nielsen, P. F. Lanzky, F. Ingerslev, H. C. Holten Lutzhoft, and S. E. Jorgensen. 1998. Occurrence, fate and effects of pharmaceutical substances in the environment--a review. *Chemosphere* 36(2):357-393.

Hedman, H. D., K. A. Vasco, and L. Zhang. 2020. A review of antimicrobial resistance in poultry farming within low-resource settings. *Animals* 10(8):1264.

Hinchliffe, S., A. Butcher, and M. M. Rahman. 2018. The amr problem: Demanding economies, biological margins, and co-producing alternative strategies. *Palgrave Communications* 4(1):142.

Hoelzer, K., L. Bielke, D. P. Blake, E. Cox, S. M. Cutting, B. Devriendt, E. Erlacher-Vindel, E. Goossens, K. Karaca, S. Lemiere, M. Metzner, M. Raicek, M. Collell Surinach, N. M. Wong, C. Gay, and F. Van Immerseel. 2018. Vaccines as alternatives to antibiotics for food producing animals. Part 1: Challenges and needs. *Veterinary Research* 49(1):64.

Hoffman, S. J., J. Savulescu, A. Giubilini, C. Kirchhelle, S. Rogers Van Katwyk, I. Weldon, B. Campus, M. Harrison, H. Maslen, and A. McLean. 2020. Governing the global antimicrobial commons: Introduction to special issue. *Health Care Analysis*.

Hogerzeil, H., G. Frank, N. Grundmann, M. Kettis, J. Larsson, M. Mendelson, M. Ndomondo-Sigonda, K. Nedog, S. Paulin, A. Singer, G. Breugelmans, F. Rafiqi, A. A. Ruiz, R. Baron, D. Calçada, and M. Hellamand. 2020. 2020 antimicrobial resistance benchmark. *Access to Medicine Foundation*

Holmes, A. H., L. S. Moore, A. Sundsfjord, M. Steinbakk, S. Regmi, A. Karkey, P. J. Guerin, and L. J. Piddock. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 387(10014):176-187.

Imanpour, S., O. Nwaiwu, D. K. McMaughan, B. DeSalvo, and A. Bashir. 2017. Factors associated with antibiotic prescriptions for the viral origin diseases in office-based practices, 2006-2012. *JRSM Open* 8(8):2054270417717668.

Iramiot, J. S., H. Kajumbula, J. Bazira, C. Kansiime, and B. B. Asiimwe. 2020. Antimicrobial resistance at the human-animal interface in the pastoralist communities of kasese district, south western uganda. *Scientific Reports* 10(1):14737.

Johanesen, P. A., K. E. Mackin, M. L. Hutton, M. M. Awad, S. Larcombe, J. M. Amy, and D. Lyras. 2015. Disruption of the gut microbiome: Clostridium difficile infection and the threat of antibiotic resistance. *Genes (Basel)* 6(4):1347-1360.

Jonas, O., I. Parry, D. Chishold, N. Banatvala, and R. Laxminarayan. 2014. Global health threats of the 21st century. *Finance & Development* 51(4).

Joosten, P., D. Ceccarelli, E. Odent, S. Sarrazin, H. Graveland, L. Van Gompel, A. Battisti, A. Caprioli, A. Franco, J. A. Wagenaar, D. Mevius, and J. Dewulf. 2020. Antimicrobial usage and resistance in companion animals: A cross-sectional study in three european countries. *Antibiotics (Basel)* 9(2):87.

Jørgensen, P. S., A. Aktipis, Z. Brown, Y. Carrière, S. Downes, R. R. Dunn, G. Epstein, G. B. Frisvold, D. Hawthorne, Y. T. Gröhn, G. T. Gujar, D. Jasovský, E. Y. Klein, F. Klein, G. Lhermie, D. Mota-Sanchez, C. Omoto, M. Schlüter, H. M. Scott, D. Wernli, S. P. Carroll, and p. Living with Resistance. 2018. Antibiotic and pesticide susceptibility and the anthropocene operating space. *Nature Sustainability* 1(11):632-641.

Jul, P., E. Okholm Nielsen, U. Wolf Sönksen, F. Bager, K. Pedersen, C. Jensen, K. Steen Pedersen, V. Pedersen Lund, J. Dahl, and T. Vig. 2019. Tackling antimicrobial use and resistance in pig production. Lessons learned in denmark. Rome: FAO and Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration.

Keighley, C., S. C. Chen, D. Marriott, A. Pope, B. Chapman, K. Kennedy, N. Bak, N. Underwood, H. L. Wilson, K. McDonald, J. Darvall, C. Halliday, S. Kidd, Q. Nguyen, K. Hajkowicz, T. C. Sorrell, S. Van Hal, and M. A. Slavin. 2019. Candidaemia and a risk predictive model for overall mortality: A prospective multicentre study. *BMC Infectious Diseases* 19(1):445.

Kirchhelle, C. 2018. Pharming animals: A global history of antibiotics in food production (1935–2017). *Palgrave Communications* 4(1):96.

Knapp, C. W., J. Dolfing, P. A. Ehlert, and D. W. Graham. 2010. Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940. *Environmental Science & Technology* 44(2):580-587.

Knowles, R., M. Sharland, Y. Hsia, N. Magrini, L. Moja, A. Siyam, and E. Tayler. 2020. Measuring antibiotic availability and use in 20 low-and middle-income countries. *Bulletin of the World Health Organization* 98(3):177.

Kraupner, N., M. Hutinel, K. Schumacher, D. A. Gray, M. Genheden, J. Fick, C. F. Flach, and D. G. J. Larsson. 2021. Evidence for selection of multi-resistant e. Coli by hospital effluent. *Environment International* 150:106436.

Kristiansson, E., J. Fick, A. Janzon, R. Grabic, C. Rutgersson, B. Weijdegard, H. Soderstrom, and D. G. Larsson. 2011. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PloS One* 6(2):e17038.

Lam, Y., J. Fry, E. Hu, B. Kim, and K. Nachman. 2016. Industrial food animal production in low-and middle-income countries: A landscape assessment. *Center for a Livable Future, Johns Hopkins* 13:2018.

Lambraki, I. A., S. E. Majowicz, E. J. Parmley, D. Wernli, A. Leger, T. Graells, M. Cousins, S. Harbarth, C. Carson, P. Henriksson, M. Troell, and P. S. Jorgensen. 2021. Building social-ecological system resilience to tackle antimicrobial resistance across the one health spectrum: Protocol for a mixed methods study. *JMIR Research Protocols* 10(6):e24378.

Law, A., O. Solano, C. J. Brown, S. S. Hunter, M. Fagnan, E. M. Top, and T. Stalder. 2021. Biosolids as a source of antibiotic resistance plasmids for commensal and pathogenic bacteria. *Frontiers in Microbiology* 12:606409.

Laxminarayan, R. 2016. Slowing the race, addressing antibiotic resistance. *Imagine*.

Laxminarayan, R., A. Duse, C. Wattal, A. K. Zaidi, H. F. Wertheim, N. Sumpradit, E. Vlieghe, G. L. Hara, I. M. Gould, H. Goossens, C. Greko, A. D. So, M. Bigdeli, G. Tomson, W. Woodhouse, E. Ombaka, A. Q. Peralta, F. N. Qamar, F. Mir, S. Kariuki, Z. A. Bhutta, A. Coates, R. Bergstrom, G. D. Wright, E. D. Brown, and O. Cars. 2013. Antibiotic resistance-the need for global solutions. *Lancet Infectious Diseases* 13(12):1057-1098.

Laxminarayan, R., P. Matsoso, S. Pant, C. Brower, J. A. Rottingen, K. Klugman, and S. Davies. 2016. Access to effective antimicrobials: A worldwide challenge. *Lancet* 387(10014):168-175.

Laxminarayan, R., T. Van Boeckel, and A. Teillant. 2015. The economic costs of withdrawing antimicrobial growth promoters from the livestock sector.

Lee, R. A., R. M. Centor, L. L. Humphrey, J. A. Jokela, R. Andrews, and A. Qaseem. 2021. Appropriate use of short-course antibiotics in common infections: Best practice advice from the american college of physicians. *Annals of Internal Medicine*.

Leekha, S., C. L. Terrell, and R. S. Edson. 2011. General principles of antimicrobial therapy. Paper read at Mayo Clinic Proceedings.

Lekagul, A., V. Tangcharoensathien, and S. Yeung. 2019. Patterns of antibiotic use in global pig production: A systematic review. *Veterinary and Animal Science* 7:100058.

Leventini, M. 2018. Interview: "No antibiotics ever at perdue farms in the US", edited by E. Koeleman: Poultry World.

Levy, S. 2014. Reduced antibiotic use in livestock: How denmark tackled resistance: NLM-Export.

Lhermie, G., L. Verteramo Chiu, K. Kaniyamattam, L. W. Tauer, H. M. Scott, and Y. T. Grohn. 2019a. Antimicrobial policies in united states beef production: Choosing the right instruments to reduce antimicrobial use and resistance under structural and market constraints. *Frontiers in Veterinary Science* 6(245):245.

Lhermie, G., D. Wernli, P. S. Jørgensen, D. Kenkel, C. Y. C. Lin Lawell, L. W. Tauer, and Y. T. Gröhn. 2019b. Tradeoffs between resistance to antimicrobials in public health and their use in agriculture: Moving towards sustainability assessment. *Ecological Economics* 166:106427.

Li, D., M. Yang, J. Hu, L. Ren, Y. Zhang, and K. Li. 2008. Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. *Environmental Toxicology and Chemistry* 27(1):80-86.

Lim, W. S., S. V. Baudouin, R. C. George, A. T. Hill, C. Jamieson, I. Le Jeune, J. T. Macfarlane, R. C. Read, H. J. Roberts, M. L. Levy, M. Wani, M. A. Woodhead, and B. T. S. S. o. C. C. Pneumonia Guidelines Committee of the. 2009. Bts guidelines for the management of community acquired pneumonia in adults: Update 2009. *Thorax* 64 Suppl 3(Suppl 3):iii1-55.

Liss, B., and O. A. Cornely. 2016. Burden and benefit of antibiotic prophylaxis in cancer chemotherapy. *Lancet Infectious Diseases* 16(6):640.

Littman, J., A. Viens, and D. S. Silva. 2020. The super-wicked problem of antimicrobial resistance. *Ethics and drug resistance: Collective responsibility for global public health*.

Liu, P., C. Ohl, J. Johnson, J. Williamson, J. Beardsley, and V. Luther. 2016. Frequency of empiric antibiotic de-escalation in an acute care hospital with an established antimicrobial stewardship program. *BMC Infectious Diseases* 16(1):751.

Loosli, K., A. Davis, A. Muwonge, and T. Lembo. 2021. Addressing antimicrobial resistance by improving access and quality of care-a review of the literature from east africa. *PLoS Neglected Tropical Diseases* 15(7):e0009529.

Lowy, F. 2009. Antibiotic resistance. http://www.columbia.edu/itc/hs/medical/pathophys/id/2004/lecture/notes/resistance_Lowy.pdf (accessed October 12, 2021).

Lubick, N. 2011. Antibiotic resistance shows up in india's drinking water. *Nature*.

Lulijwa, R., E. J. Rupia, and A. C. Alfaro. 2019. Antibiotic use in aquaculture, policies and regulation, health and environmental risks: A review of the top 15 major producers. *Reviews in Aquaculture* 12(2):640-663.

MacFadden, D. R., S. F. McGough, D. Fisman, M. Santillana, and J. S. Brownstein. 2018. Antibiotic resistance increases with local temperature. *Nature Climate Change* 8(6):510-514.

Mackenzie, J. S., and M. Jeggo. 2019. The one health approach—why is it so important?: Multidisciplinary Digital Publishing Institute.

Mahadevia, A. 2017. Tackling multi-drug resistant bacteria. *Drug Discovery World*.

Mandell, L. A., R. G. Wunderink, A. Anzueto, J. G. Bartlett, G. D. Campbell, N. C. Dean, S. F. Dowell, T. M. File, Jr., D. M. Musher, M. S. Niederman, A. Torres, C. G. Whitney, A. Infectious Diseases Society of, and S. American Thoracic. 2007. Infectious diseases society of america/american thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases* 44 Suppl 2(1537-6591 (Electronic)):S27-72.

Manohar, P., B. Loh, R. Nachimuthu, X. Hua, S. C. Welburn, and S. Leptihn. 2020. Secondary bacterial infections in patients with viral pneumonia. *Frontiers in Medicine* 7(420):420.

Manyi-Loh, C., S. Mamphweli, E. Meyer, and A. Okoh. 2018. Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications. *Molecules* 23(4):795.

Mapipa, Q., T. O. Digban, N. E. Nnolim, and U. U. Nwodo. 2021. Antibiogram profile and virulence signatures of pseudomonas aeruginosa isolates recovered from selected agrestic hospital effluents. *Scientific Reports* 11(1):11800.

McEwen, S. A., and P. J. Collignon. 2018. Antimicrobial resistance: A one health perspective. *Microbiology Spectrum* 6(2):521-547.

McGough, S. F., D. R. MacFadden, M. W. Hattab, K. Molbak, and M. Santillana. 2020. Rates of increase of antibiotic resistance and ambient temperature in europe: A cross-national analysis of 28 countries between 2000 and 2016. *Euro Surveillance* 25(45).

McManus, P. S., V. O. Stockwell, G. W. Sundin, and A. L. Jones. 2002. Antibiotic use in plant agriculture. *Annual Review of Phytopathology* 40:443-465.

McMichael, A. J., D. H. Campbell-Lendrum, C. F. Corvalán, K. L. Ebi, A. Githeko, J. D. Scheraga, and A. Woodward. 2003. *Climate change and human health: Risks and responses*: World Health Organization.

Meara, J. G., A. J. Leather, L. Hagander, B. C. Alkire, N. Alonso, E. A. Ameh, S. W. Bickler, L. Conteh, A. J. Dare, and J. Davies. 2015. Global surgery 2030: Evidence and solutions for achieving health, welfare, and economic development. *The Lancet* 386(9993):569-624.

Meeusen, E. N., J. Walker, A. Peters, P. P. Pastoret, and G. Jungersen. 2007. Current status of veterinary vaccines. *Clinical Microbiology Reviews* 20(3):489-510.

Mellon, M. 2013. *CDC's "get smart about antibiotics" campaign still ignoring animals*. https://blog.ucsusa.org/margaret-mellon/cdcs-get-smart-about-antibiotics-campaign-still-ignoring-animals-30/ (accessed September 16, 2021).

Morley, P. S., M. D. Apley, T. E. Besser, D. P. Burney, P. J. Fedorka-Cray, M. G. Papich, J. L. Traub-Dargatz, J. S. Weese, and M. American College of Veterinary Internal. 2005. Antimicrobial drug use in veterinary medicine. *Journal of Veterinary Internal Medicine* 19(4):617-629.

MSU (Michigan State University). 2011. *Prophylactic or metaphylactic use*. http://amrls.cvm.msu.edu/pharmacology/antimicrobial-usage-in-animals/non-therapuetic-use-of-antimicrobials-in-animals/use-of-antibiotics-in-animals-for-prophylactic-or-metaphylactic-purposes (accessed April 28, 2021).

Muloi, D., M. J. Ward, A. B. Pedersen, E. M. Fevre, M. E. J. Woolhouse, and B. A. D. van Bunnik. 2018. Are food animals responsible for transfer of antimicrobial-resistant escherichia coli or their resistance determinants to human populations? A systematic review. *Foodborne Pathogens and Disease* 15(8):467-474.

Munir, M., and I. Xagoraraki. 2011. Levels of antibiotic resistance genes in manure, biosolids, and fertilized soil. *Journal of Environmental Quality* 40(1):248-255.

Murphy, J. L., N. Fenn, L. Pyle, H. Heizer, S. Hughes, Y. Nomura, J. Child, and S. K. Parker. 2016. Adverse events in pediatric patients receiving long-term oral and intravenous antibiotics. *Hospital Pediatrics* 6(6):330-338.

Murray, K. A., L. E. Escobar, R. Lowe, J. Rocklov, J. C. Semenza, and N. Watts. 2020. Tracking infectious diseases in a warming world. *BMJ* 371:m3086.

Nadimpalli, M., E. Delarocque-Astagneau, D. C. Love, L. B. Price, B. T. Huynh, J. M. Collard, K. S. Lay, L. Borand, A. Ndir, T. R. Walsh, D. Guillemot, I. Bacterial, and G. antibiotic-Resistant Diseases among Young children in low-income countries Study. 2018. Combating global antibiotic resistance: Emerging one health concerns in lower- and middle-income countries. *Clinical Infectious Diseases* 66(6):963-969.

National Chicken Council. 2014. *The national chicken council releases inaugural sustainability report to recognize progress and identify future growth opportunities* (accessed September 10, 2021).

Nepogodiev, D., J. Martin, B. Biccard, A. Makupe, A. Bhangu, and S. National Institute for Health Research Global Health Research Unit on Global. 2019. Global burden of postoperative death. *Lancet* 393(10170):401.

Nnadi, N. E., and D. A. Carter. 2021. Climate change and the emergence of fungal pathogens. *PLoS Pathogens* 17(4):e1009503.

NORM/NORM-VET. 2019. *Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway.* Tromsø / Oslo.

Norris, J. M., A. Zhuo, M. Govendir, S. J. Rowbotham, M. Labbate, C. Degeling, G. L. Gilbert, D. Dominey-Howes, and M. P. Ward. 2019. Factors influencing the behaviour and perceptions of australian veterinarians towards antibiotic use and antimicrobial resistance. *PloS One* 14(10):e0223534.

NWF. 2021. *Ecosystem services*. https://www.nwf.org/Educational-Resources/Wildlife-Guide/Understanding-Conservation/Ecosystem-Services (accessed April 8, 2021).

Odoi, A., R. Samuels, C. N. Carter, and J. Smith. 2021. Antibiotic prescription practices and opinions regarding antimicrobial resistance among veterinarians in kentucky, USA. *PloS One* 16(4):e0249653.

OIE (World Organization for Animal Health). 2021. *Annual report on antimicrobial agents intended for use in animals- better understanding of the global situation.*

Olaganathan, R. T. K. M., Alicia. 2017. Impact of aquaculture on the livelihoods and food security of rural communities. *International Journal of Fisheries and Aquatic Studies* 5:278-283.

Ombelet, S., B. Barbe, D. Affolabi, J. B. Ronat, P. Lompo, O. Lunguya, J. Jacobs, and L. Hardy. 2019. Best practices of blood cultures in low- and middle-income countries. *Frontiers in Medicine* 6:131.

Partridge, S. R. 2015. Resistance mechanisms in enterobacteriaceae. *Pathology* 47(3):276-284.

PCAST (President's Council of Advisors on Science and Technology). 2015. *National action plan for combating antibiotic-resistant bacteria.* Washington, DC: White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

Pham, M. 2017. Using a complex adaptive systems approach to understand antimicrobial resistance. *American Association for the Advancement of Science*.

Pichichero, M. E. 2002. Diagnostic accuracy, tympanocentesis training performance, and antibiotic selection by pediatric residents in management of otitis media. *Pediatrics* 110(6):1064-1070.

Plumb, I. D., C. A. Schwensohn, L. Gieraltowski, S. Tecle, Z. D. Schneider, J. Freiman, A. Cote, D. Noveroske, J. Kolsin, J. Brandenburg, J. C. Chen, K. A. Tagg, P. B. White, H. J. Shah, L. K. Francois Watkins, M. E. Wise, and C. R. Friedman. 2019. Outbreak of salmonella newport infections with decreased susceptibility to azithromycin linked to beef obtained in the united states and soft cheese obtained in mexico - united states, 2018-2019. *MMWR: Morbidity and Mortality Weekly Report* 68(33):713-717.

Plunkett, A., and J. Tong. 2015. Sepsis in children. *BMJ* 350:h3017.

Podolsky, S. H. 2018. The evolving response to antibiotic resistance (1945–2018). *Palgrave Communications* 4(1):124.

Poole, N. M., D. J. Shapiro, K. E. Fleming-Dutra, L. A. Hicks, A. L. Hersh, and M. P. Kronman. 2019. Antibiotic prescribing for children in united states emergency departments: 2009-2014. *Pediatrics* 143(2).

Pruden, A., M. Arabi, and H. N. Storteboom. 2012. Correlation between upstream human activities and riverine antibiotic resistance genes. *Environmental Science & Technology* 46(21):11541-11549.

PSNet. 2019. *Surgical site infections*. https://psnet.ahrq.gov/primer/surgical-site-infections (accessed April 8, 2021).

Queenan, K., J. Garnier, N. Rosenbaum, S. Buttigieg, D. de Meneghi, M. Holmberg, J. Zinsstag, S. R. Rüegg, B. Häsler, and R. Kock. 2017. Roadmap to a one health agenda 2030. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources* 12(014):1-12.

Rahube, T. O., R. Marti, A. Scott, Y. C. Tien, R. Murray, L. Sabourin, Y. Zhang, P. Duenk, D. R. Lapen, and E. Topp. 2014. Impact of fertilizing with raw or anaerobically digested sewage sludge on the abundance of antibiotic-resistant coliforms, antibiotic resistance genes, and pathogenic bacteria in soil and on vegetables at harvest. *Applied and Environmental Microbiology* 80(22):6898-6907.

Ramirez, M. S., G. M. Traglia, D. L. Lin, T. Tran, and M. E. Tolmasky. 2014. Plasmid-mediated antibiotic resistance and virulence in gram-negatives: The klebsiella pneumoniae paradigm. *Microbiology Spectrum* 2(5):1-15.

Resendiz Sharpe, A., K. Lagrou, J. F. Meis, A. Chowdhary, S. R. Lockhart, P. E. Verweij, and I. E. A. R. S. w. group. 2018. Triazole resistance surveillance in aspergillus fumigatus. *Medical Mycology* 56(suppl_1):83-92.

Review on AMR. *Review on antimicrobial resistance: Tackling drug-resistance infections globally*. https://amr-review.org (accessed October 12, 2021).

Rickard, J., G. Beilman, J. Forrester, R. Sawyer, A. Stephen, T. G. Weiser, and J. Valenzuela. 2020. Surgical infections in low- and middle-income countries: A global assessment of the burden and management needs. *Surgical Infections* 21(6):478-494.

Ritchie, H. 2017. *How do we reduce antibiotic resistance from livestock?* https://ourworldindata.org/antibiotic-resistance-from-livestock (accessed October 12, 2021).

Ritchie, H., and M. Roser. 2018. Causes of death. In *Our World in Data*.

Robinson, T. P., D. Bu, J. Carrique-Mas, E. M. Fèvre, M. Gilbert, D. Grace, S. I. Hay, J. Jiwakanon, M. Kakkar, and S. Kariuki. 2016. Antibiotic resistance is the quintessential one health issue. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 110(7):377-380.

Rudd, K. E., S. C. Johnson, K. M. Agesa, K. A. Shackelford, D. Tsoi, D. R. Kievlan, D. V. Colombara, K. S. Ikuta, N. Kissoon, S. Finfer, C. Fleischmann-Struzek, F. R. Machado, K. K. Reinhart, K. Rowan, C. W. Seymour, R. S. Watson, T. E. West, F. Marinho, S. I. Hay, R. Lozano, A. D.

Lopez, D. C. Angus, C. J. L. Murray, and M. Naghavi. 2020. Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the global burden of disease study. *Lancet* 395(10219):200-211.

Rutgersson, C., S. Ebmeyer, S. B. Lassen, A. Karkman, J. Fick, E. Kristiansson, K. K. Brandt, C. F. Flach, and D. G. J. Larsson. 2020. Long-term application of swedish sewage sludge on farmland does not cause clear changes in the soil bacterial resistome. *Environment International* 137:105339.

Schar, D., E. Y. Klein, R. Laxminarayan, M. Gilbert, and T. P. Van Boeckel. 2020. Global trends in antimicrobial use in aquaculture. *Scientific Reports* 10(1):21878.

Schar, D., A. Sommanustweechai, R. Laxminarayan, and V. Tangcharoensathien. 2018. Surveillance of antimicrobial consumption in animal production sectors of low-and middle-income countries: Optimizing use and addressing antimicrobial resistance. *PLoS Medicine* 15(3):e1002521.

Schoenmakers, K. 2020. How china is getting its farmers to kick their antibiotics habit. *Nature* 586:2.

Schroeder, M., B. D. Brooks, and A. E. Brooks. 2017. The complex relationship between virulence and antibiotic resistance. *Genes (Basel)* 8(1).

Schug, D., K. Baxter, and K. Wellman. 2009. Valuation of ecosystem services from shellfish restoration, enhancement and management: A review of the literature. *Northern Economics Inc., Report*.

SfAM. 2018. Microbiologist. *Society for Applied Microbiology* 19(4).

Shallcross, L. J., S. J. Howard, T. Fowler, and S. C. Davies. 2015. Tackling the threat of antimicrobial resistance: From policy to sustainable action. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 370(1670):20140082.

Shapiro, D. J., L. A. Hicks, A. T. Pavia, and A. L. Hersh. 2014. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. *Journal of Antimicrobial Chemotherapy* 69(1):234-240.

Sharland, M., C. Pulcini, S. Harbarth, M. Zeng, S. Gandra, S. Mathur, N. Magrini, W. H. O. E. C. o. S. st, and M. Use of Essential. 2018. Classifying antibiotics in the who essential medicines list for optimal use-be aware. *Lancet Infectious Diseases* 18(1):18-20.

Shawar, Y. R., and L. G. Crane. 2017. Generating global political priority for urban health: The role of the urban health epistemic community. *Health Policy and Planning* 32(8):1161-1173.

Shreiner, A. B., J. Y. Kao, and V. B. Young. 2015. The gut microbiome in health and in disease. *Current Opinion in Gastroenterology* 31(1):69-75.

Shrime, M. G., S. W. Bickler, B. C. Alkire, and C. Mock. 2015. Global burden of surgical disease: An estimation from the provider perspective. *The Lancet Global Health* 3 Suppl 2:S8-9.

Simonsen, G. S. 2020. *The norwegian national strategy against antibiotic resistance*. Paper presented at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 2, Webinar.

Sinclair, J. R. 2019. Importance of a one health approach in advancing global health security and the sustainable development goals. *Revue Scientifique et Technique* 38(1):145-154.

Singer, A. C., H. Shaw, V. Rhodes, and A. Hart. 2016a. Review of antimicrobial resistance in the environment and its relevance to environmental regulators. *Frontiers in Microbiology* 7:1728.

Singer, M., C. S. Deutschman, C. W. Seymour, M. Shankar-Hari, D. Annane, M. Bauer, R. Bellomo, G. R. Bernard, J. D. Chiche, C. M. Coopersmith, R. S. Hotchkiss, M. M. Levy, J. C. Marshall, G. S. Martin, S. M. Opal, G. D. Rubenfeld, T. van der Poll, J. L. Vincent, and D. C. Angus. 2016b. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA* 315(8):801-810.

Singh Gill, A., H. Morrissey, and A. Rahman. 2018. A systematic review and meta-analysis evaluating antibiotic prophylaxis in dental implants and extraction procedures. *Medicina (Kaunas, Lithuania)* 54(6):95.

Sirota, M., T. Round, S. Samaranayaka, and O. Kostopoulou. 2017. Expectations for antibiotics increase their prescribing: Causal evidence about localized impact. *Health Psychology* 36(4):402-409.

Sneeringer, S. 2015. Restrictions on antibiotic use for production purposes in us livestock industries likely to have small effects on prices and quantities. United states department of agriculture. *Economic Research Service*.

Soto, S. M. 2013. Role of efflux pumps in the antibiotic resistance of bacteria embedded in a biofilm. *Virulence* 4(3):223-229.

Stanley, L. 2020. *Reducing surgical site infection and antimicrobial resistance: New guidelines issued*. https://www.birminghamhealthpartners.co.uk/reducing-surgical-site-infection-and-antimicrobial-resistance-new-guidelines-issued/ (accessed April 8, 2021).

Stapleton, P. J., M. Murphy, N. McCallion, M. Brennan, R. Cunney, and R. J. Drew. 2016. Outbreaks of extended spectrum beta-lactamase-producing enterobacteriaceae in neonatal intensive care units: A systematic review. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 101(1):F72-78.

Stockwell, V. O., and B. Duffy. 2012. Use of antibiotics in plant agriculture. *Revue Scientifique et Technique* 31(1):199-210.

Ström, G. H., H. Björklund, A. C. Barnes, C. T. Da, N. H. Y. Nhi, T. T. Lan, U. Magnusson, A. Norman Haldén, and S. Boqvist. 2019. Antibiotic use by small-scale farmers for freshwater aquaculture in the upper mekong delta, vietnam. *Journal of Aquatic Animal Health* 31(3):290-298.

Szogi, A. A., M. B. Vanotti, and K. S. Ro. 2015. Methods for treatment of animal manures to reduce nutrient pollution prior to soil application. *Current Pollution Reports* 1(1):47-56.

Tabak, Y. P., L. Vankeepuram, G. Ye, K. Jeffers, V. Gupta, and P. R. Murray. 2018. Blood culture turnaround time in us acute care hospitals and implications for laboratory process optimization. *Journal of Clinical Microbiology* 56(12).

Tamma, P. D., E. Avdic, D. X. Li, K. Dzintars, and S. E. Cosgrove. 2017. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Internal Medicine* 177(9):1308-1315.

Tansarli, G. S., and E. Mylonakis. 2018. Systematic review and meta-analysis of the efficacy of short-course antibiotic treatments for community-acquired pneumonia in adults. *Antimicrobial Agents and Chemotherapy* 62(9):e00635-00618.

Taylor, P., and R. Reeder. 2020. Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors. *CABI Agriculture and Bioscience* 1(1):1.

Teillant, A., S. Gandra, D. Barter, D. J. Morgan, and R. Laxminarayan. 2015. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: A literature review and modelling study. *Lancet Infectious Diseases* 15(12):1429-1437.

Thakur, S. D., and A. Panda. 2017. Rational use of antimicrobials in animal production: A prerequisite to stem the tide of antimicrobial resistance. *Current Science*:1846-1857.

The Nutrition Source. 2021. *The microbiome*. https://www.hsph.harvard.edu/nutritionsource/microbiome/ (accessed June 30, 2021).

Thomson, K. M., C. Dyer, F. Liu, K. Sands, E. Portal, M. J. Carvalho, M. Barrell, I. Boostrom, S. Dunachie, R. Farzana, A. Ferreira, F. Frayne, B. Hassan, E. Jones, L. Jones, J. Mathias, R. Milton, J. Rees, G. J. Chan, D. Bekele, A. Mahlet, S. Basu, R. K. Nandy, B. Saha, K. Iregbu, F. Modibbo, S. Uwaezuoke, R. Zahra, H. Shirazi, N. U. Syed, et al. 2021. Effects of antibiotic resistance, drug target attainment, bacterial pathogenicity and virulence, and antibiotic access and affordability on outcomes in neonatal sepsis: An international microbiology and drug evaluation prospective substudy (barnards). *Lancet Infectious Diseases*.

Tiseo, K., L. Huber, M. Gilbert, T. P. Robinson, and T. P. Van Boeckel. 2020a. Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics (Basel)* 9(12).

Toda, M., K. D. Beer, K. M. Kuivila, T. M. Chiller, and B. R. Jackson. 2021. Trends in agricultural triazole fungicide use in the united states, 1992-2016 and possible implications for antifungal-resistant fungi in human disease. *Environmental Health Perspectives* 129(5):55001.

UN (United Nations). 2016a. *High-level meeting on antimicrobial resistance.* https://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/ (accessed April 8, 2021).

UN. 2016b. Political declaration of the high-level meeting of the general assembly on antimicrobial resistance. *United Nations, Technical report*.
UN. 2018. World urbanization prospects: The 2018 revision. *United Nations*
USDA (U.S. Department of Agriculture). 2019. *2017 census of agriculture.* United States Department of Agriculture.
Van, T. T. H., Z. Yidana, P. M. Smooker, and P. J. Coloe. 2020. Antibiotic use in food animals worldwide, with a focus on africa: Pluses and minuses. *Journal of Global Antimicrobial Resistance* 20:170-177.
Van Boeckel, T. P., C. Brower, M. Gilbert, B. T. Grenfell, S. A. Levin, T. P. Robinson, A. Teillant, and R. Laxminarayan. 2015. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* 112(18):5649-5654.
Vikesland, P., E. Garner, S. Gupta, S. Kang, A. Maile-Moskowitz, and N. Zhu. 2019. Differential drivers of antimicrobial resistance across the world. *Accounts of Chemical Research* 52(4):916-924.
Wald-Dickler, N., and B. Spellberg. 2019. Short-course antibiotic therapy-replacing constantine units with "shorter is better". *Clinical Infectious Diseases* 69(9):1476-1479.
Wall, B., A. Mateus, L. Marshall, D. Pfeiffer, J. Lubroth, H. Ormel, P. Otto, and A. Patriarchi. 2016. Drivers, dynamics and epidemiology of antimicrobial resistance in animal production. *Food and Agriculture Organization of the United Nations*.
Walsh, T. L., B. E. DiSilvio, C. Hammer, M. Beg, S. Vishwanathan, D. Speredelozzi, M. A. Moffa, K. Hu, R. Abdulmassih, J. T. Makadia, R. Sandhu, M. Naddour, N. H. Chan-Tompkins, T. L. Trienski, C. Watson, T. J. Obringer, J. Kuzyck, and D. N. Bremmer. 2018. Impact of procalcitonin guidance with an educational program on management of adults hospitalized with pneumonia. *American Journal of Medicine* 131(2):201 e201-201 e208.
Walsh, T. R., J. Weeks, D. M. Livermore, and M. A. Toleman. 2011. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: An environmental point prevalence study. *Lancet Infectious Diseases* 11(5):355-362.
Waltner-Toews, D. 2017. Zoonoses, one health and complexity: Wicked problems and constructive conflict. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 372(1725):20160171.
Wee, B. A., D. M. Muloi, and B. A. D. van Bunnik. 2020. Quantifying the transmission of antimicrobial resistance at the human and livestock interface with genomics. *Clinical Microbiology and Infection* 26(12):1612-1616.
Weiner-Lastinger, L. M., S. Abner, J. R. Edwards, A. J. Kallen, M. Karlsson, S. S. Magill, D. Pollock, I. See, M. M. Soe, M. S. Walters, and M. A. Dudeck. 2020. Antimicrobial-resistant pathogens associated with adult healthcare-associated infections: Summary of data reported to the national healthcare safety network, 2015-2017. *Infection Control and Hospital Epidemiology* 41(1):1-18.
Weiser, T. G., A. B. Haynes, G. Molina, S. R. Lipsitz, M. M. Esquivel, T. Uribe-Leitz, R. Fu, T. Azad, T. E. Chao, W. R. Berry, and A. A. Gawande. 2016. Size and distribution of the global volume of surgery in 2012. *Bulletin of the World Health Organization* 94(3):201-209F.
Wellcome. 2020. The global response to amr: Momentum, success, and critical gaps: Wellcome.
Welte, T., A. Torres, and D. Nathwani. 2012. Clinical and economic burden of community-acquired pneumonia among adults in europe. *Thorax* 67(1):71-79.
Wen, X., A. M. Langevin, and M. J. Dunlop. 2018. Antibiotic export by efflux pumps affects growth of neighboring bacteria. *Scientific Reports* 8(1):15120.
White, A., and J. M. Hughes. 2019. Critical importance of a one health approach to antimicrobial resistance. *Ecohealth* 16(3):404-409.
WHO. (World Health Organization). 2015a. Health care-associated infections fact sheet. *World Health Organization* 4.
WHO. 2015b. *Vaccinating salmon: How norway avoids antibiotics in fish farming*. https://www.euro.who.int/en/health-topics/disease-prevention/antimicrobial-

resistance/news/news/2015/10/vaccinating-salmon-how-norway-avoids-antibiotics-in-fish-farming (accessed September 22, 2021).
WHO. 2018a. *Antimicrobial resistance and primary health care.* World Health Organization Regional Office for South-East Asia.
WHO. 2018b. *Noncommunicable diseases*. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases (accessed April 8, 2021).
WHO. 2018c. *Substandard and falsified medical products*. https://www.who.int/news-room/fact-sheets/detail/substandard-and-falsified-medical-products (accessed September 30, 2021).
WHO. 2019a. *Drinking-water*. https://www.who.int/news-room/fact-sheets/detail/drinking-water (accessed April 28, 2021).
WHO. 2019b. *Sanitation*. https://www.who.int/news-room/fact-sheets/detail/sanitation (accessed April 28, 2021).
WHO. 2019c. *Ten threats to global health in 2019*. https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 (accessed April 8, 2021).
WHO. 2019d. *WHO releases the 2019 aware classification antibiotics*. https://www.who.int/news/item/01-10-2019-who-releases-the-2019-aware-classification-antibiotics (accessed April 8, 2021).
WHO. 2020a. *Antimicrobial resistance*. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed April 8, 2021).
WHO. 2020b. *Children: Improving survival and well-being*. https://www.who.int/news-room/fact-sheets/detail/children-reducing-mortality (accessed April 8, 2021).
WHO. 2020c. *Children's immature immune systems threatened by increasing 'superbugs'*. https://www.who.int/news-room/commentaries/detail/children-s-immature-immune-systems-threatened-by-increasing-superbugs (accessed April 8, 2021).
WHO. 2020d. *Urgent health challenges for the next decade*. https://www.who.int/news-room/photo-story/photo-story-detail/urgent-health-challenges-for-the-next-decade (accessed April 8, 2021).
WHO. 2021. *WHO antibiotic categorization*. https://aware.essentialmeds.org/groups (accessed April 8, 2021).
Widmar, D. 2017. How big? A look at the size of beef operations in the u.S., https://aei.ag/2017/08/21/size-of-beef-operations/ (accessed April 28, 2021).
Williams-Nguyen, J., J. B. Sallach, S. Bartelt-Hunt, A. B. Boxall, L. M. Durso, J. E. McLain, R. S. Singer, D. D. Snow, and J. L. Zilles. 2016. Antibiotics and antibiotic resistance in agroecosystems: State of the science. *Journal of Environmental Quality* 45(2):394-406.
Wilson, H. L., K. Daveson, and C. B. Del Mar. 2019. Optimal antimicrobial duration for common bacterial infections. *Australian Prescriber* 42(1):5-9.
Woodhead, M., F. Blasi, S. Ewig, J. Garau, G. Huchon, M. Ieven, A. Ortqvist, T. Schaberg, A. Torres, G. van der Heijden, R. Read, T. J. Verheij, S. Joint Taskforce of the European Respiratory, M. European Society for Clinical, and D. Infectious. 2011. Guidelines for the management of adult lower respiratory tract infections--full version. *Clinical Microbiology and Infection* 17 Suppl 6:E1-59.
Woolhouse, M., M. Ward, B. van Bunnik, and J. Farrar. 2015. Antimicrobial resistance in humans, livestock and the wider environment. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences* 370(1670):20140083.
Word, A. B., T. A. Wickersham, L. A. Trubenbach, G. B. Mays, and J. E. Sawyer. 2020. Effects of metaphylaxis on production responses and total antimicrobial use in high-risk beef calves. *Applied Animal Science* 36(2):265-270.
Wright, G. D. 2010. The antibiotic resistome. *Expert Opinion on Drug Discovery* 5(8):779-788.
Zangaro, C. 2018. *Use of antibiotics administered in water to pigs in the post-vfd era*. https://www.canr.msu.edu/news/use-of-antibiotics-administered-in-water-to-pigs-in-the-post-vfd-era (accessed September 10, 2021).

Zhu, Y. G., Y. Zhao, B. Li, C. L. Huang, S. Y. Zhang, S. Yu, Y. S. Chen, T. Zhang, M. R. Gillings, and J. Q. Su. 2017. Continental-scale pollution of estuaries with antibiotic resistance genes. *Nature Microbiology* 2(4):16270.

# 3

# The Health and Economic Burden of Resistance

As the previous chapter mentioned, antimicrobial-resistant infections are difficult to treat and contribute to a general increase in morbidity and mortality, while simultaneously adding high costs to the health system. But estimating disease burden associated with antimicrobial resistance is not straightforward. Analysis of death certificates and international diagnosis codes, common in epidemiological studies of disease burden, are not suitable to studies of antimicrobial-resistant infections (CDC, 2019; Denison and AV, 2010; Lopez et al., 2006). This is because the effects of resistant pathogens can manifest in many different ways. Methicillin-resistant *Staphylococcus aureus* (MRSA), for example, commonly causes skin, wound, and bone infections, pneumonia, and bloodstream infections (CDC, 2019). Though caused by the same pathogen, any one of these presentations would be diagnosed and coded differently. Should the patient die, the cause of death might be recorded as sepsis or pneumonia, but not MRSA. For these reasons, population estimates of the consequences of resistant infection have underestimated the true burden of disease (CDC, 2019).

There is also wide variability in where studies are conducted. Most research takes place in high-income countries where microbiological confirmation of a resistant infection is more readily available. Fewer studies have attempted to estimate the health or economic burden of resistance in low- or middle-income countries. Gradual improvements in surveillance of both antimicrobial use and resistance patterns, a topic discussed in more detail in the next chapter, could facilitate better understanding of the true burden of resistant infections in the future.

This chapter will review a cross section of relevant literature, mostly from the last several years. First, it discusses a series of recent landmark publications on the topic; next, it discusses some of the challenges of estimating the effects of resistance on health, the economy, and on animal agriculture. Though primarily a literature review, this chapter is not an exhaustive analysis of every publication on the question; rather, it presents an overview of trends in the literature and important patterns to emerge.

## REVIEW OF RECENT REPORTS

Attention to the problem of antimicrobial resistance has grown in recent years, driven in part by a series of high-profile international reports. This section reviews the touchstone reports from the Centers for Disease Control and Prevention (CDC), the Organisation for Economic Co-

operation and Development (OECD), the UK Prime Minister's commission to Jim O'Neill, called the O'Neill report, and the World Bank.

### *Antibiotic Resistance Threats in the United States, 2019*

The CDC's *Antibiotic Resistance Threats in the United States, 2013*, was one of the earliest of the recent reports to attempt to quantify the health burden of resistance and to categorize pathogens by the level of threat they pose to public health (CDC, 2013). The CDC revisited this report in 2019, and the more recent publication contains estimates of the burden of resistant pathogens based on laboratory and population surveillance data, complemented with research from electronic medical records, and is weighted to allow for some extrapolation to the national level (CDC, 2019; Kadri, 2020).[1]

This analysis indicated there are 2.8 million resistant infections every year in the United States, causing 35,900 deaths; *Clostridioides difficile* (*C. difficile*) infection, a problem caused by antimicrobial disruption of the gut flora, kills another 12,800 people a year (CDC, 2019). Despite sudden increases in certain infections, multidrug-resistant *Candida auris*, for example, was not spreading in the United States until 2015, total deaths from resistant infections declined 18 percent between 2013 and 2019 and deaths in hospitals have declined 28 percent (CDC, 2019). Table 3-1 shows the percentage change for those pathogens for which a longitudinal comparison was possible.

**TABLE 3-1** Change in Infections Caused by Some CDC Priority Pathogens Between 2013 and 2019

| Pathogen | Increase or Decrease | % Change 2013 to 2019 |
|---|---|---|
| Vancomycin-resistant *Enterococcus* | Decrease | 41% |
| Multidrug-resistant *Pseudomonas aeruginosa* | Decrease | 29% |
| Carbapenem-resistant *Acinetobacter* | Decrease | 33% |
| Drug-resistant *Candida auris* | Decrease | 25% |
| Carbapenem-resistant Enterobacterales | Stable | - |
| Drug-resistant *Neisseria gonorrhoeae* | Increase | 124% |
| ESBL-producing Enterobacterales | Increase | 50% |
| Methicillin-resistant *Staphylococcus aureus* | Decrease | 21% |
| Erythromycin-resistant invasive group A strep | Increase | 315% |

NOTE: ESBL = extended-spectrum beta-lactamases.
SOURCE: CDC, 2019.

The report also explained that the economic costs of resistance can be difficult to estimate with any credibility. Resistant infections undoubtedly cost the health system more in terms of

[1] The CDC report's technical appendix thoroughly explains the methods used to estimate the burden of the 21 resistant pathogens included (CDC, 2019). The CDC's Active Bacterial Core surveillance through the Emerging Infections Program was the starting point for many of the estimates presented including those for group A and B *Streptococcus*, and *Streptococcus pneumonia;* a combination of active laboratory and population surveillance in study sites across the country informed estimates for several pathogens including *Acinetobacter baumanii*, *Clostriodioides difficile,* MRSA, and certain *Candida* spp. (CDC, 2019). Cohort studies using patient data from three nationally used electronic health record systems collected over 5 years were pooled and weighted to inform estimates of MRSA and another six pathogens (CDC, 2019). The National Antimicrobial Resistance Monitoring System data on the number of infections and the prevalence of resistance was used to estimate the prevalence of resistance among isolates of several species (CDC, 2019). The published, peer-reviewed methods papers describing how CDC researchers arrived at disease burden estimates for each pathogen are included in the report's references.

person hours needed to treat them and extended hospital stays. The medicines needed to treat them can be expensive and less well tolerated (CDC, 2019). Nevertheless, there is no consensus methodology to estimate the economic burden of resistant infections.

To put some economic parameters on the problem, the CDC used retrospective cost analysis of patients with six common resistant infections in the Veterans Health Administration medical centers, adjusted for the general population by the Veterans Affairs (VA) Health Economics Resource Center (Nelson et al., 2021). The analysis for *C. difficile* drew from peer-reviewed literature, and for some pathogens, no reliable cost estimate was available. Table 3-2 shows only the direct medical costs associated with a positive culture for the pathogens of interest, not the downstream costs associated with future disability or the cost to the patient of missed work or even the cost to the health system after discharge. (The long-term asymptomatic nature of resistant gonorrhea infection made it necessary to present a lifetime estimate of costs.) The direct costs of treating six, common multidrug-resistant pathogens was $4.6 billion a year, *C. difficile* another billion, and drug-resistant gonorrhea another $133.4 million (CDC, 2019; Nelson et al., 2021).

**TABLE 3-2** Costs Attributable to Antimicrobial-Resistant Pathogens in the United States, in Constant 2017 Dollars

| Pathogen | Estimated Attributable Health Care Costs | Annual Direct Medical Costs | Annual Discounted Lifetime Direct Medical Costs |
|---|---|---|---|
| Carbapenem-resistant *Acinetobacter* | $281 million | - | - |
| Hospital-associated *Clostridioides difficile* | $1 billion | - | - |
| Carbapenem-resistant Enterobacterales | $130 million | - | - |
| Drug-resistant *Neisseria gonorrhoeae* | - | - | $133.4 million |
| Drug-resistant *Campylobacter* | - | $270 million | - |
| Drug-resistant *Candida* | - | $3 billion | - |
| ESBL-producing Enterobacterales | $1.2 billion | - | - |
| Vancomycin-resistant *Enterococcus* | $539 million | - | - |
| Multidrug-resistant *Pseudomonas aeruginosa* | $767 million | - | - |
| Drug-resistant nontyphoidal *Salmonella* | - | $400 million | - |
| Drug-resistant *Shigella* | - | $93 million | - |
| Methicillin-resistant *Staphylococcus aureus* | $1.7 billion | - | - |
| Drug-resistant *Streptococcus pneumoniae* | - | $1.3 billion | - |

NOTE: ESBL = extended-spectrum beta-lactamase.
SOURCE: CDC, 2019.

## OECD Development Work on Antimicrobial Resistance

The OECD, an intergovernmental economic organization, has also published several influential reports on antimicrobial resistance since 2015, often in collaboration with the European Centre for Disease Prevention and Control (ECDC).

The first of these publications, *Antimicrobial Resistance in G7 Countries and Beyond* was released shortly after the O'Neill report and drew attention to the fact that only a quarter of

the world's countries had a national antimicrobial resistance plan (Cecchini et al., 2015). The OECD's 2016 publication drew on data from the ECDC's Surveillance of Antimicrobial Consumption Network and the Center for Disease Dynamics, Economics, and Policy's national and subnational resistance data to analyze trends in the emergence of resistance between 2005 and 2014 (OECD, 2016). Using an aggregate measure of resistance based on six, high priority pathogen–drug combinations, the report concluded that the prevalence of antimicrobial resistance had increased in 23 of 26 OECD countries (see Figure 3-1), though human use of antimicrobials remained largely stable (OECD, 2016).

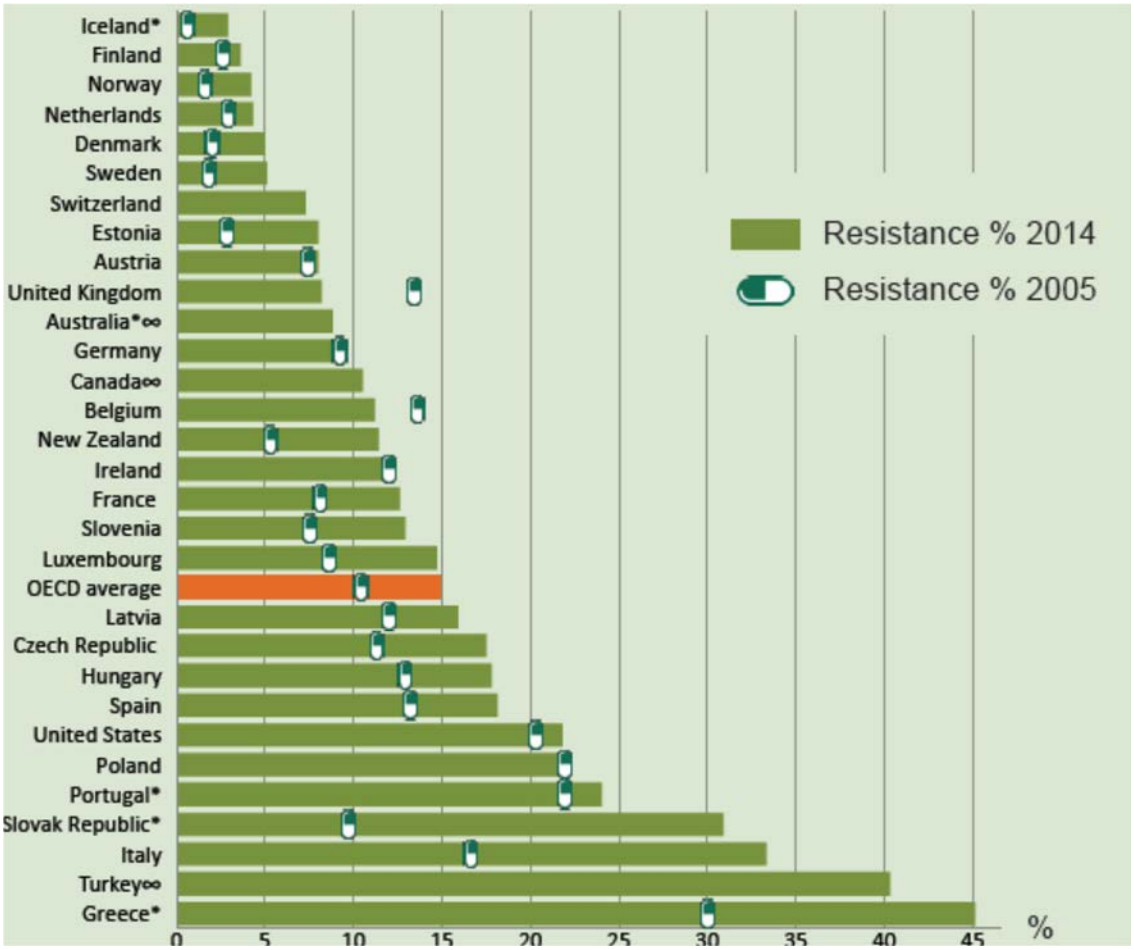



**FIGURE 3-1** Trends in antimicrobial resistance across OECD countries, 2005 to 2014.
SOURCE: OECD, 2016.
NOTE: * Greece missing *S. pneumoniae* (resistant to penicillin) 2005 and 2014, Slovakia and Belgium missing *K. pneumoniae* (resistant to 3rd generation cephalosporins and carbapenem) 2005, Portugal missing *K. pneumoniae* (resistant to carbapenem) 2005, New Zealand missing MRSA 2014, Australia missing *S. pneumoniae* (resistant to penicillin) 2014, Iceland missing *K. pneumoniae* (resistant to carbapenem) 2014; ∞ Includes resistant and intermediate data.

The OECD Health Committee, in collaboration with the European Centre for Disease Prevention and Control, has also given considerable attention to estimating the future health and economic burden of antimicrobial-resistant infections (OECD, 2018). Their analysis was undertaken at the direction of the European Commission and published in *Stemming the*

*Superbug Tide.* The researchers drew on data from the ECDC European Antimicrobial Resistance Surveillance Network and the laboratory networks that inform the Center for Disease Dynamics, Economics, and Policy's Resistance Map (OECD, 2018). Their estimates of resistance in pathogen–drug combinations accounted for uncertainty using multiple imputation of missing historical values and estimating correlates of resistance from UN population data and weighted modelling, described in detail in the report (OECD, 2018). The analysis indicated that around 17 percent of bacterial infections in OECD countries *overall* are resistant to antibacterial medicines, but this prevalence is more than a third in some OECD countries such as Greece, Republic of Korea, and Turkey (OECD, 2018). Resistance proportions are much higher outside the OECD, over 40 percent in some G20 countries, including China, India, and Russia (OECD, 2018).

The large variation among countries in burden of resistant infections influences projections of mortality. OECD models indicate that there are about 60,000 deaths from resistant infections every year in the Unites States and Europe (OECD, 2018). By 2050, the OECD model suggests resistant infections will have caused 2.4 million deaths in the same countries (plus Canada, Mexico, and Australia), roughly 30,000 deaths a year in the United States alone (Figure 3-2) (OECD, 2018). The effects of resistance on quality of life are even stronger. The OECD models of disability-adjusted life years (DALYs), an indicator that accounts for both untimely deaths and time spent in relatively compromised health, suggest 1.75 million years of healthy life are lost every year across 33 study countries (see Figure 3-3). In Italy alone, up to one person out of every 205 could lose a year of life because of infections caused by resistant organisms (OECD, 2018).

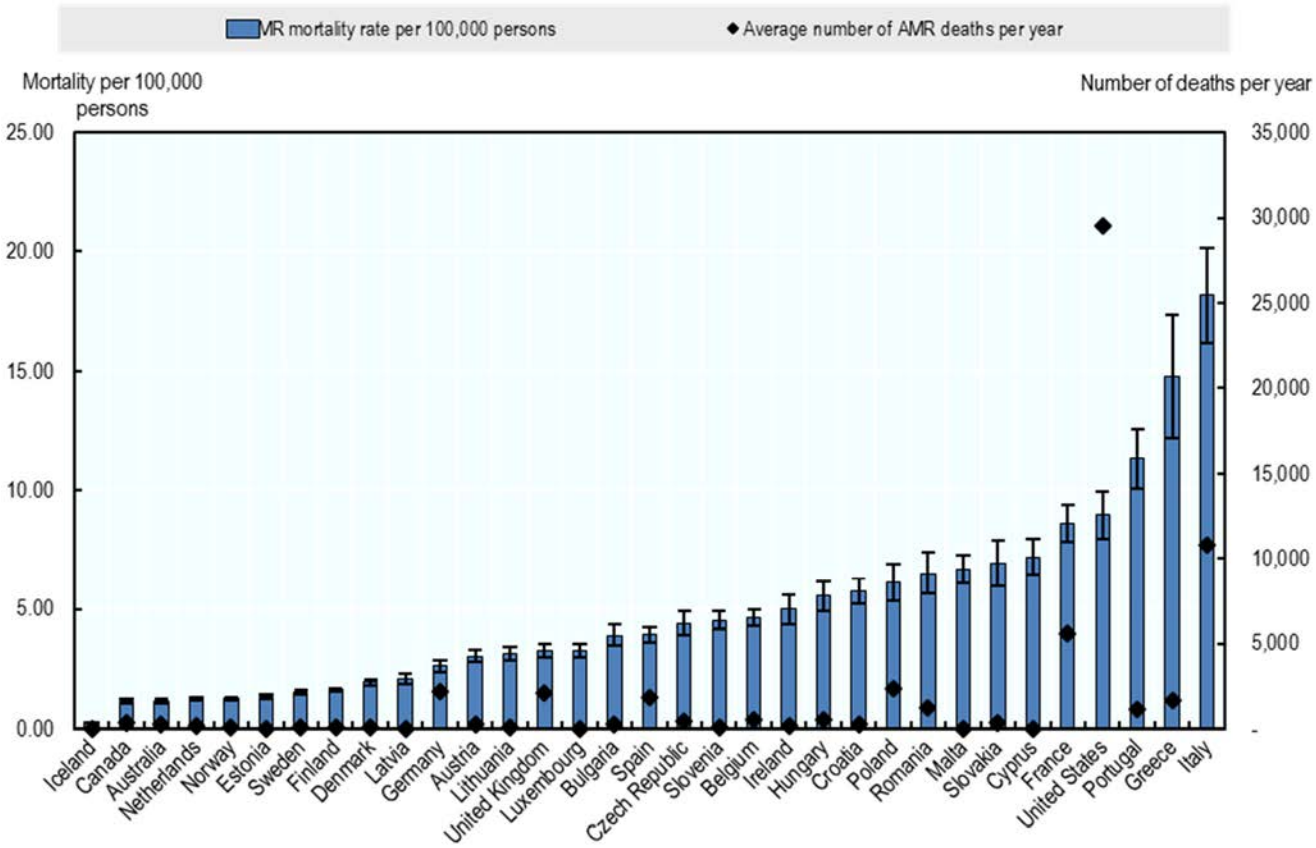


**FIGURE 3-2** Projected average annual number of deaths from resistant infections and mortality rate per 100,000, 2015 to 2050.
SOURCE: OECD, 2018.

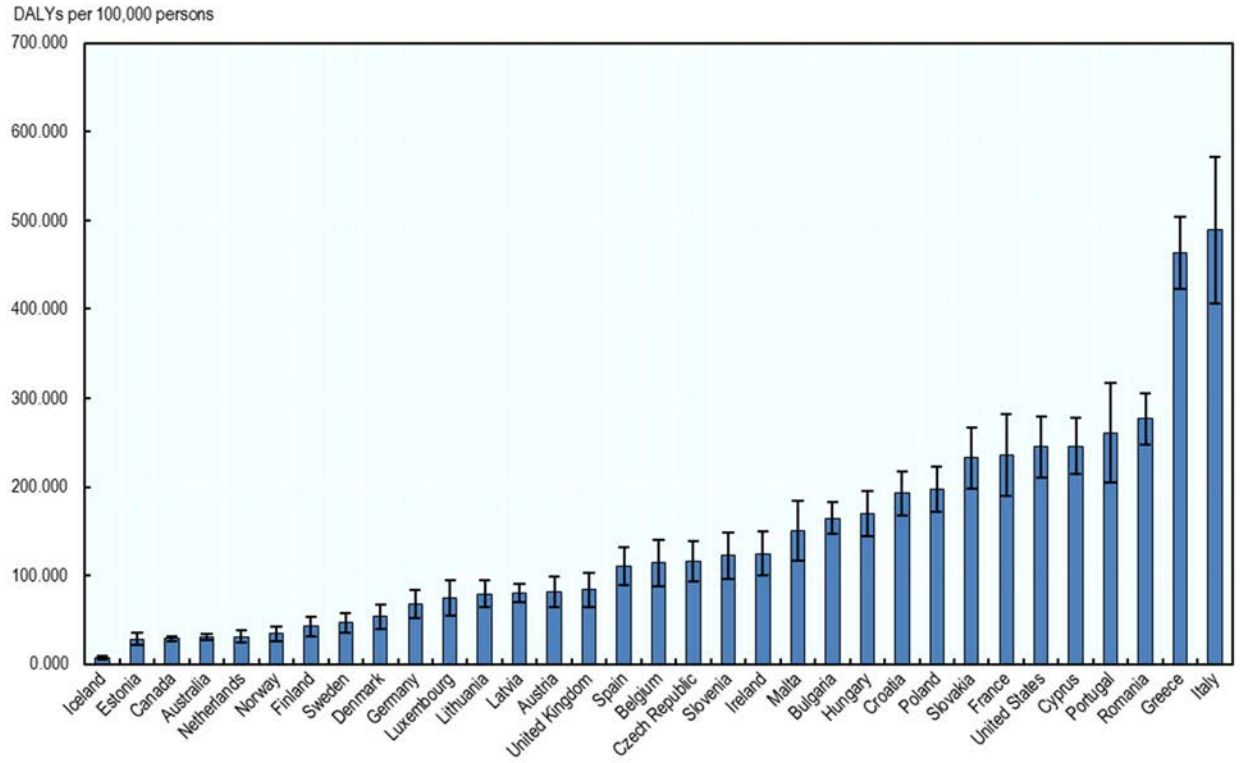



**FIGURE 3-3** Projected average annual burden of antimicrobial resistance expressed in disability-adjusted life years, 2015 to 2050.
SOURCE: OECD, 2018.

The OECD's estimates of mortality and morbidity are the output of published models, the assumptions of which are clearly explained. There are only so many parameters modelling can accommodate, however. All the models presented in *Stemming the Superbug Tide* were based on resistance in eight common pathogen-drug combinations.[2] Other resistance patterns will emerge between now and 2050; there are other pathogen–drug combinations that cause serious excess illness and death even today. Accepting the methodological limitations of modelling, the work shows a clear and consistent increasing threat to human health from antimicrobial resistance.

OECD research has also made valuable contributions to understanding the economic consequences of resistant infections. Based on their calculations of morbidity and mortality associated with resistant infections, the report estimated that resistance costs the health system of the 33 countries studied about $3.5 billion a year (adjusted for purchasing power parity), $2 billion a year in the United States alone (OECD, 2018). This finding was consistent with a similar study that estimated the cost to the U.S. health system around $2.2 billion a year (Thorpe et al., 2018).

[2] Third-generation cephalosporin-resistant *E. coli*; fluoroquinolones-resistant *E. coli*; penicillin-resistant *S. pneumonia*; Methicillin-resistant *S. aureus*; carbapenem-resistant *K. pneumonia*; third-generation cephalosporin-resistant *K. pneumonia*; carbapenem-resistant *P. aeruginosa*; vancomycin-resistant *E. faecalis* and *E. faecium.*

The OECD also drew attention to the negative externalities (costs to parties other than the patient and prescriber) associated with antimicrobial resistance (OECD, 2018). For example, antimicrobial resistance can undermine confidence in the health system, causing people to avoid in-patient treatment if possible; it can also hurt livelihoods dependent on tourism or agriculture (Thorpe et al., 2018). These kinds of effects are harder to model with any amount of precision, but are useful as a reminder of the potentially devastating downstream effects of a health problem with already devastating short-term consequences.

## The O'Neill Report

One of the most influential reports on antimicrobial resistance was the O'Neill report, the 2014 commission from then UK Prime Minister David Cameron to economist Jim O'Neill to analyze the problem of antimicrobial resistance and suggest a mitigating strategy (O'Neill). The commission's final report, *Tackling Drug-Resistant Infections Globally*, was published in 2016 (O'Neill, 2018). The report immediately attracted considerable attention in the scientific literature (Matthiessen et al., 2016; O'Neill, 2016; PLOS Medicine Editors, 2016; Price, 2016; Sugden et al., 2016), from international organizations (FAO and UN; IACG, 2019; World Bank, 2016, 2017b), and in the lay media (*BBC News*, 2016; Boseley, 2016; Roland, 2015; *The Economist*, 2016). Much of this attention centered around the report's projection that by 2050 antimicrobial resistance would cause 10 million deaths a year, costing the global economy a cumulative $100 trillion in the same time (O'Neill, 2018).

These estimates were based on analyses by the Rand Corporation, a nonprofit think tank, and by the management consulting and tax firm KPMG (O'Neill, 2018). Both models considered resistance to medicines used to treat malaria, HIV, and tuberculosis, as well as hospital-acquired *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* (KPMG LLP, 2014; Taylor et al., 2014). Although both models report having made projections for different burden of resistance scenarios, only the extreme high-burden scenario were reflected in the O'Neill report (KPMG LLP, 2014; Taylor et al., 2014).

The pathogens causing HIV, malaria, and tuberculosis are not usually central to the discussion of antimicrobial resistance. The burden of disease associated with these infections is vastly greater than those caused by the CDC or the World Health Organization (WHO) priority pathogens, making it difficult to interpret estimates of their combined affects.

The Rand model assumed that in 15 years none of the medicines licensed to treat these infections will be effective, an assumption that lacks face validity (Friedman, 2020; Taylor et al., 2014). Even in the model appendices, the Rand team cite contemporary estimates of resistance to HIV drugs (~5 percent worldwide) and treatments for multidrug-resistant tuberculosis treatments (~3 percent globally, between 2 and 5 percent in every region except Europe where it is ~16 percent) (Taylor et al., 2014). It is not credible to conclude that total resistance to these medicines in 15 years is in any way likely.

Table 3-3 presents some key results from the Rand and KPMG analyses. This results informed the O'Neill report's widely publicized estimates of 10 million lives lost to antimicrobial resistance every year by 2050 and $100 trillion cumulative loss in global production (O'Neill, 2018).

**TABLE 3-3** Key Results from the RAND and KPMG Analyses Informing the O'Neill Report and from the O'Neill Report

| | Lives Lost by 2050 | Cumulative GDP Loss by 2050 |
|---|---|---|
| **Rand model** | 11 to 444 million adults, cumulative | $5.8–$125 trillion |
| **KPMG model** | 200 to 700 million, cumulative | $5–$14.2 trillion |
| **O'Neill report** | 10 million a year by 2050 | $60–$100 trillion |

SOURCES: KPMG LLP, 2014; Taylor et al., 2014.

None of the analysis informing the estimates in Table 3-3 were formally peer reviewed (de Kraker et al., 2016). The relationship between the commissioned models and the O'Neill report's conclusions are also somewhat murky (de Kraker et al., 2016; O'Neill, 2014). The O'Neill report's authors refer to original analyses and information not included in the Rand or KPMG models (e.g., "We estimate that caesarean sections contribute about 2% to world GDP"), but their methods and data are not presented (Friedman, 2020; O'Neill, 2014).

The O'Neill team started from a reasonably credible 2014 base estimate of 700,000 deaths a year from resistant infections (about a third from multidrug-resistant tuberculosis alone) (O'Neill, 2018; WHO, 2019b). This estimate also has methodological limitations (Schnall et al., 2019). Few if any of the other numbers in the report have such a clear attribution. Though their analytic steps are not clear, one critique concluded, "the scenario that seems to be underlying the most often quoted line [10 million death a year] entails a sharp initial rise of current resistance rates by 40 percentage points, after which rates remain stable until 2050, and doubled infection rates" (de Kraker et al., 2016). A 40-percentage point increase in not consistent with what is presented in the CDC or the OECD analyses discussed previously. One may assume the O'Neill commission believed this to be plausible based on more (rightly) dire predictions in low- and middle-income countries, but it is not clear what scientific research informed their estimates or what their assumptions regarding resistance in different parts of the world might have been. A lack of data from low- and middle-income countries, where the burden of resistant infection is undoubtedly greatest, is a reason to support these countries in routine surveillance for, and prevalence surveys of, resistant infections (Islam et al., 2019). But no estimate of the global burden of resistance can be made in the absence of such data.

The O'Neill report writers may have damaged their credibility by promoting what appears to be only the upper limit of the uncertainty intervals for their conclusions (de Kraker et al., 2016). The writers give no confidence interval for their estimate of 10 million excess deaths a year by 2050 (O'Neill, 2014). (For comparison, 10 million deaths a year is comparable to the global sum of all cancer deaths combined [Sung et al., 2021]). Their estimate that resistance could "cost the world up to 100 trillion USD" contained an uncertainty interval ($60 to $100 trillion) which is usually dropped (O'Neill, 2014).

This is not to say that the O'Neill commission did not produce valuable policy analysis or that its report did not raise the global prominence of the problem. Nor is the modelling of extreme assumptions or worst-case scenarios without value (OECD, 2018). Such models can be useful, especially when they are presented as sensitivity analyses and the caveats on their interpretation made clear. But unfortunately, the O'Neill report's estimates of both projected mortality and economic consequences of resistance took on a life of their own (Friedman, 2020). When cited, which is often, it is usually without mention of their limitations or the murky analysis that informed them. As a 2016 essay concluded, "Unreliable global estimates like those

provided in the [O'Neill report] potentially undermine, rather than support, the fight against a post-antibiotic era" (de Kraker et al., 2016).

## The World Bank Report

The World Bank report *Drug-Resistant Infections: A Threat to Our Economic Future,* came out in 2017, building on the momentum of the previous year's O'Neill report (World Bank, 2017). The report presented estimates of the threat antimicrobial resistance poses to the global economy in terms of lost gross domestic product (GDP) between 2015 and 2050, giving particular attention to costs to international trade, livestock agriculture, and health (World Bank, 2017).

The World Bank models drew on the Rand estimates that informed the O'Neill report (Ahmed et al., 2017). The model's low-case scenario was based on the Rand scenario 1, assuming 5 percent antimicrobial resistance from 2015 on; the high-case scenario projected current rates of resistance for 15 years and 100 percent resistance to available treatments after year 15 (Ahmed et al., 2017). Possibly motivated by concerns about the validity of the Rand analyses, the working paper explained, "we avoid the [Rand report's] extreme cases of absolute resistance"[3] (Ahmed et al., 2017). In its final report the World Bank team further clarified that its "simulations are not predictions (rather, a range of outcomes that are possible)" (World Bank, 2017).

The caveats on the World Bank models are helpful. At the same time, using models driven mostly by data on HIV, tuberculosis, and malaria to inform conclusions about other resistant pathogens in humans and livestock is of questionable validity and should be kept in mind in reviewing the report's main conclusions.

The World Bank report emphasized that trade and livestock production stand to be seriously affected by antimicrobial resistance, especially livestock production in low-income countries (World Bank, 2017). Livestock is only a small part (about 2 percent) of the global economy, but its relative value—both in direct terms and as determinant of the health and economic mobility of women and children—is greater in low- and lower-middle-income countries (Ahmed et al., 2017). The World Bank working paper reported that livestock production in low-income countries could fall between 3.1 and 11.1 percent and, in lower-middle income countries between 3.1 and 8.9 percent (Ahmed et al., 2017). The effects of reductions in livestock production also influence, but only partially, the projected 1.1 to 3.8 percent deficit in global exports (World Bank, 2017).

The cost of health services could be perhaps the most directly affected by antimicrobial resistance, given that resistant infections cost more to treat. Increased health expenditures could be felt in cost of medicines, with more expensive antimicrobials being needed, as well as more days spent hospitalized, more consultation time with providers, and increased demand on laboratory diagnostic services. Increasing need for health services puts more pressure on both public and private spending for health, which coupled with decreasing trade and livestock production, could drive a public deficit. The World Bank models estimate that under a low burden of antimicrobial resistance health costs could increase $330 billion; under a high-burden scenario this increase could be $1.2 trillion (World Bank, 2017).

[3] Meaning the Rand projections that assumed 100 percent resistance starting immediately (Ahmed et al., 2017; Taylor et al., 2014).

Figure 3-4 shows how protracted effects on global economic output might extend for the next 30 years, costing the world between 1.1 and 3.8 percent of annual gross domestic product by 2050 (World Bank, 2017). These shortfalls could be as serious as during the 2008–2009 global financial crisis (see Figure 3-5) but could extend for much longer. (The shocks of the 2008–2009 crisis lasted only a few years.)

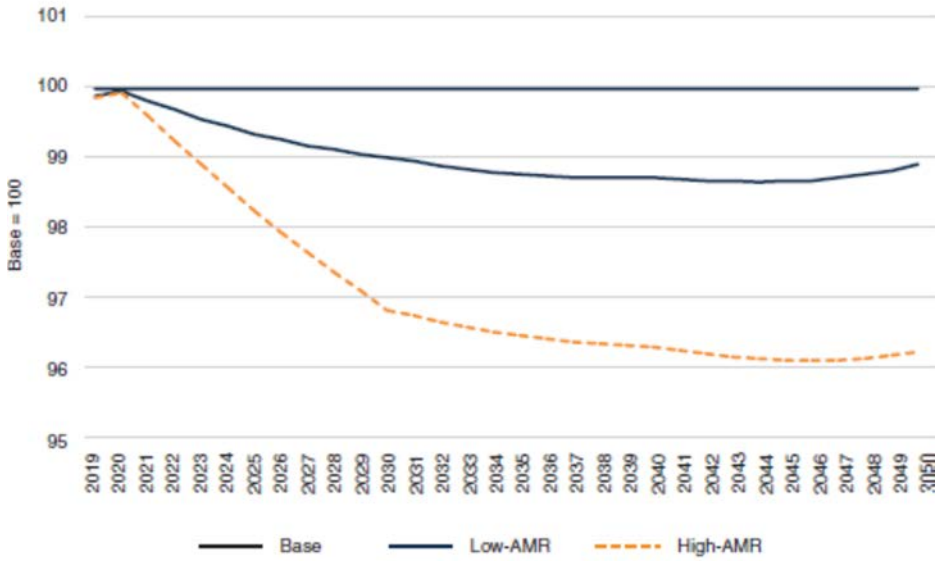



**FIGURE 3-4** Shortfalls in global economic output assuming low- and high-burden of resistance relative to a baseline scenario, 2019 to 2050.
SOURCE: World Bank, 2017.

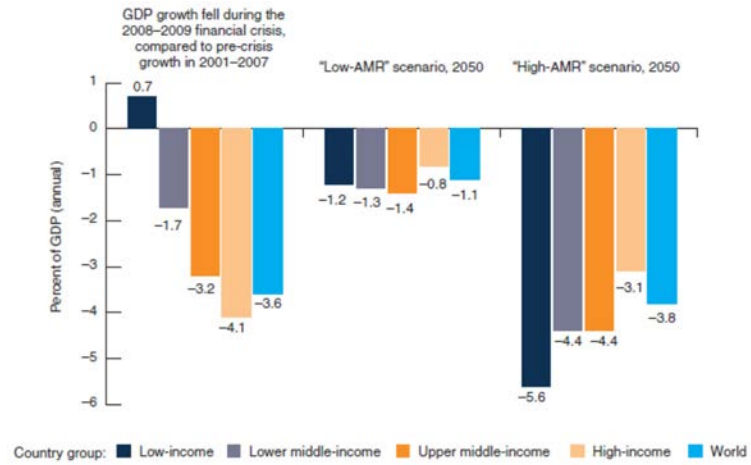



**FIGURE 3-5** Costs to the economy of antimicrobial resistance compared to those of the 2008–2009 financial crisis, annual cost expressed as percentage of GDP.
SOURCE: World Bank, 2017.

By taking a disproportionate toll on developing countries, antimicrobial resistance could derail progress on the Sustainable Development Goals, the United Nations' goals for international development between 2015 and 2030 (UN, 2021; World Bank, 2017). Through its

effects on health costs, trade, and livestock production, the World Bank models indicate that antimicrobial resistance could push between 8 and 28 million people into extreme poverty by 2050 (World Bank, 2017) (see Figure 3-6).[4]

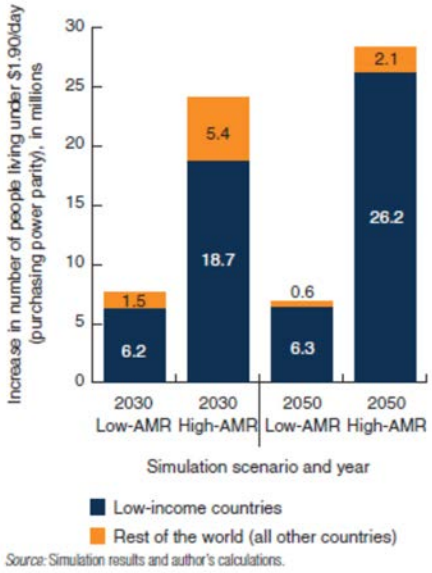



**FIGURE 3-6** Number of people falling into extreme poverty (living on < $1.90 a day adjusted for purchasing power parity) by 2050.
SOURCE: World Bank, 2017.

## CHALLENGES OF QUANTIFYING THE BURDEN OF RESISTANCE

The O'Neill report and the World Bank report it inspired are examples of how a lack of empirical evidence about antimicrobial resistance influences the discussion of the problem. Reliable modelling of the true burden of resistance is extremely challenging. Part of the challenge stems from uncertainty regarding the best ways to measure antimicrobial resistance in humans, animals, the environment (Wernli et al., 2017). The global COVID-19 pandemic has made this task more challenging, increasing the strain on health systems and possibly leading to less interest in antimicrobial resistance (Kwon and Powderly, 2021; Pelfrene et al., 2021; Rodriguez-Bano et al., 2021). Information on the epidemiology of resistance, through surveillance of known risks and attention to emerging resistant pathogens, and their consequences for health, are essential pieces of information to quantify this burden (Wernli et al., 2017).

### The Health Effects of Resistance in Humans

Chapter 4 discusses the challenges of surveillance for antimicrobial resistance. In short, measuring antimicrobial resistance requires a laboratory capacity and trained clinical microbiologists that are not widely available in low- and middle-income countries (Iskandar et al., 2021). The large, tertiary-care hospitals that can support the required microbiology labs

[4] Defined as living on less than $1.90 a day, adjusted for purchasing power parity (World Bank, 2017).

provide a narrow window into the scope of resistance (Gandra et al., 2020; Tadesse et al., 2017; Walia et al., 2019; Wang, 2019). While valuable, this window is not necessarily representative of the national situation. Even in the United States, with its sophisticated laboratory infrastructure, there are challenges in reporting resistant isolates through the regional and national Antibiotic Resistance Laboratory Network, a problem discussed more in Chapter 5.

Regardless of the capacity of the national surveillance systems, there are also challenges in measuring mortality and morbidity from resistant infections. First of all, most resistant infections are seen in patients who have other underlying conditions, making it difficult to know what portion of the clinical outcomes observed can be attributed to the resistant infection (Cassini et al., 2019). For this reason, "scientific debate is ongoing on the appropriate epidemiological study design and statistical inference methods to measure reliable estimates of untoward clinical outcomes attributable to infections with antibiotic-resistant bacteria" (Cassini et al., 2019). For the time being, most research on the clinical outcomes associated with antimicrobial resistance is limited to readily observable, relatively short-term clinical outcomes, including deaths, number of days hospitalized, and risk of developing sequelae (e.g., developing *C. difficile* infection after treatment for a resistant infection) (Cassini et al., 2019). Risk of death is clearly the most potentially devastating consequence of resistant infection, though only about half of the studies included in a recent systematic review found an increased risk of death in patients infected with a resistant pathogen relative to those infected with a susceptible one (Naylor et al., 2018). It is possible that these differing results are influenced by widely varying methodological approaches, a topic discussed later in the chapter.

Scientists from the ECDC recently published one such analysis of the health outcomes of resistant infections. Drawing on data from the European Antimicrobial Resistance Surveillance Network and health outcome models for specific types of infection (e.g., bloodstream infection, surgical site infection), they estimated between 583,148 and 763,966 infections with resistant bacteria occurred in Europe in 2015, almost two-thirds of them acquired during health care (Cassini et al., 2019). These infections ended in over 33,000 deaths, with the burden of disease (in terms of healthy life years lost) being most severe in infants and older adults, see Figure 3-7 (Cassini et al., 2019).

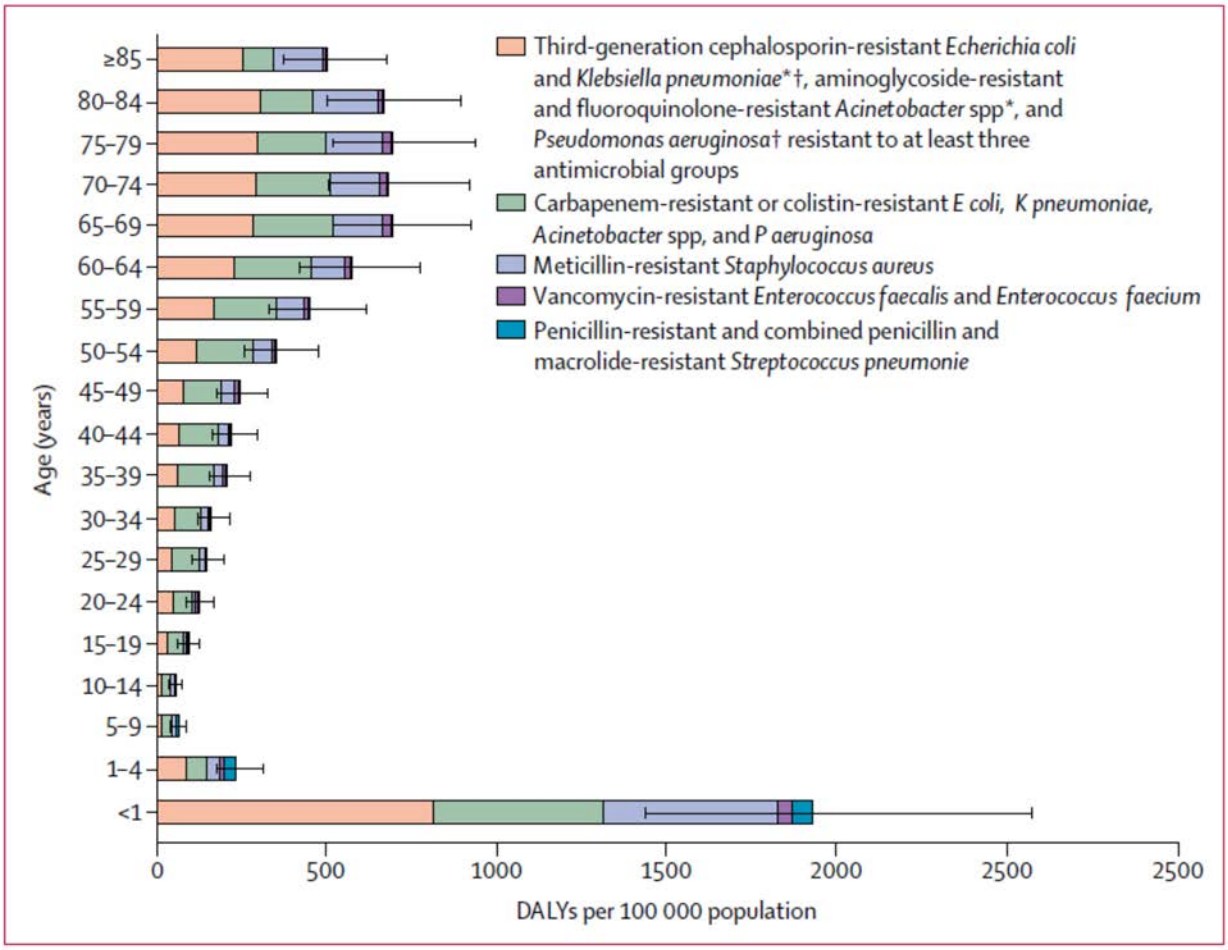



**FIGURE 3-7** Estimates of the burden of drug-resistant bacterial infections in DALYs by age group, European Union and European Economic Area, 2015 data.
SOURCE: Cassini et al., 2019.

Studies such as these help put concrete parameters on the consequences of resistance, parameters that are compelling to policy makers precisely because of their narrow scope and clear boundaries. Nevertheless, some of the most potentially devastating consequences of resistance are the downstream effects that can manifest in increased mortality and complications from seemingly unrelated conditions.

As the previous chapter discussed, antimicrobials are essential for the medical management of surgical care, cancer, and transplant patients, many of whom are immunocompromised. A 2015 model, based on review of randomized and quasi-randomized, controlled trials, estimated how loss of effective antibiotic prophylaxis might increase the burden of serious infections and related deaths in the United States (Teillant et al., 2015). The models presented scenarios of a loss of antibiotic efficacy of 10, 30, 70, and 100 percent (Teillant et al., 2015). The authors estimate that a 30 percent reduction in the efficacy of prophylactic antimicrobial treatment for 10 common surgeries and blood cancer chemotherapy would result in an additional 120,000 infections and 6,300 deaths a year (Teillant et al., 2015). Even a relatively minimal 10 percent loss of efficacy would result in 40,000 additional infections and 2,100 additional deaths; the more dire prediction of a 70 percent loss of efficacy would result in

280,000 additional infections and 15,000 additional deaths, as Figures 3-8 and 3-9 show (Teillant et al., 2015).

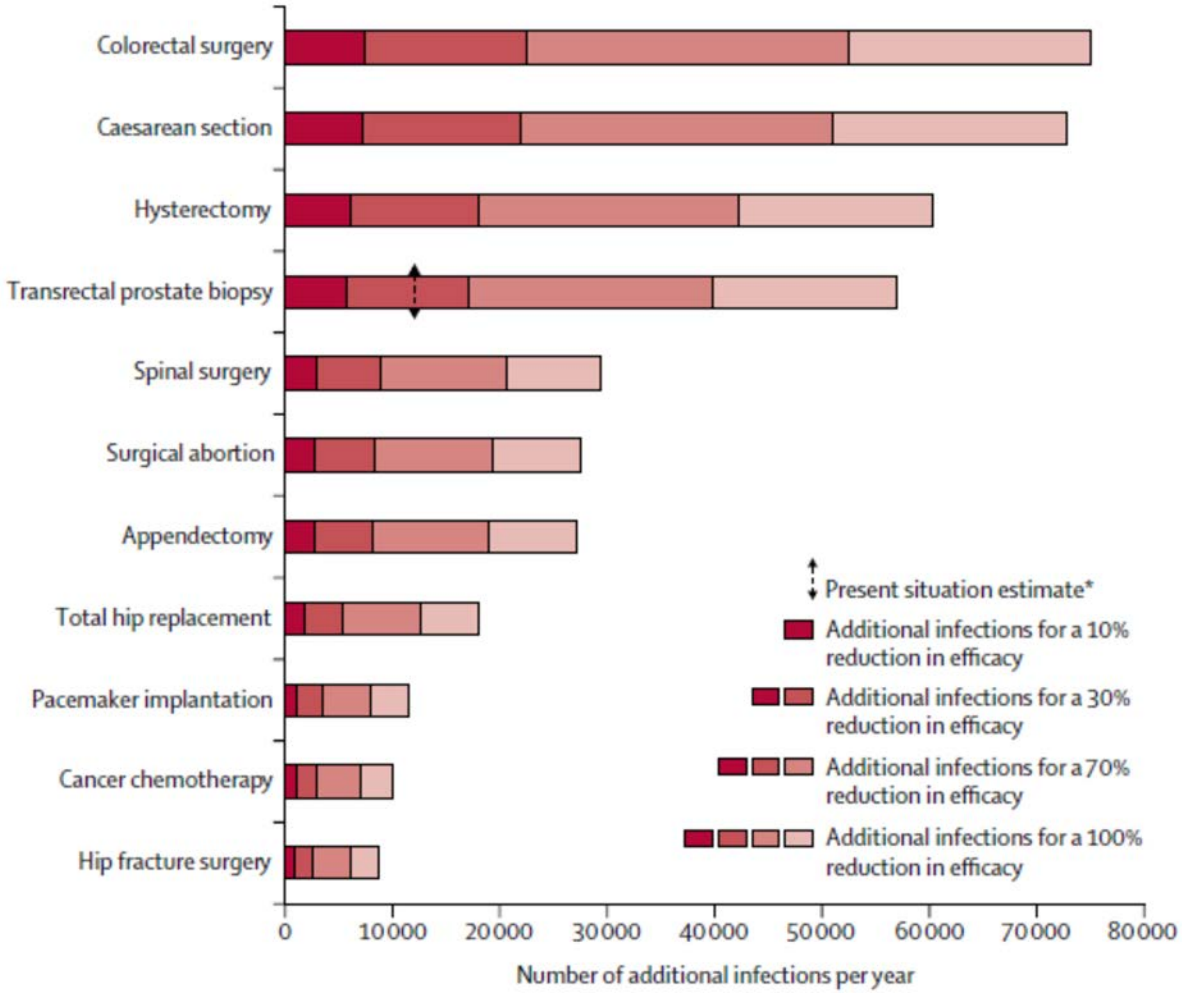



**FIGURE 3-8** Additional infections per year in the United States under 10%, 30%, 70%, and 100% reduction in efficacy of antibiotic prophylaxis.
SOURCE: Teillant et al., 2015.

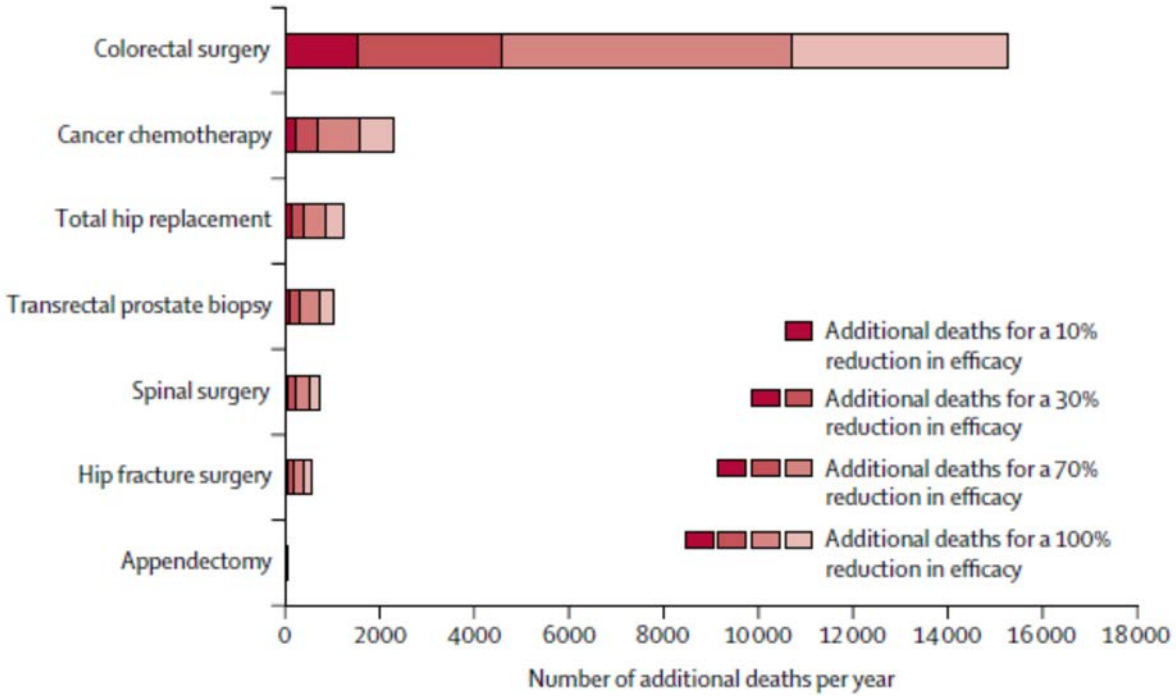



**FIGURE 3-9** Number of additional deaths per year in the United States under 10%, 30%, 70%, and 100% reduction in efficacy of antibiotic prophylaxis.
SOURCE: Teillant et al., 2015.

Models such as those of Teillant and colleagues draw on an extensive body of research on infection in cancer and surgery patients. The consequences of resistance associated with other common infections, though sometimes more serious, are less amenable to modeling. Drug-resistant infections in the bone and brain, for example, are serious because it is difficult to achieve clinically meaningful concentrations of antimicrobial medicines in these tissues (Nau et al., 2010; Nau et al., 1998; Thabit et al., 2019). Moreover, even small changes in susceptibility of pathogens to medicines can make more surgeries necessary and prompt months-long, or even lifelong, antimicrobial therapy with uncertain results.

Resistant infections can compromise the outcomes of almost every medical treatment. They could also have psychological affects that reduce public confidence in the health system (Foster, 2011; WHO, 2019a). The COVID-19 pandemic has made clear that an infectious disease crisis, accompanied by disruptions in health services and widespread fear or anxiety, can have profound effects on health. English models indicate that cancer mortality may have increased by an estimated 20 percent during the pandemic because of avoided or delayed treatments (Lai et al., 2020). Globally, about 28 million surgeries were cancelled or postponed in the first wave of COVID-19 alone (COVIDSurg Collaborative, 2020). It is not clear how long it will take to clear this backlog or how far-reaching the health consequences could be (Carr et al., 2021). In some ways the most serious risks antimicrobial resistance poses to society are some of the most challenging to quantify.

The overall effects of the COVID-19 pandemic on antimicrobial resistance are hard to predict. On one hand the increased emphasis on hygiene and the decrease in travel and elective medical procedures may have decreased the spread of resistant pathogens both in community and clinical practice (Knight et al., 2021). On the other hand, the vast majority of COVID-19 patients were treated with antimicrobials (Knight et al., 2021). One study found that despite only 7

percent of COVID-19 patients having bacterial infections over 70 percent were treated with antibiotics (Langford et al., 2020). Research in India found that COVID-19 drove over 200 million excess doses of antimicrobials (Sulis et al., 2021). Such extensive exposure to antimicrobials can predispose patients to colonization with resistant organisms. There may also be a cohort of COVID-19 survivors with residual predisposition to lung infections who will need more frequent antimicrobial therapy (Knight et al., 2021).

There has also been considerable presumptive antimicrobial use during the pandemic, both in COVID-19 patients presenting with nonspecific symptoms and "just in case" prescribing to patients with other illnesses who were deflected from care (Knight et al., 2021). As Figure 3-10 shows, the ways COVID-19 has and will continue to influence antimicrobial resistance are varied and warrant further research.

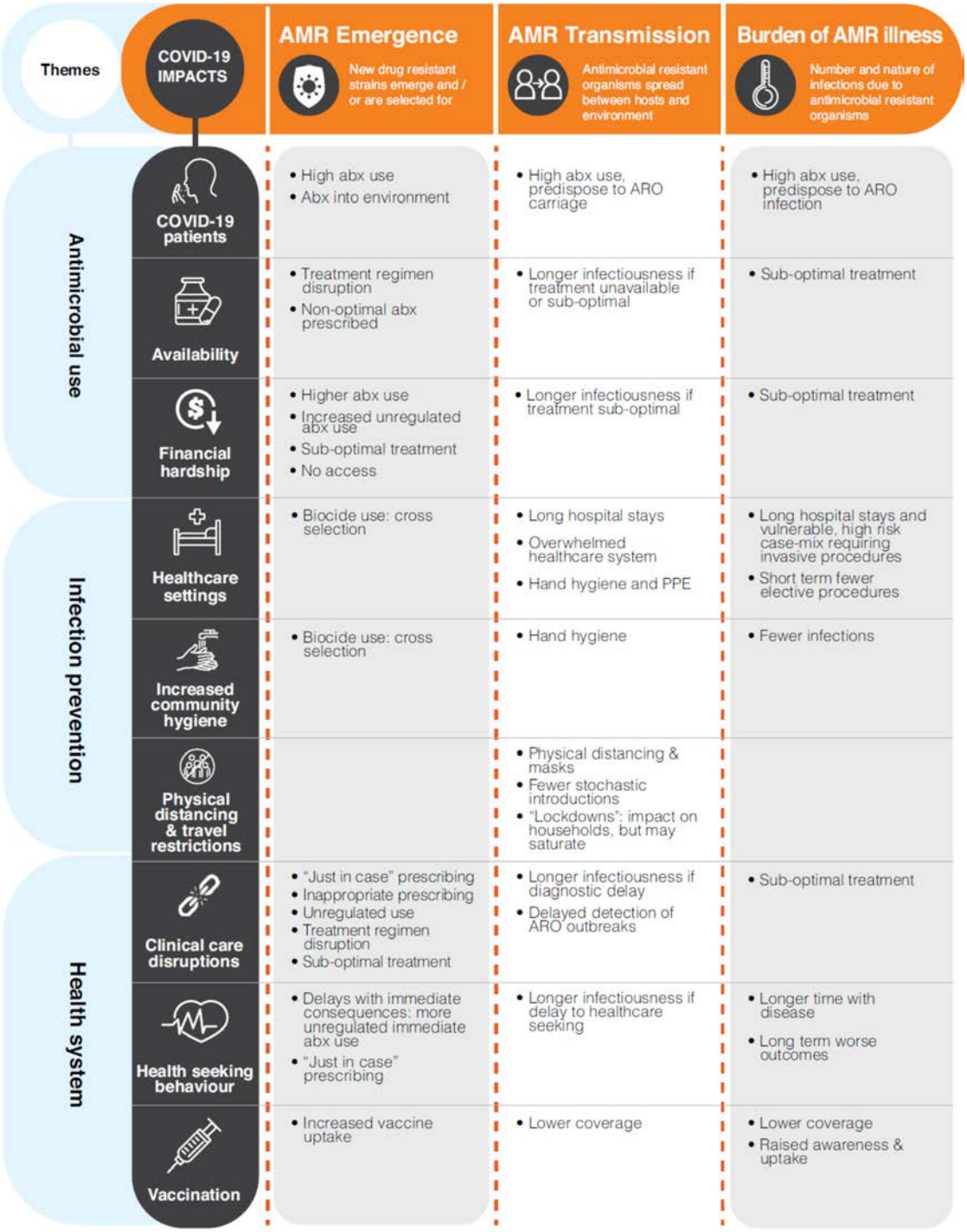



**FIGURE 3-10** Interactions between COVID-19 and the emergence of antimicrobial resistance.
NOTE: abx = antibiotics; AMR = antimicrobial resistance; ARO = antibiotic-resistant organisms.
SOURCE: Knight et al., 2021.

### The Economic Effects of Resistance in Humans

Loss of life and disability are devastating health outcomes in their own right. They also affect society indirectly, through the loss of what might have been achieved in years of healthy

life. Estimates of how health problems affect the workforce are often of particular interest to policy makers. Most health problems, resistant infections included, hurt the workforce in two ways: the lost productivity among patients suffering from resistant infections and, in some cases, the lost productivity of the workers looking after them (Tillotson and Zinner, 2017). In the same way the health effects of resistant infections can be both direct and indirect, so can the social and economic effects. Table 3-4 shows the many pathways through which health care-associated infections draw a social and economic toll.[5]

**TABLE 3-4** The Social Costs of Hospital-Acquired Infections

| Categories of Cost | | |
|---|---|---|
| Direct Hospital Costs | Fixed Costs | Buildings |
| | | Utilities |
| | | Equipment/Technology |
| | | Labor (laundry, environmental control, administration) |
| | Variable Cost: | Medications |
| | | Food |
| | | Consultations |
| | | Treatments |
| | | Procedures |
| | | Devices |
| | | Testing (laboratory and radiographic) |
| | | Supplies |
| Indirect Costs | Lost/Wages | |
| | Diminished worker productivity on the job | |
| | Short term and long term morbidity | |
| | Mortality | |
| | Income lost by family members | |
| | Forgone leisure time | |
| | Time spent by family/friends for hospital visits, travel costs, home care | |
| Intangible Cost | Psychological Costs (i.e., anxiety, grief disability, job loss) | |
| | Pain and suffering | |
| | Change in social functioning/daily activities | |

SOURCES: Scott, 2009. Adapted from Haddix AC and Shaffer PA. Cost-effectiveness analysis. In Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation. Oxford University Press, 1996.

In estimating the economic consequences of resistance, researchers must base their analysis on estimates of the health effects. Therefore, the uncertainties and limitations in measuring the health consequences of resistance carry forward to discussion of the costs. For this reason, there are fewer economic studies on antimicrobial resistance (Naylor et al., 2018). The quality of what is published is also lower, a recent systematic review concluded, and held back

[5] Infections acquired as a result of medical care, often stemming from inappropriate use of antimicrobials or problems with infection controls; health care-acquired infections are often drug resistant (CDC et al., 2021).

by a "lack of rigorous, transparent modelling studies which appropriately present or incorporate uncertainty" (Naylor et al., 2018).

The potential for bias in the economic evaluation of antimicrobial resistance is at the root of the many widely variable estimates ($3 billion to $100 trillion) of the economic consequences of antimicrobial resistance published in recent years (Wozniak et al., 2019). In a systematic review on the economic burden of resistant infections, Wozniak and colleagues commented on this variability, "erroneous or unclear estimates of impact can have alarming effects some of which may contribute to greater action but they also create confusion and potentially undermine the fight against antimicrobial resistance" (Wozniak et al., 2019).

Even a relatively straightforward economic outcome, excess time spent hospitalized, for example, is highly vulnerable to analytic and methodological bias (Naylor et al., 2018; Nelson et al., 2021). Figure 3-11 shows how one recent systematic review identified that different analytic methods, sometimes even reported in the same study, can influence the study's estimate of excess days hospitalized (Naylor et al., 2018). When measuring excess costs associated with length of hospital stay, for example, studies will often fail to adjust the outcome (i.e., length of stay) to count only those days *after* the resistant infection started (Wozniak et al., 2019). This time-dependent bias tends to inflate estimates of costs. A recent systematic review found that of 14 studies on the excess costs associated with resistant infections, only two properly accounted for bias in their analyses (Wozniak et al., 2019). After reviewing over 1,000 abstracts the researchers concluded that, while economic valuations of the excess costs associated with resistant infections are sorely needed, especially in low- and middle-income countries, currently the only rigorous and unbiased research available is on health care-associated bloodstream infections with resistant Enterobacterales and MRSA (Wozniak et al., 2019).

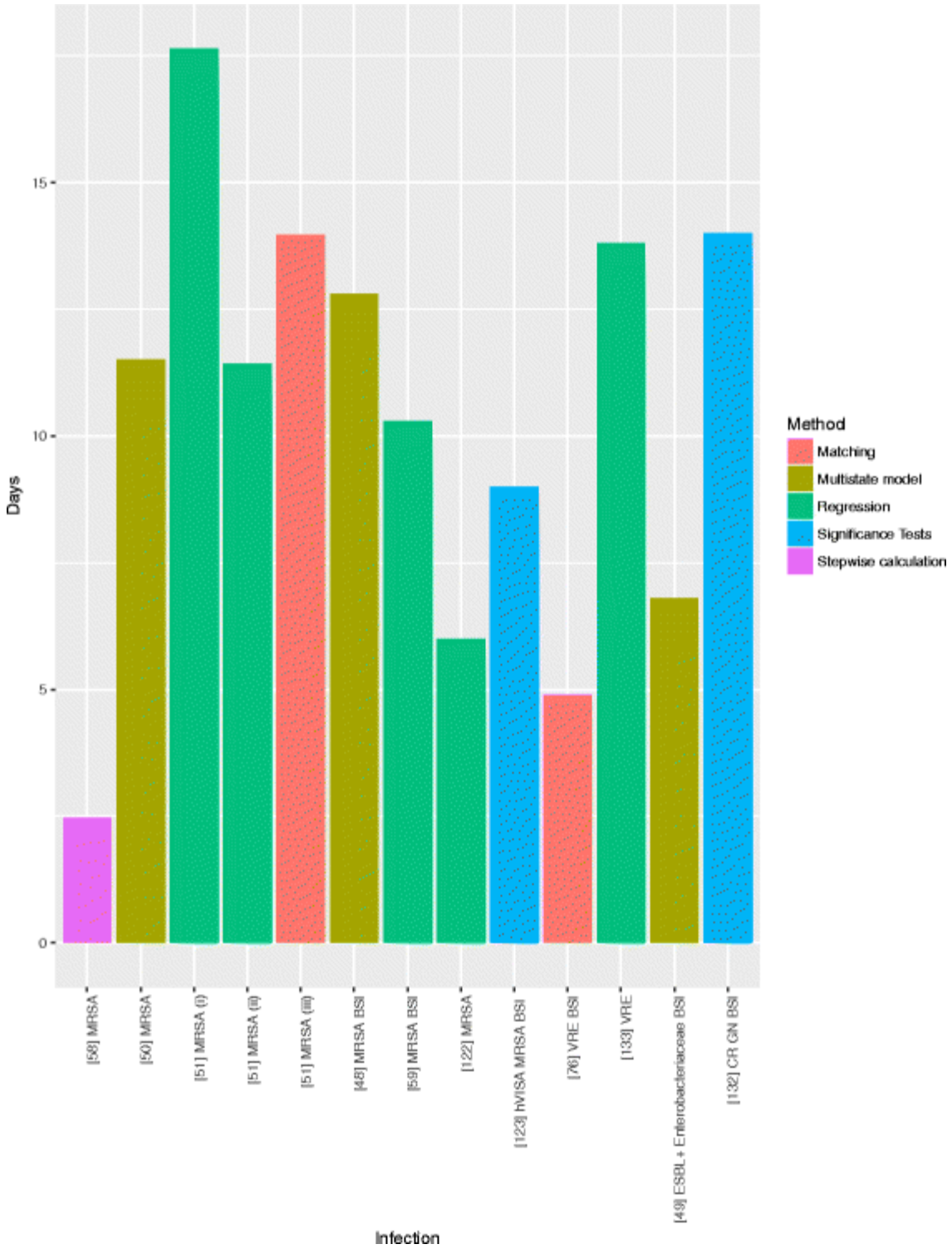



**FIGURE 3-11** Estimates of excess length of hospitalization cause by antimicrobial resistance and different analytic methods; (i) through (iii) indicate different methods used in a single study.
NOTE: BSI = bloodstream infection; CR = carbapenem-resistant; GN = gram-negative; hVISA = heterogeneous vancomycin-intermediate *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococci.*
SOURCE: Naylor et al., 2018.

Since Wozniak and colleagues published this meta-analysis, some U.S. papers meeting their criteria for adjusting for bias and confounders have come out. Data from the Department of Veterans Affairs (VA), the largest integrated health system in the United States, with linked records containing cost, microbiological, and clinical information, informed the CDC estimates of costs attributable to resistant pathogens presented earlier in this chapter (Nelson et al., 2021). From a final dataset that included almost 25,000 infections, researchers estimated the costs associated with both community- and hospital-acquired infection for six common resistant pathogens (see Table 3-5). Adjusted over the entire United States, estimates of the direct costs associated with these infections is between $4.1 and $5.1 billion (Nelson et al., 2021).

**TABLE 3-5** Adjusted Attributable Cost by Pathogen for Community and Hospital Onset Infections

| | **Invasive**[a] | | | **Noninvasive**[a] | | |
|---|---|---|---|---|---|---|
| **Pathogen** | Estimate | 95% Confidence Interval | | Estimate | 95% Confidence Interval | |
| Community Onset | | | | | | |
| MRSA | $19,749 | $17,414 | $22,084 | $596 | -$162 | $1,355 |
| VRE | $17,490 | $8,475 | $26,505 | $7,590 | $4,796 | $10,384 |
| ESBL | $7,352 | $3,903 | $10,802 | $3,914 | $1,880 | $5,948 |
| CRE | $8,354 | -$1,191 | $17,899 | $5,154 | $908 | $9,400 |
| CR *Acinetobacter* | $62,396 | $20,370 | $104,422 | $29,265 | $11,412 | $47,119 |
| MDR *Pseudomonas* | $13,442 | -$5,257 | $32,140 | $11,882 | $5,987 | $17,776 |
| Hospital Onset | | | | | | |
| MRSA | $30,998 | $25,272 | $36,724 | $9,588 | $7,088 | $12,087 |
| VRE | $37,893 | $31,598 | $44,188 | $6,835 | $3,630 | $10,039 |
| ESBL | $33,637 | $20,074 | $47,200 | $16,240 | $11,316 | $21,163 |
| CRE | $54,614 | $26,992 | $82,236 | $16,606 | $8,684 | $24,529 |
| CR *Acinetobacter* | $74,306 | $20,377 | $128,235 | $30,590 | $12,784 | $48,396 |
| MDR *Pseudomonas* | $66,934 | $32,943 | $100,925 | $50,810 | $41,062 | $60,558 |

NOTE: CI = confidence interval; CR = carbapenem-resistant; CRE = carbapenem-resistant Enterobacterales; ESBL = extended-spectrum beta-lactamase; ICU = intensive care unit; MDR = multidrug-resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococci*.

[a] The CDC defines invasive disease as when pathogens invade parts of the body, like blood, that are normally free from germs (CDC, 2020). Noninvasive infections refer to bacteria that does not spread to or damage internal organs and tissues (New Mexico Department of Health, 2021).

SOURCE: Nelson et al., 2021.

Another recent U.S. study compared costs and mortality in MRSA patients to those in patients infected with methicillin-susceptible *Staphylococcus aureus* (MSSA) (Klein et al., 2019). After adjusting for the many confounders that can influence difference between these groups of patients, the researchers found that costs of hospitalization for MRSA was roughly the same or less than those for hospitalization with MSSA (Klein et al., 2019). This may, ironically, stem from the increasing burden of MRSA infections acquired in the community (as opposed to in a health care setting), as community-acquired MRSA is generally susceptible to second-line medicines, bringing down the overall costs of treatment (Klein et al., 2019). Heightened attention to MRSA in hospitals may have led to the identification and treatment of some minimally invasive MRSA, which in turn influenced these results. It is also possible that *aureus* infections, even when susceptible to treatment, are simply difficult to manage in clinical practice.

A 2017 study of the burden of carbapenem-resistant Enterobacterales (CRE) found that the cost of one such infection to the hospital was between $22,993 and $35,503, to the insurer or payer between $13,701 and $18,286 (Bartsch et al., 2017). The authors also considered the cost such infections have on society, a cost influenced mainly by assumptions about mortality attributable to such infections. Assuming mortality attributable to the resistant infection was 35 percent, infection with CRE causes between 1,131 and 5,790 deaths a year, costing society between $681 and $3,489 million (Bartsch et al., 2017). Assuming an attributable mortality of 9 percentage points higher would mean 1,422 to 7,279 deaths, costing society between $819 million and $4.2 billion (Bartsch et al., 2017). As a reference, this means the cost of CRE infection alone is higher than many chronic diseases such as high blood pressure (estimated cost to society $672 per patient per year), asthma (estimated direct cost $4,008 per patient per year) and diabetes ($13,015 estimated per patient per year) (Bartsch et al., 2017).

The incurred costs to society from resistant infections is an important point to capture in economic analysis of antimicrobial resistance, partly because of the negative externalities, or the harm associated with antimicrobial use not incurred to the patients or prescriber (Broughton, 2017). The largest part of the negative externality associated with misuse of antimicrobials is the loss of useful antimicrobial medicines in the future. As the previous section explained, the loss of these drugs would influence the risk calculation underlying many basic surgeries as well as more sophisticated treatments such as organ transplantation and cancer chemotherapy. It is difficult to even imagine the potential health consequences of antimicrobial resistance, making the consequent economic burden, “at present inestimable” (Smith and Coast, 2013).

### The Effects of Antimicrobial Resistance in Food-Producing Animals

As the previous chapter discussed, the contribution of antimicrobial use in food-producing animals to total antimicrobial use and the concentration of resistance genes and drug residues in the environment are a serious concern. Resistance traits that emerge in animals will be found also in manure and water; resistant pathogens from animals can be passed to their handlers, and from them to their family members (Ma et al., 2021). As early as the 1980s researchers have shown an association and plausible pathway through which resistant pathogens emerging in livestock eventually cause human infections (Ma et al., 2021). These include direct contact through consuming food from an infected animal, or indirect routes involving water or a shared environment. Produce can also be a link between resistant bacteria in water or soil and humans (ASM, 2017).

Part of the challenge is that, as in human medicine, it is difficult to know what antimicrobials are being used in livestock and in what doses. The best estimates of use come from U.S. Department of Agriculture (USDA) surveys, which, coupled with the Food and Drug Administration sales data give a rough picture of trends in use (although very little about actual consumption can be inferred from sales data, discussed more in Chapter 5) (Hope et al., 2020). In low- and middle-income countries, the matter is much more difficult to discern. As emerging economies such as Brazil, Russia, India, and China face an increased demand for animal protein they are shifting to more intensive and more efficient systems for raising chickens and pigs (Van Boeckel et al., 2015). Intensive farming of cattle is generally limited to North America, Argentina, and Brazil (Laxminarayan et al., 2015). The shift in production systems will have an effect on global antimicrobial consumption (Laxminarayan et al., 2015).

The projected rise in the use of antimicrobials in livestock, mostly related to an increased demand for animal protein in low- and middle-income countries, has raised a more urgent need

for clarity on if and to what extent antimicrobials use in livestock influences human health. Especially in regards to growth promoters, if the gains in efficiency of production are marginal, then it would be easy to justify prohibitions on antimicrobial growth promoters citing only public health concerns (Laxminarayan et al., 2015). But if the gains are larger, then the burden of proof shifts to establishing that the use of antimicrobial growth promoters in agriculture affects human health (Laxminarayan et al., 2015). This question is difficult to answer. Use of antimicrobial growth promoters has been banned in many countries, including the United States (EU, 2005; FDA, 2021). Data on antimicrobial use on farms are often high-level (i.e., sales data), few countries have farm-level data on antimicrobial use (Mesa Varona et al., 2020). What is more, linking antimicrobial use or resistance data from animals to human health outcomes is tenuous.

*Antimicrobial Use and Productivity*

Research from Denmark, Sweden, and the United States indicates that in modern production systems, when implemented against a background of good hygiene, feeding practices, and selective breeding, the gains in productivity from using antimicrobial growth promoters is minimal (Laxminarayan et al., 2015). A 2007 analysis found that, in the United States, antimicrobial growth promoters had a negligible effect on poultry productivity, insufficient to offset the cost of medicines used (Graham et al., 2007).

The same is not true in low- and middle-income countries. Research in Brazil and China, for example, has shown antimicrobials to be essential for optimal growth (Ryan, 2019). In China this production advantage helps ensure national food security; antimicrobials use is seen as a cost-effective alternative to expensive biosecurity and farm management systems, a way to compensate for problems with hygiene controls (Ryan, 2019). In Brazil, the economic calculation also favors the use of antimicrobial growth promoters, though the reasons have more to do with maximizing production efficiency in the face of very lean profit margins (Ryan, 2019). As a recent OECD paper concluded, "farmers will use preventative medicines such as antibiotics up to the point where the marginal cost of the input is equal to the marginal benefit from the use of this input in their production system" (Ryan, 2019).

Across countries, more attention to animal housing, breeding, feed, and the density of animals on the farm can reduce the need for antimicrobial growth promoters (Ryan, 2019). The same steps help prevent infection in animals, limiting the need for therapeutic antimicrobials as well. Some encouraging evidence indicates that, at least in China, government and public concern about antimicrobial growth promoters is leading to increased restrictions on antimicrobial growth promoters and improvements to infection control measures (Luo et al., 2020; Ryan, 2019; Schoenmakers, 2020).

In low- and middle-income countries, the most pressing economic questions concerning antimicrobial use tend to concern the economic fallout of withdrawing antimicrobial growth promoters. In the United States, European Union, and other high-income countries, where the use of medically important antibiotics as growth promoters is banned, growing momentum for restricting antimicrobial use in food-producing animals is driven by food companies in response to consumer pressure (FDA, 2021; Kesmodel et al., 2014; Singer et al., 2019; WHO, 2017). A major concern of restricting therapeutic and preventive antimicrobial use are the implications for productivity and animal welfare. Yet there is only modest empirical evidence regarding the health and welfare consequences of restricting antimicrobial use (Tang et al., 2019).

Removal of antibiotics could have serious economic consequences. By some estimates, removing preventive and therapeutic antibiotics would cost producers between $43 and $139 for

every steer entering the feedlot system in the United States (Lhermie et al., 2020). Removal of metaphylaxis, the use of antimicrobials to treat a group of animals *at risk* for infectious diseases, could result in a loss in surplus of $1.8 billion to $2.3 billion to U.S. beef producers (Dennis et al., 2018). Prohibition of antimicrobial use in dairy cows could cost the U.S. dairy industry $152 million a year, though the price increase to the consumer would be relatively modest one, about $0.42 a liter for milk (Lhermie et al., 2018). Modelling these effects is difficult, however, because price volatility of agricultural markets and potential unintended consequences on other domestic markets (increasing sales of organic meat, for example) (Lhermie et al., 2016). As the United States is a major exporter of animal commodities, there could also be effects in foreign markets (Lhermie et al., 2016).

For most farmers and veterinarians, such concerns pale in comparison to questions of animal welfare. Antimicrobial use prohibitions on farms would mean that sick animals were either left untreated or culled and euthanized (Lhermie et al., 2020). The removal of antimicrobials in poultry production would lead to increasing eye burns, footpad lesions, and airsacculitis,[6] for example (Karavolias et al., 2018). There are also, depending on the infection in question, moral obligations to treat and prevent the spread of infection in a flock or herd (Lhermie et al., 2020). In the case of highly contagious and potentially serious diseases, such as bovine respiratory disease, this imperative is more clear than for a disease like infectious liver abscess, which has fewer associated animal welfare consequences (Lhermie et al., 2020).

Removal of antimicrobials from animal agriculture could decrease productivity and increase infectious diseases harming the animals' health and capability to grow or produce. But these increases in cost will depend on the production systems and diseases in question. Production cycles for poultry are short (several weeks), somewhat longer for swine. For cattle the production cycle is several years long and involves multiple producers (ERS, 2021). The wide difference in production time and producers makes it difficult to generalize the effect of removing antimicrobials. It is clear, however that without effective alternatives and enhanced infection control, removal of antimicrobials could increase disease and mortality, leading to culling and productivity losses.

Serious clinical resistance in animals could also decrease food production with implications for food security, famers' livelihoods, and environmental contamination (OECD). Losses of animals to resistant infections and the premature culling of herds will mean financial losses to farmers and could cause food prices to rise (Founou et al., 2021).

The economic ramifications of antimicrobial resistance in animal agriculture extends to the cost-to-benefit analysis of upgrading to a more expensive animal management system or treating with more expensive drugs. These are all questions that would benefit from research attention.

### *The Effects of Resistance on Animal Health*

There is growing evidence that livestock are colonized with resistant pathogens (Abdelfattah et al., 2021; Chehabi et al., 2019; de Jong et al., 2018; Harrison et al., 2017). Yet there are major gaps in our knowledge of the effects of resistant infections on animal health. Resistant infections in animals are less well studied than those in humans. In dairy cattle, for example, *Staphylococcus aureus* causes considerable clinical mastitis, though MRSA and beta-lactam resistance are uncommon (Patel et al., 2021). A better understanding of *S. aureus* in cattle

[6] An inflammation of the air sacs that can cause respiratory distress and watery eyes (Clarke, 2014).

would be helpful because the pathogen is highly contagious and aggressive culling can be necessary to control it in a herd (Cousin et al., 2018).

In both livestock and companion animals there is concern that resistant infections may be increasing, but it is difficult to say precisely; there are no accepted, standardized definitions of multidrug resistance, extensive drug resistance, and pandrug resistance in veterinary medicine (Sweeney et al., 2018). There is also a lack of epidemiological research on the health consequences of resistant infections in animals.

As with resistant infections in humans, the burden of resistant infections varies considerably by country. Research on the pathogen causing clinical mastitis in dairy cows in Demark found generally low levels of resistance, with the exception of about 83 percent of *Klebsiella pneumoniae* isolates being resistant to ampicillin (Chehabi et al., 2019). Research on feedlot cattle across southern Alberta, Canada, found that over 90 percent of the pathogens causing bovine respiratory disease were resistant to macrolide antimicrobials, almost half of the pathogens were resistant to four or five different antimicrobial classes, and about a quarter were resistant to six of the nine available drug classes (Anholt et al., 2017). In general, resistance was less common among the antimicrobials of critical importance to human health and more common among the tetracycline and macrolide medicines often added to cattle feeds to prevent liver abscess in the feedlot-raised cattle (Anholt et al., 2017).

As in humans, MRSA infections in livestock are difficult to treat. Contamination from retail meat is a source of MRSA infections in humans (Anjum et al., 2019; O'Brien et al., 2012). Heavy metal contamination, common on farms and in food production systems, can co-select for resistance in *S. aureus* and may be contributing to an increasing burden of MRSA infections in livestock (Dweba et al., 2018). At the same time, humans are the main reservoir of MRSA infections (Dweba et al., 2018). The transmission of MRSA from animals to human handlers is relatively well documented (Pirolo et al., 2019). Meta-analysis indicates that veterinarians and livestock workers, especially pig farmers, are at elevated risk for acquiring MRSA from animals (Chen and Wu, 2020). There are also examples of humans transmitting MRSA to animals (Magro et al., 2018). Most of the research on these pathways is from North America and Europe, however. It is likely in parts of the world where contact between humans and livestock is more common in the general population the risk of interspecies transmission is more general and not limited to farmers, animal handlers, or veterinarians.

In general, the way resistant pathogens spread between humans and animals is not well-studied (Wee et al., 2020). Genomic sequencing has the potential to illuminate major pathways from which resistant bacteria travel directly between species and indirectly through a shared environmental element, such as water or soil (Wee et al., 2020). Genomic analysis has, for example, indicated that *Acinetobacter baumannii* has likely spread from humans to animals (directly or via an environmental intermediary) (Argudin et al., 2017). Genomic studies also suggest that *mecA*, a gene that confers resistance to methicillin, may have originated in staphylococcal infections in animals (Argudin et al., 2017). In the reverse pathway, resistance linked to extended-spectrum beta-lactamase and carbapenemase, enzymes that destroy commonly used antimicrobials, may be emerging in animals (Hartantyo et al., 2018). There is a need for more research across human, animal, and environmental health to determine the health burden of resistance and clarify major pathways for the spread of resistant organisms.

## DEVELOPING MORE PRECISE ESTIMATES OF THE BURDEN OF ANTIMICROBIAL RESISTANCE

Measuring antimicrobial resistance is difficult. Unlike most global health challenges, the problem is not any one disease or risk factor, but a process. Resistance can emerge in any number of microbial pathogens and resistant infections can present in different ways (e.g., pneumonia, skin infection, urinary tract infection). For these reasons, traditional tools for estimating the burden of disease, such as analysis of cause of death on death certificates, are not suited to the problem (Dunachie et al., 2020). What is more, any analysis of disease burden depends on microbiological confirmation of the infective agent. A lack of microbiology laboratories seriously holds back surveillance in low- and middle-income countries. National estimates of resistance in India, for example, a country of over 1.3 billion people are "drawn from a few thousand laboratory isolates and a handful of hospitals" (Islam et al., 2019).

The biggest barrier to producing better estimates of the burden of antimicrobial resistance is the lack of microbiological data (Dunachie et al., 2020). Figure 3-12 shows multiple barriers to producing this data, from limited capacity for microbiological analysis and difficulties with quality assurance, to difficulties linking the data to patient records (Dunachie et al., 2020). There are also biases in blood culture data. Especially in low- and middle-income countries where blood cultures are paid entirely out of pocket, this data is available only for relatively affluent, urban patients (Dunachie et al., 2020; Hay et al., 2018).

Other barriers relate to data analysis. Data sharing is challenging around the world, partly because data about resistance is sensitive and the fear of being exposed as a resistance hotspot deters sharing from the clinic to the national level (Dunachie et al., 2020). Data sharing, while desirable, has to be done in orderly and balanced way. Datasets can easily be shared with many groups of researchers biasing perceptions of resistance if the same data informed multiple, seemingly different, studies (Dunachie et al., 2020).

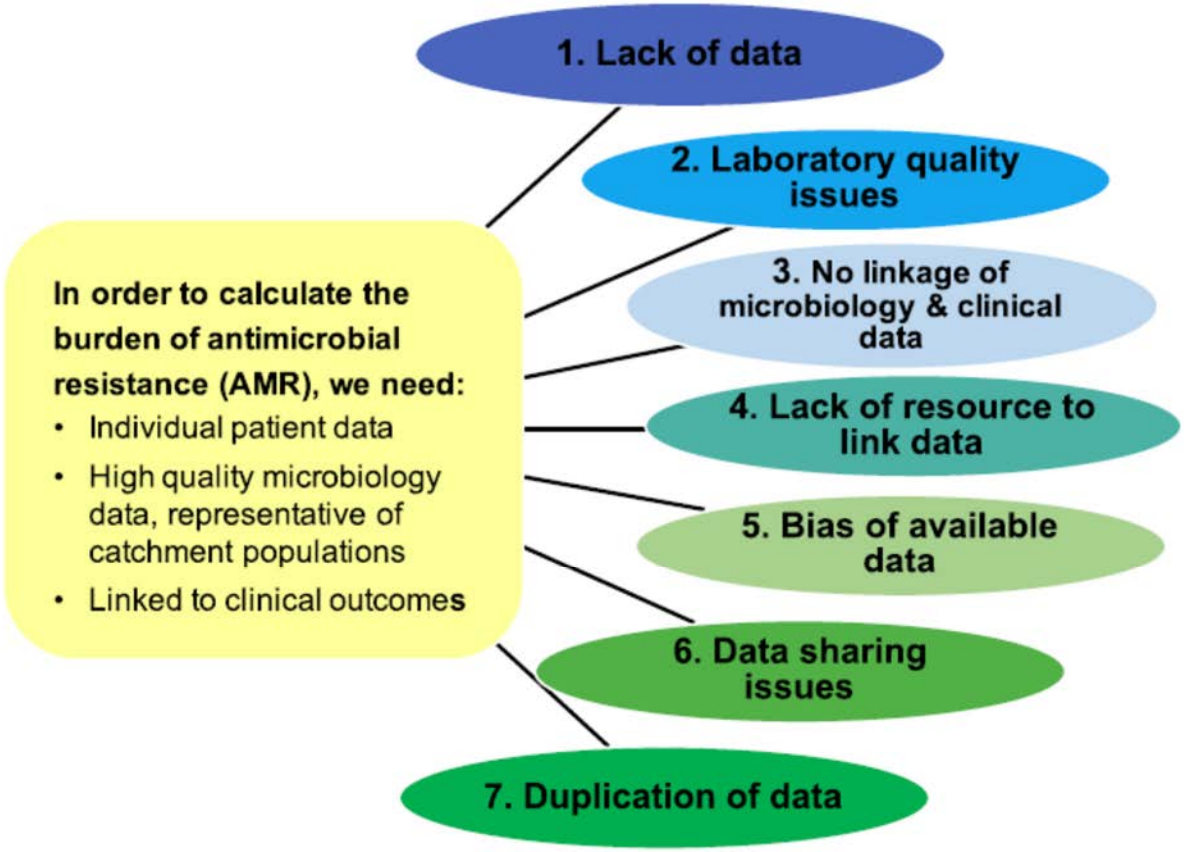



**FIGURE 3-12** Seven key challenges in collecting data to inform estimates of the burden of resistance. SOURCE: Dunachie et al., 2020.

The laboratory infrastructures that underlie surveillance are challenging to coordinate even in the United States and other high-income countries, a topic discussed more in the next chapter. While improving surveillance systems around the world will be essential to better measure the health and economic consequences of resistance, surveillance is not the only tool to this end. More research on the burden of antimicrobial resistance is needed, especially in low- and middle-income countries. But even with data of high quality, easily linked to the patient records in a single payer system, as is available in the VA data that informs the CDC estimates discussed earlier in this chapter, different analytic strategies could yield widely different conclusions about the nature of the problem (Dunachie et al., 2020). For one thing, it is difficult to know the best comparator group for patients with resistant infections. Comparison to patients with susceptible infections or without infections are both complicated as the groups would not usually have the same comorbidities (Dunachie et al., 2020). Attention to such questions in study design, drawing on research guidelines presented in Box 3-1 could help avoid some of the methodological problems studies on the burden of antimicrobial-resistant infections often face.

**BOX 3-1**
**Naylor and Colleagues' Guidelines for**
**Research Measuring the Burden of Resistant Infections**

- Utilize data from a representative sample of the population of interest. If this is not achievable due to data limitations, create and publish a clearly defined protocol that can be utilized in other institutions. This will enable future meta-analyses to be conducted.
- Choose an appropriate methodology that takes into account potential confounding factors (such as patient comorbidities or age) and biases (such as time dependency bias, competing risks, or non-informative censoring).
- Describe data collection, data cleaning, follow-up, response rates and/or censoring clearly, where appropriate.
- Estimate healthcare system and economic impact where possible.
- If performing a mathematical or economic model, clearly describe the reasons for the chosen model structure (for example by detailing a formal health economic reasoning, including for chosen time horizon) and methods of parameterization (with structured or systematic methods preferred). In addition, it is important to discuss how methodological, structural, heterogeneity and parameter uncertainty has been addressed (or discuss why these were not addressed).

SOURCE: Naylor et al., 2018, reprinted with permission.

Another challenge related to measuring the burden and consequences of resistance stem from the complex, adaptive nature of the problem described in the previous chapter. The toll of resistance, be it on human health, the economy, animal agriculture, or farmers' livelihoods, cannot be considered in isolation (Dunachie et al., 2020). This is not to say that researchers should incorporate human, animal, and environmental health indicators in all their work. Rather, across disciplines researchers, government officials, and private industry could all give better attention to capturing the costs associated with resistant infections.

The Global Antimicrobial Resistance Platform for ONE-Burden Estimates, an international research network, recently released a One Health framework for estimating the costs of resistance (Morel et al., 2020). This framework, introduced in Figure 3-13, articulates what costs, both direct and indirect, will be affected by resistance in human and animal health and in the environment (Morel et al., 2020).

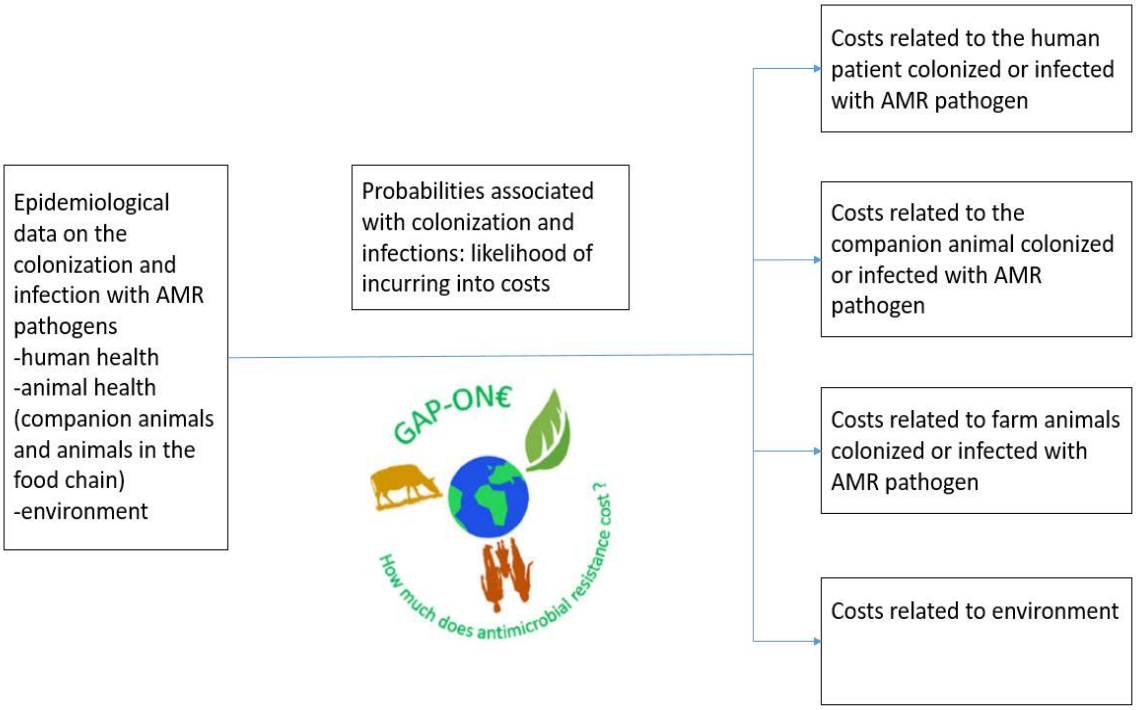



**FIGURE 3-13** The global antimicrobial resistance platform for ONE-burden estimates.
SOURCE: Adapted from Morel et al., 2020.

The international momentum for action against antimicrobial resistance driven by the O'Neill report and the other recent landmark publications described at the beginning of this chapter is commendable. Following through on this energy and translating it into meaningful policy changes requires good evidence on the true burden of resistance and what interventions work to reduce that burden (Hay et al., 2018; IHME, 2020a; Morel et al., 2020).

## The Global Research on Antimicrobial Resistance Project

The Global Burden of Disease, Injuries, and Risk Factors program on antimicrobial resistance (the Global Research on Antimicrobial Resistance project) is a welcome addition to the literature on the health consequences of antimicrobial resistance (IHME, 2020a).[7] This analysis of the health consequences of 23 resistant bacteria (88 microbe–drug combinations) drew on 471 million patient records or isolates from collaborators and public data from around the world (AMR Collaborators). Under a counterfactual assumption of infection with a susceptible pathogen, the authors estimated that antimicrobial resistance killed 1.27 million people in 2019 (95% confidence interval [CI]: 0.91 to 1.71 million) (AMR Collaborators). Such analysis suggests that antimicrobial resistance is the 12th leading cause of death worldwide,[8] (AMR Collaborators). Under a counterfactual assumption of no infection the estimate was 4.95

[7] This study was in review during the committee's final deliberations, and the committee thanks the researchers for sharing some key findings.
[8] Among Global Burden of Disease level three causes, "specific causes such as tuberculosis, stroke, and road injuries," sometimes the most detailed cause of death classification available (Lancet, 2020).

million deaths associated with antimicrobial resistance (95% CI: 3.62 million to 6.57 million) (AMR Collaborators). Despite limited data from low- and middle-income countries, the models indicated that this is where the burden of resistance is worst, with death rates from antimicrobial resistance highest in sub-Saharan Africa (AMR Collaborators).

Of the 23 pathogens studied, six (*E.coli*, *S. aureus*, *K. pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*) accounted for a majority (about 72 percent) of deaths (AMR Collaborators). MRSA, a serious burden in high-income countries, caused an estimated 100,000 deaths worldwide in 2019 (AMR Collaborators).

The Global Research on Antimicrobial Resistance study provides a scientifically rigorous framework through which to evaluate antimicrobial resistance and an exhaustive review of the epidemiological data to estimate its burden (IHME, 2020b). Generating comparable estimates of the burden of resistance in key microbe-drug combinations across countries is especially valuable (IHME, 2020c). As Table 3-6 shows, even the estimates of the health consequences of resistant infections vary so widely, including variability in the way they are reported, that it is difficult to identify trends in the literature.

**TABLE 3-6** Estimates of the Effect of Antimicrobial Resistance on Mortality from Recent Prominent Reports

| Publication Year | Report | Measure | Quantity | Geographic Area |
|---|---|---|---|---|
| 2019 | *AR Threats Report* | Deaths per year | 35,900 | United States |
| 2019 | *AR Threats Report* | Deaths per year (drug-resistant *C. difficile*) | 12,800 | United States |
| 2018 | *Stemming the Superbug Tide* | Deaths per year, 2015 to 2050 | 30,000 | United States |
| 2018 | *Stemming the Superbug Tide* | Deaths per year | 60,000 | United States, Europe |
| 2018 | *Stemming the Superbug Tide* | Deaths per year, 2015 to 2050 | 2.4 million | North America, Europe, Australia |
| 2018 | *Stemming the Superbug Tide* | DALYs lost per year | 1.75 million | 33 high-income countries |
| 2014 | O'Neill report's Rand model | Cumulative deaths 2015 to 2050 | 11 to 444 million adults | Global |
| 2014 | O'Neill report's KPMG model | Cumulative deaths 2015 to 2050 | 200 to 700 million | Global |
| 2014 | The O'Neill report | Deaths per year by 2050 | 10 million | Global |
| 2019 | European CDC, Cassini and colleagues | Deaths in 2015 | 33000 | Europe |
| 2021 | The Global Burden of Disease | Deaths caused by infection with a resistant pathogen in 2019 | .91 to 1,71 million | Worldwide |
| 2021 | The Global Burden of Disease | Deaths associated with infection with a resistant pathogen in 2019 | 3.62 to 6.57 million | Worldwide |

SOURCES: AMR Collaborators; CDC, 2019; KPMG LLP, 2014; OECD, 2018; O'Neill, 2014; Taylor et al., 2014.

## The Economic Component of Antimicrobial Resistance

The problem of wide variability in research is more obvious in reviewing estimates of the economic consequences of resistance. As Table 3-3 showed, even economic researchers working on similar datasets and making ostensibly similar analytic assumptions can arrive at such widely different estimates of the problem as to be unrecognizable. It may be that the most important message regarding the economic fallout of antimicrobial resistance is that it cannot be compartmentalized. As the COVID-19 epidemic has made clear, infectious outbreaks can devastate the global economy and people's quality of life in far-reaching ways. Even estimates of the cost of the pandemic in the trillions do not account for the long-term, less tangible consequences of disrupted schooling and income (Cutler and Summers, 2020).

Antimicrobial resistance is a One Health problem, so estimating its economic component means untangling the relative contributions of resistance in any one sector and tying them to larger economic indicators. This is not a direct analytic question, and the economic fallout of resistance is not easily reduced to a number. The burden of any one resistant pathogen depends on context; the same resistant infections can have drastically different consequences in humans or animals, if acquired in hospital or outside of it, in a high-income country or a low-income one. The downstream consequences of resistant infections can be felt on food safety, on livelihoods, on social relationships and, of course, on health. A lack of communication among the different One Health disciplines may contribute a relatively one-sided body of research on the health and economic effects of resistant infections in humans. This is a major barrier to developing better estimates of the consequences of resistance.

## REFERENCES

Abdelfattah, E. M., P. S. Ekong, E. Okello, T. Chamchoy, B. M. Karle, R. A. Black, D. Sheedy, W. R. ElAshmawy, D. R. Williams, D. Califano, L. F. D. Tovar, J. Ongom, T. W. Lehenbauer, B. A. Byrne, and S. S. Aly. 2021. Epidemiology of antimicrobial resistance (AMR) on california dairies: Descriptive and cluster analyses of amr phenotype of fecal commensal bacteria isolated from adult cows. *PeerJ* 9:e11108.

Ahmed, S. A., E. Barış, D. S. Go, H. Lofgren, I. Osorio-Rodarte, and K. Thierfelder. 2017. Assessing the global economic and poverty effects of antimicrobial resistance. *World Bank Group*.

AMR Collaborators (unpublished). *Global burden of bacterial antimicrobial resistance in 2019*. Lancet. In review.

Anholt, R. M., C. Klima, N. Allan, H. Matheson-Bird, C. Schatz, P. Ajitkumar, S. J. Otto, D. Peters, K. Schmid, M. Olson, T. McAllister, and B. Ralston. 2017. Antimicrobial susceptibility of bacteria that cause bovine respiratory disease complex in alberta, canada. *Frontiers in Veterinary Science* 4:207.

Anjum, M. F., F. Marco-Jimenez, D. Duncan, C. Marin, R. P. Smith, and S. J. Evans. 2019. Livestock-associated methicillin-resistant staphylococcus aureus from animals and animal products in the uk. *Frontiers in Microbiology* 10:2136.

Argudin, M. A., A. Deplano, A. Meghraoui, M. Dodemont, A. Heinrichs, O. Denis, C. Nonhoff, and S. Roisin. 2017. Bacteria from animals as a pool of antimicrobial resistance genes. *Antibiotics (Basel)* 6(2):12.

ASM (American Society for Microbiology). 2017. *Antibiotic-resistant bacteria in ready-to-eat foods*. www.sciencedaily.com/releases/2017/06/170605121333.htm (accessed August 4, 2021).

Bartsch, S. M., J. A. McKinnell, L. E. Mueller, L. G. Miller, S. K. Gohil, S. S. Huang, and B. Y. Lee. 2017. Potential economic burden of carbapenem-resistant enterobacteriaceae (cre) in the united states. *Clinical Microbiology and Infection* 23(1):48 e49-48 e16.

*BBC News*. 2016. Global antibiotics "revolution" needed. *BBC News Media*.

Boseley, S. 2016. No antibiotics without a test, says report on rising antimicrobial resistance. *The Guardian*, 05/18/2016.

Broughton, E. I. 2017. *The economics of reducing antibiotic use to reduce antimicrobial resistance*. http://resistancecontrol.info/2017/the-economics-of-reducing-antibiotic-use-to-reduce-antimicrobial-resistance/ (accessed June 23, 2021).

Carr, A., J. A. Smith, J. Camaradou, and D. Prieto-Alhambra. 2021. Growing backlog of planned surgery due to COVID-19. *BMJ* 372:n339.

Cassini, A., L. D. Hogberg, D. Plachouras, A. Quattrocchi, A. Hoxha, G. S. Simonsen, M. Colomb-Cotinat, M. E. Kretzschmar, B. Devleesschauwer, M. Cecchini, D. A. Ouakrim, T. C. Oliveira, M. J. Struelens, C. Suetens, D. L. Monnet, and A. M. R. C. G. Burden of. 2019. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the eu and the european economic area in 2015: A population-level modelling analysis. *Lancet Infectious Diseases* 19(1):56-66.

CDC (Centers for Disease Control and Prevention). 2013. *Antibiotic resistance threats in the United States.* US Department of Health and Human Services, Centers for Disease Control and Prevention

CDC. 2019. *Antibiotic resistance threats in the United States, 2019.* Atlanta, GA: http://dx.doi.org/10.15620/cdc:82532.

CDC. 2020. *Surveillance*. https://www.cdc.gov/hi-disease/surveillance.html (accessed September 15, 2021).

CDC, NCEZID (National Center for Emerging and Zoonotic Diseases), and DHQP (Division of Healthcare Quality Promotion). 2021. *Healthcare settings and antibiotic resistance*. https://www.cdc.gov/drugresistance/solutions-initiative/healthcare.html#anchor_1576259604118 (accessed June 23, 2021).

Cecchini, M., J. Langer, and L. Slawomirski. 2015. *Antimicrobial resistance in the g7 countries and beyond.* OECD.

Chehabi, C. N., B. Nonnemann, L. B. Astrup, M. Farre, and K. Pedersen. 2019. In vitro antimicrobial resistance of causative agents to clinical mastitis in danish dairy cows. *Foodborne Pathogens and Disease* 16(8):562-572.

Chen, C., and F. Wu. 2020. Livestock-associated methicillin-resistant staphylococcus aureus (la-mrsa) colonisation and infection among livestock workers and veterinarians: A systematic review and meta-analysis. *Occupational and Environmental Medicine*.

Clarke, P. 2014. *How to control airsacculitis in broilers*. https://www.fwi.co.uk/livestock/poultry/broilers/how-to-control-airsacculitis-in-chickens (accessed July 20, 2021).

Cousin, M. E., M. C. Hardi-Landerer, V. Volk, and M. Bodmer. 2018. Control of staphylococcus aureus in dairy herds in a region with raw milk cheese production: Farmers' attitudes, knowledge, behaviour and belief in self-efficacy. *BMC Veterinary Research* 14(1):46.

COVIDSurg Collaborative. 2020. Elective surgery cancellations due to the COVID-19 pandemic: Global predictive modelling to inform surgical recovery plans. *British Journal of Surgery* 107(11):1440-1449.

Cutler, D. M., and L. H. Summers. 2020. The covid-19 pandemic and the $16 trillion virus. *JAMA* 324(15):1495-1496.

de Jong, A., F. E. Garch, S. Simjee, H. Moyaert, M. Rose, M. Youala, E. Siegwart, and G. VetPath Study. 2018. Monitoring of antimicrobial susceptibility of udder pathogens recovered from cases of

clinical mastitis in dairy cows across europe: Vetpath results. *Veterinary Microbiology* 213:73-81.

de Kraker, M. E., A. J. Stewardson, and S. Harbarth. 2016. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Medicine* 13(11):e1002184.

Denison, J., and P. AV. 2010. Accuracy of death certifications and the implications for studying disease burdens. In *Handbook of disease burdens and quality of life measures*, edited by V. R. Preedy and R. R. Watson: Springer.

Dennis, E. J., T. C. Schroeder, D. G. Renter, and D. L. Pendell. 2018. Value of arrival metaphylaxis in u.S. Cattle industry. *Faculty Publications: Agricultural Economics* 181.

Dunachie, S. J., N. P. Day, and C. Dolecek. 2020. The challenges of estimating the human global burden of disease of antimicrobial resistant bacteria. *Current Opinion in Microbiology* 57:95-101.

Dweba, C. C., O. T. Zishiri, and M. E. El Zowalaty. 2018. Methicillin-resistant staphylococcus aureus: Livestock-associated, antimicrobial, and heavy metal resistance. *Infection and Drug Resistance* 11:2497-2509.

ERS (Economic Research Service). 2021. *Sector at a glance*. https://www.ers.usda.gov/topics/animal-products/cattle-beef/sector-at-a-glance/ (accessed July 20, 2021).

EU (European Union). 2005. Ban on antibiotics as growth promoters in animal feed enters into effect. Brussels, Belgium.

FDA (U.S. Food and Drug Administration). 2021. *Timeline of FDA action on antimicrobial resistance*. https://www.fda.gov/animal-veterinary/antimicrobial-resistance/timeline-fda-action-antimicrobial-resistance (accessed June 22, 2021).

FAO and UN (Food and Agriculture of the United Nations and United Nations). 2021. *Antimicrobial resistance*. http://www.fao.org/antimicrobial-resistance/en/ (accessed September 22, 2021).

Foster, S. 2011 (unpublished). *Challenges for healthcare: The impact of amr on costs of care*.

Founou, L. L., R. C. Founou, and S. Y. Essack. 2021. Antimicrobial resistance in the farm-to-plate continuum: More than a food safety issue. *Future Science OA* 7(5):FSO692.

Friedman, E. A. 2020. Behind the headlines: 10 million deaths from antimicrobial resistance by 2050 (or not?). *Geogretown Law*, 02/12/2020.

Gandra, S., G. Alvarez-Uria, P. Turner, J. Joshi, D. Limmathurotsakul, and H. R. van Doorn. 2020. Antimicrobial resistance surveillance in low- and middle-income countries: Progress and challenges in eight south asian and southeast asian countries. *Clinical Microbiology Reviews* 33(3):e00048-00019.

Graham, J. P., J. J. Boland, and E. Silbergeld. 2007. Growth promoting antibiotics in food animal production: An economic analysis. *Public Health Reports* 122(1):79-87.

Harrison, E. M., F. Coll, M. S. Toleman, B. Blane, N. M. Brown, M. E. Torok, J. Parkhill, and S. J. Peacock. 2017. Genomic surveillance reveals low prevalence of livestock-associated methicillin-resistant staphylococcus aureus in the east of england. *Scientific Reports* 7(1):7406.

Hartantyo, S. H. P., M. L. Chau, L. Fillon, A. Ariff, J. S. L. Kang, K. T. Aung, and R. A. Gutierrez. 2018. Sick pets as potential reservoirs of antibiotic-resistant bacteria in singapore. *Antimicrobial Resistance & Infection Control* 7(1):106.

Hay, S. I., P. C. Rao, C. Dolecek, N. P. J. Day, A. Stergachis, A. D. Lopez, and C. J. L. Murray. 2018. Measuring and mapping the global burden of antimicrobial resistance. *BMC Medicine* 16(1):78.

Hope, K. J., M. D. Apley, N. F. D. Schrag, B. V. Lubbers, and R. S. Singer. 2020. Antimicrobial use in 22 u.S. Beef feedyards: 2016-2017. *Zoonoses and Public Health* 67 Suppl 1:94-110.

IACG (Interagency Coordination Group on Antimicrobial Resistance). 2019. *No time to wait: Securing the future from drug-resistant infections.* World Health Organization.

IHME (Institute for Health Metrics and Evalution). 2020a. *GRAM project deliverables and scope*. http://www.healthdata.org/gram/scope (accessed July 14, 2021).

IHME. 2020b. *Introducing the GRAM project: Estimating the global burden of antimicrobial resistance*. http://www.healthdata.org/sites/default/files/files/infographics/Infographic_GRAM_Intro_2020.pdf (accessed July 14, 2021).

IHME. 2020c. *What does the GRAM project need to estimate the global burden of antimicrobial resistance (AMR)?* http://www.healthdata.org/sites/default/files/files/infographics/Infographic_GRAM_Data%20Needs_2020.pdf (accessed July, 14, 2021).

Iskandar, K., L. Molinier, S. Hallit, M. Sartelli, T. C. Hardcastle, M. Haque, H. Lugova, S. Dhingra, P. Sharma, S. Islam, I. Mohammed, I. Naina Mohamed, P. A. Hanna, S. E. Hajj, N. A. H. Jamaluddin, P. Salameh, and C. Roques. 2021. Surveillance of antimicrobial resistance in low- and middle-income countries: A scattered picture. *Antimicrobial Resistance & Infection Control* 10(1):63.

Islam, S., J. Aldstadt, and D. Aga. 2019. Global antimicrobial resistance: A complex and dire threat with few definite answers. *Tropical Medicine and International Health* 24(6):658-662.

Kadri, S. S. 2020. Key takeaways from the u.S. Cdc's 2019 antibiotic resistance threats report for frontline providers. *Critical Care Medicine* 48(7):939-945.

Karavolias, J., M. J. Salois, K. T. Baker, and K. Watkins. 2018. Raised without antibiotics: Impact on animal welfare and implications for food policy. *Transl Anim Sci* 2(4):337-348.

Kesmodel, D., J. Bunge, and B. McKay. 2014. Meat companies go antibiotics-free as more consumers demand it. *The Wall Street Journal* 11/03/2014.

Klein, E. Y., W. Jiang, N. Mojica, K. K. Tseng, R. McNeill, S. E. Cosgrove, and T. M. Perl. 2019. National costs associated with methicillin-susceptible and methicillin-resistant staphylococcus aureus hospitalizations in the united states, 2010-2014. *Clinical Infectious Diseases* 68(1):22-28.

Knight, G. M., R. E. Glover, C. F. McQuaid, I. D. Olaru, K. Gallandat, Q. J. Leclerc, N. M. Fuller, S. J. Willcocks, R. Hasan, E. van Kleef, and C. I. Chandler. 2021. Antimicrobial resistance and covid-19: Intersections and implications. *Elife* 10.

KPMG LLP. 2014. The global economic impact of anti-microbial resistance. 12/11/2014.

Kwon, J. H., and W. G. Powderly. 2021. The post-antibiotic era is here. *Science* 373(6554):471.

Lai, A. G., L. Pasea, A. Banerjee, G. Hall, S. Denaxas, W. H. Chang, M. Katsoulis, B. Williams, D. Pillay, M. Noursadeghi, D. Linch, D. Hughes, M. D. Forster, C. Turnbull, N. K. Fitzpatrick, K. Boyd, G. R. Foster, T. Enver, V. Nafilyan, B. Humberstone, R. D. Neal, M. Cooper, M. Jones, K. Pritchard-Jones, R. Sullivan, C. Davie, M. Lawler, and H. Hemingway. 2020. Estimated impact of the covid-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: Near real-time data on cancer care, cancer deaths and a population-based cohort study. *BMJ Open* 10(11):e043828.

Lancet. 2020. Global burden of disease 2019 disease, injury, and impairment summaries. *Lancet* 396.

Langford, B. J., M. So, S. Raybardhan, V. Leung, D. Westwood, D. R. MacFadden, J. R. Soucy, and N. Daneman. 2020. Bacterial co-infection and secondary infection in patients with covid-19: A living rapid review and meta-analysis. *Clinical Microbiology and Infection* 26(12):1622-1629.

Laxminarayan, R., T. V. Boeckel, and A. Teillant. 2015. The economic costs of withdrawing antimicrobial growth promoters from the livestock sector.

Lhermie, G., Y. T. Grohn, and D. Raboisson. 2016. Addressing antimicrobial resistance: An overview of priority actions to prevent suboptimal antimicrobial use in food-animal production. *Frontiers in Microbiology* 7:2114.

Lhermie, G., L. W. Tauer, and Y. T. Gröhn. 2018. An assessment of the economic costs to the u.S. Dairy market of antimicrobial use restrictions. *Preventative Veterinary Medicine* 160(1873-1716 (Electronic)):63-67.

Lhermie, G., P. Sauvage, L. W. Tauer, L. V. Chiu, K. Kanyiamattam, A. Ferchiou, D. Raboisson, H. M. Scott, D. R. Smith, and Y. T. Grohn. 2020. Economic effects of policy options restricting antimicrobial use for high risk cattle placed in u.S. Feedlots. *PloS One* 15(9):e0239135.

Lopez, A. D., C. D. Mathers, M. Ezzati, D. T. Jamison, and C. J. L. Murray. 2006. *Global burden of disease and risk factors*, *Global burden of disease and risk factors*: The World Bank.

Luo, Q., Y. Wang, and Y. Xiao. 2020. Prevalence and transmission of mobilized colistin resistance (MCR) gene in bacteria common to animals and humans. *Biosafety and Health* 2(2):71-78.

Ma, F., S. Xu, Z. Tang, Z. Li, and L. Zhang. 2021. Use of antimicrobials in food animals and impact of transmission of antimicrobial resistance on humans. *Biosafety and Health* 3(1):32-38.

Magro, G., M. Rebolini, D. Berettac, and R. Piccinini. 2018. Methicillin-resistant staphylococcus aureus CC22-MRSA-IV as an agent of dairy cow intramammary infections. *Veterinary Microbiology*.

Matthiessen, L., R. Bergstrom, S. Dustdar, P. Meulien, and R. Draghia-Akli. 2016. Increased momentum in antimicrobial resistance research. *Lancet* 388(10047):865.

Mesa Varona, O., K. Chaintarli, B. Muller-Pebody, M. F. Anjum, T. Eckmanns, M. Norstrom, I. Boone, and B. A. Tenhagen. 2020. Monitoring antimicrobial resistance and drug usage in the human and livestock sector and foodborne antimicrobial resistance in six european countries. *Infection and Drug Resistance* 13:957-993.

Morel, C. M., R. A. Alm, C. Ardal, A. Bandera, G. M. Bruno, E. Carrara, G. L. Colombo, M. E. A. de Kraker, S. Essack, I. Frost, B. Gonzalez-Zorn, H. Goossens, L. Guardabassi, S. Harbarth, P. S. Jorgensen, S. S. Kanj, T. Kostyanev, R. Laxminarayan, F. Leonard, G. L. Hara, M. Mendelson, M. Mikulska, N. T. Mutters, K. Outterson, J. R. Bano, E. Tacconelli, L. Scudeller, and G. A.-O. network. 2020. A one health framework to estimate the cost of antimicrobial resistance. *Antimicrobial Resistance & Infection Control* 9(1):187.

Nau, R., F. Sorgel, and H. Eiffert. 2010. Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. *Clinical Microbiology Reviews* 23(4):858-883.

Nau, R., F. Sorgel, and H. W. Prange. 1998. Pharmacokinetic optimisation of the treatment of bacterial central nervous system infections. *Clinical Pharmacokinetics* 35(3):223-246.

Naylor, N. R., R. Atun, N. Zhu, K. Kulasabanathan, S. Silva, A. Chatterjee, G. M. Knight, and J. V. Robotham. 2018. Estimating the burden of antimicrobial resistance: A systematic literature review. *Antimicrobial Resistance & Infection Control* 7:58.

Nelson, R. E., K. M. Hatfield, H. Wolford, M. H. Samore, R. D. Scott, S. C. Reddy, B. Olubajo, P. Paul, J. A. Jernigan, and J. Baggs. 2021. National estimates of healthcare costs associated with multidrug-resistant bacterial infections among hospitalized patients in the united states. *Clinical Infectious Diseases* 72(Suppl 1):S17-S26.

New Mexico Department of Health. 2021. Non-invasive group a *streptococcus* (GAS).

O'Brien, A. M., B. M. Hanson, S. A. Farina, J. Y. Wu, J. E. Simmering, S. E. Wardyn, B. M. Forshey, M. E. Kulick, D. B. Wallinga, and T. C. Smith. 2012. Mrsa in conventional and alternative retail pork products. *PloS One* 7(1):e30092.

O'Neill, J. *Review on antimicrobial resistance - tackling drug resistance globally*. https://amr-review.org/ (accessed June 22, 2021).

O'Neill, J. 2014. *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations.* London, United Kingom: Wellcome Trust.

O'Neill, J. 2016. Jim O'Neill. *Nature Reviews Drug Discovery* 15(8):526.

O'Neill, J. 2018. Tackling drug-resistant infections globally: Final report and recommendations. 2016. *HM Government and Welcome Trust: UK*.

OECD (Organisation for Economic Co-operation and Development). 2016. Antimicrobial resistance policy insights.

OECD. 2018. *Stemming the superbug tide*, *OECD health policy studies*. https://doi.org/10.1787/9789264307599-en

OECD. 2021. *Anti-microbial resistance is a global challenge for food systems and public health*. https://www.oecd.org/agriculture/topics/antimicrobial-resistance-and-agriculture/ (accessed June 25, 2021).

Patel, K., S. M. Godden, E. E. Royster, B. A. Crooker, T. J. Johnson, E. A. Smith, and S. Sreevatsan. 2021. Prevalence, antibiotic resistance, virulence and genetic diversity of staphylococcus aureus isolated from bulk tank milk samples of u.S. Dairy herds. *BMC Genomics* 22(1):367.

Pelfrene, E., R. Botgros, and M. Cavaleri. 2021. Antimicrobial multidrug resistance in the era of covid-19: A forgotten plight? *Antimicrobial Resistance & Infection Control* 10(1):21.

Pirolo, M., D. Visaggio, A. Gioffre, I. Artuso, M. Gherardi, G. Pavia, P. Samele, L. Ciambrone, R. Di Natale, G. Spatari, F. Casalinuovo, and P. Visca. 2019. Unidirectional animal-to-human transmission of methicillin-resistant staphylococcus aureus st398 in pig farming; evidence from a surveillance study in southern italy. *Antimicrobial Resistance & Infection Control* 8(1):187.

PLOS Medicine Editors. 2016. Antimicrobial resistance: Is the world unprepared? *PLoS Medicine* 13(9):e1002130.

Price, R. 2016. O'Neill report on antimicrobial resistance: Funding for antimicrobial specialists should be improved. *European Journal of Hospital Pharmacy* 23(4):245-247.

Rodriguez-Bano, J., G. M. Rossolini, C. Schultsz, E. Tacconelli, S. Murthy, N. Ohmagari, A. Holmes, T. Bachmann, H. Goossens, R. Canton, A. P. Roberts, B. Henriques-Normark, C. J. Clancy, B. Huttner, P. Fagerstedt, S. Lahiri, C. Kaushic, S. J. Hoffman, M. Warren, G. Zoubiane, S. Essack, R. Laxminarayan, and L. Plant. 2021. Key considerations on the potential impacts of the covid-19 pandemic on antimicrobial resistance research and surveillance. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 115(10):1122-1129.

Roland, D. 2015. Multibillion-dollar investment needed to fight drug-resistant 'superbugs'. *The Wall Street Journal*, 05/13/2015.

Ryan, M. 2019. Evaluating the economic benefits and costs of antimicrobial use in food-producing animals. In *OECD Food, Agriculture and Fisheries Papers*. Paris: OECD Publishing.

Schnall, J., A. Rajkhowa, K. Ikuta, P. Rao, and C. E. Moore. 2019. Surveillance and monitoring of antimicrobial resistance: Limitations and lessons from the gram project. *BMC Medicine* 17(1):176.

Schoenmakers, K. 2020. How china is getting its farmers to kick their antibiotics habit. *Nature* 586:2.

Scott, R. D. 2009. The direct medical costs of healthcare-associated infections in u.S. Hospitals and the benefits of prevention, edited by D. National Center for Preparedness, C. o. I. Diseases and P. Division of Healthcare Quality. Division of Healthcare Quality Promotion National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention.

Singer, R. S., L. J. Porter, D. U. Thomson, M. Gage, A. Beaudoin, and J. K. Wishnie. 2019. Raising animals without antibiotics: U.S. Producer and veterinarian experiences and opinions. *Frontiers in Veterinary Science* 6(452):452.

Smith, R., and J. Coast. 2013. The true cost of antimicrobial resistance. *BMJ* 346:f1493.

Sugden, R., R. Kelly, and S. Davies. 2016. Combating antimicrobial resistance globally. *Nature Microbiology* 1(10):16187.

Sulis, G., B. Batomen, A. Kotwani, M. Pai, and S. Gandra. 2021. Sales of antibiotics and hydroxychloroquine in india during the covid-19 epidemic: An interrupted time series analysis. *PLoS Medicine* 18(7):e1003682.

Sung, H., J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray. 2021. Global cancer statistics 2020: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 71(3):209-249.

Sweeney, M. T., B. V. Lubbers, S. Schwarz, and J. L. Watts. 2018. Applying definitions for multidrug resistance, extensive drug resistance and pandrug resistance to clinically significant livestock and companion animal bacterial pathogens. *Journal of Antimicrobial Chemotherapy* 73(6):1460-1463.

Tadesse, B. T., E. A. Ashley, S. Ongarello, J. Havumaki, M. Wijegoonewardena, I. J. Gonzalez, and S. Dittrich. 2017. Antimicrobial resistance in africa: A systematic review. *BMC Infectious Diseases* 17(1):616.

Tang, K. L., N. P. Caffrey, D. B. Nobrega, S. C. Cork, P. E. Ronksley, H. W. Barkema, A. J. Polachek, H. Ganshorn, N. Sharma, J. D. Kellner, S. L. Checkley, and W. A. Ghali. 2019. Examination of unintended consequences of antibiotic use restrictions in food-producing animals: Sub-analysis of a systematic review. *One Health* 7:100095.

Taylor, J., M. Hafner, E. Yerushalmi, R. Smith, J. Bellasio, R. Vardavas, T. Bienkowska-Gibbs, and J. Rubin. 2014. *Estimating the economic costs of antimicrobial resistance: Model and results*: RAND Corporation.

Teillant, A., S. Gandra, D. Barter, D. J. Morgan, and R. Laxminarayan. 2015. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: A literature review and modelling study. *Lancet Infectious Diseases* 15(12):1429-1437.

Thabit, A. K., D. F. Fatani, M. S. Bamakhrama, O. A. Barnawi, L. O. Basudan, and S. F. Alhejaili. 2019. Antibiotic penetration into bone and joints: An updated review. *International Journal of Infectious Diseases* 81:128-136.

*The Economist*. 2016. When the drugs don't work- how to combat the dangerous rise of antibiotic resistance. *The Economist*, 05/21/2016.

Thorpe, K. E., P. Joski, and K. J. Johnston. 2018. Antibiotic-resistant infection treatment costs have doubled since 2002, now exceeding $2 billion annually. *Health Affairs* 37(4):662-669.

Tillotson, G. S., and S. H. Zinner. 2017. Burden of antimicrobial resistance in an era of decreasing susceptibility. *Expert Review of Anti-Infective Therapy* 15(7):663-676.

UN (United Nations). 2021. *The 17 sustainable development goals*. https://sdgs.un.org/goals (accessed June 23, 2021).

Van Boeckel, T. P., C. Brower, M. Gilbert, B. T. Grenfell, S. A. Levin, T. P. Robinson, A. Teillant, and R. Laxminarayan. 2015. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* 112(18):5649-5654.

Walia, K., J. Madhumathi, B. Veeraraghavan, A. Chakrabarti, A. Kapil, P. Ray, H. Singh, S. Sistla, and V. C. Ohri. 2019. Establishing antimicrobial resistance surveillance & research network in india: Journey so far. *Indian Journal of Medical Research* 149(2):164-179.

Wang, J. 2019. The challenges of antimicrobial resistance surveillance in china. *American Journal of Infection Control* 47(11):1403-1404.

Wee, B. A., D. M. Muloi, and B. A. D. van Bunnik. 2020. Quantifying the transmission of antimicrobial resistance at the human and livestock interface with genomics. *Clinical Microbiology and Infection* 26(12):1612-1616.

Wernli, D., P. S. Jorgensen, S. Harbarth, S. P. Carroll, R. Laxminarayan, N. Levrat, J. A. Rottingen, and D. Pittet. 2017. Antimicrobial resistance: The complex challenge of measurement to inform policy and the public. *PLoS Medicine* 14(8):e1002378.

WHO (World Health Organization). 2017. Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance. Geneva: WHO.

WHO. 2019a. *Antimicrobial resistance (AMR) - a major public threat*. https://www.who.int/infection-prevention/tools/IPC_AMR_A4.pdf?ua=1 (accessed June 25, 2021).

WHO. 2019b. New report calls for urgent action to avert antimicrobial resistance crisis. New York.

World Bank. 2016. By 2050, drug-resistant infections could cause global economic damage on par with 2008 financial crisis. New York: The World Bank

World Bank. 2017. *Drug-resistant infections: A threat to our economic future.* Washington D.C.: World Bank.

Wozniak, T. M., L. Barnsbee, X. J. Lee, and R. E. Pacella. 2019. Using the best available data to estimate the cost of antimicrobial resistance: A systematic review. *Antimicrobial Resistance & Infection Control* 8:26.

# 4

# Strengthening Surveillance

Surveillance is an essential public health service. The information gained through the monitoring of a health threat, in this case antimicrobial resistance, informs public policy and communication; it also helps direct research attention (OPHSS and CDC, 2018). In this discussion, surveillance refers to the timely collection, analysis, and communication of data on resistance patterns (that is, the extent, spread, evolution, and impact) for pathogens of public health importance (WHO, 2014). Improving surveillance is a key component of global and national action plans for combatting antimicrobial resistance (Ranjalkar and Chandy, 2019; The White House, 2015; WHO, 2014).

Monitoring resistance is also a component of some disease surveillance programs. Resistance to the drugs that treat tuberculosis is an important part of national tuberculosis surveillance, for example. But unlike disease surveillance systems, surveillance for antimicrobial resistance requires monitoring a range of targets not just in human health, but in animals, crops, and the environment as well. The targets for monitoring include resistant pathogens or indicator organisms, antimicrobials and their metabolites, resistance genes, and mobile genetic elements. For these reasons the setting feeding into surveillance for antimicrobials includes not just hospitals or clinical microbiology labs, although they are important, but also animal health laboratories, watershed and soil monitoring programs, and routine animal health surveillance. Collecting and interpreting such varied data then using it to inform public health programming is challenging.

This chapter will first give a broad introduction to surveillance for antimicrobial resistance, explaining the types of systems collecting information and the way information moves through them, paying particular attention to various surveillance systems operating globally and the challenge of integrating data from these disparate sources. Next, it discusses the main types of relevant data collected and the inferences that can be made from them, with some attention to making better use of routinely collected clinical phenotype information and integrating this data into public health surveillance. The last section gives more attention to questions of monitoring resistance in water, sewage, and other environmental reservoirs, with the committee proposing steps to better characterize the relatively neglected environmental dimension of surveillance.

## SURVEILLANCE SYSTEMS

Surveillance systems are critically important for understanding the burden of antimicrobial resistance, detecting the emergence and spread of resistant pathogens, targeting interventions to prevent and control the emergence of resistance, and measuring their effectiveness. Whether at the local, national or international level, surveillance systems for antimicrobial resistance can differ considerably regarding their objectives, scope, and methods.

Surveillance systems can be passive or active. A passive system relies on self-reporting from organizations with relevant data, (e.g., health care facilities, animal health laboratories, or water monitoring programs) depending on the monitoring scope of the system. Passive surveillance is relatively inexpensive to manage because the labor costs to get the data are low, but the information gained is not likely to be complete, timely, or representative of the target population (Lee et al., 2010). In the context of antimicrobial resistance, active surveillance can involve the deployment of public health staff to monitor a target pathogen by actively contacting institutions and collecting information about the incidence of infections caused by that pathogen. Active surveillance can minimize problems with data completeness and representativeness and is available on a predictable timetable, but these advantages come at a cost. An example of an active surveillance is the Active Bacterial Core within the Emerging Infections Program of the Centers for Disease Control and Prevention (CDC), which has collected clinical information and resistance data for community-acquired infections of five invasive bacteria since the 1990s (Fridkin et al., 2015; GAO, 2020). The Active Bacterial Core surveillance program was able to identify important health disparities in risk of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in certain states, informing health policy and outreach decisions to counter this disparity (Fridkin et al., 2015).

Sentinel surveillance systems (active or passive) are based on surveillance of selected sites rather than being comprehensive across a location or population. These sites collect data from a large population in areas likely to find antimicrobial resistance hospitals or clinical laboratories, for example (Lee et al., 2010). The CDC's Gonococcal Isolate Surveillance Program, which tracks antimicrobial resistance in gonococcal isolates submitted by 33 health departments across the United States, is an example of sentinel surveillance for resistant pathogens (CDC, 2021a).

Historically, surveillance for antimicrobial resistance has been built around human medicine, especially acute care. Data from acute-care hospitals are often a starting point for surveillance as the clinical microbiology services in hospitals afford good quality data on the resistant pathogens causing infections in hospitalized patients. Newer tools for surveillance include genomic analysis that can be used to trace the source of infectious outbreaks, thereby contributing to a better understanding of the burden of antimicrobial resistance.

The design of a surveillance system to monitor antimicrobial resistance depends on decisions regarding the target to monitor, such as the microbial species, as well as the public health questions of interest. A concern with the effect of antimicrobial resistance on the environment might lead to a relatively greater interest in monitoring effluent (i.e., the discharging wastewater from treatment plants into the natural environment); an interest in characterizing the resistome of a mostly health population would lead to monitoring of a sample representative of this population,[1] such as sewage. After considering such questions, there are

[1] "All the genes [in a microbial community] that directly or indirectly contribute to resistance" make up the resistome (Wright, 2010).

also technical questions regarding how surveillance data will be shared, sampling strategy, and geographical scope. Box 4-1 gives an overview of some of these foundational questions as they relate to monitoring antimicrobial resistance.

**BOX 4-1**
**Foundational Steps for Surveillance of Antimicrobial Resistance**

- Clearly define the public health question of interest, the population catchment, and sampling frame.
- Train and support workers to collect and analyze samples, manage the data, and disseminate relevant clinical and public health information.
- Record antimicrobial susceptibility test results, ideally making them accessible to laboratory information management systems at sentinel sites, and at human, animal, or environmental reference microbiology laboratories.
- Harmonize standards and procedures for collecting and transmitting susceptibility and related test results.
- Set up quality assurance and control for data collection, analysis, and management.
- Analyze data and interpret results to support clinical decision making and antimicrobial stewardship.

Laboratory data reporting into surveillance systems can take several different forms. A labor-intensive approach is manual reporting with data entered via internet questionnaire forms. Manual file extraction followed by uploading to a central webpage or online database is another common method for reporting resistance data into surveillance systems. Both these approaches add to the workload for laboratory staff and health workers and to delays on data availability. A more efficient approach is direct, automated transmission from the laboratory information system to the surveillance system. This can facilitate real- or near real-time reporting, allowing for more useful analysis of emerging trends.

Real-time, cloud-based surveillance sometimes draws on proprietary data. In the United States, where automated testing for antimicrobial susceptibility is the norm, medical device companies can access considerable information about resistance trends if the laboratories using their systems are willing to share their (anonymized) test results (Ruzante et al., 2021). A recent analysis of such data from 29 clinical laboratories using the BioFire gastrointestinal panel was able to monitor trends in acute gastrointestinal infection for almost 2 years, finding about 70 percent of infections caused by bacteria, especially *Clostridioides difficile* and enteropathogenic *Escherichia coli* (Ruzante et al., 2021). Such results should be interpreted with caution, as they were not obtained from a deliberate sampling frame designed to be representative of the population, but were nevertheless largely similar to CDC surveillance data in the relative rank and proportion of pathogens detected (Ruzante et al., 2021). It can also be difficult to interpret some of the results from the medical device company's data, as patient confidentiality requires it be de-identified. Without data on patient age and medical history, for example, it is difficult to comment on the public health implications of the observed *C. difficile* colonization.

## WHO and Multilateral Support for Surveillance

In the United States and other high-income countries there are many ways to monitor indicators of antimicrobial resistance in humans, animals, and the environment. There are fewer options in low- and middle-income countries, partly because of constraints on laboratory

capacity. Across settings, the most effective surveillance for antimicrobial resistance needs to integrate confidential patient data with information from other sources, making an agreement for data management and confidentially of paramount importance (Seale et al., 2017). Procedures for integrating confidential data are set out in the World Health Organization's (WHO's) Global AMR Surveillance System (GLASS) manual (WHO, 2015). Implementing the systems outlined in the manual is beyond the capacity of many low-income countries, however (Seale et al., 2017). For these countries, a road map to surveillance of resistant pathogens sets out the data governance agreements required, as well as the choice of sentinel sites and coordinating laboratories, even arrangements for storing and transporting isolates and data management (Seale et al., 2017). This road map allows that automated testing systems may not be in place in these countries (Seale et al., 2017). Box 4-2 gives more background on the WHO GLASS program.

**BOX 4-2**
**The WHO's Global Antimicrobial Surveillance and Use System**

A 2014 WHO report revealed little or no data on antimicrobial resistance were available from many low- and middle-income countries. In 2015, WHO launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS) to support the standardized collection, analysis, and sharing of antimicrobial resistance data at the global level. GLASS encourages countries to establish national surveillance systems that are capable of monitoring trends in resistance to eight priority, resistant pathogens with reliable data that can be compared across countries. To this end, GLASS provides a standardized information technology platform, standards, and tools for surveillance of priority bacterial infections in humans. Since 2019, GLASS has also had a system to monitor antimicrobial consumption including the quantity of medicines reportedly used in both hospital and community practice, as well as both public and private sectors. Though only a rough measure of use, the estimated consumption measures for humans and animals helps countries identify patterns in the amounts and types of antimicrobial medicines used. As of April 2021, 109 countries or territories participate in the GLASS antimicrobial resistance surveillance program; 19 of these are also in the program for monitoring antimicrobial consumption and an additional 2 countries participate in the antimicrobial consumption monitoring only.

GLASS represents a relatively low bar for national surveillance and reporting but one that makes surveillance of antimicrobial resistance and use possible in countries where it would not otherwise have been an option. WHO acknowledges that the data are not necessarily nationally representative. While the involvement of multiple sentinel surveillance sites is encouraged, only one site is required. This means that, especially in low-income countries, the country's GLASS data may be based on a few isolates from only one hospital. Furthermore, there is considerable variability in the type of data reported (e.g., types of isolates and their patient specimen sources), its representativeness, and completeness among reporting countries. Countries are required to report to GLASS only once a year, so trends are not identified quickly. The program supports the development of sentinel sites and developing stewardship programs and laboratory capacity; there's a strong emphasis on peer support for capacity building. Other capacity-building programs, such as those supported by the UK Fleming Fund, use GLASS parameters and enrollment as targets for supported countries. Starting in 2021, GLASS will have a capacity-building program for environmental aspects of surveillance for antimicrobial resistance.

SOURCES: WHO, 2017, 2021a.

Recent work from the WHO indicates an interest in expanding GLASS to microbes from animal and environmental sources. This includes helping countries to increase their capacity to monitor, collect, and report data on resistance of extended-spectrum beta-lactamase-producing *Escherichia coli* in humans, poultry, and water bodies, including those containing wastewater from human and food animal sources (WHO, 2021c). In its implementation guidance for One Health surveillance in low- and middle-income countries, the WHO recommended that the protocol be "simplified, integrated, [and] trans-sectoral" (WHO, 2021c).

The WHO also collaborates with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (known by the historical acronym OIE) to build a Tripartite Integrated Surveillance System on Antimicrobial Resistance and Antimicrobial Use (FAO and WHO, 2019). The Tripartite system envisions a global, web-based repository for resistance and use data from human, animals, animal, food, plant, and environmental sources; a request for proposals to develop such a platform was issued in March 2021 (WHO, 2021b). The Tripartite surveillance system is one of the four global projects supported by the United Nations (UN) AMR Multi-Partner Trust Fund, a pooled funding compact established in 2019 to support the Tripartite's joint One Health effort to combat antimicrobial resistance (FAO et al., 2020; UN MPTF Office, 2020).

The WHO's GLASS model of surveillance is a major step forward in monitoring antimicrobial resistance in low- and middle-income countries. The information gleaned from this network could be complemented by active surveillance, and there are numerous systems in place for active surveillance of antimicrobial resistance in low- and middle income countries (Ashley et al., 2018). As Figure 4-1 shows, global programs to fight malaria, tuberculosis, and HIV usually have a resistance-monitoring component; there is also considerable attention to surveillance in industry and academia.

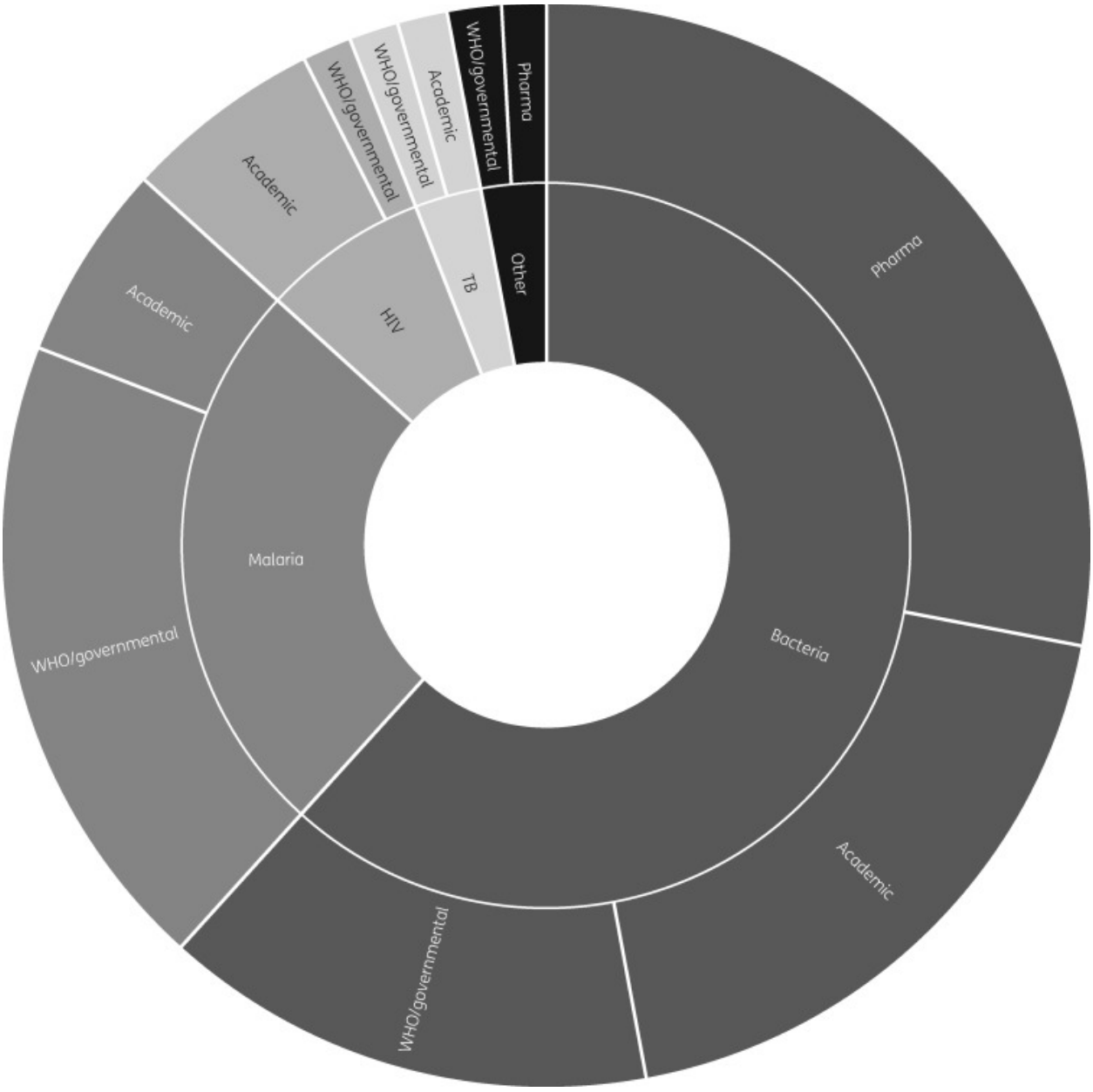



**FIGURE 4-1** Sunburst chart of international networks performing surveillance for antimicrobial resistance in low- or middle-income countries since 2000.
SOURCE: Ashley et al., 2018.

## Integrating Information from Disparate Sources

The challenge of effective surveillance for resistant pathogens comes in part from the useful information being collected by a wide and disparate group of systems. A recent review found that of 72 international surveillance networks developed since 2000, 34 were still active in 2018 (Ashley et al., 2018). Of the 45 networks conducting surveillance for resistance in bacteria or fungi, 21 were still active in 2018 (Ashley et al., 2018). A more recent review identified 71 surveillance networks, mostly in Europe and the Americas, that monitored at least one species of resistant bacteria, though only 26 of these networks appear to be active (Diallo et al., 2020).

Many of these were national networks, but others had a regional scope, such as the European Antimicrobial Resistance Surveillance Network, the Central Asian and Eastern European Surveillance of Antimicrobial Resistance.

More attention to monitoring resistance might yield more and better data to inform policy decisions, but it is not always so. Different systems collect data differently, and report results on different schedules, sometimes only once a year (Diallo et al., 2020). Only three of the active surveillance networks that Diallo and colleagues reviewed have real-time monitoring with an alarm for the detection of critical pathogens (Diallo et al., 2020). In general, different networks monitor animal and human health indicators. Some, such as the United States' National Antimicrobial Resistance Monitoring System for Enteric Bacteria look at both, but environmental monitoring is not a common component (Diallo et al., 2020). Harmonization efforts could do much to improve comparability of data and the speed at which it is shared (Diallo et al., 2020).

As Figure 4-1 shows, the private sector also operates surveillance networks. GlaxoSmithKline has a regular survey of community-acquired respiratory tract infections in more than 30 countries, for example; Merck has a program to look at antimicrobial resistance in isolates from intra-abdominal, blood stream, urinary tract, and respiratory tract infections in more than 60 countries (AMR Industry Alliance, 2017a,b; Enne et al., 2016; Hermsen et al., 2020; Torumkuney et al., 2016). The Pfizer Antimicrobial Testing Leadership and Surveillance database allows public access to both antifungal and antibiotic resistance data (Pfizer, 2021). Sometimes multiple companies collaborate in a surveillance consortium, as in the over 20-year SENTRY Antimicrobial Surveillance Program that collects and tests isolates from sentinel medical centers around the world (Fuhrmeister and Jones, 2019). Because of the large number of collaborators, isolates can be tested against 20 to 30 drugs, including investigational drugs (Fuhrmeister and Jones, 2019). This in turn informs antibiograms with scarce, valuable information about susceptibility to new drugs (a topic discussed more in Chapters 5 and 6) (Fuhrmeister and Jones, 2019).

In an effort to better understand private surveillance networks for antimicrobial resistance, the Wellcome Trust and the Open Data Institute established AMR Register, a clearinghouse for pharmaceutical companies' human surveillance data (AMR Research Initiative, 2021a). In May 2021, Wellcome announced that it would work with the nonprofit organization Vivli to evolve the pilot project into a public website that publishes these data (AMR Research Initiative, 2021b; Vivli Center for Global Clinical Research Data, 2021).

Figure 4-1 also notes academic surveillance efforts. Some such programs are related to ongoing academic research projects, and as such have a set duration. Academic surveillance networks can also be run in collaboration with industry. The Global Point Prevalence Survey of Antimicrobial Consumption and Resistance, for example, relies on the sponsorship of bioMerieux, a diagnostics company, and the University of Antwerp to conduct point prevalence studies of antimicrobial consumption and resistance in over 800 hospitals in 80 countries (Biomerieux, 2020; Global PPS, 2021a,b). These surveys help in the evaluation of hospital stewardship programs, charting whether they are effective at reducing antimicrobial consumption or the emergence of resistance. Some academic networks are wholly or partly devoted to low- or middle-income countries. The International Nosocomial Infection Control Consortium is one such network, with over 300 participating study sites in Latin America, Asia, North Africa and the Middle East (INICC, 2013). The consortium works to identify infection control strategies suitable to low- and middle-income countries; its surveillance component has helped quantify the

higher risk of surgical site infections and device-acquired infections both three to five times higher in low- and middle-income countries than in high-income ones (Rosenthal, 2016).

These networks could provide a useful source of complementary data to inform estimates of the burden of the antimicrobial resistance. There is also ample room to make better use of, and have better access to, some of the data these networks collect, a topic discussed later in this chapter.

## Automated Reporting

Automated surveillance systems have clear advantages over methods that rely on people to report data. Automation makes the reporting faster and easier, and it causes minimal disruptions to routine work. Nevertheless, a 2018 assessment of automated reporting from clinical diagnostic laboratories across Europe found that the most common barriers to automated reporting to the national surveillance systems were technological and financial (Leitmeyer et al., 2020). The laboratory software developers and vendors might not have developed ways to make their data compatible with the national surveillance systems as this is not their primary business (Leitmeyer et al., 2020). The protection of confidential information is a barrier to automated surveillance, especially in countries where there is no legal framework to support automated surveillance.

A lack of information technology is often cited as a barrier to comprehensive surveillance for antimicrobial resistance in low- and middle-income countries (Vong et al., 2017). Limited internet connectivity is a related challenge, as are the cost of the hardware, software, and staff to support automated surveillance networks (Vong et al., 2017). The WHO Collaborating Center for Surveillance of Antimicrobial Resistance has developed WHONET, a free, Windows-based software for microbiology laboratories to use for analysis of susceptibility test results (Vong et al., 2017). WHONET also provides a data conversion tool to ease the transfer of raw susceptibility data from the laboratory system to surveillance systems such as GLASS (Vong et al., 2017). Lab managers simply have to opt-in to have the data uploaded to a surveillance system. Figure 4-2 illustrates the flow of information from hospitals or national sentinel sites to the national data hub, also highlighting some of the country support the WHO is providing for the surveillance of antimicrobial resistance.

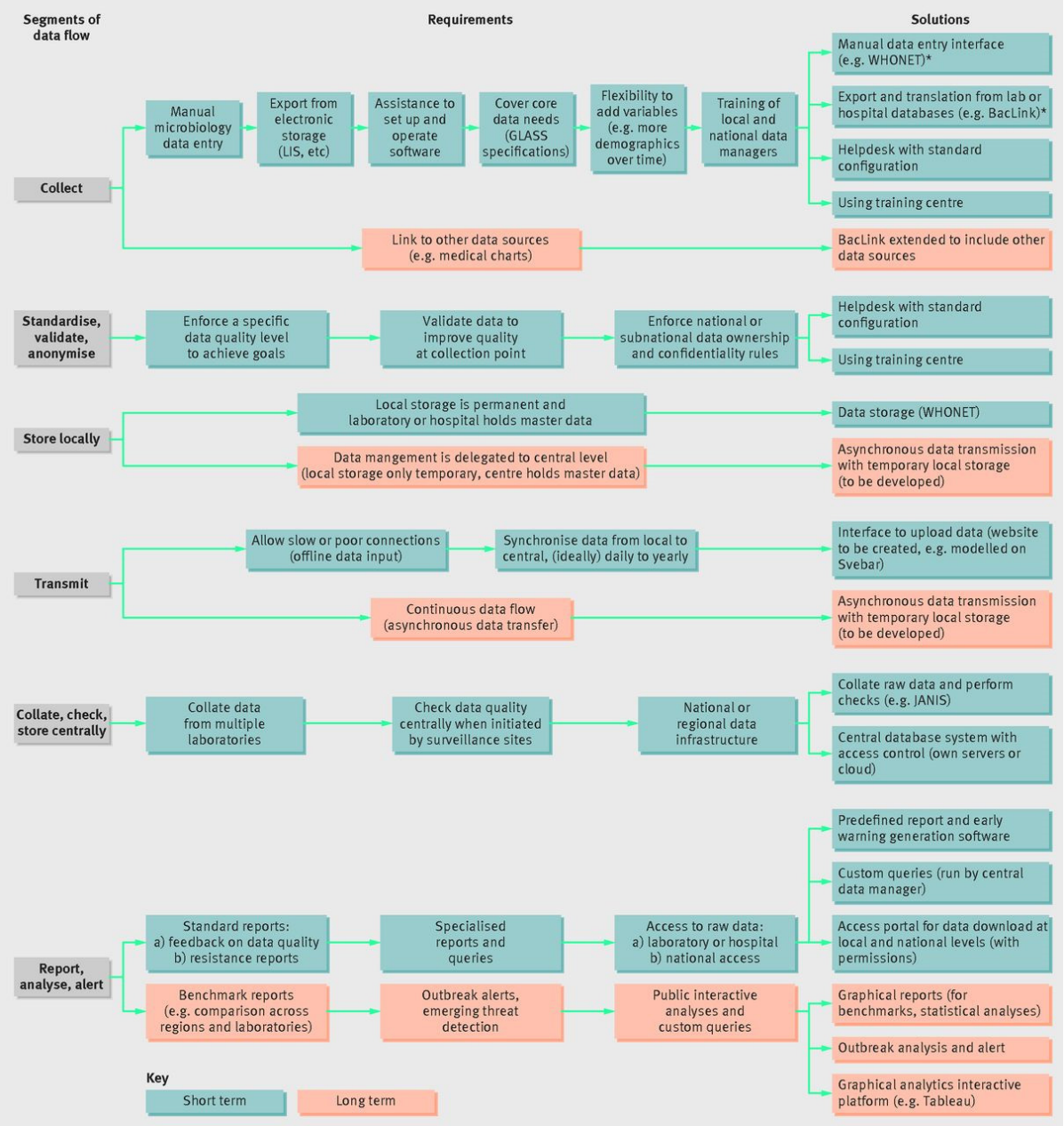



**FIGURE 4-2** Requirements for the flow of surveillance data and proposed solutions to key challenges.
NOTE: Short-term actions are shown in green, long-term actions in salmon.
SOURCE: Vong et al., 2017.

FAO is working to adapt WHONET to collect antimicrobial resistance data on food and food-producing animals, with consideration to the elements of database design that allow for compatible automated data capture (FAO, 2019b, 2021a). To this end, the organization has developed a data management template and an online database from which information on antimicrobial resistance in food and animals will eventually be uploaded to the Tripartite surveillance system (FAO, 2019b, 2021b).

Such developments are promising, but in order for countries to participate in these nascent networks, they first have to have the capacity to collect data. To this end, FAO provides

assessment tools to measure capacity to monitor antimicrobial resistance in food systems and to set specific priorities for improvement (FAO, 2021a; FAO and UN, 2021). FAO also encourages regional cooperation to ensure harmonized data collection and regional comparability of results (FAO, 2019a). The WHO and FAO's Codex Alimentarius Commission has produced draft guidelines on monitoring foodborne antimicrobial resistance (FAO and WHO, 2021).

## DATA COLLECTION AND ANALYSIS

Antibacterial resistance can be determined through two main sets of tools: phenotypic and genotypic. Phenotypic antimicrobial susceptibility tests determine the effectiveness of an antimicrobial compound in killing or inhibiting the growth of specific bacterial types. Such test results are vital for clinical decision making, including the drug and regimen for antimicrobial therapy. At a population level, susceptibility data are valuable indicators of trends in antimicrobial resistance (Cusack et al., 2019). There are also a wealth of genotypic tools, more widely used in research, that can help inform a better understanding of the burden of resistance. This includes multiplexed molecular panels incorporating resistance markers, which are becoming increasingly common in clinical and environmental laboratories and offer rapid and accurate genotypic susceptibility results, and next-generation sequencing approaches.

### Phenotypic Tests

The two most commonly used methods to test antimicrobial susceptibility are diffusion and microdilution. As Figures 4-3 and 4-4 show, both types of test rely on established clinical breakpoints to determine if an organism is resistant or susceptible to an antimicrobial compound or at an intermediate point between resistance and susceptibility, from which the microbiologist measures the minimum drug concentration needed to inhibit microbial growth (the minimum inhibitory concentration or MIC). Of the two methods, broth microdilution provides more information on the extent of susceptibility or resistance that facilitates comparison of susceptibility profiles over space and time. The microtiter plate format is also more amenable to automation from setup to reading, as Figure 4-4 shows, although automated disc dispensers are commercially available to facilitate the setup of diffusion tests.

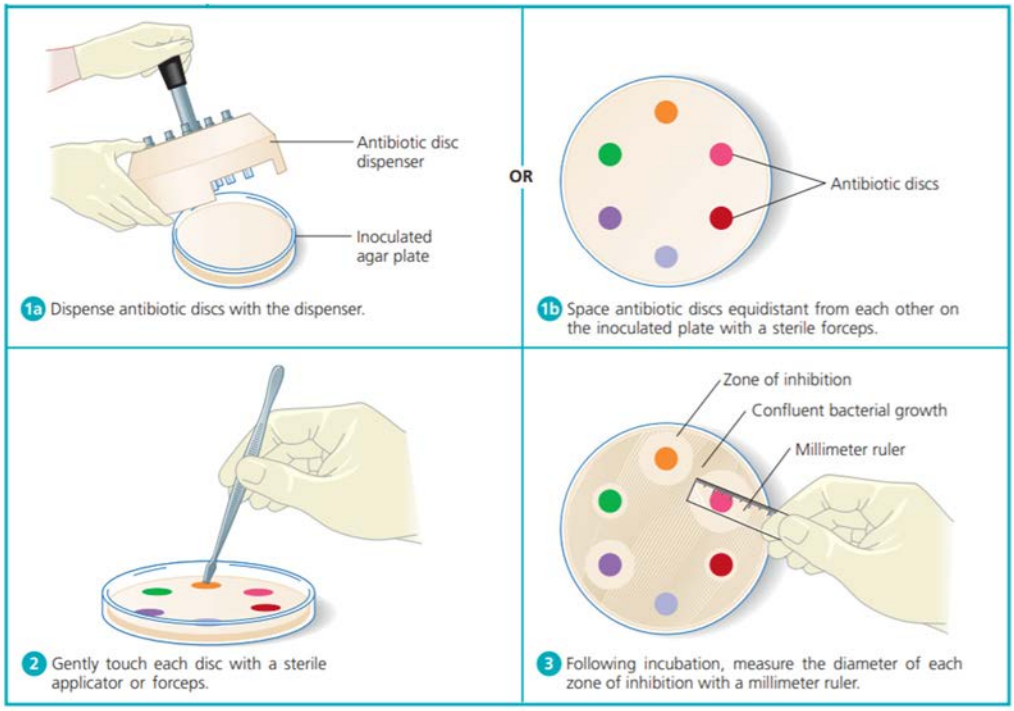



**FIGURE 4-3** Steps in disk diffusion
NOTE: In disk diffusion, different antimicrobials or different concentrations of the same antimicrobial are spaced on a culture plate inoculated with the pathogen of interest. After incubation, the diameter of the zone of inhibition around each disk is measured.
SOURCE: Cappuccino and Sherman, 2014.

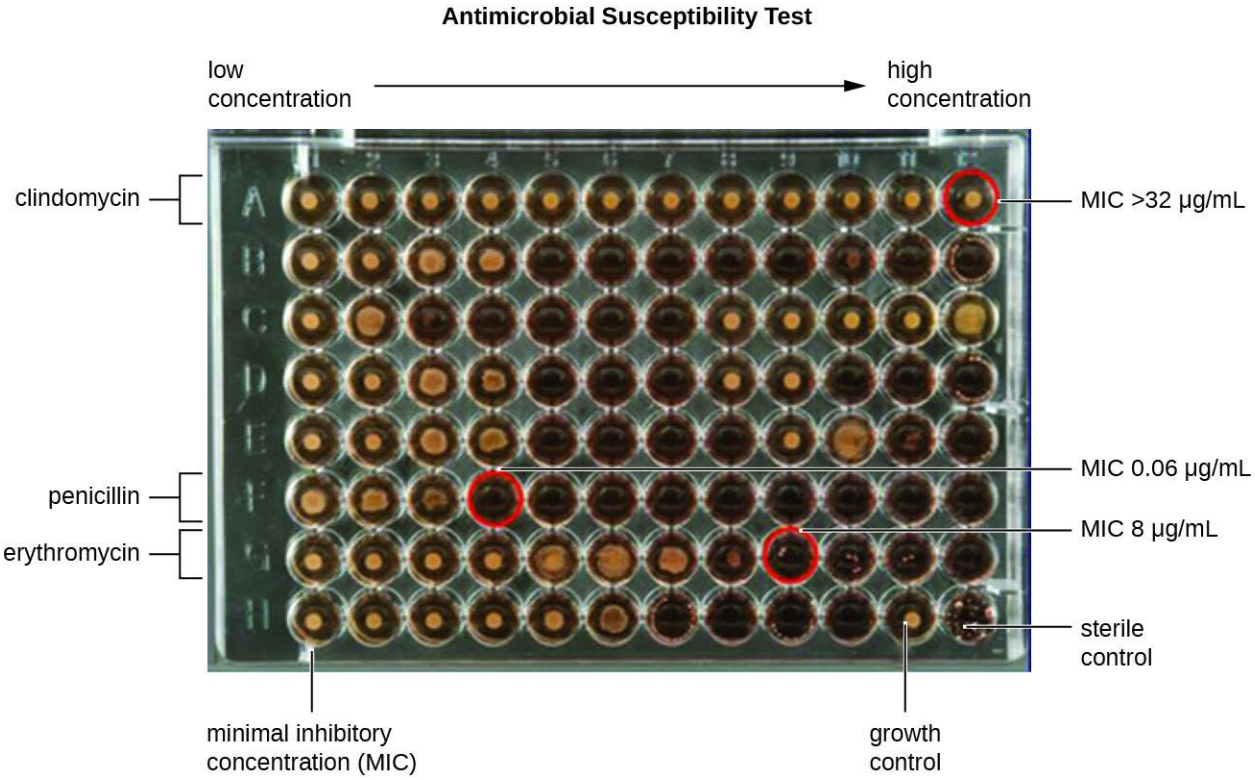


**FIGURE 4-4** A microdilution tray viewed from above, microtubes filled with progressively more concentrated dilutions of drug in both are inoculated with an equal number of bacterial cells. The microbiologist identifies the lowest drug concentration to inhibit cloudiness in the sample.
SOURCE: Lumen, 2021.

Both diffusion and microdilution tests are used in medicine to understand the clinical susceptibility of a pathogen to an antimicrobial. This is information a physician or veterinarian would need to identify a resistant infection and treat a patient. This clinical resistance is driven at the molecular level by traits in the pathogen that convey resistance to antimicrobials. Recent advances in testing have given better insight into the genetic basis of resistance, information which can be monitored in academic and public health surveillance efforts.

### Genotypic Tests

Genotypic tools for identifying resistance look for sequences in the genetic code that indicate mechanisms of resistance to antimicrobials. Genotypic analyses include many tools based on molecular analysis, (i.e., polymerase chain reaction or PCR), which amplify sections of bacterial DNA to detect the presence of resistant traits. In clinical settings, molecular tests typically look for genes known to convey resistance to relevant drugs. The results can be helpful in informing clinical treatment by ruling out treatments for which the target pathogen carries resistance genes. At the same time, the presence of resistance genes does not necessarily predict treatment failure, nor does the absence of resistance genes necessarily indicate the clinical susceptibility of the pathogen, especially in gram-negative organisms (Bard and Lee, 2018; Galhano et al., 2021). Quantitative PCR (qPCR), also known as real-time PCR, not only detects the presence of a resistance gene but can also measure the concentration of the gene in the sample. For this reason, qPCR is frequently used to detect resistance genes in the environment. Its usefulness has increased with the introduction of high-throughput, real-time quantitative PCR, a technique that can analyze the presence and quantity of many resistance genes or mobile genetic elements at the same time, performing multiple assays using samples of only nanoliters (Franklin et al., 2021; Luby et al., 2016).

Whole genome sequencing identifies resistance by comparing the sequenced genome of the pathogen in question to known sequences that encode antimicrobial resistance (see Figure 4-5). Through the use of computerized algorithms and pattern recognition (called machine learning), genome sequences can be rapidly compared to their phenotypic resistance patterns to identify novel resistance mechanisms or mutations (Hendriksen et al., 2019a; Schurch and van Schaik, 2017).

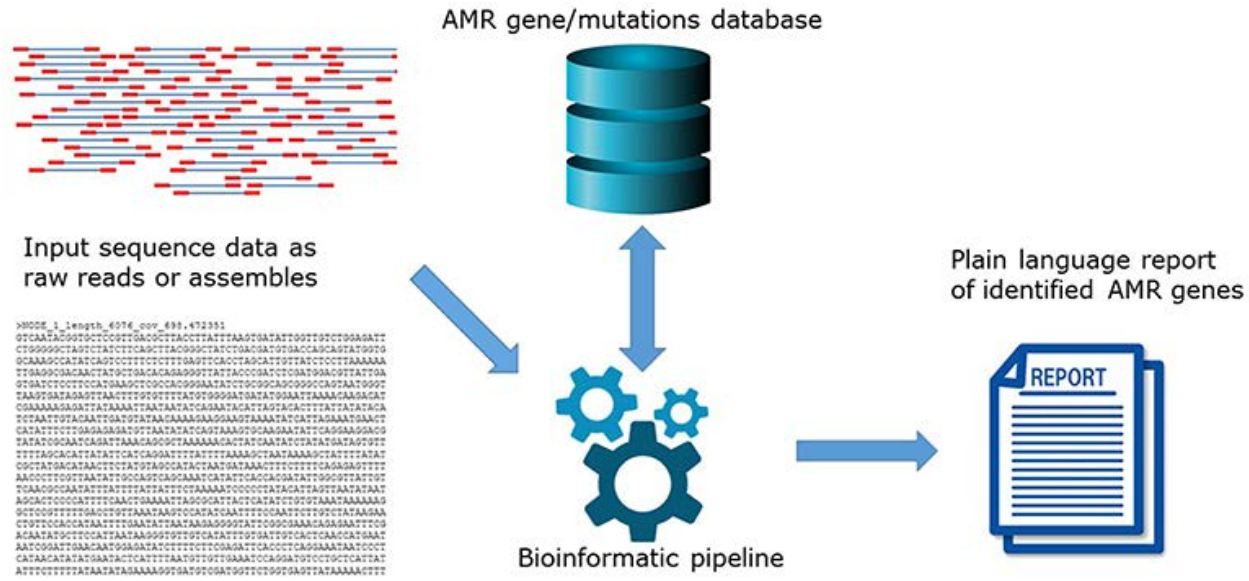



**FIGURE 4-5** Whole genome sequencing compares DNA sequence data to AMR determinants in reference databases.
SOURCE: Hendriksen et al., 2019a.

Whole genome sequencing has been essential to the recent COVID-19 response, and using this tool in surveillance can be essential for outbreak response (Africa CDC, 2020) For this reason, a group of public, private, and nonprofit organizations, led by the African Union Commission through the Africa Centres for Disease Control and Prevention, recently invested $100 million to expand the use of genomic sequencing tools in public health surveillance and laboratory networks across Africa (Africa CDC, 2020).

There are also genotypic tools to describe the composition of microbial communities rather than single (cultured) organisms. As Figure 4-6 shows, metagenomic analysis can be especially useful in environmental monitoring (Schmieder and Edwards, 2012). Sequence-based metagenomic analysis involves extraction of DNA from an environmental sample and sequencing all or portions of it. The sequenced DNA—the metagenome—is then compared to a reference database of resistance genes and other determinants of resistance. (Examples of such reference databases include the Comprehensive Antibiotic Resistance Database, ResFiner, and the Reference Gene Catalog [Alcock et al., 2020; Bortolaia et al., 2020; Feldgarden et al., 2021a].) Functional metagenomics involves cloning the collective genome of all the organisms in a sample into a bacterial host, often *E.coli*, to identify resistance genes or genetic elements that may not be apparent from the sequence alone (Allen et al., 2010). This functional metagenomic analysis can be highly exploratory; no specific target pathogen, resistance gene, or mobile genetic element needs to be identified prior to the analysis. This can, therefore, be a very time-consuming approach to analysis, sometimes described as “tedious” or like searching for a needle in a haystack (Kowalchuk et al., 2007).

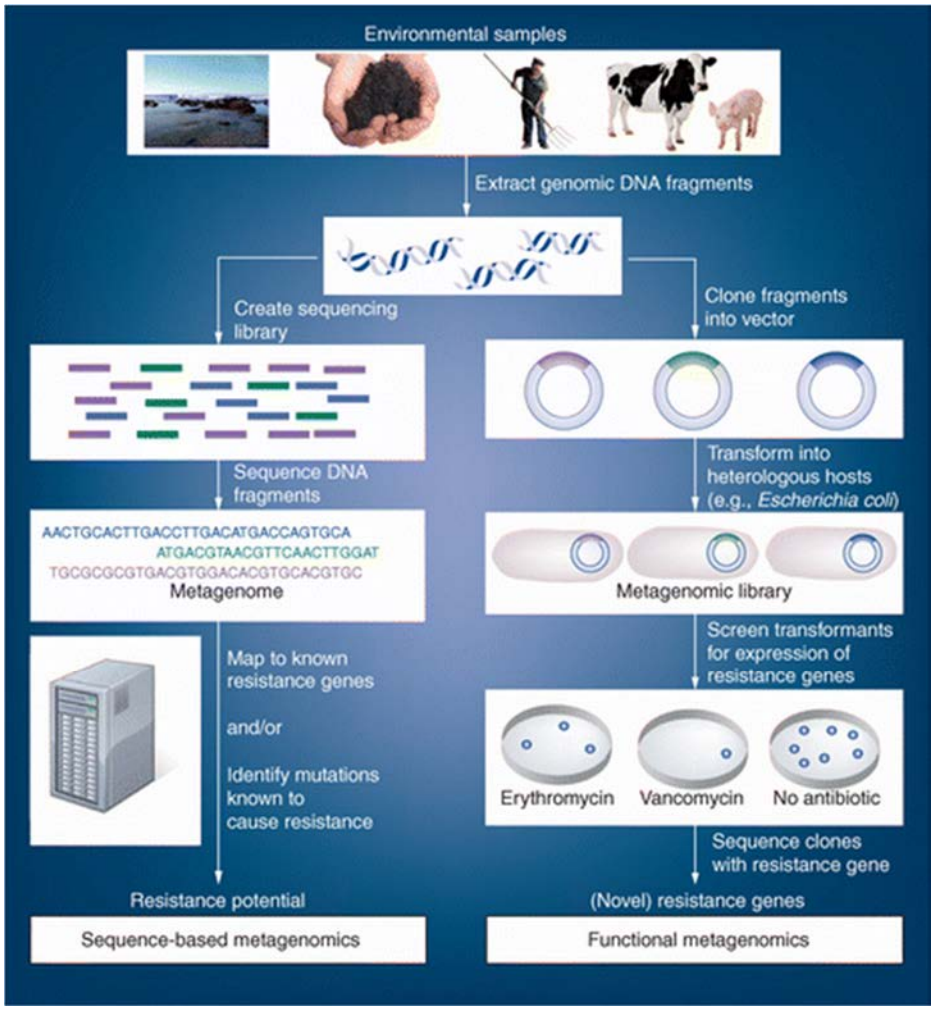



**FIGURE 4-6** Examples of metagenomic analysis of antimicrobial resistance in microbial communities
NOTES: Cloning fragments into an expression vector to create a metagenomic expression library is a new approach, especially valuable in identifying genes involved in resistance to target antimicrobials. It is a complement to the more widely used metagenomic approaches delineated on the left.
SOURCE: Schmieder and Edwards, 2012.

Genotypic tools are useful in surveillance: they are fast and require relatively small sample volumes. The ability to detect the presence of a resistance mechanism, even at low levels, is useful in surveillance. (The same is not true in clinical medicine, where the presence of resistance genes is not necessarily clinically useful information.) Genotypic tools are valuable in studying bacteria that are difficult to culture (Franklin et al., 2021). They have the potential to identify drivers of resistance, such as the presence of genes associated with resistance to heavy metals or multiple drugs or with mobile genetic elements (Franklin et al., 2021; Hendriksen et al., 2019a; Sundsfjord et al., 2004). They can also detect resistance mechanisms regardless of whether the pathogen is alive, a determination that does not rely on phenotypic breakpoints, which may be defined differently depending on the testing standard used (Sundsfjord et al., 2004).

At the same time, genotypic tests are currently expensive and require more sophisticated equipment and analysis than phenotypic susceptibility tests (Wellcome Trust, 2018). What is

more, resistance encoded by a previously unknown gene will be missed by genotypic methods based on sequencing. Furthermore, the *presence* of a resistance gene or determinant is not the same thing as its functional expression in a pathogen, something a phenotypic susceptibility test determines (Dunne et al., 2017). Looking at the RNA in a transcriptome can give insight into the genetically active and inactive components of a genome or microbiome (Shakya et al., 2019). The sequencing of RNA in microbial communities (called metatranscriptomics) can clarify the ways in which genes function (Franzosa et al., 2014; Korry et al., 2020; Shakya et al., 2019). While metagenomic analysis gives insight into the structure and potential function of the microbial community, metatranscriptomic analysis gives insights into gene expression and function in response to specific conditions. Tools used together can provide a good understanding of changes in microbial communities and the functional response of antibiotic resistant genes in response to antibiotic exposure, if they can be adequately assembled and annotated from sequencing datasets (Korry et al., 2020). At the same time, obtaining intact RNA from an environmental sample is technically difficult and time consuming, challenges that should be weighed against their use (Maki et al., 2017).

Analysis of an environmental sample using PCR to search for particular resistance markers cannot determine the microbial host of the resistance gene, making it difficult to interpret if or how the resistance is conveyed to key pathogens (Luby et al., 2016). While the new high-throughput, real-time PCR techniques can test for multiple resistance genes at the same time, they are incapable of identifying novel resistance genes or emerging genetic elements (Franklin et al., 2021). There is also a need for standardization of procedures, especially for whole genome sequencing and metagenomic analysis (Hendriksen et al., 2019a). Table 4-1 summarizes advantages and disadvantages of different methods to identify the presence of antimicrobial resistance.

**TABLE 4-1** Advantages and Disadvantages of Current Methods Available to Characterize Antimicrobial Resistance

| Methods | Advantages | Disadvantages |
|---|---|---|
| Phenotypic tests | Low technical requirements | Labor intensive and time consuming |
| | Low cost per test | |
| | Capable of identifying and quantifying antimicrobial resistance bacteria | Inherent cultivation bias for fast-growing, easily cultivable bacteria |
| | Allows determining the phenotypic response of bacteria to selection pressure from antimicrobials | Unculturable environmental bacteria that may serve as a reservoir of resistance are neglected |
| | Already in widespread use in clinical settings and water quality monitoring programs | For environmental surveillance, lack of benchmarking against culture-independent methods |
| | Ongoing global efforts to provide guidelines on collecting and reporting data | Results take days, necessitating prolonged use of broad-spectrum antimicrobials in clinical practice |
| qPCR and reverse transcriptase qPCR | Rapid quantification of target resistance genes for tracking, transport, and risk-assessment models | High technical requirements |

| | | |
|---|---|---|
| | With new high-throughput technologies, able to analyze a large suite of target genes simultaneously | Inability to directly discriminate extracellular from intracellular DNA or the presence of resistance genes in live versus dead bacteria (qPCR only) |
| | Ability to detect low-abundance genes (i.e., high sensitivity) | In the case of reverse transcriptase qPCR, need for methods to avoid RNA degradation and preserve sample quality before processing. |
| | Do not need live organism | Sensitivity can be influenced by qPCR inhibition |
| | High specificity compared to many culture-based assays for environmental samples | |
| | | Difficult to distinguish location of the gene (e.g., chromosome, plasmid, phage) |
| | | Only amplifies a small region of the genome and may therefore detect pseudogenes (i.e., nonfunctional genes) |
| Whole genome sequencing | Antimicrobial-resistant bacteria can be typed and tracked by individual allele profile | Generally, cost prohibitive for large studies |
| | Achieves much higher resolution than traditional typing methods | Limited to the individual bacterial cells that can be cultured and sequenced; newer technologies like single-cell genomics can capture unculturable microbes |
| | Determines co-carriage of specific genes causing different multidrug-resistance patterns | Requires accurate and up-to-date reference databases |
| | | Very high technical requirements |
| Metagenomics | Able to analyze large numbers of relevant genes in environmental samples | Highest cost and technical requirements of all the methods |
| | Can potentially carry out bacterial taxonomy and functional gene analysis simultaneously | Poor repeatability due to limitations in current analysis methods (in development); repeatability will increase with the development of guidelines and standards of analysis and the growth of curated reference databases |
| | Using PCR-free library preparation removes problems with unsuitable primer design and PCR biases | Labor intensive with complex sample preparation and analysis |
| | Can predict new variations on resistance genes | Difficult to directly link the presence of a resistance gene with a specific resistant bacteria |
| | Datasets can be compared between studies | No live, dead, or active discrimination when not culturing first |

| | | |
|---|---|---|
| | Helps to expand ARG databases | When PCR-dependent library preparation is used, PCR biases can affect analytical sensitivity and accuracy (e.g., exaggerations of dominant taxa or omitting low number abundance taxa) |
| | | Does not provide enough sequencing depth to enrich and assemble genomes of a single strain (especially in complex matrices); however, this limitation depends on the platform |
| | | Results dependent on library preparation and bioinformatics workflows |
| Metatranscriptomics | Allows the characterization and quantification of antimicrobial resistance genes that are metabolically active (being expressed) | Only characterizes resistance genes that are actively expressed at the particular time of sample collection and in that particular environmental condition |
| | | Expensive |
| | | Requires samples to be frozen immediately at ultra-low temperatures or stored in special preservatives |

SOURCES: Based on Franklin et al., 2021; Korry et al., 2020.

## Identifying Resistance Patterns

Some systems in place for surveillance of antimicrobial resistance are designed to monitor resistance in particular pathogens or to a certain antimicrobial. AstraZeneca monitored susceptibility to meropenems in 21 countries for almost a decade, for example (Ashley et al., 2018). However, as protocols for phenotypic detection are streamlined and genotypic tools become cheaper and more accessible, coordinated monitoring across human, animal, and environmental samples will be more feasible.

One commonly used tool to monitor resistance patterns is the antibiogram, a "profile of antimicrobial susceptibility testing results of a specific microorganism to a battery of antimicrobial drugs" (Minnesota Department of Health, 2015). Antibiograms are usually presented in tables, pulling aggregate data from a hospital or health system (Minnesota Department of Health, 2015). Antibiograms are useful for monitoring trends in pathogens' phenotypic resistance to different drugs; for this reason they are invaluable in both clinical medicine and surveillance. The production of antibiograms is part of the CDC's *Core Elements of Hospital Antibiotic Stewardship Programs* (CDC, 2019a). Hospital reports, in turn, feed into state and county antibiograms that are used to both inform treatment decisions and monitor trends in resistance.

Useful as they are, antibiograms do not typically give information into mechanisms of resistance, information that can be used to predict resistance patterns in microbe–drug combinations that are not part of the antibiogram (Sundsfjord et al., 2004). As Figure 4-5 showed, automated test panels have limited space, so the ability to make inferences about susceptibility in microbe–drug combinations that are not included in automated susceptibility

tests is helpful. The use of whole genome sequencing to identify root causes of resistance is also useful when phenotypic resistance patterns change. In the Philippines, for example, the pairing of sequencing data with local antibiograms revealed that an increase in carbapenem resistance was attributable to horizontal gene transfer rather than the spread of a single resistant genetic clone (Argimon et al., 2020).

Whole genome sequencing is especially valuable in connection resistance patterns that emerge in different places or species or over a long time. It has been used in neonatal intensive care units to connect outbreaks of MRSA even when months pass between cases (Harris et al., 2013). Whole genome sequencing can also identify genetic links between resistant pathogens affecting humans and livestock (Davis et al., 2015).

The effectiveness of using phenotypic and genotypic data together to combat antimicrobial resistance can be seen in the Walter Reed Army Institute of Research's Multidrug-Resistant Organism Repository and Surveillance Network (MRSN). Established to identify and prevent the spread of gram-negative multidrug-resistant organisms in military hospitals, the network provides a standardized system to interpret and compare resistance data across diverse settings (Chandrasekera et al., 2015). The MRSN also emphasizes prompt turnaround on testing to inform clinical practice. Pathogen identification and susceptibility are confirmed within 48 hours, along with PCR results screening for resistance genes (Chandrasekera et al., 2015). Information derived from whole genome sequencing and other advanced genomic tests are made available within a week (Chandrasekera et al., 2015). Through these efforts, MRSN supports attention to standard minimum data included on antibiograms, allowing for greater comparability of antibiograms across sites (Chandrasekera et al., 2015).

The MRSN allows clinicians prompt access to valuable information about resistant pathogens, informing treatment decisions and allowing them to put infection control measures in place quickly if necessary. It can also identify new resistant pathogens and genes. The value of the information gained is amplified through the Department of Defenses' ongoing surveillance for resistant pathogens in host country military and civilian hospitals as part of the Global Emerging Infections Surveillance program (Health.mil, 2021; Meyer et al., 2011). Such monitoring can track the spread of antimicrobial resistance globally, informing clinical practice and national policy for combatting antimicrobial resistance (Meyer et al., 2011).

### *NIH Efforts to Curate Information About Resistance*

The MRSN may be unique in the population it serves and in the speed at which it is able to collect, analyze, and act on a signal, but it feeds into an even larger data collection effort. The National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) at the National Institutes of Health (NIH), has collected and made publicly available considerable information about resistance genes, genome sequences, antimicrobial susceptibility data, and bacterial genomes (NLM, 2019a). In 2016, it launched the Pathogen Detection Isolates Browser, an evolving tool that collects and analyzes gene sequences of pathogen isolates from human, food, animal, and environmental sources (NLM, 2019b). Submissions to the isolate browser come from a range of U.S. federal health agencies (including the DOD, CDC, Food and Drug Administration, and U.S. Department of Agriculture [USDA]), state public health and agriculture laboratories, universities and hospitals, and international partners in the United Kingdom, Denmark, Australia, Canada, and Mexico (NLM). Figure 4-7 shows resources available in the Pathogen Detection Project and the relationships among them.

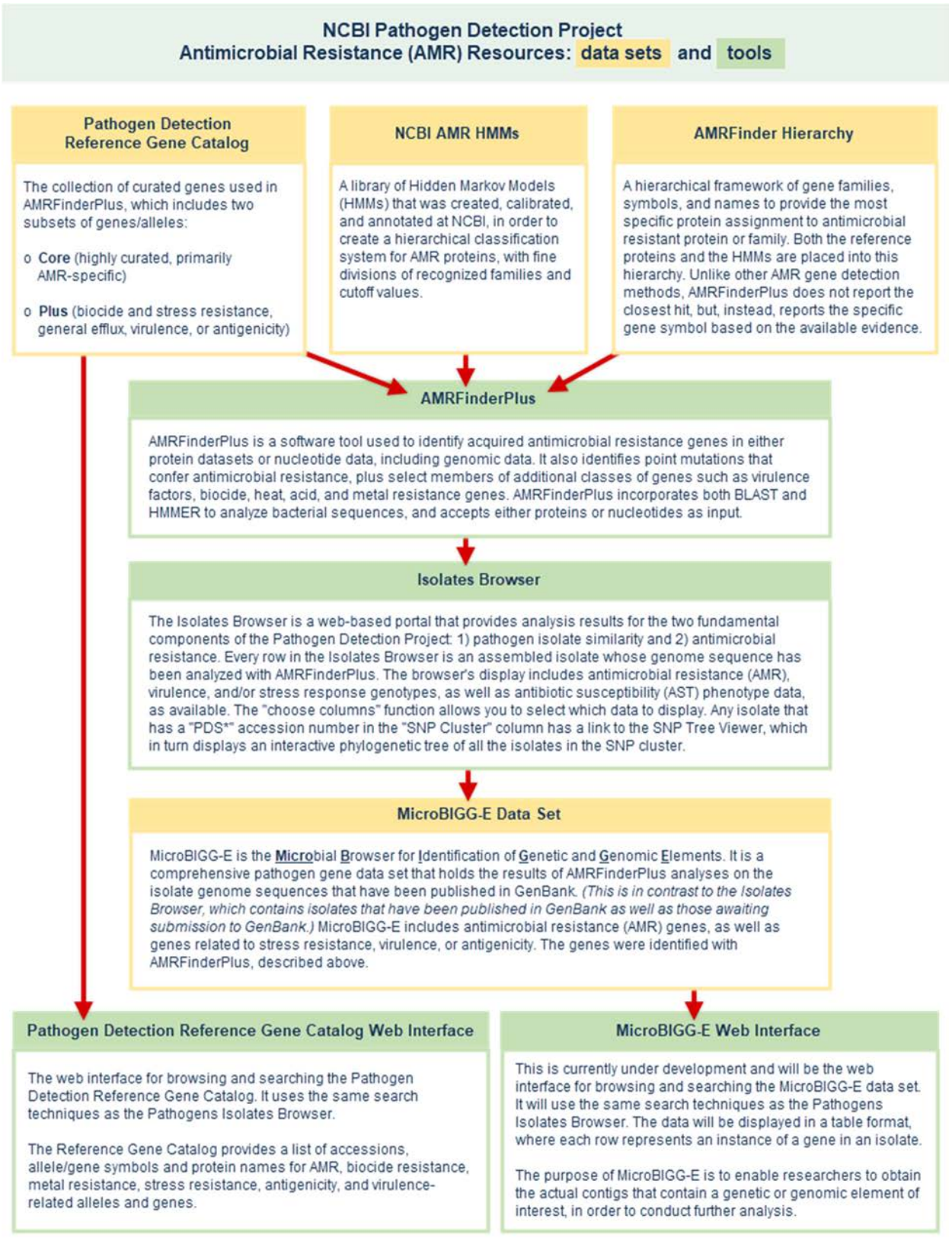



**FIGURE 4-7** Antimicrobial resistance resources in the NCBI pathogen detection project and the relationships among them.

SOURCE: NLM, 2020.

As Figure 4-7 indicates, public health and clinical laboratories can submit data to the NCBI databases, as can researchers or the managers of various data repositories (NLM).[2] As of June 2021, the Pathogen Detection Isolates Browser contained nearly 900,000 isolates from 33 bacteria and the fungus *Candida auris* (NLM, 2021b). All data are publicly available.

The Pathogen Detection project has two objectives. The first is to identify relationships among disparate clones as part of the source investigation and response to on an outbreak (NLM). The other is to facilitate monitoring and research on resistance genes and other relevant genetic information that encode antimicrobial resistance. To this end, NCBI has built the National Database of Antibiotic Resistant Organisms (NDARO) (NLM). This database includes a reference catalog with the capability to search for acquired resistance genes and proteins and point mutations as well as genes encoding for co-resistances (including metal and biocides) and virulence (Sayers et al., 2021). It includes software that analyzes all uploaded isolates, with the exception of *C. auris*, for resistance genes identified in the databases, with the capacity to identify co-resistance and point mutations for some pathogens (Feldgarden et al., 2021a). Antibiogram data from phenotypic susceptibility tests can be uploaded and stored with the sequence. The phenotypic information is included as a column in the Isolate Browser next to the column of identified resistance genes, as well as details of the antibiogram, including minimum inhibitory concentrations and the testing standard used. Additional information about the isolates (e.g., clinical or environmental sample; from blood, urine, meat from retail or wholesale) is included in the metadata. The database can be searched for combinations of phenotypic and genotypic resistances, including co-resistances and virulence. As of January 2021, the project has included the Microbial Browser for Identification of Genetic and Genomic Elements, which allows users to download protein and nucleotide sequences as well as isolate metadata about assumed phenotypic expression (Sayers et al., 2021).

The committee commends NCBI for its Pathogen Detection and NDARO programs, both for scope of the programs and the breadths of contributors they are accessible to. These databases are not only invaluable tools for researchers and public health investigators, but they are useful to inform discussion about priorities for medicine and diagnostic development.

However, the focus of the programs on genotypic data leaves much available data on resistance unmined. Of the almost 900,000 isolates submitted to the browser, only a little more than 10,000 entries (about 1 percent) have associated antibiogram data (Hendriksen et al., 2019a; Prasad, 2021). Most of these antibiograms have been entered by federal agencies, and more than half are for *Salmonella* spp. (Strain, 2021). Antibiogram data from many hospitals, universities, and public health laboratories around the country are not being uploaded. The committee encourages NCBI to continue its efforts to communicate about the Pathogen Detection Project to all parties who may have data to contribute, emphasizing the importance of including antibiogram data when available.

As seen with the example of MRSN, collecting phenotypic data within a broader database can facilitate the aggregation of antibiograms and bolster efforts to depict the emergence and spread of resistance (CDDEP, 2021) The sequencing of resistance genes and associated mechanisms of resistance can increasingly predict pathogens' susceptibility to different

[2] Submission requires a record of the project in NCBI's BioProject database, a record in NCBI's BioSample database with the isolate metadata for each pathogen sequenced, and a submission of the raw sequence data to NCBI's Sequence Read Archive database (NLM, 2021a).

antimicrobials (Hendriksen et al., 2019a; Schurch and van Schaik, 2017) (see Table 4-2). It is still too expensive and resource intensive to be useful in clinical practice, especially in low- and middle-income countries, however (NIHR Global Health Research Unit on Genomic Surveillance of AMR, 2020). For surveillance purposes, genome sequences may be sufficiently reliable for identifying patterns of antimicrobial resistance of public health importance (Bortolaia et al., 2020; Koser et al., 2014; Schurch and van Schaik, 2017). As the GLASS protocols acknowledge, phenotypic testing is the common denominator of global surveillance (Bard and Lee, 2018).

**TABLE 4-2** Concordance Between Phenotypic Susceptibility Testing and Whole Genome Sequencing-Based Predicted Antimicrobial Resistance

| | Pathogen | No. of pathogens | AST method | No. of antimicrobials | Bioinformatic tool | Sequencing data | Concordance | Sensitivity | Specificity | Comment | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | *S. Typhimurium* | 49 | MIC | 17 | ResFinder | Assembled, Velvet | 99.74% | | | Disagreement: 7 isolates including 6 *E. coli* resistent to Spec | (7) |
| | *E. coli* | 48 | | | | | | | | | |
| | *E. faecalis* | 50 | | 14 | | | | | | | |
| | *E. faecium* | 50 | | | | | | | | | |
| 2013 | *E. coli* (ESBL) | 74 | DD | 7 | BLASTn, selected panel | Assembled, Velvet | | 96% | 97% | VM rate: 1.2%/M rate: 2.1% | (8) |
| | *K. pneumonia* (ESBL) | 69 | | | | | | | | | |
| 2014 | *S. aureus* | 501 | DD/MIC (Vitek) | 12 | BLASTn, selected panel | Assembled, Velvet | | 97% | 99% | VM rate: 0.5%/M rate: 0.7% | (9) |
| 2016 | *C. jejuni* | 32 | MIC | 9 | BLASTx | Assembled, CLC-bio | 99.2% | | | Lower concordance to | (10) |
| | *C. coli* | 82 | | | | | | | | Gen, Azi, Clin, Tel | |
| 2016 | *S. enterica* | 104 | MIC | 14 | ResFinder/ ARG-ANNOT/ CARD/BLAST | Assembled, CLC-bio | 99.0% | 99.2% | 99.3% | Lower concordance to | (11) |
| | | 536 | | | | | | 97.6% | 98.0% | aminoglycosides/β-lactams | |
| 2017 | *E. coli* | 31 | MIC | 4 | Custom DB based on ARDB/CARD/β-lactamase alleles | | | 87% | 98% | Neg. predictive value: 97% | (12) |
| | *K. pneumonia* | 24 | | | | | | | | Pos. Predictive value: 91% | |
| | *P. aeruginosa* | 22 | | | | | | | | | |
| | *E. cloacae* | 13 | | | | | | | | | |
| 2017 | *S. enterica* | 50 | MIC | 4 | ResFinder/ PointFinder | Assembled, SPAdes | 98.4% | | | Disagreement: 2/2 C.jejuni to FQ/ERY | (13) |
| | *E. coli* | 50 | | 6 | | | | | | | |
| | *C. jejuni* | 50 | | 4 | | | | | | 5 *E. coli* to COL (pmrB) | |
| 2018 | *E. faecalis* | 97 | MIC | 11 | ResFinder/NCBI Pathogen DB/BLAST | Assembled, CLC-bio | 96.5% | | | | (14) |
| | *E. faecium* | 100 | | | | | | | | | |
| 2018 | *S. aureus* | 501 | DD/MIC | 12 | GeneFinder/ Mykrobe/ Typewriter | FASTQ/assembled, BLAST | 98.3% | | | Disagreements: 0.7% predicted resistant | (15) |
| | | 491 | | | | | | | | | |
| | | 397 | MIC | | | | | | | 0.6% predicted susceptible | |
| 2018 | *M. tuberculosis* | 10,209 | MGIT 960 | 4 | Cortex | Assembled | 89.5% | | | 97.1%/99.0% predicted R/S | (16) |
| | | | | 4 | | | | | | 97.5%/98.8% predicted R/S | |
| | | | | 4 | | | | | | 94.6%/93.6% predicted R/S | |
| | | | | 4 | | | | | | 91.3%/96.8% predicted R/S | |
| 2019 | *H. pylori* | 140 | MIC (E-test) | 5 | ARIBA | FASTQ | 99% | | | Phenotype issues to metronidazole | (17) |

*1) ESBL: Extended Spectrum Beta-Lactamase, 2) MIC: Minimum Inhibitory Concentration, 3) DD: Disk diffusion, 4) VM: Very Major, 5) M: Major, 6) R/S: Resistant/Susceptible, 7) SPEC: Spectinomycin, 8) GEN: Gentamicin, 9) AZI: Azithromycin, 10) CLIN: Clindamycin, 11) TEL: Telithromycin, 12) FQ: Fluoroquinolone, 13) ERY: Erythromycin, 14) COL: colistin.*

SOURCE: Hendriksen et al., 2019a.

## A Phenotypic Database

Phenotypic susceptibility tests are a mainstay of clinical microbiology. They are also valuable in environmental surveillance as they are relatively inexpensive and allow for comparison with other epidemiological data. Some water monitoring programs already rely on phenotypic susceptibility tests (Bard and Lee, 2018; Franklin et al., 2021; McLain et al., 2016). There is a great deal of susceptibility data generated daily at U.S. hospitals, nursing homes, diagnostic laboratories, and environmental monitoring sites on phenotypic resistance that is not captured by the Pathogen Detection Project because no genomic data are collected to which the phenotypic results can be attached. Even if there are genomic data to which susceptibility results can be linked, adding this information creates an extra manual step on the part of the submitter.

Furthermore, as evidenced by the efforts of the Wellcome Trust and the Open Data Institute to establish the AMR Register, there is considerable relevant industry data that is not yet public and therefore not captured in the NCBI databases. The phenotypic information from these sources would be useful for understanding the prevalence, spread, and evolution of resistance. A reasonable approach to incorporating genomic data is to monitor markers of genomic resistance alongside phenotypic susceptibility data when available. Resistance detection assays, as part of multiplexed molecular panels including syndromic panels, have increased the availability of such results that may also inform treatment decisions (Dien Bard and McElvania, 2020).

The committee recognizes the rapid advancements that have been made in genome sequencing. Genomic tools are increasingly used to identify patterns in antimicrobial resistance and predict susceptibility to antimicrobials. Chapter 6 discusses how such tools can be used to inform drug discovery. The wealth of research tools presented in Table 4-1 are all used, individually and together, to better understand the way resistant pathogens move through human and animal hosts and the environment. Rapid sequencing can help detect emerging pathogens passing between humans and animals (GAO, 2021). USDA and the CDC use these tools to track emerging variants of SARS-CoV-2 in humans and animals (APHIS, 2021; GAO, 2021). Similarly, these tools drive forward research on antimicrobial resistance and efforts to counter it.

Excitement over the immense potential of new analytic technologies should not blind us to the value of the vast amounts of information on phenotypic antimicrobial susceptibility currently generated in clinical laboratories and health departments all over the world. There is useful data in ordinary antibiograms that could inform a better understanding of the trends in antimicrobial resistance. Failure to make full use of this data for understanding disease burden and emerging trends is wasteful.

Phenotypic data are useful for surveillance, even in the absence corresponding genotypic information. Furthermore, the amount of phenotypic data generated regularly in clinical laboratories, both from animal and human samples, dwarfs that being produced via whole genome sequencing and metagenomics. Central collection and analysis of phenotypic data would give better insight into the regional and global distribution of resistant pathogens than genomic results from the smaller subset of sequenced isolates. It could also provide a more representative picture of disease burden, as most investigators would only sequence pathogens that seem out of the ordinary.

**Recommendation 4-1: The National Library of Medicine (NLM) should establish an open-source, unified antimicrobial resistance database that integrates raw phenotypic data from national and international efforts. This database should support automatic importation from hospitals, laboratories, and surveillance networks and linking to genotypic data when available. NLM should engage the Centers for Disease Control and Prevention, the U.S. Department of Agriculture, and other relevant stakeholders to determine the necessary data elements and confidentiality procedures.**

An automated data ingestion pipeline would mitigate the additional burden on clinical laboratories imposed by such a database by taking disparate formats of collected antimicrobial resistance data and, either by a simple set of translation rules or potentially using more advanced machine learning techniques, automatically format and deposit the data in a consistent fashion. As commonly used automatic testing machines, including the bioMérieux Vitek and BD Phoenix are already internet connected; once an initial pipeline from the laboratory information system is

established, data deposition from these devices could be almost fully automated with laboratory intervention only in the case of errors. A standard data deposition form could also help new laboratories or regional laboratories that currently do not generate their own standardized antibiograms by providing a default template, contributing to more standardized measurements across the United States and internationally.

*Automating Data Deposition*

The WHONET software could be useful to diagnostic laboratories looking to automate data deposition, the process by which data is consolidated for analysis. WHONET does not require adoption of any specific laboratory information system, which can be costly (WHONET, 2020). For laboratories that already use such information management systems, WHONET has a free data importing tool (BacLink) to capture and standardize existing data (AHRQ, 2014; WHONET, 2021). Given its convenience and ease of use, over 2,300 laboratories (including human and animal clinical laboratories, public health, and food safety laboratories) in 130 countries use WHONET, including for generating antibiograms (AHRQ, 2014; WHONET, 2021). By simply granting a centralized database permission to extract their data from WHONET, lab managers could contribute raw susceptibility data to a centralized database without any additional labor, much as is done for uploading data to GLASS. FAO is currently using WHONET tools for surveillance in food and food-producing animals. Further expansion of WHONET into animal health and environmental monitoring labs could ease automated data collection that the proposed database would draw from. The committee envisions the proposed database would pull phenotypic data from various human, animal, and environmental sources. Private-sector information, such as that the nascent AMR Register is collecting, would further enrich this repository, as would submissions from academic researchers.

*Database Development and Use*

One of NLM's main concerns with expanding antimicrobial resistance data collection will be protecting privacy. For example, hospitals may not want antibiograms identifiable for fear of bad publicity or being labeled as a resistance hotspot. Some care must be taken to make the database anonymized while still useful. The use of WHONET is also relevant to this concern as software automatically removes identifiers from raw data (WHONET, 2020).

NLM has experience in the technical work of database development and familiarity with common stumbling blocks such as insufficient attention to controlling the reporting burden or removing data identifiers. NLM has already given attention to how to collect this type of information in the Pathogen Detection Isolate Browser discussed earlier, providing precedent for some important variables to collect data on (NCBI, 2019). Key variables found in data collection for the Isolate Browser that would also be collected in the proposed phenotypic database include pathogen species, the type of isolate (e.g., clinical or environmental), its source (differentiating, for example, between human and animal isolates, and among them isolates from blood, urine, tissue), and collection date (NCBI, 2019). Other optional, but useful, information would include where the sample was collected and patient diagnostic information if relevant and available.

The Pathogen Detection Isolate Browser also has a field for susceptibility test phenotypes, listing all the medicines tested against the isolate (NCBI, 2019). However, this field is currently limited to the categorical interpretation that the pathogen is resistant, intermediate, or susceptible to a drug (or "other" for pathogen–drug combinations for which breakpoints are not established). In the browser's current capabilities, minimum inhibitory concentrations are

available if an antibiogram is attached to the genomic data (NLM, 2018). The committee notes that the usefulness of this tool and its comparability to other databases would be improved by the inclusion of numerical minimum inhibitory concentrations.

In a unified antimicrobial resistance database, numerical measurements or ranges of minimum inhibitory concentrations would be a crucial data field. Simply knowing that a pathogen is sensitive to a treatment is sufficient to guide therapy, but some susceptible pathogens are much closer to developing resistance than others. At the riskier end of the spectrum are sensitive pathogens that are only a few mutations away from resistance; such pathogens are of concern for public health surveillance. Increasing minimum inhibitory concentrations can provide forewarning of pathogens that may develop resistance (Baquero, 2001). Furthermore, the categorical cutoff points of susceptible, intermediate, and resistant are not fully standardized by pathogen, drug, or region, making comparisons difficult. Access to the minimum inhibitory concentrations would also allow researchers to reinterpret data as susceptibility criteria change (McLain et al., 2016). The proposed database would also be equipped to capture zone diameter measurements for data produced from manual susceptibility tests such as disk diffusion, discussed more in Chapter 6.

More information about minimum inhibitory concentrations could also inform determinations of epidemiological cutoff values (Martinez et al., 2015; McLain et al., 2016). Including phenotypic results from environmental monitoring sites increases the amount of data available to support this determination. As of June 2021, more than 62 percent of the sequenced isolates in the Pathogen Detection Project were from clinical settings (Feldgarden et al., 2021b). Efforts to diversify the sources of information will capture a more accurate, One Health picture of the true burden of resistance (Berendonk et al., 2015; McLain et al., 2016).

Finally, it would be helpful for the proposed database to capture information about genotypic resistance markers if available. Some resistance patterns are commonly monitored in clinical settings, including *mecA*, a gene associated with methicillin-resistant *Staphylococcus aureus* (MRSA) and *van A* and *van B*, conferring vancomycin resistance (CDC, 2019b; Saadat et al., 2014). Tests for extended-spectrum beta-lactamases (ESBL), enzymes that can break down the beta-lactam family of antibacterials, and carbapenemase-producing organisms, which can break down carbapenems, are also sometimes available and would be useful optional data to include. It could also be helpful to know, for clinical specimens, whether the infection was acquired in a hospital or in the community, allowing that this distinction is not always clear.

In the implementation of this recommendation, NLM would work with the CDC and USDA as well as other relevant industry and academic stakeholders to further discuss what data would be essential and what would be optional. This cooperation would also ensure that the database was set up to be most useful to the agencies responsible for surveillance and to set up a system easily mined by researchers from different disciplines. It would also be important to clarify a communication strategy or mix of incentives to encourage people to submit their data. The relevant professional societies for microbiology, including the American Society for Microbiology, the American Society for Clinical Pathology, and the Association for Molecular Pathology would be valuable stakeholders to involve in any discussion of incentives for participation. The societies could help draw attention to the program and support laboratory staff to implement it.

The committee recognizes the value of contributions to surveillance of antimicrobial resistance already undertaken by the CDC; USDA's National Agricultural Research and Monitoring Surveys (NARMS), discussed later in this chapter, give similar insight into resistance

patterns in agriculture. At the same time, there is considerable information generated outside of these networks, much of it having little life beyond the immediate purpose it was generated for. Hospital antibiograms, for example, may inform some mandatory reporting to county or state health authorities but are otherwise not used beyond the hospital.

Over time, the implementation of this recommendation could also allow for greater representation of surveillance data from low- and middle-income countries. Automated susceptibility testing is less common in low- and middle-income countries, partly because of the expense of the equipment and unreliable distribution systems for the consumables needed to operate them (Iskandar et al., 2021; Pascucci et al., 2021). However, most large hospitals in low- and middle-income countries do produce antibiograms (Iskandar et al., 2021; Pascucci et al., 2021; Tiwari et al., 2009). The Clinical Laboratory Standards Institute has guidance on how to standardize antibiograms, making them more accessible in places that rely on manual testing (CLSI, 2014). There is also growing interest in the use of widely accessible technology such as smart phones to generate antibiograms in settings with few resources (Pascucci et al., 2021). Eventually this could mean more phenotypic data to characterize antimicrobial resistance in parts of the world where the problem is worst, and potentially more antibiogram data to contribute to international surveillance efforts.

## MONITORING ANTIMICROBIAL RESISTANCE IN WATER

Increasing the availability of information about environmental isolates collected by surveillance networks and stored in the proposed NLM database would contribute to a more holistic understanding of antimicrobial resistance. However, environmental monitoring of resistance is still new. Most environmental bacteria cannot be cultured, so until the recent advent of genomic tools, they could not be easily assessed for resistance mechanisms (Allen et al., 2010). As the field is still developing, methods for evaluating resistance in environmental isolates are not standardized (Berendonk et al., 2015; Murray et al., 2021; Pruden et al., 2018). As discussed in Chapters 1 and 2, antimicrobial resistance exists naturally in the environment. It is difficult to distinguish background levels of resistance from that caused by humans (Rothrock et al., 2016). The geographic scale of the area to be monitored adds to the challenge, as do the numerous targets for surveillance of antimicrobial resistance (e.g., pathogens, resistance genes, antimicrobials and residues, mobile genetic elements).

Furthermore, the number of antimicrobial resistance genes isolated from human and animal pathogens is much greater than what has been described in environmental bacteria (Berendonk et al., 2015). Some of the metagenomic data from environmental samples are thought to be resistance genes in the sample, but this characterization is often based on genetic similarity to resistance genes described in clinical samples, not on a functional demonstration (Berendonk et al., 2015). The Comprehensive Antibiotic Resistance Database is unique in that it only includes genes that have been characterized clinically or experimentally (Alcock et al., 2020). In other public databases, the description of resistance genes is more frequently putative (Berendonk et al., 2015).

The evolution of resistance in the environment and its transmission to humans is a serious concern, and the first step to improve understanding of that risk is monitoring resistant pathogens, resistances genes, and related genetic elements in the environment (Manaia, 2017). The mechanisms through which resistance moves from the environment to humans and other animals are not clear, and it is difficult to demonstrate if and how resistance traits in the

environment influence clinical presentation in humans or other animals (Vaz-Moreira et al., 2014). Determinants of resistance in soil, surface water, and groundwater are thought to contribute to a reservoir of antimicrobial resistance in the environment (Dantas et al., 2008). Though the concentration of antimicrobials in water is generally low, it may still be enough to encourage the emergence of resistance (Murray et al., 2021). The challenge for environmental monitoring is to determine what factors amplify resistance genes in the environment and what factors encourage their transmission.

Monitoring sewage can provide access to samples from a large and diverse population, reflecting exposure to pathogens, resistant organisms, resistance genes, antimicrobials and residues, and heavy metals. Unlike surveillance methods that rely on clinical laboratory data, surveillance of wastewater gives insight into a largely healthy population and can capture a wider range of relevant bacteria and resistance traits; sewage can sample, in essence, an entire city at one time (Aarestrup and Woolhouse, 2020; Brinch and Aarestrup, 2020). For this reason, the Global Sewage Surveillance project has been monitoring markers of antimicrobial resistance in sewage in 60 countries since 2016 (Aarestrup and Woolhouse, 2020; Brinch and Aarestrup, 2020; Hendriksen et al., 2019b). This project's metagenomic analysis of sewage allows insight into the composition of the resistome, all the resistance genes in a bacterial community, including those of clinical interest as well as those in nonpathogenic bacteria that are not as well-studied (Hendriksen et al., 2019b; Wright, 2010). This research has established geographic clustering of resistance patterns (Hendriksen et al., 2019b). In low- and middle-income countries metagenomic analysis of sewage samples has shown the relative abundance of resistance genes expressed are broadly consistent with patterns of antimicrobial use (i.e., genes that convey resistance to macrolide antibacterials are more abundant in places where macrolides are more commonly used) (Hendriksen et al., 2019b).

Box 4-3 describes how the COVID-19 pandemic has brought a renewed attention to monitoring wastewater for infectious disease surveillance. It is possible that the pandemic will hasten use of wastewater for infectious disease monitoring more broadly. Monitoring sewage discharged from hospitals, for example, could give insight into the burden of both antimicrobial residues and pathogens in a point of likely antimicrobial pollution. Hospital sewage has been implicated in the dissemination of resistance, though the extent to which this risk is diluted at wastewater treatment is not clear (Buelow et al., 2020). Research on how the indicators of antimicrobial pollution move through the water supply, from hospital or factory effluent through wastewater treatment, through the environment and into the community would be invaluable for both characterizing this risk and identifying points where additional monitoring would be valuable. The comparison of resistance indicators at different points in the wastewater supply could identify resistance trends as they emerge including during the treatment process. Research on indicators of resistance in water and the effect of sewage and wastewater treatment and their downstream activity could also inform mitigating actions in water policy.

**BOX 4-3**
**Wastewater Surveillance and COVID-19**

Wastewater surveillance to detect pathogens or substances of public health importance is not new, but the COVID-19 pandemic has created a significant increase in interest and investment in this public health strategy. Several countries, communities, and college campuses have implemented wastewater testing as a means to detect presence of SARS-CoV-2 RNA to allow early interventions to contain its spread. Wastewater epidemiology experts and the companies that work in this field have quickly adapted their methods to detect SARS-CoV-2 RNA in sewage.

Wastewater monitoring is a surveillance approach that can be adapted to different scales, from a single hospital or dormitory to an entire county or state. It is also largely anonymous, minimizing concerns with privacy or confidentiality. But since wastewater surveillance is a relatively new approach, there is still considerable variability in the way samples are collected, processed, and analyzed.

In response to the demands for wastewater epidemiology brought on by COVID-19, the CDC has introduced the National Wastewater Surveillance System to monitor the spread of SARS-CoV-2 across the United States. This system will monitor wastewater in state, tribal, local, and territorial health departments. The program has already made considerable progress in setting out standard methods to prepare, store, and transport sewage samples, standardized procedures for extracting and measuring RNA, as well as laboratory controls on the process.

The system for wastewater monitoring could be adapted to monitor resistant pathogens and resistance genes. Wastewater monitoring is already used to track infectious diseases such as polio, cholera, and seasonal influenza in some countries. The WHO Collaborating Center Risk Assessment of Pathogens in Food and Water is currently producing a guidance document on a harmonized global strategy for monitoring COVID-19, polio, and antimicrobial resistance in wastewater. Such efforts could be useful in the longer term to characterize the relationship between COVID-19 and resistance and to track and map resistance genes and other pathogens.

SOURCES: Ardal et al., 2021; Berendonk et al., 2015; CDC, 2021b; Harris-Lovett et al., 2021; Keshaviah et al., 2021; Kreier, 2021; Murray et al., 2021; Norman, 2020.

Additional research could clarify how or where to monitor antimicrobial residues to inform environmental surveillance (Polianciuc et al., 2020). As Figure 4-8 shows, antimicrobial medicines and resistant pathogens can both enter the water supply through many paths. Industrial effluent, including factory effluent from pharmaceutical plants, is one avenue, as are agricultural runoff and human sewage (Fouz et al., 2020; Murray et al., 2021). Concentrations of antimicrobials in industrial waste are generally highest, about a thousand times higher than in wastewater, and a million times higher than in surface water (Murray et al., 2021). The concentrations that select for resistant bacteria in water are difficult to establish, partly because the aquatic microbial community is so complex, with many antimicrobials and resistance genes mixing, as well larger forces—such as competition for nutrients—at work (Bengtsson-Palme and Larsson, 2016). Recent research efforts to predict antimicrobial concentrations at which the environmental resistomes would be unaffected are a valuable starting point for ecological testing and environmental risk assessment (Bengtsson-Palme and Larsson, 2016).

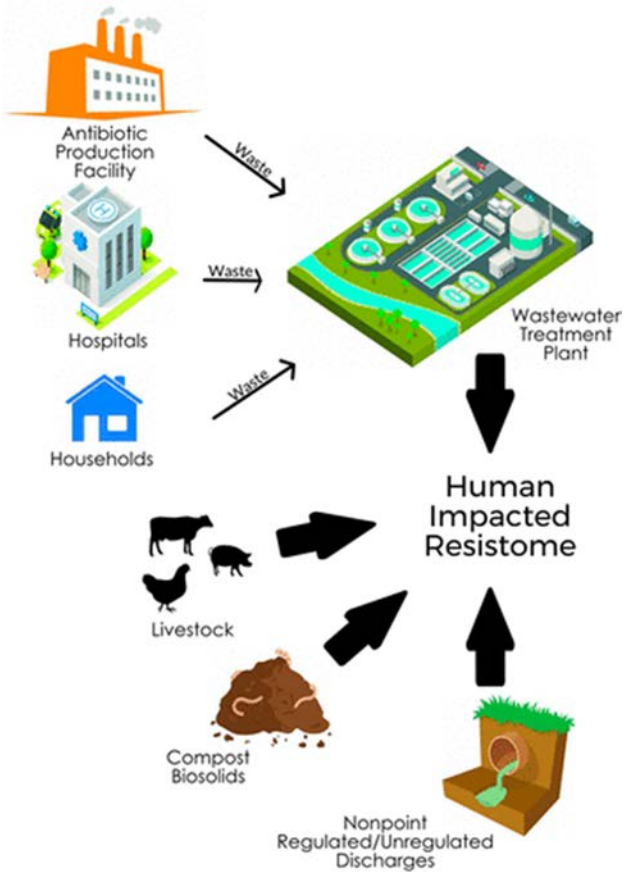



**FIGURE 4-8** Key environmental matrices and flows relevant to the dissemination of antimicrobial resistance in the environment.
NOTES: Small arrows reflect waste flows from environmental reservoirs to a wastewater treatment plant. Large arrows reflect direct effects of different reservoirs on the human-affected resistome.
SOURCE: Vikesland et al., 2017.

Environmental risk assessment is required in the United States and Europe when medicines are predicted to be found in a concentration in water above a certain threshold, but most environmental toxicological testing does not target bacteria and the current thresholds might not protect against the emergence of antimicrobial resistance (Murray et al., 2021). What is more, this concentration is difficult to predict (Bengtsson-Palme and Larsson, 2016). Some evidence suggests that the minimum concentration at which an antimicrobial can select for resistance in microbial communities in water can be up to 200 times lower than the clinically meaningful minimum inhibitory concentrations (Murray et al., 2021). It is difficult to predict minimum selective concentrations because of a dynamic effect any one antimicrobial residue can have on a microbial community, and the interplay different medicines residues would have with each other and with other stressors in the environment (Pruden et al., 2018).

Lack of consensus over what indicators of resistance to monitor in the environment holds back the ability of policy makers to monitor it. Some researchers have suggested the need for a composite antimicrobial contamination measure that could help identify environmental hotspots—nutrient-rich environments with high concentrations of bacteria (Pruden et al., 2018; Vikesland et al., 2017). Such an indicator could help distinguish the pathogenic resistance driven by humans from background levels resistance that may not be a meaningful threat to health. One

standard that could be used to narrow resistance genes of possible threat to human health is the likelihood that a resistance gene could be acquired and expressed in human pathogens (Martinez et al., 2015). Genes that are known to confer resistance in bacteria and are found in mobile genetic elements are of particular concern, especially if they are found in environments closely associated with people (Martinez et al., 2015). Berendonk and colleagues proposed 16 genetic determinants to use as possible indicators based on these criteria;[3] other genes have been added more recently. The authors also suggested six bacterial groups as priorities for water monitoring efforts because of their likelihood to carry resistance genes or acquire them from environmental sources,[4] their usefulness as indicators of water quality, and their frequency in both animal gut and environmental samples (Berendonk et al., 2015).

## U.S. Government Work to Monitor Antimicrobial Resistance in Water

The 2021–2025 strategic plan for the National Antimicrobial Resistance Monitoring System includes a pilot project to monitor surface water for evidence of antimicrobial resistance (Garland, 2020). The project will also set out a standardized system for sampling and analysis of evidence of resistance in surface water (Garland, 2020). The program's choice of surface water to monitor stems from the constant human exposure to surface water both directly through drinking, swimming, or other recreational use, and indirectly as with exposure of food crops to irrigation water (Franklin et al., 2021). Surface water is also an attractive candidate for monitoring because it is a natural endpoint and mixing site for treated wastewater, agricultural runoff, and other nonpoint water sources.

The Environmental Protection Agency (EPA) is in the process of analyzing samples collected from national surveys for the presence of six resistance genes and the mobile genetic element marker *intI1* (most of them among the Berendonk and colleagues' proposed indicators) and fecal indicators (Berendonk et al., 2015; Garland et al., 2018). Preliminary analyses indicate high concentrations of *intlI1* with apparent hotspots in the Northeast and northern Midwest, *sul1* with hotspots in the Northeast and central states, and *tetW* with hotspots mostly across the northern central states (Garland et al., 2018). Continued monitoring will give better insight into where and how the selected resistance indicators emerge and change over time.

The CDC also has pilot programs looking at resistant bacteria in surface water. *E. coli* is a commonly monitored indicator of water quality, and those *E. coli* that produce ESBL are a serious threat to human health (FDA, 2021). After a year of monitoring, CDC researchers found that about 70 percent of samples contained detectable ESBL-producing *E.coli,* with 84 percent of isolates resistant to two or more classes of antimicrobials (FDA, 2021).

---

[3] *intI1* (integrase gene of class 1 integrons, a genetic platform for resistance gene capture), *sul1* and *sul2* (sulfonamide-resistant dihydropteroate synthase), *bla*CTX-M and *bla*TEM (beta-lactamases, frequently identified in *Enterobacteriaceae*), *bla*NDM-1 (New Delhi metallo-beta-lactamase), *bla*VIM (carbapenemase, frequent in clinical *Pseudomonas aeruginosa* in certain areas), *bla*KPC (*Klebsiella pneumoniae* carbapenemase), *qnrS* (quinolone pentapeptide repeat family), *aac*-(6´)-*Ib-cr* (aminoglycoside acetyltransferase), *vanA* (vancomycin resistance operon gene), *mecA* (penicillin binding protein), *ermB* and *ermF* (rRNA adenine N-6-methyltransferase, associated with macrolide resistance), *tetM* (ribosomal protection protein, associated with tetracycline resistance), and *aph* (aminoglycoside phosphotransferase).

[4] *Escherichia coli*, *Klebsiella pneumonia*, *Aeromonas* spp., *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and *Enterococcus faecium.*

*Monitoring Point Source Discharge*

While useful, surface water monitoring does not give insight into the source of the resistance genes, resistant pathogens, or medicines residues in the environment. Such insight could come from analyzing the places contaminants enter water, broadly classified as either point sources, which are single, identifiable entry points such as pharmaceutical factories or sewage treatment, and nonpoint sources, meaning coming from many sources diffusing through seepage or natural water cycling (EPA, 2021c; NOAA, 2021). The Clean Water Act requires monitoring at point sources, but discharge from nonpoint sources, including farms and feedlots, is not regulated (EPA, 2020b).

Given the uncertainty in measuring meaningful resistance traits in the environment, the way resistance-encoding genes move through the environment, and the sheer geographical scale involved, efforts to monitor resistance in the environment will likely have to start with a relatively narrow scope. Point source discharge is a good starting point given EPA's statutory mandate to monitor them and their known association with resistance indicators (Fouz et al., 2020).

Wastewater treatment plants are a good entry point to monitor for resistance genes, resistant bacteria, and antimicrobial residues. This is primarily because wastewater treatment is equipped to contain and remove water contaminants, but not to remove resistance genes or drug residues (Berendonk et al., 2015). Treatment plants typically discharge directly to aquatic environments, making them an important bridge between human-made contamination and the natural environment (Berendonk et al., 2015). Multiple studies have reported elevated levels of antimicrobial resistance downstream of wastewater discharges (Ashbolt et al., 2019; Zhang et al., 2009). Wastewater discharges also include waste streams from hospitals, which are of particular concern because of the antimicrobials residues and resistant pathogens found there. Research in Europe has shown indicators of antimicrobial resistance in wastewater largely parallel the relative burden of clinical resistance (Parnanen et al., 2019). Whether hospital effluent contributes disproportionately to the presence of antimicrobial resistance genes in wastewater treatment plants is as yet an unresolved scientific question, however (Buelow et al., 2018; Kraupner et al., 2021; Muller et al., 2018).

The monitoring of risk factors for resistance in manure would be particularly challenging. Given the broad variability when the manure is applied to fields and its runoff enters water, land application is typically classified as a nonpoint source. While certain kinds of animal agriculture such as contained animal feeding operations are regulated as point sources, monitoring waste collection facilities would likely be met with understandable pushback from farmers (EPA, 2020a). In most of the country there are too few farms even at the county level to make anonymization possible. Monitoring wastewater has the advantage of anonymity, and there is ample tie-in to resistance risk in agriculture as biosolids from treatment plants can be used to fertilize farm lands, bringing the readily exchangeable genetic information from resistant pathogens into contact with terrestrial organisms (Buta et al., 2021; EPA, 2021b; Mackie et al., 2006).

EPA had begun a project to validate hospital discharge as a high-strength source of antimicrobial resistance, looking specifically at ESBL *E. coli* and vancomycin-resistant *Enterococcus* spp. isolates and resistance genes, but this work was suspended because of the COVID-19 pandemic (Garland, 2020). The agency is now working with the CDC and the Department of Health and Human Services on surveillance for SARS-CoV-2 in wastewater, with

plans to expand this system to look for resistant pathogens in the future (Anthes, 2021). Thus, as Box 4-3 described, the foundation on which to build surveillance is already in place.

**Recommendation 4-2: The Environmental Protection Agency should provide guidance and funding to states for testing point source discharge at wastewater treatment plants for antimicrobial resistance traits and integrating these data with other surveillance networks.**

Monitoring wastewater discharge will provide a broader dataset to relate local environmental and clinical patterns of resistance. This includes relating indicators of antimicrobial resistance in waste to clinical resistance profiles and relating waste discharge to downstream resistance detected through other monitoring networks, such as EPA's monitoring of streams and rivers. This monitoring will contribute to better linking of resistance indicators in waste to those found downstream in surface waters. Information from the proposed surveillance would, if included in the NCBI Pathogen Detection Database and the proposed NLM database described in Recommendation 4-1, contribute to a more complete mapping of the geographic distribution of resistance genes.

A recent EPA publication concluded that no one of the vast array of molecular methods available can fully characterize the burden of antimicrobial resistance in surface water (Franklin et al., 2021). A combination of genotypic and phenotypic tools will be needed in surveillance, at least until there is better consensus on what indicators best measure risk to human or animal health (Franklin et al., 2021). Bacterial culture may be best suited to link surface water resistance to animal or human infections, while molecular-genotypic approaches provide better insight into the movement of resistance genes and the transfer of resistance genes or traits to other bacteria (Franklin et al., 2021).

As a starting point, testing could focus on the subset of resistance genes and mobile genetic elements currently monitored in EPA surface water programs (Garland et al., 2018). Similar monitoring in Europe provided a useful baseline for understanding the relative abundance of key resistance genes in wastewater treatment and downstream (Cacace et al., 2019). It also allowed for identification of the resistance gene best suited to tracking as a proxy for resistance in the environment ($bla_{OXA58}$) and shed light on wastewater treatment practices that can reduce the burden of resistance genes in the water supply (Cacace et al., 2019).[5] It may take time to identify the analytic techniques best suited to identify the resistance genes or genetic elements in water that pose the most serious risk to human or animal health. In the short term, a combination of culture-based methods paired with genome sequencing and metagenomic analysis may be necessary (Franklin et al., 2021).

Some evidence indicates that the amounts of resistant pathogens or genes discharged through wastewater treatment is directly related to the composition of the effluent discharged into the environment (Ju et al., 2019). Characterizing the relative abundance of resistance traits at this point source would be a valuable first step to understanding the extent to which water can amplify and convey antimicrobial resistance in the environment. The proposed surveillance of point source discharge would also make a solid foundation upon which EPA could build future water monitoring efforts. As better clarity about the monitoring of antimicrobial residues and

[5] A gene associated with carbapenem-resistance in *Acinetobacter* spp, $bla_{OXA58}$, was isolated in clinical *Proteus mirablis* in 2017 (Girlich et al., 2017).

concentrations in water emerge from research, this system could be expanded to monitor other resistance indicators in other water sources.

*Understanding Water as a Conduit of Resistance*

Monitoring waste streams and advancing analytical methods will help characterize the role of water as a conduit of antimicrobial resistance. This characterization may inform selection of water quality indicators. EPA provides state and local governments with water quality criteria for aquatic life, recreational and drinking water (EPA, 2020c). These include measures of fecal contamination as indicated by *E. coli* and *Enterococcus* species (EPA, 2015). Recreational water sites are regularly monitored during high-use seasons to ensure the criteria are met. EPA could eventually develop similar water quality criteria with threshold limits for antimicrobial resistance risk. There is evidence that ingesting resistant *E. coli* while surfing or swimming leads to colonization with the resistant pathogen (Leonard et al., 2018). The information gleaned from water surveillance could eventually feed in to the longer-term goal of monitoring recreational water for resistant pathogens or other indicators of resistance that pose risk to human health (Huijbers et al., 2019).

In the same way, it is possible that with sufficient evidence of health risk, EPA may eventually identify certain pathogens, medicines or residues, or resistance genes that qualify as pollutants that would need to be removed above a certain threshold. Removing antimicrobials at wastewater treatment plants is possible, though the efficiency of the process depends on both the physical and chemical properties of the medicine and the operating conditions at the treatment plant (Michael et al., 2013). Some evidence suggests that macrolide antimicrobials are difficult to remove from wastewater, though this may depend on the treatment methods used (Barbosa et al., 2021; Pan and Yau, 2021). There is evidence that current action at these plants can reduce the abundance of some resistance genes, though genes associated with resistance to vancomycin are notably unaffected (Parnanen et al., 2019). Older research indicated that resistance genes survive tertiary treatment and contribute to the burden of resistance genes in the environment (LaPara et al., 2011).

Lessons learned from mitigating resistance at point source discharge could then be applied to other discharge sites. Discharge from nonpoint sources would be monitored and mitigation strategies implemented through Section 319 of the Clean Water Act, which provides federal funding for state, tribal, and territorial authorities in their work to manage water quality at nonpoint sources (EPA, 2021a). Understanding the environmental fate and transport of antimicrobials and their metabolites, resistant organisms, and resistance genes, as well as their decay patterns, will be a precursor to any nonpoint source action against antimicrobial resistance. In particular, understanding environmental transport mechanisms will inform more efficient design of environmental monitoring systems.

## REFERENCES

Aarestrup, F. M., and M. E. J. Woolhouse. 2020. Using sewage for surveillance of antimicrobial resistance. *Science* 367(6478):630-632.

Africa CDC (Centres for Disease Control and Prevention). 2020. US$100 million africa pathogen genomics initiative to boost disease surveillance and emergency response capacity in africa, edited by A. CDC. ADDIS ABABA, ETHIOPIA: Africa CDC.

AHRQ (Agency for Healthcare Research and Quality). 2014. Concise antibiogram toolkit using whonet to create your antibiogram, edited by AHRQ.

Alcock, B. P., A. R. Raphenya, T. T. Y. Lau, K. K. Tsang, M. Bouchard, A. Edalatmand, W. Huynh, A. V. Nguyen, A. A. Cheng, S. Liu, S. Y. Min, A. Miroshnichenko, H. K. Tran, R. E. Werfalli, J. A. Nasir, M. Oloni, D. J. Speicher, A. Florescu, B. Singh, M. Faltyn, A. Hernandez-Koutoucheva, A. N. Sharma, E. Bordeleau, A. C. Pawlowski, H. L. Zubyk, D. Dooley, E. Griffiths, F. Maguire, G. L. Winsor, R. G. Beiko, F. S. L. Brinkman, W. W. L. Hsaio, G. V. Domselaar, and A. G. McArthur. 2020. Card 2020: Antibiotic resistome surveillance with the comprehensive antibiotic resistance database. *Nucleic Acids Research* 48(D1):D517-D525.

Allen, H. K., J. Donato, H. H. Wang, K. A. Cloud-Hansen, J. Davies, and J. Handelsman. 2010. Call of the wild: Antibiotic resistance genes in natural environments. *Nature Reviews: Microbiology* 8(4):251-259.

AMR Industry Alliance. 2017a. *Merck & Co., Inc. – study for monitoring antimicrobial resistance trends (SMART)*. https://www.amrindustryalliance.org/case-study/study-for-monitoring-antimicrobial-resistance-trends-smart/ (accessed July 30, 2021).

AMR Industry Alliance. 2017b. *GSK – survey of antibiotic resistance (SOAR)*. https://www.amrindustryalliance.org/case-study/gsks-survey-of-antibiotic-resistance-soar/ (accessed July 30, 2021).

AMR Research Initiative. 2021. *Project overview*. https://amr.theodi.org/project-overview (accessed July 30, 2021).

AMR Research Initiative. 2021. *About*. https://amr.theodi.org/ (accessed July 27, 2021).

Anthes, E. 2021. From the wastewater drain, solid pandemic data. *New York Times*, May 7 2021.

APHIS (Animal and Plant Health Inspection Service). 2021. *APHIS' american rescue plan (ARP) surveillance program: Strategic framework* https://www.aphis.usda.gov/publications/aphis_general/arp-strategic-framework.pdf (accessed September 17, 2021).

Ardal, C., D. McAdams, A. L. Wester, and S. Mogedal. 2021. Adapting environmental surveillance for polio to the need to track antimicrobial resistance. *Bulletin of the World Health Organization* 99(3):239-240.

Argimon, S., M. A. L. Masim, J. M. Gayeta, M. L. Lagrada, P. K. V. Macaranas, V. Cohen, M. T. Limas, H. O. Espiritu, J. C. Palarca, J. Chilam, M. C. Jamoralin, Jr., A. S. Villamin, J. B. Borlasa, A. M. Olorosa, L. F. T. Hernandez, K. D. Boehme, B. Jeffrey, K. Abudahab, C. M. Hufano, S. B. Sia, J. Stelling, M. T. G. Holden, D. M. Aanensen, and C. C. Carlos. 2020. Integrating whole-genome sequencing within the national antimicrobial resistance surveillance program in the philippines. *Nature Communications* 11(1):2719.

Ashbolt, N., A. Pruden, J. Miller, M. V. Riquelme, A. Maile-Moskowitz, A. Pruden, N. Ashbolt, and J. Miller. 2019. Antimicrobal resistance: Fecal sanitation strategies for combatting a global public health threat. In *Water and sanitation for the 21st century: Health and microbiological aspects of excreta and wastewater management (global water pathogen project)*, edited by J. B. Rose and B. Jiménez-Cisneros.

Ashley, E. A., J. Recht, A. Chua, D. Dance, M. Dhorda, N. V. Thomas, N. Ranganathan, P. Turner, P. J. Guerin, N. J. White, and N. P. Day. 2018. An inventory of supranational antimicrobial resistance

surveillance networks involving low- and middle-income countries since 2000. *Journal of Antimicrobial Chemotherapy* 73(7):1737-1749.

Baquero, F. 2001. Low-level antibacterial resistance: A gateway to clinical resistance. *Drug Resistance Updates* 4(2):93-105.

Barbosa, V., M. Morais, A. Silva, C. Delerue-Matos, S. A. Figueiredo, and V. F. Domingues. 2021. Comparison of antibiotic resistance in the influent and effluent of two wastewater treatment plants. *AIMS Environmental Science* 8(2):101-116.

Bard, J. D., and F. Lee. 2018. Why can't we just use PCR? The role of genotypic versus phenotypic testing for antimicrobial resistance testing. *Clinical Microbiology Newsletter* 40(11):87-95.

Bengtsson-Palme, J., and D. G. Larsson. 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International* 86:140-149.

Berendonk, T. U., C. M. Manaia, C. Merlin, D. Fatta-Kassinos, E. Cytryn, F. Walsh, H. Burgmann, H. Sorum, M. Norstrom, M. N. Pons, N. Kreuzinger, P. Huovinen, S. Stefani, T. Schwartz, V. Kisand, F. Baquero, and J. L. Martinez. 2015. Tackling antibiotic resistance: The environmental framework. *Nature Reviews: Microbiology* 13(5):310-317.

Biomerieux. 2020. *Global point prevalence survey*. https://amr.biomerieux.com/en/our-commitment/global-point-prevalence-survey/ (accessed July 27, 2021).

Bortolaia, V., R. S. Kaas, E. Ruppe, M. C. Roberts, S. Schwarz, V. Cattoir, A. Philippon, R. L. Allesoe, A. R. Rebelo, A. F. Florensa, L. Fagelhauer, T. Chakraborty, B. Neumann, G. Werner, J. K. Bender, K. Stingl, M. Nguyen, J. Coppens, B. B. Xavier, S. Malhotra-Kumar, H. Westh, M. Pinholt, M. F. Anjum, N. A. Duggett, I. Kempf, S. Nykasenoja, S. Olkkola, K. Wieczorek, A. Amaro, L. Clemente, J. Mossong, S. Losch, C. Ragimbeau, O. Lund, and F. M. Aarestrup. 2020. Resfinder 4.0 for predictions of phenotypes from genotypes. *Journal of Antimicrobial Chemotherapy* 75(12):3491-3500.

Brinch, C., and F. M. Aarestrup. 2020. *Global sewage situation report.* The Global Sewage Surveillance Project Consortium.

Buelow, E., J. R. Bayjanov, E. Majoor, R. J. Willems, M. J. Bonten, H. Schmitt, and W. van Schaik. 2018. Limited influence of hospital wastewater on the microbiome and resistome of wastewater in a community sewerage system. *FEMS Microbiology Ecology* 94(7).

Buelow, E., A. Rico, M. Gaschet, J. Lourenco, S. P. Kennedy, L. Wiest, M. C. Ploy, and C. Dagot. 2020. Hospital discharges in urban sanitation systems: Long-term monitoring of wastewater resistome and microbiota in relationship to their eco-exposome. *Water Research X* 7:100045.

Buta, M., J. Hubeny, W. Zielinski, M. Harnisz, and E. Korzeniewska. 2021. Sewage sludge in agriculture - the effects of selected chemical pollutants and emerging genetic resistance determinants on the quality of soil and crops - a review. *Ecotoxicology Environmental Safety* 214:112070.

Cacace, D., D. Fatta-Kassinos, C. M. Manaia, E. Cytryn, N. Kreuzinger, L. Rizzo, P. Karaolia, T. Schwartz, J. Alexander, C. Merlin, H. Garelick, H. Schmitt, D. de Vries, C. U. Schwermer, S. Meric, C. B. Ozkal, M. N. Pons, D. Kneis, and T. U. Berendonk. 2019. Antibiotic resistance genes in treated wastewater and in the receiving water bodies: A pan-european survey of urban settings. *Water Research* 162:320-330.

Cappuccino, J. G., and N. Sherman. 2014. *Microbiology: A laboratory manual* 10 ed: Pearson Education.

CDC (Centers for Disease Control and Prevention). 2019a. *Core elements of hospital antibiotic stewardship programs.* Atlanta, GA.

CDC. 2019b. *Laboratory testing*. https://www.cdc.gov/mrsa/lab/index.html#anchor_1548442775 (accessed July 30, 2021).

CDC. 2021a. *Gonococcal isolate surveillance project (GISP)* (accessed September 17, 2021).

CDC. 2021b. *Waterborne disease & outbreak surveillance reporting - wastewater surveillance*. https://www.cdc.gov/healthywater/surveillance/wastewater-surveillance/wastewater-surveillance.html (accessed June 30, 2021).

CDDEP (Center for Disease Dynamics, Economics & Policy). 2021. *Resistancemap: Antibiotic resistance*. https://resistancemap.cddep.org/AntibioticResistance.php (accessed September 14, 2021).

Chandrasekera, R. M., E. P. Lesho, U. Chukwuma, J. F. Cummings, and P. E. Waterman. 2015. The state of antimicrobial resistance surveillance in the military health system: A review of improvements made in the last 10 years and remaining surveillance gaps. *Military Medicine* 180(2):145-150.

CLSI (Clinical and Laboratory Standards Institute). 2014. Analysis and presentation of cumulative antimicrobial susceptibility test data; approved guideline—fourth edition: Clinical and Laboratory Standards Institute.

Cusack, T. P., E. A. Ashley, C. L. Ling, S. Rattanavong, T. Roberts, P. Turner, T. Wangrangsimakul, and D. A. B. Dance. 2019. Impact of clsi and eucast breakpoint discrepancies on reporting of antimicrobial susceptibility and amr surveillance. *Clinical Microbiology and Infection* 25(7):910-911.

Dantas, G., M. O. Sommer, R. D. Oluwasegun, and G. M. Church. 2008. Bacteria subsisting on antibiotics. *Science* 320(5872):100-103.

Davis, G. S., K. Waits, L. Nordstrom, B. Weaver, M. Aziz, L. Gauld, H. Grande, R. Bigler, J. Horwinski, S. Porter, M. Stegger, J. R. Johnson, C. M. Liu, and L. B. Price. 2015. Intermingled klebsiella pneumoniae populations between retail meats and human urinary tract infections. *Clinical Infectious Diseases* 61(6):892-899.

Diallo, O. O., S. A. Baron, C. Abat, P. Colson, H. Chaudet, and J. M. Rolain. 2020. Antibiotic resistance surveillance systems: A review. *Journal of Global Antimicrobial Resistance* 23:430-438.

Dien Bard, J., and E. McElvania. 2020. Panels and syndromic testing in clinical microbiology. *Clinics in Laboratory Medicine* 40(4):393-420.

Dunne, W. M., Jr., M. Jaillard, O. Rochas, and A. Van Belkum. 2017. Microbial genomics and antimicrobial susceptibility testing. *Expert Review of Molecular Diagnostics* 17(3):257-269.

Enne, V. I., A. P. Johnson, and J. D. Perry. 2016. Preface. *Journal of Antimicrobial Chemotherapy* 71 Suppl 1(suppl_1):i1.

EPA (U.S. Environmental Protection Agency). 2015. *Recreational water quality criteria.* EPA.

EPA. 2020a. *Animal feeding operations (AFOS)*. https://www.epa.gov/npdes/animal-feeding-operations-afos (accessed July 30, 2021).

EPA. 2020b. *Summary of the clean water act*. https://www.epa.gov/laws-regulations/summary-clean-water-act; (accessed July 20, 2021).

EPA. 2020c. *Water quality criteria*. https://www.epa.gov/wqc (accessed July 30, 2021).

EPA. 2021a. *319 grant: Current guidance*. https://www.epa.gov/nps/319-grant-current-guidance (accessed October 11, 2021).

EPA. 2021b. *Basic information about biosolids*. https://www.epa.gov/biosolids/basic-information-about-biosolids (accessed July 30, 2021).

EPA. 2021c. *Basic information about nonpoint source (NPS) pollution*. https://www.epa.gov/nps/basic-information-about-nonpoint-source-nps-pollution (accessed July 30, 2021).

FAO (Food and Agriculture Organization of the United Nations). 2019a. Monitoring and surveillance of antimicrobial resistance in bacteria from healthy food animals intended for consumption. In *Regional Antimicrobial Resistance Monitoring and Surveillance Guidelines*. Bangkok, Thailand: FAO.

FAO. 2019b. Monitoring and surveillance of antimicrobial resistance in bacteria from healthy food animals intended for consumption. In *Regional Antimicrobial Resistance Monitoring and Surveillance Guidelines – Volume 1*. Bangkok.

FAO. 2021a. Evaluation of fao's role and work on antimicrobial resistance (AMR). In *Thematic Evaluation Series*. Rome.

FAO. 2021b. *Fao action plan on antimicrobial resistance 2021-2025* FAO.

FAO. 2021c. *FAO and WHO activities to support monitoring and surveillance of antimicrobial resistance in the food and agriculture sectors*. http://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/en/c/1381093 (accessed July 30, 2021).

FAO, OIE (World Organisation for Animal Health), and WHO (World Health Organization). 2020. *Annual progress report 2020- antimicrobial resistance multi-partner trust fund.* Geneva: WHO.

FAO and UN (United Nations). 2021. *Antimicrobial resistance*. http://www.fao.org/antimicrobial-resistance/en/ (accessed September 22, 2021).

FAO and WHO. 2019. Joint FAO/WHO food standards programme - ad hoc codex intergovernmental task force on antimicrobial resistance.

FAO and WHO. 2021. *Request for comments on the guidelines on integrated monitoring and surveillance of foodborne antimicrobial resistance (at step 3).*

FDA (U.S. Food and Drug Administration). 2021. 2020 virtual public meeting of the national antimicrobial resistance monitoring system.

Feldgarden, M., V. Brover, N. Gonzalez-Escalona, J. G. Frye, J. Haendiges, D. H. Haft, M. Hoffmann, J. B. Pettengill, A. B. Prasad, G. E. Tillman, G. H. Tyson, and W. Klimke. 2021a. Amrfinderplus and the reference gene catalog facilitate examination of the genomic links among antimicrobial resistance, stress response, and virulence. *Scientific Reports* 11(1):12728.

Feldgarden, M., V. B., B. Fedorov, D. H. Haft, A. B. Prasad, W. Klimke. 2021b. NCBI's pathogen detection system and microbigg-e enable evolutionary analysis of aac(6')-ib family aminoglycoside modifying enzymes: World Microbe Forum.

Fouz, N., K. N. A. Pangesti, M. Yasir, A. L. Al-Malki, E. I. Azhar, G. A. Hill-Cawthorne, and M. Abd El Ghany. 2020. The contribution of wastewater to the transmission of antimicrobial resistance in the environment: Implications of mass gathering settings. *Tropical Medicine and Infectious Disease* 5(1).

Franklin, A. M., N. E. Brinkman, M. A. Jahne, and S. P. Keely. 2021. Twenty-first century molecular methods for analyzing antimicrobial resistance in surface waters to support one health assessments. *Journal of Microbiological Methods* 184:106174.

Franzosa, E. A., X. C. Morgan, N. Segata, L. Waldron, J. Reyes, A. M. Earl, G. Giannoukos, M. R. Boylan, D. Ciulla, D. Gevers, J. Izard, W. S. Garrett, A. T. Chan, and C. Huttenhower. 2014. Relating the metatranscriptome and metagenome of the human gut. *Proceedings of the National Academy of Sciences of the United States of America* 111(22):E2329-2338.

Fridkin, S. K., A. A. Cleveland, I. See, and R. Lynfield. 2015. Emerging infections program as surveillance for antimicrobial drug resistance. *Emerging Infectious Diseases* 21(9):1578-1581.

Fuhrmeister, A. S., and R. N. Jones. 2019. The importance of antimicrobial resistance monitoring worldwide and the origins of sentry antimicrobial surveillance program. *Open Forum Infectious Diseases* 6(Suppl 1):S1-S4.

Galhano, B. S. P., R. G. Ferrari, P. Panzenhagen, A. C. S. de Jesus, and C. A. Conte-Junior. 2021. Antimicrobial resistance gene detection methods for bacteria in animal-based foods: A brief review of highlights and advantages. *Microorganisms* 9(5):923.

GAO (U.S. Government Accountability Office). 2020. Antibiotic resistance: Additional federal actions needed to better determine magnitude and reduce impact. Washington, DC: U.S. Government Accountability Office.

GAO. 2021. *Science & tech spotlight: Genomic sequencing of infectious pathogens*. https://www.gao.gov/products/gao-21-426sp (accessed September 17, 2021).

Garland, J. 2020. Narms surface water pilot overview: Annual Meeting of the National Institute of Animal Agriculture, Cincinnati, Ohio.

Garland, J. L., N. Brinkman, S. Keely, and M. Jahne. 2018. Geospatial distribution of antimicrobial resistance genes in us rivers and streams.

Girlich, D., R. A. Bonnin, P. Bogaerts, M. De Laveleye, D. T. Huang, L. Dortet, P. Glaser, Y. Glupczynski, and T. Naas. 2017. Chromosomal amplification of the blaoxa-58 carbapenemase

gene in a proteus mirabilis clinical isolate. *Antimicrobial Agents and Chemotherapy* 61(2):e01697-01616.

Global PPS. 2021a. *About the global PPS project*. https://www.global-pps.com/project/ (accessed July 30, 2021).

Global PPS. 2021b. *Acknowledgements*. https://www.global-pps.com/acknowledgements/ (accessed July 27, 2021).

Harris, S. R., E. J. Cartwright, M. E. Torok, M. T. Holden, N. M. Brown, A. L. Ogilvy-Stuart, M. J. Ellington, M. A. Quail, S. D. Bentley, J. Parkhill, and S. J. Peacock. 2013. Whole-genome sequencing for analysis of an outbreak of meticillin-resistant staphylococcus aureus: A descriptive study. *Lancet Infectious Diseases* 13(2):130-136.

Harris-Lovett, S., K. Nelson, P. Beamer, H. N. Bischel, A. Bivins, A. Bruder, C. Butler, T. D. Camenisch, S. K. De Long, S. Karthikeyan, D. A. Larsen, K. Meierdiercks, P. Mouser, S. Pagsuyoin, S. Prasek, T. S. Radniecki, J. L. Ram, D. K. Roper, H. Safford, S. P. Sherchan, W. Shuster, T. Stalder, R. T. Wheeler, and K. S. Korfmacher. 2021. Wastewater surveillance for sars-cov-2 on college campuses: Initial efforts, lessons learned and research needs. *medRxiv* 18(9).

Health.mil. 2021. *Global emerging infections surveillance*. health.mil/Military-Health-Topics/Combat-Support/Armed-Forces-Health-Surveillance-Branch/Global-Emerging-Infections-Surveillance-and-Response (accessed September 17, 2021).

Hendriksen, R. S., V. Bortolaia, H. Tate, G. H. Tyson, F. M. Aarestrup, and P. F. McDermott. 2019a. Using genomics to track global antimicrobial resistance. *Front Public Health* 7(242):242.

Hendriksen, R. S., P. Munk, P. Njage, B. van Bunnik, L. McNally, O. Lukjancenko, T. Roder, D. Nieuwenhuijse, S. K. Pedersen, J. Kjeldgaard, R. S. Kaas, P. Clausen, J. K. Vogt, P. Leekitcharoenphon, M. G. M. van de Schans, T. Zuidema, A. M. de Roda Husman, S. Rasmussen, B. Petersen, The Global Sewage Surveillance Project Consortium, C. Amid, G. Cochrane, T. Sicheritz-Ponten, H. Schmitt, J. R. M. Alvarez, A. Aidara-Kane, S. J. Pamp, O. Lund, T. Hald, M. Woolhouse, M. P. Koopmans, H. Vigre, T. N. Petersen, and R. M. Aarestrup. 2019b. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nature Communications* 10(1):1124.

Hermsen, E. D., R. L. Sibbel, and S. Holland. 2020. The role of pharmaceutical companies in antimicrobial stewardship: A case study. *Clinical Infectious Diseases* 71(3):677-681.

Huijbers, P. M. C., C. F. Flach, and D. G. J. Larsson. 2019. A conceptual framework for the environmental surveillance of antibiotics and antibiotic resistance. *Environment International* 130:104880.

INICC (International Nosocomial Infection Control Consortium). 2013. *Multicentric network of cities and countries*. http://www.inicc.org/multicentric/ (accessed July 27, 2021).

Iskandar, K., L. Molinier, S. Hallit, M. Sartelli, T. C. Hardcastle, M. Haque, H. Lugova, S. Dhingra, P. Sharma, S. Islam, I. Mohammed, I. Naina Mohamed, P. A. Hanna, S. E. Hajj, N. A. H. Jamaluddin, P. Salameh, and C. Roques. 2021. Surveillance of antimicrobial resistance in low- and middle-income countries: A scattered picture. *Antimicrobial Resistance & Infection Control* 10(1):63.

Ju, F., K. Beck, X. Yin, A. Maccagnan, C. S. McArdell, H. P. Singer, D. R. Johnson, T. Zhang, and H. Burgmann. 2019. Wastewater treatment plant resistomes are shaped by bacterial composition, genetic exchange, and upregulated expression in the effluent microbiomes. *ISME J* 13(2):346-360.

Keshaviah, A., X. C. Hu, and M. Henry. 2021. Developing a flexible national wastewater surveillance system for covid-19 and beyond. *Environmental Health Perspectives* 129(4):45002.

Korry, B. J., D. J. Cabral, and P. Belenky. 2020. Metatranscriptomics reveals antibiotic-induced resistance gene expression in the murine gut microbiota. *Frontiers in Microbiology* 11:322.

Koser, C. U., M. J. Ellington, and S. J. Peacock. 2014. Whole-genome sequencing to control antimicrobial resistance. *Trends in Genetics* 30(9):401-407.

Kowalchuk, G. A., A. G. Speksnijder, K. Zhang, R. M. Goodman, and J. A. van Veen. 2007. Finding the needles in the metagenome haystack. *Microbial Ecology* 53(3):475-485.

Kraupner, N., M. Hutinel, K. Schumacher, D. A. Gray, M. Genheden, J. Fick, C. F. Flach, and D. G. J. Larsson. 2021. Evidence for selection of multi-resistant e. Coli by hospital effluent. *Environment International* 150:106436.

Kreier, F. 2021. The myriad ways sewage surveillance is helping fight covid around the world. *Nature*, 10 May 2021.

LaPara, T. M., T. R. Burch, P. J. McNamara, D. T. Tan, M. Yan, and J. J. Eichmiller. 2011. Tertiary-treated municipal wastewater is a significant point source of antibiotic resistance genes into duluth-superior harbor. *Environmental Science & Technology* 45(22):9543-9549.

Lee, L. M., S. M. Teutsch, S. B. Thacker, and M. E. St. Louis. 2010. *Principles & Practice of Public Health Surveillance*.

Leitmeyer, K. C., L. Espinosa, E. K. Broberg, M. J. Struelens, ECDC National Focal Points Laboratory E-reporting Survey Group Members, and ECDC National Focal Points Laboratory E-reporting Survey Group. 2020. Automated digital reporting of clinical laboratory information to national public health surveillance systems, results of a EU/EEA survey, 2018. *Euro Surveillance* 25(39).

Leonard, A. F. C., L. Zhang, A. J. Balfour, R. Garside, P. M. Hawkey, A. K. Murray, O. C. Ukoumunne, and W. H. Gaze. 2018. Exposure to and colonisation by antibiotic-resistant e. Coli in uk coastal water users: Environmental surveillance, exposure assessment, and epidemiological study (beach bum survey). *Environment International* 114:326-333.

Luby, E., A. M. Ibekwe, J. Zilles, and A. Pruden. 2016. Molecular methods for assessment of antibiotic resistance in agricultural ecosystems: Prospects and challenges. *Journal of Environmental Quality* 45(2):441-453.

Lumen. 2021. *Testing the effectiveness of antimicrobials*. https://courses.lumenlearning.com/microbiology/chapter/testing-the-effectiveness-of-antimicrobials/ (accessed May 19, 2021).

Mackie, R. I., S. Koike, I. Krapac, J. Chee-Sanford, S. Maxwell, and R. I. Aminov. 2006. Tetracycline residues and tetracycline resistance genes in groundwater impacted by swine production facilities. *Animal Biotechnology* 17(2):157-176.

Maki, A., P. Salmi, A. Mikkonen, A. Kremp, and M. Tiirola. 2017. Sample preservation, DNA or rna extraction and data analysis for high-throughput phytoplankton community sequencing. *Frontiers in Microbiology* 8(1848):1848.

Manaia, C. M. 2017. Assessing the risk of antibiotic resistance transmission from the environment to humans: Non-direct proportionality between abundance and risk. *Trends in Microbiology* 25(3):173-181.

Martinez, J. L., T. M. Coque, and F. Baquero. 2015. What is a resistance gene? Ranking risk in resistomes. *Nature Reviews: Microbiology* 13(2):116-123.

McLain, J. E., E. Cytryn, L. M. Durso, and S. Young. 2016. Culture-based methods for detection of antibiotic resistance in agroecosystems: Advantages, challenges, and gaps in knowledge. *Journal of Environmental Quality* 45(2):432-440.

Meyer, W. G., J. A. Pavlin, D. Hospenthal, C. K. Murray, K. Jerke, A. Hawksworth, D. Metzgar, T. Myers, D. Walsh, M. Wu, R. Ergas, U. Chukwuma, S. Tobias, J. Klena, I. Nakhla, M. Talaat, R. Maves, M. Ellis, G. Wortmann, D. L. Blazes, and L. Lindler. 2011. Antimicrobial resistance surveillance in the afhsc-geis network. *BMC Public Health* 11 Suppl 2(2):S8.

Michael, I., L. Rizzo, C. S. McArdell, C. M. Manaia, C. Merlin, T. Schwartz, C. Dagot, and D. Fatta-Kassinos. 2013. Urban wastewater treatment plants as hotspots for the release of antibiotics in the environment: A review. *Water Research* 47(3):957-995.

Minnesota Department of Health. 2015. About antibiograms - antimicrobial susceptibilities of selected pathogens, edited by M. D. o. Health.

Muller, H., E. Sib, M. Gajdiss, U. Klanke, F. Lenz-Plet, V. Barabasch, C. Albert, A. Schallenberg, C. Timm, N. Zacharias, R. M. Schmithausen, S. Engelhart, M. Exner, M. Parcina, C. Schreiber, and

G. Bierbaum. 2018. Dissemination of multi-resistant gram-negative bacteria into german wastewater and surface waters. *FEMS Microbiology Ecology* 94(5).

Murray, A. K., I. Stanton, W. H. Gaze, and J. Snape. 2021. Dawning of a new era: Environmental risk assessment of antibiotics and their potential to select for antimicrobial resistance. *Water Research* 200:117233.

NCBI (National Center for Biotechnology Information). 2019. NCBI pathogen detection.

NIHR (National Institute for Health Research) Global Health Research Unit on Genomic Surveillance of AMR. 2020. Whole-genome sequencing as part of national and international surveillance programmes for antimicrobial resistance: A roadmap. *BMJ Global Health* 5(11).

NLM (National Library of Medicine). *About the NCBI pathogen detection system*. https://www.ncbi.nlm.nih.gov/pathogens/about/ (accessed June 30, 2021).

NLM. *Major contributors*. https://www.ncbi.nlm.nih.gov/pathogens/contributors (accessed June 30, 2021).

NLM. *National database of antibiotic resistant organisms (NDARO)*. https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance (accessed June 30, 2021).

NLM. 2018. Introducing the ncbi pathogen detection isolates browser: YouTube.

NLM. 2019a. *Amrfinderplus*. https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/AMRFinder/ (accessed June 30, 2021).

NLM. 2019b. *Pathogen detection*. https://www.ncbi.nlm.nih.gov/pathogens/ (accessed June 30, 2021).

NLM. 2020. *Pathogen detection help document*. https://www.ncbi.nlm.nih.gov/pathogens/pathogens_help/#amr-resources-schematic (accessed June 30, 2021).

NLM. 2021a. *How to submit data for real-time analysis*. https://www.ncbi.nlm.nih.gov/pathogens/submit-data/ (accessed June 30, 2021).

NLM. 2021b. *Organism groups*. https://www.ncbi.nlm.nih.gov/pathogens/organisms/ (accessed June 30, 2021).

NOAA (National Oceanic and Atmospheric Administration). 2021. *Point source pollution tutorial*. https://oceanservice.noaa.gov/education/tutorial_pollution/03pointsource.html (accessed July 30, 2021).

Norman, R. S. 2020. Amr and sars-cov-2 surveillance in sewage. Paper read at 14th Public Virtual Meeting of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria 09/10/2020.

OPHSS (Office of Public Health Scientific Services) and CDC. 2018. *Public health surveillance: Preparing for the future.* Atlanta, GA: Centers for Disease Control and Prevention.

Pan, M., and P. C. Yau. 2021. Fate of macrolide antibiotics with different wastewater treatment technologies. *Water, Air, and Soil Pollution* 232(3):103.

Parnanen, K. M. M., C. Narciso-da-Rocha, D. Kneis, T. U. Berendonk, D. Cacace, T. T. Do, C. Elpers, D. Fatta-Kassinos, I. Henriques, T. Jaeger, A. Karkman, J. L. Martinez, S. G. Michael, I. Michael-Kordatou, K. O'Sullivan, S. Rodriguez-Mozaz, T. Schwartz, H. Sheng, H. Sorum, R. D. Stedtfeld, J. M. Tiedje, S. V. D. Giustina, F. Walsh, I. Vaz-Moreira, M. Virta, and C. M. Manaia. 2019. Antibiotic resistance in european wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. *Science Advances* 5(3):eaau9124.

Pascucci, M., G. Royer, J. Adamek, M. A. Asmar, D. Aristizabal, L. Blanche, A. Bezzarga, G. Boniface-Chang, A. Brunner, C. Curel, G. Dulac-Arnold, R. M. Fakhri, N. Malou, C. Nordon, V. Runge, F. Samson, E. Sebastian, D. Soukieh, J. P. Vert, C. Ambroise, and M. A. Madoui. 2021. Ai-based mobile application to fight antibiotic resistance. *Nature Communications* 12(1):1173.

Pfizer. 2021. *Antimicrobial surveillance*. https://www.pfizer.com/science/therapeutic-areas/anti-infectives/antimicrobial-surveillance (accessed August 5, 2021).

Polianciuc, S. I., A. E. Gurzau, B. Kiss, M. G. Stefan, and F. Loghin. 2020. Antibiotics in the environment: Causes and consequences. *Medicine and Pharmacy Reports* 93(3):231-240.

Prasad, A. B., V. B., M. Feldgarden, B. Fedorov, D. H. Haft, W. Klimke. 2021. NCBI's amrfinderplus, isolates browser, and microbigg-e identify quinolone resistance mutations and their sources: World Microbe Forum.

Pruden, A., R. E. Alcalde, P. J. J. Alvarez, N. Ashbolt, H. Bischel, N. L. Capiro, E. Crossette, D. Frigon, K. Grimes, C. N. Haas, K. Ikuma, A. Kappell, T. LaPara, L. Kimbell, M. Li, X. Li, P. McNamara, Y. Seo, M. D. Sobsey, E. Sozzi, T. Navab-Daneshmand, L. Raskin, M. V. Riquelme, P. Vikesland, K. Wigginton, and Z. Zhou. 2018. An environmental science and engineering framework for combating antimicrobial resistance. *Environmental Engineering Science* 35(10):1005-1011.

Ranjalkar, J., and S. J. Chandy. 2019. India's national action plan for antimicrobial resistance - an overview of the context, status, and way ahead. *Journal of Family Medicine and Primary Care* 8(6):1828-1834.

Rosenthal, V. D. 2016. International nosocomial infection control consortium (INICC) resources: INICC multidimensional approach and INICC surveillance online system. *American Journal of Infection Control* 44(6):e81-e90.

Rothrock, M. J., P. L. Keen, K. L. Cook, L. M. Durso, A. M. Franklin, and R. S. Dungan. 2016. How should we be determining background and baseline antibiotic resistance levels in agroecosystem research? *Journal of Environmental Quality* 45(2):420-431.

Ruzante, J. M., K. Olin, B. Munoz, J. Nawrocki, R. Selvarangan, and L. Meyers. 2021. Real-time gastrointestinal infection surveillance through a cloud-based network of clinical laboratories. *PloS One* 16(4):e0250767.

Saadat, S., K. Solhjoo, M. J. Norooz-Nejad, and A. Kazemi. 2014. Vana and vanb positive vancomycin-resistant staphylococcus aureus among clinical isolates in shiraz, south of iran. *Oman Medical Journal* 29(5):335-339.

Sayers, E. W., J. Beck, E. E. Bolton, D. Bourexis, J. R. Brister, K. Canese, D. C. Comeau, K. Funk, S. Kim, W. Klimke, A. Marchler-Bauer, M. Landrum, S. Lathrop, Z. Lu, T. L. Madden, N. O'Leary, L. Phan, S. H. Rangwala, V. A. Schneider, Y. Skripchenko, J. Wang, J. Ye, B. W. Trawick, K. D. Pruitt, and S. T. Sherry. 2021. Database resources of the national center for biotechnology information. *Nucleic Acids Research* 49(D1):D10-D17.

Schmieder, R., and R. Edwards. 2012. Insights into antibiotic resistance through metagenomic approaches. *Future Microbiology* 7(1):73-89.

Schurch, A. C., and W. van Schaik. 2017. Challenges and opportunities for whole-genome sequencing-based surveillance of antibiotic resistance. *Annals of the New York Academy of Sciences* 1388(1):108-120.

Seale, A. C., N. C. Gordon, J. Islam, S. J. Peacock, and J. A. G. Scott. 2017. Amr surveillance in low and middle-income settings - a roadmap for participation in the global antimicrobial surveillance system (glass). *Wellcome Open Research* 2:92.

Shakya, M., C. C. Lo, and P. S. G. Chain. 2019. Advances and challenges in metatranscriptomic analysis. *Frontiers in Genetics* 10:904.

Strain, E. 2021. Machine learning for mic predictions using whole-genome sequencing for FDA narms: World Microbe Forum.

Sundsfjord, A., G. S. Simonsen, B. C. Haldorsen, H. Haaheim, S. O. Hjelmevoll, P. Littauer, and K. H. Dahl. 2004. Genetic methods for detection of antimicrobial resistance. *APMIS* 112(11-12):815-837.

The White House. 2015. *National action plan for combating antibiotic resistant bacteria.*

Tiwari, H. K., A. K. Das, D. Sapkota, K. Sivrajan, and V. K. Pahwa. 2009. Methicillin resistant staphylococcus aureus: Prevalence and antibiogram in a tertiary care hospital in Western Nepal. *Journal of Infection in Developing Countries* 3(9):681-684.

Torumkuney, D., R. Chaiwarith, W. Reechaipichitkul, K. Malatham, V. Chareonphaibul, C. Rodrigues, D. S. Chitins, M. Dias, S. Anandan, S. Kanakapura, Y. J. Park, K. Lee, H. Lee, J. Y. Kim, Y. Lee, H. K. Lee, J. H. Kim, T. Y. Tan, Y. X. Heng, P. Mukherjee, and I. Morrissey. 2016. Results from

the survey of antibiotic resistance (SOAR) 2012-14 in thailand, india, south korea and singapore. *Journal of Antimicrobial Chemotherapy* 71(Suppl 1):i3-19.

UN MPTF (Multi-Partner Trust Fund) Office. 2020. *2020 annual report UN multi-partner trust fund office.* United Nations Center of Expertise on pooled financing instruments for the Sustainable Development Goals.

Vaz-Moreira, I., O. C. Nunes, and C. M. Manaia. 2014. Bacterial diversity and antibiotic resistance in water habitats: Searching the links with the human microbiome. *FEMS Microbiology Reviews* 38(4):761-778.

Vikesland, P. J., A. Pruden, P. J. J. Alvarez, D. Aga, H. Burgmann, X. D. Li, C. M. Manaia, I. Nambi, K. Wigginton, T. Zhang, and Y. G. Zhu. 2017. Toward a comprehensive strategy to mitigate dissemination of environmental sources of antibiotic resistance. *Environmental Science & Technology* 51(22):13061-13069.

Vivli Center for Global Clinical Research Data. 2021. *News & events* https://vivli.org/vivli-awarded-contract-to-improve-access-to-antimicrobial-resistance-surveillance-data/ (accessed July 27, 2021).

Vong, S., A. Anciaux, A. Hulth, J. Stelling, V. Thamlikitkul, S. Gupta, J. M. Fuks, K. Walia, P. Rattanumpawan, S. Eremin, K. Tisocki, T. R. Sedai, and A. Sharma. 2017. Using information technology to improve surveillance of antimicrobial resistance in south East Asia. *BMJ* 358:j3781.

Welcomme Trust. 2018. *Initiatives for addressing antimicrobial resistance in the environment - current situation and challenges.*

WHO (World Health Organization). 2014. *Antimicrobial resistance- global report on surveillance.*

WHO. 2015. *Global antimicrobial resistance surveillance system - manual for early implementation.*

WHO. 2017. *Global antimicrobial resistance surveillance system (GLASS) report- early implementation.* WHO.

WHO. 2021a. Global antimicrobial resistance and use surveillance system (GLASS) report: 2021. *World Health Organization*.

WHO. 2021b. *Tripartite integrated system for surveillance on amr and antimicrobial use (tissa)*. https://www.ungm.org/Public/Notice/124127 (accessed July 30, 2021).

WHO. 2021c. *Who integrated global surveillance on ESBL-producing e. Coli using a "one health" approach.* Geneva: WHO.

WHONET. 2020. *Whonet for caesar: Manual*. https://www.whonet.org/docserv/Manual_WHONET_for_CAESAR.pdf (accessed July 28, 2021).

WHONET. 2021. *The microbiology laboratory database software.* (accessed July 30, 2021).

Wright, G. D. 2010. The antibiotic resistome. *Expert Opinion on Drug Discovery* 5(8):779-788.

Zhang, X. X., T. Zhang, and H. H. Fang. 2009. Antibiotic resistance genes in water environment. *Applied Microbiology and Biotechnology* 82(3):397-414.

# 5

# Stewardship and Infection Prevention

As Chapter 2 discussed, there are many factors driving the misuse and overuse of antimicrobials and the emergence of resistance. Limited local laboratory capacity, for example, can force the extensive use or prolonged courses of empiric antimicrobial treatment. In this regard, the overuse of these medicines is in many ways a proxy indicator of other gaps in the health system, such as problems with infection control and uneven access to medicines, preventative services, or primary care (Denyer Willis and Chandler, 2019). Efforts to promote rational antimicrobial use will be futile without attention to these underlying problems.

The Centers for Disease Control and Prevention (CDC) defines antimicrobial stewardship as "the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients" (CDC, 2021e). Stewardship can also be thought of as an effort to match antimicrobial use to need, with an emphasis on the right medicine, in the right dose, for the right length of time. Drug selection, dose, and duration influence potential adverse effects to patients and contribute to the development of resistance (Gerding, 2001). More recent frameworks emphasize duration of treatment and correct de-escalation (described in Chapter 2) as other important dimensions of stewardship (Goebel et al., 2021).

In its *Global Action Plan on AMR*, the World Health Organization (WHO) cites the optimal use of antimicrobial medicines in human and animal health as one of its main objectives (Mendelson and Matsoso, 2015). In the United States, both the 2015 and 2020 National Action Plans for Combating Antibiotic-Resistant Bacteria emphasized supporting stewardship programs and infection prevention in humans and animals (CARB, 2020; Mendelson and Matsoso, 2015).

Successful antimicrobial stewardship will protect the drugs we have, thereby prolonging their useful life in recognition of the fact that the pace of drug development has not and cannot keep pace with the emergence of resistance (Doron and Davidson, 2011). Good stewardship strikes the optimal balance between prescribing effective treatment and avoiding unnecessary risks, be they the short-term risk to the patient or long-term risks to society by encouraging resistance.

This chapter presents the committee's analysis of key bottleneck problems related to stewardship and infection prevention, in both humans and animals. This is not an exhaustive analysis of every possible tool for stewardship or infection prevention. Education of providers, for example, is one necessary precursor for better stewardship. In training and in professional development, health professionals are taught the essentials of antimicrobial treatment including, most obviously, correct diagnosis, but also drug choice and dose, duration of treatment, and de-

escalation (Goebel et al., 2021). The committee commends the greater attention to antimicrobial stewardship in preclinical and continuing education emerging across health professions (Augie et al., 2021; Espinosa-Gongora et al., 2021; Gotterson et al., 2021; Holz et al., 2021; Nasr et al., 2021; Van Katwyk et al., 2018).

At the same time, knowledge of correct stewardship practices is rarely enough to alter providers' behavior. Qualitative research across six low- and middle-income countries found awareness of antimicrobial resistance and knowledge of the role of providers to combat it consistently very high (Goebel et al., 2021). This does not necessarily translate into changes in prescribing patterns, however, as such decisions are influenced by larger social and economic factors (Goebel et al., 2021). In the face of environmental conditions that encourage infection, the cost, time, and tools required for diagnosis, and managing the expectations of patients, their families, or, in veterinary medicine, animal owners, it can be difficult for providers to change behavior, or to argue that, in some cases, such change would be advisable (Goebel et al., 2021). In short, the relationship between providers' knowledge and their practice is not direct or linear (Denyer Willis and Chandler, 2019). For this reason, attention to providers' behavior and their awareness of good stewardship practices has been described as "the tip of the iceberg" (Chandler et al., 2016).

This chapter presents the committee's judgement regarding key points where policy intervention could improve antimicrobial stewardship in the United States. It also discusses tools that could help mitigate the problem in low- and middle-income countries where the burden of resistance is greatest. Though not an exhaustive list, the steps recommended in this chapter have potential to encourage more judicious use of antimicrobials as well as promising preventive measures.

## STEWARDSHIP IN HUMAN MEDICINE IN THE UNITED STATES

In its definition of antimicrobial stewardship, the CDC emphasizes both the prescription and use of antimicrobials, a distinction that can be difficult to track (CDC, 2021e).

Stewardship in hospitals was the focus of the agency's 2014 report *Core Elements of Hospital Antibiotic Stewardship*, the first in a series of guidance documents (Sanchez, 2016). This immediate emphasis on hospital stewardship was well founded. By CDC estimates, 30 to 50 percent of antimicrobial use in hospitals is unnecessary (e.g., to treat a viral infection) or inappropriate (e.g., use of the wrong drug for a particular bacteria) (CDC, 2021b). Because of the lag time on microbiological diagnosis, hospital prescribing relies heavily on the broad-spectrum drugs that are often used inappropriately (Doron and Davidson, 2011).

The frequency of misuse in hospitals is a concern as infections can spread quickly and because hospitals are, by definition, places for infirm and immunocompromised people for whom infections pose serious risks. Box 5-1 describes how, even when hospital staff have heightened attention to infection control, drug-resistant pathogens can spread quickly. Hospitals are also, compared to other practice settings, structured environments with multiple checks on medicine use and patient compliance as well as in-house laboratory and pharmacy systems. For these reasons, hospitals are an obvious starting point for efforts to promote antimicrobial stewardship.

**BOX 5-1**
**Multidrug-Resistant *Candida auris* and COVID-19**

The multidrug-resistant fungus, *Candida auris,* first identified in the United States in 2015, has rapidly become a CDC urgent microbial threat. *C. auris* can live on skin and spread easily; it is not readily destroyed with hospital disinfectants. *C. auris* infection can be difficult to diagnose since it requires specialized methods for identification and additional infection control precautions are recommended for patients who are infected or colonized. Though the infection is still rare in the United States, some evidence indicates overall mortality from *C. auris* infection around 17 percent; higher estimates of case fatality for the more severe *C. auris* infection in the bloodstream can occur, but vary widely.

The COVID-19 epidemic brought new attention to *C. auris,* driven by a *C. auris* outbreak in a COVID-19 unit in Florida. In July 2020, the Florida Department of Health was alerted to three *C. auris* bloodstream infections and one urinary tract infection in four patients with COVID-19 who had been treated in the same, dedicated COVID-19 unit. Among 67 patients admitted to the unit in question and screened during subsequent point prevalence surveys in August 2020, 35 (52 percent) were colonized with *C. auris*. Even in a COVID-19 specialty care unit, with all its emphasis on infection prevention, *C. auris* was able to spread rapidly.

The investigation noted multiple opportunities for contamination of health care worker's personal protective equipment through direct contact with patients, their surroundings, and contaminated surfaces. The need to conserve and reuse gowns and other protective equipment, lapses in cleaning and disinfection of shared medical equipment, and lapses in hand hygiene likely contributed to widespread *C. auris* transmission.

SOURCES: Arensman et al., 2020; CDC, 2019a; Prestel et al., 2021.

National attention to stewardship in hospitals has elicited considerable progress over a relatively short time. Starting in 2017, the Joint Commission, the organization that accredits hospitals, has assessed hospital stewardship programs as part of their review (Joint Commission, 2016). Between 2014 and 2017 the number of U.S. hospitals with stewardship programs conforming to CDC guidelines almost doubled (CDC, 2019b). A Centers for Medicare & Medicaid Services (CMS) rule that went into effect in 2019 requires hospitals to have antibiotic stewardship as part of their infection control efforts (ASM, 2019). Attention from CMS and the Joint Commission command the attention of hospital administrators, making it easier to ask for financial support for stewardship activities (Joint Commission, 2016). In 2014 less than 40 percent of U.S. hospitals had a stewardship program (Pollack et al., 2016). By 2019, almost 89 percent did (see Figure 5-1).

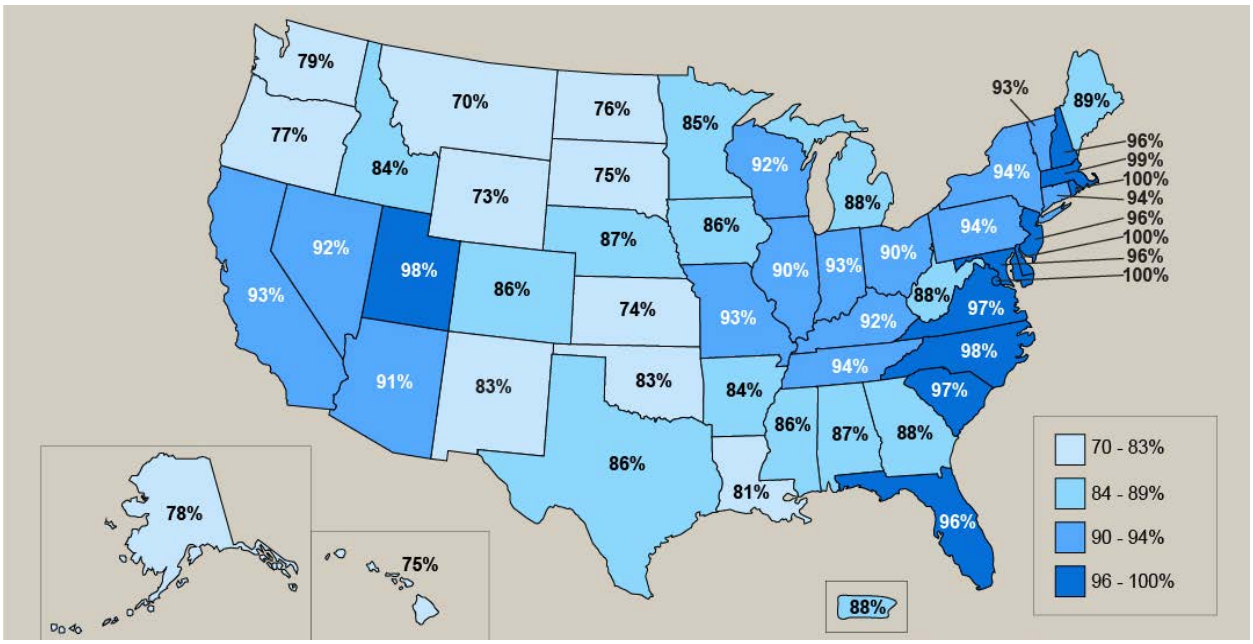



**FIGURE 5-1** Percentage of hospitals meeting all seven core elements of hospital antibiotic stewardship programs by state, 2019.
SOURCE: Adapted from CDC, 2020d.

The success in improving hospital stewardship over the last 5 years is heartening, but the institutions left without functional stewardship programs are some of the most challenging ones to reach. CDC surveys indicate that hospitals with 25 or fewer beds, many of them designated Critical Access Hospitals that support rural or remote areas, account for most of the remaining hospitals without complete stewardship programs (CDC, 2020g). These hospitals have fewer staff, a reflection of their smaller patient load, and cannot often support the expertise in infectious disease and specialty pharmacy outlined in CDC guidance. Collaborations with other hospitals are one effective way to overcome this barrier (CDC, 2018; StratisHealth, 2020). Using telemedicine to connect to academic medical centers is one particularly promising strategy, as discussed in Box 5-2.

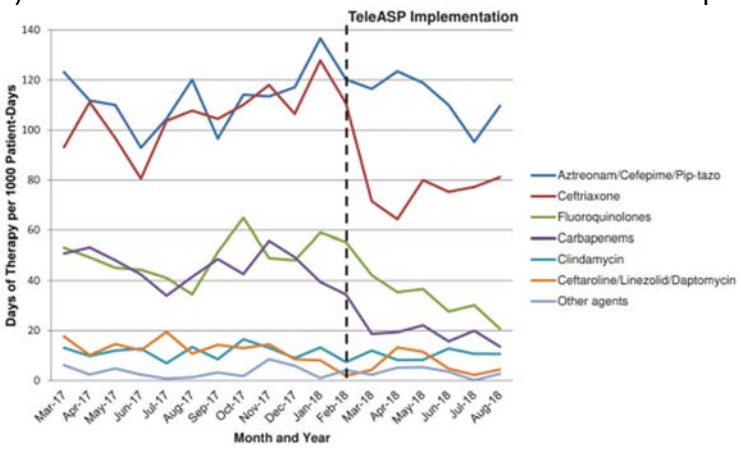
**BOX 5-2**
**University of Washington Tele-ASP**

Antimicrobial stewardship programs in academic medical centers have proven to be successful, but many small, rural hospitals do not have the staffing depth or resources to replicate these programs. The state of Washington has 39 federally designated Critical Access Hospitals. In 2016, the Washington State Department of Health approved a program that uses telehealth to connect stewardship teams at these rural hospitals to experts and the University of Washington Medical Center.

The University of Washington (UW) tele-antimicrobial stewardship program (or UW tele-ASP) uses a hub and spoke model, meaning that the UW team, including infectious disease doctors, infection prevention specialists, pharmacists, and microbiologists, connect to multiple rural centers at the same time. This makes most efficient use of their time and helps foster relationships among rural providers who may have fewer opportunities for networking and professional development. Weekly video conferences typically involve a 10- to 15-minute teaching session. Topics covered include the pros and cons of differ types of treatment and guidelines on the treatment of common infections. The teaching sessions are meant to give the rural providers sufficient background to be able to provide stewardship interventions in their hospitals. Each session also includes the presentation and discussion of de-identified case studies.

Tele-ASP uses tools such as prospective audit and feedback to support pharmacists at community hospitals. This involves daily review of antibiotic prescriptions at the community hospital to identify irregularities. Several times a week the pharmacists review their audit flags with infectious disease doctors who see complicated patients more often.

The goal of tele-ASP is to build local skills and knowledge of antimicrobial stewardship. It also expands the rural health knowledge of the UW participants in the central hub. Almost all of Washington's rural hospitals and several in Oregon, Idaho, Utah, Montana, Arizona, and Maine, participate in the program. Furthermore, the evidence from other similar programs indicates that tele-ASP can reduce use of broad-spectrum antimicrobials (see graph) and increase consultations with infectious disease specialists.




SOURCE: Shively et al., 20201.

SOURCES: Lynch, 2021; Shively et al., 2020; UWTASP, 2018; Zhou et al., 2017.SOURCE for figure: Shively et al., 2020.

It is difficult to overstate the importance of federal leadership in bringing attention to antimicrobial stewardship in hospitals. Joint Commission standards and a CMS rule command

the attention of hospital leadership and make it easier for stewardship staff to get protected time and salary support for their work (StratisHealth, 2020). In the absence of such a rule, it can be difficult to persuade hospital administrators of the value of the antimicrobial stewardship activities (Kapadia et al., 2018; StratisHealth, 2020). This is partly because the relationship between stewardship activities and changes in burden of resistance are not clear or direct; even the best stewardship program will not necessarily improve indicators of resistance in the hospital (Doron and Davidson, 2011).

The rapid improvement in hospital stewardship programs in the United States is a success; tele-health programs and outreach to smaller community hospitals are promising tools to reach remaining hospitals (Shively et al., 2020). By 2020, 88.9 percent of hospitals had implemented all seven of the CDC's core elements of antimicrobial stewardship, falling short of the agency's goal of 100 percent of hospitals having quality stewardship programs in place by 2020 (CDC, 2020b).

There are other clinical settings where there is room for improvement in the rational use of antimicrobials. In its 2019 report, *Antibiotic Use in the United States*, the CDC identified problems with outpatient prescribing practices including unnecessary use of fluoroquinolones for urinary tract and respiratory tract infections, overly long antibiotic treatment for sinus infections and community-acquired pneumonia, and the misuse of azithromycin in children (CDC, 2019b). The agency's *Core Elements of Outpatient Antibiotic Stewardship* emphasized that a responsibility for stewardship was distributed across the health system including primary care providers, and also urgent and emergent care, pharmacies, dental practices, and many outpatient specialty providers and clinics (Sanchez, 2016). Rapid, reliable diagnostic information could do much to improve these troubling practices, a matter discussed in more detail later in this chapter.

## Nursing Homes, Long-Term Acute Care Hospitals, and Dialysis Centers

There are several clinical practice settings similar to hospitals in their misuse of antimicrobials, vulnerable patient populations, and an administrative structure conducive to implementing change. Recent government response to the COVID-19 pandemic recognizes the unique importance of these practice settings, with the CDC creating special outbreak control teams to deploy to nursing homes, dialysis clinics, and other skilled nursing settings to prevent and control the spread of SARS-CoV-2 and other infectious diseases (CDC, 2021c). Nursing homes, long-term acute care hospitals, and dialysis centers all have a financial relationship with CMS. These settings are an obvious choice as the next step in the push for improved antimicrobial stewardship.

### *Nursing Homes*

Nursing homes, the live-in health facilities that provide 24-hour supervision and skilled nursing support, are home to an estimated 1.3 million Americans (Harris-Kojetin et al., 2019; NIA, 2017b). Some nursing home residents are admitted for short stays, for physical or occupational therapy after an injury or surgery, for example, but the vast majority are there permanently because their conditions require constant skilled nursing and supervision (Harris-Kojetin et al., 2019; NIA, 2017b). About 80 percent of nursing home residents are over 65 years of age (Harris-Kojetin et al., 2019). Their care is often complicated by comorbidities such as dementia (36 percent prevalent), diabetes (37 percent prevalent), heart disease (36 percent prevalent), and hypertension (77 percent prevalent) (Harris-Kojetin et al., 2019). Limiting

infections through stewardship is especially important in nursing homes, as infection control measures such as isolation and donning gowns and gloves are not always practical or suitable in the setting (Cohen et al., 2015). Unlike in hospitals, where the attending physician or other in-house provider is often responsible for prescriptions, nursing home residents are free to choose their provider (CMS, 2021g; LaBore, 2014). This person is not generally affiliated with the nursing home, and would not necessarily have the same perspective on the institution's stewardship goals as the in-house staff.

The CDC released its *Core Elements of Antibiotic Stewardship for Nursing Homes* in 2015, setting out steps for nursing homes to improve their antibiotic prescribing and reduce inappropriate use (CDC, 2015b). Yet a recent survey found that only a third of nursing homes had comprehensive antimicrobial stewardship programs (Fu et al., 2020). The most recent compendium of data on CMS-certified nursing homes reported that problems with infection control were the most common citation for nursing homes in the years 2010 to 2014; citations for improper use of medicines have also become more common (CMS, 2015).

An estimated 70 percent of nursing home residents receive antimicrobials in a year (CDC, 2020a). Point prevalence surveys indicate about 8 percent of nursing home residents are using antimicrobial medicines at any given time, with about a third of these being broad-spectrum antibiotics (Thompson et al., 2021b). Data from nursing homes in 10 states indicate that for every hundred nursing home residents, 2.7 are being treated with antibiotics for urinary tract infections (Thompson et al., 2020).

Such trends are concerning, as nursing home residents are often frail and have immune systems compromised by advanced age and comorbidities. *Clostridioides difficile* infection, an infection often stemming from inappropriate or excessive use of antimicrobials, is endemic in nursing homes and can be deadly for residents (MayoClinic, 2020; Yu et al., 2016). About 10 percent of patients who acquire *C. difficile* infection in nursing homes die within 30 days (Yu et al., 2016).

### *Long-Term Acute Care Hospitals*

Long-term acute care hospitals (also called long-term care hospitals) are sometimes confused with long-term care (i.e., nursing home), but they are different (NIA, 2017a,b). Long-term acute care is a specialized hospital for patients who are too infirm to be discharged to a nursing home, but not dynamic enough to warrant care in a regular, acute care hospital (ASHA, 2021). Many are discharged directly from intensive care units, bringing with them the associated risks of gram-negative, drug-resistant infections (ASHA, 2021; Kadri, 2020; Strich and Kadri, 2019). At admission, more than 60 percent of these patients are either infected or colonized with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, or both (Gould et al., 2006).

An estimated 120,000 Medicare beneficiaries are treated in long-term care hospitals every year (Makam et al., 2019). Medicare national data indicate that only about 19 percent of patients successfully return home after time in long-term acute care (CMS, 2021f). Fewer than half survive 12 months after admission; median survival is about 8 months (Makam et al., 2019). Patients in long-term care hospitals stay, on average, for 25 days or longer, often for conditions that involved prolonged use of ventilators and central lines, wound or burn care, and dialysis (ASHA, 2021; CMS, 2019b; Jacob et al., 2019). Infections associated with central lines, catheters, and ventilators are common. National surveys of long-term acute care have found 84 percent of *S. aureus* bloodstream infections acquired from central lines are resistant to

methicillin; 44 percent of *Enterococcus faecalis* urinary tract infections acquired from catheters are resistant to vancomycin (Chitnis et al., 2012; Gould et al., 2006). A regional study found that the highly resistant *Klebsiella pneumoniae* that produce an enzyme (carbapenemase) that renders them non-susceptible to the carbapenem class antibiotics, are 10 to 54 percent prevalent in long-term acute care (Lin et al., 2013). Colonization with resistant bacteria (meaning the presence of a pathogen without its damaging tissue or causing illness) can easily become chronic among these patients (O'Fallon et al., 2009). Resistant *K. pneumoniae* can be especially persistent; 83 percent of colonized patients retain *K. pneumoniae* for the duration of their stay in long-term acute care (Haverkate et al., 2016).

Survey data indicate a mismatch between perception and actual risk of antimicrobial-resistant infections in long-term acute care. A study in Detroit found that while almost two-thirds of staff consider antimicrobial resistance to be a serious national problem, only 38 percent saw it as a problem in their hospital (Mushtaq et al., 2017). The same respondents showed low awareness of some stewardship principles, missing 77 percent of opportunities to de-escalate antimicrobial treatment (Mushtaq et al., 2017).

*Dialysis Centers*

The vast majority (98 percent) of the estimated 520,000 hemodialysis patients in the United States receive maintenance dialysis at outpatient centers (Apata et al., 2021). These patients are immunocompromised almost by definition, and dialysis involves repeated bloodstream access, often with central venous catheters (Apata et al., 2021; CDC, 2020e). Bloodstream infections are a serious risk for dialysis patients and mortality after sepsis is 100 to 300 times higher for them than for the general population (Sarnak and Jaber, 2000).

Partly because of their elevated risk, about 30 percent of dialysis patients receive intravenous antibiotics in a year; 68 percent of these prescriptions are for vancomycin, a powerful, broad-spectrum drug often held in reserve to treat resistant infections (Apata et al., 2021; NIDDK, 2012). Audit data indicates that dialysis patients are often treated empirically with vancomycin even when a better tolerated, beta-lactam family drug was indicated (Apata et al., 2021; Zvonar et al., 2008). Third- and fourth-generation cephalosporins and cefazolin are also frequently used in ways not consistent with any treatment guidelines (D'Agata et al., 2018). Failure to de-escalate empiric treatment and the treatment of skin contaminants sampled in blood culture are other common misuses of antimicrobials in dialysis (D'Agata et al., 2018).

The balancing of risk and benefit that all prescribers confront in the use of antimicrobials is heightened in people with kidney disease. The relationship between drug concentration and time that underlies decisions about dosing is altered in dialysis patients because they cannot filter medicines effectively between sessions (Eyler and Shvets, 2019). As a group, these patients also have some of the highest rates of colonization with drug-resistant bacteria in the world, making effective dosing clinically important but difficult in practice (Wang et al., 2019). Colonization with vancomycin-resistant enterococci and methicillin-resistant *Staphylococcus aureus* are both about 6 percent prevalent in dialysis patients (Zacharioudakis et al., 2014, 2015).

There are serious problems with antimicrobial stewardship in nursing homes, long-term acute care, and dialysis centers. These practice settings also all have a financial relationship with CMS that could be used to encourage implementation of good stewardship practices.

**Recommendation 5-1: The Centers for Medicare & Medicaid Services should require nursing homes, long-term acute care hospitals, and dialysis centers to**

**have antimicrobial stewardship programs and include that information on the Care Compare website. These programs should, at a minimum, designate key staff, a system for preauthorization of restricted antimicrobials, and a process for regular review of all antimicrobial prescriptions.**

This recommendation is consistent with recent action at CMS. In a 2016 rule, the agency required nursing homes to have antimicrobial stewardship program in place by late 2017 that would set out a system for monitoring use and recording lapses in infection control (CMS, 2016; Cooper, 2020). Similarly, the CMS rule requiring antimicrobial stewardship in hospitals would apply to long-term acute care hospitals as well, though there is no implementing guidance specific to this setting (CMS, 2019a). Plans to expand stewardship requirement for dialysis centers and other practice settings that participate in CMS are pending (Cooper, 2020).

The CDC 2015 guidance *Core Elements of Antibiotic Stewardship in Nursing Homes* will be invaluable in implementing this recommendation. Although there are no parallel, tailored antimicrobial stewardship guidelines for dialysis or for long-term acute care, the core elements outlined in other CDC stewardship documents (leadership, accountability, pharmacy expertise, action, tracking, reporting, and education) are broadly applicable to a range of these settings (see Figure 5-2). The CDC cites the same core elements in its 2015 guidance on antimicrobial stewardship in nursing homes (CDC, 2015b).


**FIGURE 5-2** The CDC's core elements of hospital antibiotic stewardship programs.
SOURCE: CDC, 2019c.

There are also similarities among the three types of practice settings. All rely heavily on nurses and pharmacists (Apata et al., 2021; Katz et al., 2017; Sloane et al., 2016). Physicians are not necessarily, or even commonly, on site; they base their prescribing decisions heavily on nurses' reports. When physicians are on site, it tends to be on a rotating basis making it difficult to find one sufficiently integrated into day-to-day activities to have a sense of ownership of a stewardship program. As in critical access hospitals, infectious disease specialists are not

generally on staff and telehealth may be the best option when specialist consultations are needed (Apata et al., 2021; Petrak, 2014).

There are steps that could make stewardship a higher priority for the in-person staff in these settings. The Agency for Healthcare Research and Quality (AHRQ) provides simple tool kits to help nursing homes implement their stewardship programs. These tool kits emphasize the appointing of stewardship champions on staff, and the clear assigning of responsibility for different pieces of the program (AHRQ, 2016a,b). The AHRQ guidance encourages involving external pharmacy consultants and prescribing physicians in the implementation of stewardship programs (AHRQ, 2016a). Hospital research suggests that pharmacists are often willing to take responsibility for stewardship, acting as champions of the stewardship program (Livorsi et al., 2021). In addition to reviewing culture data, pharmacists can serve as a check on appropriate ordering, dosing, duration of treatment, and de-escalation. The structure of the stewardship program will vary based on the size and resources of the setting, but coordination with prescribers will be important across settings.

Regardless of who leads the stewardship program, regular review of all antimicrobial use will be an essential first step to ensuring rational use. This review is difficult when recordkeeping is inadequate, as is common in dialysis clinics (D'Agata et al., 2018). Record keeping in nursing homes can also be uneven; a recent national survey found only about half used electronic medical records (Bjarnadottir et al., 2017). While the electronic system is not absolutely necessary for reviewing antimicrobial use, it greatly eases the process, making strategies like remote audit and feedback on prescribing possible. This strategy significantly decreased antimicrobial use and *C. difficile* infection in long-term acute care (Beaulac et al., 2016).

Expanding stewardship may be an opportunity to modernize documentation processes, especially in nursing homes and dialysis centers. At a minimum, records should clearly cite the indication for every antimicrobial prescribed; the dose and duration of treatment; as well recording antibiotic "time-outs" or breaks in treatment to determine of the drug is working. The review would give the stewardship team a chance to encourage de-escalation and to avoid parenteral therapy when oral treatment is possible.

Medical records are also useful in developing a pre-authorization process for restricted antimicrobials. Pre-authorization is a key part of hospital stewardship; it refers to the standing approval of an infectious disease specialist (physician or pharmacist) for empiric treatment with antimicrobials (Eljaaly et al., 2018). In dialysis, preauthorization could emphasize the rational use of vancomycin, properly a drug of last resort and not one that should be used out of habit. In nursing homes, preauthorization might give more attention to the treatment of a positive urine culture, discouraging the use of antimicrobials to treat asymptomatic presence of microbes in urine. Whenever possible the pre-authorized treatment would be integrated into the electronic medical record system. Automatic prompts in electronic medical records have been shown to improve antimicrobial prescribing practices in outpatient medicine, and could be used in these settings as well (Meeker et al., 2016).

*Payment and Cost Savings*

The committee recognizes that implementing stewardship programs adds work for managers and staff at these facilities. But historical evidence from hospitals suggests these costs can be more than made up in savings on medicines, both from defaulting to cheaper antibiotics and using shorter treatment courses (CDC, 2015a). Given the common overuse and misuse of antibiotics in the settings targeted by this recommendation, the benefits of more rational use,

both to the individual facility and to society, are likely to be even greater. Modelling indicates that implementing stewardship programs in hemodialysis clinics would save between $100 and $229 million, prevent between 2,000 and 4,645 *C. difficile* and multidrug-resistant infections, and avoid between 600 and 1340 deaths every year (D'Agata et al., 2018). Research in nursing homes has not found evidence that stewardship programs reduce infection, hospitalization, or mortality rates among residents, but do tend to reduce unnecessary antibiotic use and improve adherence to stewardship guidelines (Feldstein et al., 2018). Less can be said about long-term acute care, though a pilot study in Michigan found that reductions in spending on antibiotics alone saved $55,000 in the first 3 months after implementing a stewardship program (Mushtaq et al., 2017).

Medicare is the primary payer for nursing homes and long-term acute care, as these patients are mostly over 65; it is also the primary payer for dialysis patients (CMS, 2021d). Indeed, long-term acute care as a separate clinical setting came about as a way to manage similar kinds of complicated patients more efficiently and to control Medicare spending on lengthy hospital stays (Munoz-Price, 2009). For this reason, CMS has considerable influence over these settings.

There are also similarities in business models among these practice settings. In the United States, almost 70 percent of nursing home care and 79 percent of long-term acute care is for-profit (CDC, 2021f; MedPAC, 2020). Dialysis clinics are even less diverse; two for-profit chains alone control 72 percent of the U.S. dialysis market (Childers et al., 2019; Levin et al., 2020). In this situation, it may help to frame antimicrobial stewardship as a step to lowering future costs, especially if coupled with wider use of electronic records, as the cost savings might accrue to a different department than the one making the investment in stewardship.

### *Care Compare and Implementation*

What is more, implementation does not have to be an overnight, disruptive change. The CDC guidance to nursing homes encourages gradual implementation, starting with one or two changes and adding more pieces to the strategy over time (CDC, 2021e). To start, CMS could work with providers in these settings to define the barriers to good stewardship and strategies to change their practices (Resman, 2020). When inappropriate use is driven more by the expectations of patients or their families, then strategies to improve communication and education might be an early starting point. Some research indicates ways of describing patients or residents may encourage behavior at odds with good stewardship or patient care (Chambers et al., 2019). The pattern of describing a resident as having frequent urinary tract infections, for example, tends to lead to the over treating of asymptomatic infection (Chambers et al., 2019). These patterns can change, especially when the stewardship program has an educational emphasis rather than a punitive one.

CMS could also help draw attention to stewardship by including it in the quality measures that inform its star rating system for nursing homes and dialysis and its Care Compare database (CMS, 2021c). CMS created the star rating system for nursing homes in 2008; it draws on inspection reports, staffing review, and quality measures such as vaccination coverage, percentage of residents with urinary tract infections, pressure sores, and in physical restraints (CMS, 2020; Horton et al., 2020). The rating system for dialysis is a more recent development, first implemented in 2015 and revised in 2019 (University of Michigan Kidney Epidemiology and Cost Center, 2018). The dialysis rating system relies on quality measures relating to

mortality, hospitalization, transfusions; bloodstream infection is also included (Horton et al., 2020).

The rating systems for nursing homes and dialysis is primarily a tool to help consumers and their families navigate their options (CMS, 2021c; University of Michigan Kidney Epidemiology and Cost Center, 2018). Over time, insurance companies and state regulators have used the rating system for incentive payments, referrals, and loans (AHCA/NCAL, 2020). Today the Medicare Care Compare database acts as a clearinghouse for independent quality assessments, as well as patient surveys when available (CMS, 2021b). For long-term acute care, the website also allows for benchmarking against national averages on the hospital's rates of *C. difficile* infection and catheter- and central line-associated infections (CMS, 2021c).

The Care Compare database is meant to be easy to use and to consolidate relevant information into one website (CMS News and Media Group, 2020). By giving more emphasis to antimicrobial stewardship in the public indicators on Care Compare, Medicare could help draw attention to the importance of stewardship programs among providers and Medicare beneficiaries.

## STEWARDSHIP IN ANIMAL MEDICINE IN THE UNITED STATES

While the basic concepts of antimicrobial stewardship are the same in human and animal medicine, the practices differ considerably. CDC guidance on antimicrobial stewardship in hospitals, outpatient medicine, nursing homes, and critical access facilities all emphasize the role of executive leadership and accountability for stewardship throughout health system; they all also stress the role of pharmacists (CDC, 2019c, 2020g, 2021a). These intervention points have no direct parallel in veterinary medicine. Despite recent trends toward consolidation, about half of veterinarians work in practices that employ fewer than 100 people (Ouedraogo et al., 2018). Most veterinarians dispense medicines from their practice without a pharmacy intermediary (Morley et al., 2005). For these reasons, the American Veterinary Medical Association (AVMA) emphasizes the role of the veterinarian "individually and as a profession" in antimicrobial stewardship (AVMA, 2021a).

One core element of antimicrobial stewardship that does apply across a range of human and animal medicine practices is tracking. It is impossible to measure progress against any goal, especially a complex, multifaceted endpoint like antimicrobial stewardship without understanding patterns of use or being able to measure the effect of interventions. Better information about antimicrobial use in animals is a serious barrier to better stewardship. Of particular concern is the veterinary use of antimicrobials thought to promote pathogens' cross-resistance to human antimicrobials (Singh and Bhunia, 2019).

### Tracking Antimicrobial Use in Animals

The United States does not have a strong system to track antimicrobial use in animals. While the Food and Drug Administration (FDA) requires companies that make animal medicines to report their annual antimicrobial sales, the actual use of the drugs is harder to measure (FDA, 2020e). Veterinarians may buy medicines that they do not use or do not use immediately (FDA, 2020e). It is also difficult to make inferences about use without information about the number and species of animals treated. Large differences in size and metabolism among species make it impossible to draw meaningful conclusions about trends in consumption from sales information

(FDA, 2020e). Even sales data are only available for food-producing animals. Much less can be said about antimicrobial use in pets, as Box 5-3 explains.

**BOX 5-3**
**Antimicrobial Use in Companion Animals**

Most of the attention given to antimicrobial use in animals concerns food-producing animals, but pets can also harbor drug-resistant pathogens. Humans live closely with pets; there are many opportunities for resistant pathogens to pass between them. Surveillance data and focused research suggest increasing problems with drug-resistant infections in pets. Methicillin-resistant *staphylococcus* is a problem in dogs; ESBL-producing Enterobacterales, drug-resistant *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Enterococcus* species are all increasingly common in dogs and cats.

Treating these infections is challenging because no antimicrobials have been approved for companion animals since 2012, and only six have been approved since 1997. Antimicrobials approved before 1997 may have label approvals dating from the 1960s, meaning the doses and indications entirely predate the pathogens and susceptibility profiles veterinarians are seeing today. The use of outdated drugs and dosages is a risk for therapeutic failure; it also encourages the evolution of resistance.

There are regulatory restrictions on use of medically important antibiotics in animals that will enter the food chain. There are no such restrictions in pets (or in zoos and aquariums), nor is off-label use of human medicines in pets restricted. Injectable third-generation cephalosporins are commonly used, as are WHO watch group medicines such as levofloxacin, ciprofloxacin, meropenem, and the tuberculosis drug rifampin, and the reserve group drug linezolid. A recent survey across three academic veterinary hospitals in the United States found fluoroquinolones and third-generation cephalosporins to be the most frequently used critically important antimicrobials.

Veterinarians recognize the problems with using medically important human medicines in pets, but there are no other options to treat these animals. Veterinary hospitals may have stewardship or restriction programs, and recent treatment guidelines encourage as short a treatment course as possible. It is difficult to say how well such efforts work, however, because there is no formal surveillance or monitoring of antimicrobial use in companion animals. Veterinarians generally dispense medicines from their clinics purchased directly from a distributor. They may also write prescriptions to retail pharmacies, but there is no way to track those prescriptions, nor is there a system for monitoring antimicrobial sales as there is with food-producing animals. Surveys of veterinary practices may give some insight into antimicrobial use, so, in theory, could the internal sales data of drug distributors, animal hospitals, or laboratories. But there is no national monitoring system for antimicrobial use in pets.

SOURCES: Goggs et al., 2021; Papich, 2020.

More accurate information about antimicrobial use on farms comes from U.S. Department of Agriculture (USDA) and FDA research. USDA's National Animal Health Monitoring System (NAHMS) conducts regular (every 5 to 10 years) surveys of antimicrobial use and resistance in different animals (Bright-Ponte, 2020). Recent surveys in cattle and swine feedlots provided a baseline for comparisons of how FDA guidance on judicious antimicrobial use may change practices (Bright-Ponte, 2020; USDA, 2017, 2019). These surveys include questions about the farmer's relationship with a veterinarian and include analysis of biological

samples from the animals and the farms' records (USDA, 2017, 2019). Collecting these data more frequently or widely would be complicated logistically. Cattle agriculture in particular is characterized by considerable market fragmentation (Bright-Ponte, 2020). There are also wide differences in record keeping on farms (Bright-Ponte, 2020). Despite agreement that the indication for using an antimicrobial, the dose, duration, and route administered (e.g., injected, orally, in feed) are key data to capture, it remains challenging to do so (Bright-Ponte, 2020).

At the writing of this report, the FDA Center for Veterinary Medicine had pilot projects under way to get additional information on antimicrobial use in animals. In 2016, it funded two 5- year cooperative agreements, one characterizing antimicrobial use in U.S. beef feedlots and dairies, the other collecting data on antibiotic use in U.S. poultry and swine production (USDA, 2018). The agency announced another cooperative agreement examining antimicrobial use in dogs and cats in 2020 (FDA, 2020d). The committee commends the FDA on these efforts that will give valuable insight into the relationship between antimicrobial use in animals and the emergence of the resistance and will inform long-term strategies on how best to monitor antimicrobial use. The CDC also has projects in place to strengthen tracking and data collection on farms (CDC, 2021d).

*Capturing Prescription Data*

At the same time, considerable information on drug choice, indication, dose, route of administration, and species is lost at the farm level. Prescriptions are one way to measure consumption of, and indication for, antimicrobials. Since 2017, FDA rules have required a veterinarian's written authorization for the use of certain drugs in animal feeds (Clark, 2017). The same rules disallow the use of medically important antimicrobials without veterinary oversight (Clark, 2017). Since veterinary medicines do not necessarily go through a pharmacy, however, not all states require veterinarians to provide prescriptions, though AVMA recommends they always be made available upon request (AVMA, 2021b,c). To this end, some states encourage veterinarians to use electronic prescribing systems, and the electronic prescribing software is already in use (AVMA, 2021d).

The FDA Center for Veterinary Medicine has the mandate to monitor animal medicines and to conduct research that advances this work (FDA, 2020b). The center could promote better antimicrobial stewardship by investing in strategies to advance the use of electronic prescriptions and to encourage the sharing of prescription information in proprietary hands. In the near term, the agency can continue to research ways to better estimate antimicrobial use in animals.

**Recommendation 5-2: The Food and Drug Administration's Center for Veterinary Medicine should establish a process and clear metrics to facilitate better tracking of antimicrobial consumption in animals. This information would support the design and implementation of stewardship programs.**

Prescription data would help make more sense of raw antimicrobial use information as it would clarify what species is being treated; it would also allow insight into where stewardship programs are working and what practices help promote them (Pinto Ferreira, 2017). Better prescription data would also afford better understanding of antimicrobial use in companion animals, something not currently tracked. Unfortunately, there are no user-friendly technologies to collect prescription information (Pinto Ferreira, 2017). Therefore, mandatory electronic

prescriptions are a valuable *long-term* goal in veterinary medicine. The FDA should encourage veterinarians and farmers to work towards this goal, communicating how better tracking of antimicrobial use in animals would do much to improve our understanding of effective stewardship. With better data, it would be possible to reward producers for good antimicrobial stewardship through tax breaks or other incentive programs (Pinto Ferreira, 2017).

The agency could also emphasize the accompanying benefits of electronic prescribing. For example, it can help veterinarians, particularly those who work a diverse range of species, automatically calculate correct dosages. It would also allow insight into the extra-label (called off-label) prescribing of human medicines in animals, a practice not uncommon in companion animals (Goggs et al., 2021; Papich, 2020). Although the FDA prohibits the off-label use of certain antimicrobials, notably fluoroquinolones and cephalosporins, in food-producing animals, there is considerable ambiguity regarding other drugs, and better insights into the need for—and real-world use of—medicines in veterinary practice would be useful (FDA, 2021a).

Electronic prescriptions also provide an entry point for steps to control the prescription of critically important human antimicrobials. A recent randomized, controlled trial in the United Kingdom found that by monitoring electronic prescriptions it was possible to alert veterinarians when their prescribing of the highest priority human medicines was above the median (Singleton et al., 2021). When combined with regular meetings and education about stewardship and benchmarking of the practice prescribing patterns, also facilitated through review of electronic records, prompts about prescription practice reduced the use of critically important antimicrobials by almost 40 percent in cats and over 23 percent in dogs (Singleton et al., 2021).

In human medicine, research on electronic records is difficult as the data is usually proprietary (Adibuzzaman et al., 2017; Gliklich et al., 2014). There is time to avoid or control this problem in animal medicine by encouraging data accessibility in the early stages of the shift to electronic prescribing.

The goal of this recommendation is to make accessible the information about dose, duration, and indication for how antimicrobials are used and in what species. Advancing this goal may mean better outreach to private industry. The largest veterinary provider in the United States, for example, is Mars, Incorporated, which owns one of the largest veterinary laboratory chains in the country (Kelloway, 2018; Veterinary Practice News Editors, 2017). As the FDA has relationships with Mars and other animal health companies, it could involve them in the discussion about accessibility and monitoring of antimicrobial consumption data.

In its communication, the agency should emphasize the value of aggregate information about antimicrobial use and the need to identify patterns of judicious use as well as misuse. This is consistent with international trends. In Denmark, for example, the VetStat central database, a national repository of electronic prescribing and other reporting requirements for farmers and pharmacies, has been in use since 2001 (AACTING, 2021). VetStat data have been used to estimate daily doses of active ingredients per 100 animals, a much higher level of precision than is now possible in the United States (AACTING, 2021). By tracking VetStat data, Danish authorities identified a rise in antimicrobial consumption between 2001 and 2009, mostly driven by use in pigs (FAO and Denmark Ministry of Environment and Food, 2019). The national regulatory authority used this information to establish antibiotic use thresholds and a warning system for farms exceeding this threshold, reducing antimicrobial consumption by 90 percent (relative to 2009 levels) in less than 5 years (DVFA, 2017).

Similar monitoring systems are taking hold across Europe. In 2019, the European Medicines Agency issued regulations on monitoring the use of antimicrobials in animals,

encouraging the monitoring of veterinary prescriptions as a means to understand use (EMA, 2020). In response, European countries are developing national databases similar to Denmark's VetStat to collect and store electronic prescriptions (Chirollo et al., 2021; Government of Ireland, 2021; Koper et al., 2020).

The committee recognizes that additional data accessibility requirements put a burden on veterinarians and may be met with resistance from producers. The shift to electronic prescribing and the central monitoring systems similar to what can be found in Europe is, to be clear, a long-term goal. Production systems in the United States are different from those in Europe, so it is unlikely that duplicating the VetStat system would be a suitable goal for this country. There are other ways to monitor antimicrobial use to inform stewardship programs in each state. In any case, the monitoring system used is less important than the measures of use derived.

There is no standardized system to measure antimicrobial use in animals (Kasabova et al., 2019). Units of measurement for antimicrobial use include expressions of the mass of the active substance administered, the dose (how many milliliters of medicine used multiplied by the mg/ml concentration of active ingredient), or a count of days treated or courses of medicine administered (Sanders et al., 2020). Mass and dose measures then need to be divided by some indicator of the target animal population: average number of animals treated, mass of the meat produced, or standardized weight of the animals treated, for example (Sanders et al., 2020). Different estimates of the population treated and animal weights affect the estimates of use (Kasabova et al., 2019). Count-based measures such as the number of days treated per year have some advantage in being essentially indicators of treatment incidence, something relatively direct to calculate and meaningful to both farmer and veterinarian (Sanders et al., 2020). For this reason, count measures may be more amenable to benchmarking and comparisons among farms (Sanders et al., 2020).

Measuring antimicrobial use and prescribing practices in animals is related to concerns about veterinary drug labeling. Not all veterinary antimicrobials have up-to-date labels that reflect current standards of judicious use (The Pew Charitable Trusts, 2016). For example, 28 percent of medically-important antimicrobials used in animal feed have no defined duration of use, introducing guesswork for the veterinarian and possibly exposing the animal to an unnecessarily prolonged treatment (FDA, 2021b). The FDA Center for Veterinary Medicine's recent work to support better antimicrobial stewardship calls for updating the approved use and conditions of antimicrobials and to the labels that inform their use (FDA Center for Veterinary Medicine, 2018). To this end, the agency has mobilized funding for research to establish duration limits for antimicrobials in the feed of food-producing animals (FDA, 2020c). The committee commends these steps, and sees that attention to monitoring prescribing patterns could be a complement to FDA's work to revise and update antimicrobial labels. Ultimately, action in both areas is needed to promote judicious use of antimicrobials in veterinary medicine.

In any effort to measure antimicrobial use or to promote stewardship in animal agriculture, the FDA should work with and strengthen collaboration with USDA. The ongoing and proposed additional surveillance studies conducted through USDA's NAHMS program are valuable tools to this end (USDA, 2014). USDA also has a valuable agricultural extension network that can be used for education and outreach. Research has shown agricultural extension staff to be a trusted source of information on antimicrobial stewardship for farmers (Ekakoro et al., 2019; Wemette et al., 2020). Extension programs can also do much to improve information management on the farm and promote the best practices in biosecurity, both of which control antimicrobial use (Baudoin et al., 2021; Clark et al., 2012; Henriksson et al., 2018). For these

reasons, agricultural extension is already highlighted in USDA and CDC's antimicrobial resistance programming (NIMSS, 2017).

Implementation of this recommendation would pave the way for better information on how antimicrobials are used in animals. This is an important and necessary step for better antimicrobial stewardship. Generating these data is not, in itself, enough to inform policy, however. In setting up a system for tracking antimicrobial use, the FDA would need to consider steps to ensure the information was properly analyzed and interpreted. This could come from within the agency, though designating an independent third-party for analysis might be a better way to overcome industry reluctance to share sensitive information.

### The Need for Animal-Specific Breakpoints

In addition to better understanding how veterinarians use antimicrobials, the cause of good stewardship (using the right drug, in the right dose, for right duration) in veterinary medicine is held back by challenges in availability and use of veterinary diagnostic tests. Some of the factors that encourage reliance on empiric treatment in human medicine apply to veterinary medicine as well (e.g., slow turnaround time for diagnostic test results). These problems are amplified, however, by several factors unique to animals. First is the logistical challenge of collecting diagnostic samples on a farm. If the sample can be drawn in a minimally disruptive way, during milking for example, the logistical burden is lower than if testing disrupts the animal's routine (Lubbers, 2021). The process of bringing the animal into a chute to draw a sample is stressful for the animal and sometimes dangerous for its handlers (Lubbers, 2021). Especially when large animals are involved, the safety concerns alone are enough to encourage empiric treatment (Lubbers, 2021). There are also financial barriers. In veterinary medicine the animal owner generally pays out of pocket not only for medicines, but for diagnostic testing used to inform treatment. The veterinarian and his or her client must weigh this additional expense, around $20 to $110 per sample, against the likelihood of the result yielding novel information that would alter clinical treatment (ISU, 2021). Finally, even after the samples are drawn and submitted for testing, the veterinarian may not be able to act on the information returned because there are no established susceptibility breakpoints for that microbe–drug combination in the species tested.

Establishing susceptibility breakpoints requires balancing information on the mechanism by which an organism is resistant to a drug, the range and distribution of observed minimum inhibitory concentrations, the pharmacokinetic and pharmacodynamic properties that influences drug concentration in tissue, and data on clinical outcomes from similar cases (Humphries et al., 2019). As a recent review paper explained, "breakpoint decisions are rarely clear-cut" and are therefore often the work of expert committees convened by international organizations (Weinstein and Lewis, 2020). The best known of these are the Clinical Laboratory Standards Institute (CLSI), run in partnership with the International Standards Organization, and the European Committee in Antimicrobial Susceptibility Testing (EUCAST) (Kahlmeter et al., 2019). CLSI breakpoints and interpretative criteria are widely used in the United States and internationally (Weinstein and Lewis, 2020). CLSI is also approved by the FDA as a "standards development organization," meaning that the FDA accepts most CLSI interpretative criteria for susceptibility tests (FDA, 2020a). EUCAST, founded in 1997 by the European Society for Microbiology and Infectious Disease, serves a similar role in Europe; its breakpoints are also used internationally (EUCAST, 2021).

Most antimicrobial susceptibility test guidelines were developed for human pathogens, but work on veterinary breakpoints has followed. Since the late 1980s, CLSI has convened the Sub-Committee on Veterinary Antimicrobial Susceptibility Testing to develop interpretive breakpoints for bacterial pathogens in animals (Lubbers, 2021). EUCAST convened its Veterinary Committee on Antimicrobial Susceptibility Testing (VetCAST) in 2015 (EUCAST, 2021). These two volunteer groups develop interpretative standards and guidelines for their respective organizations and the regulatory agencies that reference them. Both groups rely heavily on independent research and on clinical trial data submitted by the drug companies.

Breakpoints in veterinary medicine are specified not just by microbe–drug combination, but also by species and disease process (Toutain et al., 2017; Watts et al., 2018). Even when the drug and pathogen are constant, the drug may be administered differently in different animals. Differences in physiology and metabolism among species further influence the way the drug moves (pharmacokinetics) and its ultimate efficacy. Therefore, the ability to develop new susceptibility test breakpoints depends on collecting and creating pharmacokinetic-pharmacodynamic data for different drugs in different species and on convening experts to review and interpret this data. Both the data and the expertise to review it are somewhat scarce (Damborg, 2021; Toutain et al., 2017). Despite agreement that more animal-specific breakpoints are needed, it is difficult to keep up momentum for the process (FAO, 2019; Toutain et al., 2017). The time and expense of building the evidence base to inform breakpoint analysis is a complicated precursor to any interpretation of test criteria.

There are, therefore, too few interpretive breakpoints for antimicrobial susceptibility tests in animals, especially in food-producing animals (Toutain et al., 2017; Watts et al., 2018). Such breakpoints are vital to antimicrobial stewardship in veterinary medicine; they are also a cornerstone of surveillance and monitoring resistance patterns. Despite decades of effort from standard setting organizations, development of needed breakpoints has not kept pace with the demand for them, especially in light of increasing emphasis on antimicrobial stewardship in veterinary medicine. Deliberate effort at the level of the federal government would encourage the research needed to develop these breakpoints for key drug, pathogen, and species combinations.

**Recommendation 5-3: The Food and Drug Administration's Center for Veterinary Medicine should convene an advisory committee to coordinate development of antimicrobial susceptibility test breakpoints in animals and identify priority animal, drug, and pathogen combinations. When necessary, the Center for Veterinary Medicine would fund the research needed to develop the priority breakpoints.**

There are many combinations of pathogen, drug, and animal species of interest in veterinary medicine. Choosing priorities for breakpoint development from among these many combinations should be done in a more deliberate way, with more open communication among clinicians who use the test results and the diagnostics laboratories that generate them, as well as the standards organizations that set the breakpoints, and the scientists who do the pharmacokinetic and pharmacodynamic research. The FDA advisory committee system is designed to bring such varied stakeholder groups together and to get advice from niche subject-matter experts outside of government (FDA, 2020f).

This committee would work with the CLSI Veterinary Antimicrobial Susceptibility Testing subcommittee and with clinical stakeholders to assess the various microbe–drug–species combinations and identify the most urgent needs for animal health and public health. The committee need not start from scratch. AVMA recently published an assessment of species-specific antimicrobial-resistant pathogens that affect animal health (AVMA, 2020). Pathogens identified in this document could serve as the starting point for the proposed advisory committee. This list could be immediately narrowed to pathogens treated with antibiotics that are important to human medicine (e.g., cephalosporins, fluoroquinolones, and macrolides) and to zoonotic pathogens that affect both animals and humans (e.g., *Salmonella* and *Campylobacter*).

The committee would still face a problem of insufficient data about veterinary pathogens. In general, information about veterinary antimicrobials are scarce, and often the proprietary data of pharmaceutical companies. The FDA has the authority to ask drug sponsors to collect more data during the approval process and to encourage them to work with CLSI's VAST (Veterinary Antimicrobial Susceptibility Testing) subcommittee to generate the information needed to develop susceptibility test breakpoints. The advisory committee could provide guidance on what data are needed for establishing breakpoints and what methods should be used to generate the data. These may include epidemiological studies, pharmacokinetic and pharmacodynamic data, and clinical trials.

Currently, CLSI's Veterinary Antimicrobial Susceptibility Testing subcommittee develops breakpoints with volunteer effort, based on data availability and willingness of an individual committee member to champion an effort (Watts et al., 2018). This process is not efficient or sustainable. The proposed advisory committee would evaluate the current process and identify ways to improve it. Particularly, the committee could consider funding research to generate data that are critically needed for developing breakpoints.

In the longer term, the committee could consider ways to increase the pool of qualified experts to participate in veterinary breakpoint development. This may include training strategies in the United States and enhanced collaboration and coordination between CLSI-VAST and VetCAST to take advantage of expertise available in different countries. Increasing international collaboration may have the added benefit of paving the way for more harmonized methods internationally.

The advisory committee could also work with veterinary organizations such as the USDA National Animal Health Laboratory Network, the FDA Veterinary Laboratory Investigation and Response Network, and the American Association of Veterinary Laboratory Diagnosticians to educate their members about the relationship between antimicrobial susceptibility test data and antimicrobial stewardship. Both epidemiological and clinical studies are needed to assess the effectiveness of national and regional stewardship programs. Better education and member outreach, something the associations have experience with, could help strengthen efforts to increase diagnostic testing.

There is also a need for new quality control and testing methods that these organizations could help develop. Although progress has been made in standardizing susceptibility test methods, there are still considerable needs remaining. For example, some pathogens grow slowly or require special culture conditions. There is a special need for testing methods for the so-called fastidious pathogens, organisms that will only grow in the presence of specific nutrients or atmosphere, such as mycoplasma, mycobacteria, and anaerobes (Watts et al., 2018). Since these pathogens grow slowly or require special culture conditions, they are not amenable to standard

laboratory methods, but are important for animal health. Attention to speeding the development of tests for them would be a meaningful use of the advisory committee's effort.

The advisory committee could also identify a standardized system for veterinary diagnostic labs to report susceptibility test data to veterinarians. Currently, most veterinary diagnostic labs in the United States use disc diffusion and broth microdilution (Dargatz et al., 2017). Yet there is considerable variability in how the results are reported (e.g., a numeric or categorical measures of susceptibility) and the forms used for reporting. This variability arises in part from the uncertainty in breakpoints this recommendation aims to reduce. It also causes confusion among the users of the data and inconsistency in their ability to act on the results (Dargatz et al., 2017). The standardized reporting system would be developed with input from commercial test developers, veterinarians, and other end users and would provide not only interpretation of the results (e.g., pathogen is susceptible, intermediate, or resistant) but also quantitative data (e.g., minimum inhibitory concentrations).

Attention from the FDA could help make veterinary susceptibility testing less ad hoc, but after setting out the priority pathogen, drug, and species combinations there will still be a need for pharmacokinetic and pharmacodynamic data to establish the needed breakpoints, especially for generic drugs. By designating funding for this research, the agency could remove another major barrier to better antimicrobial stewardship in animals.

## DIAGNOSTIC STEWARDSHIP IN THE UNITED STATES

Across human and animal medicine, accurate, fast diagnostic tests are needed to promote antimicrobial stewardship. By making test results available to clinicians before they start empiric treatment, diagnostic testing can avoid much unnecessary empiric treatment. In a 2018 commentary, Jim O'Neill, the lead commissioner of the O'Neill report, described rapid diagnostics as "the single biggest potential game changer in the fight against antimicrobial resistance" (Collier and O'Neill, 2018). In low- and middle-income countries, diagnostics have the potential to save millions of lives; an estimated 405,000 child deaths from bacterial pneumonia could be avoided with diagnostic tests (Moeller et al., 2007). In the United States, their value would be more on the side of avoided unnecessary or poorly targeted treatments.

As this report has explained, much of the error in treating infectious disease stems from uncertainty, an abundance of caution weighted in favor of the patient, even if the patient's interests are not aligned with the larger interests of society. This human calculus encourages treatment, and treatment with broad-spectrum antibiotics, on the *possibility* that the patient would benefit. Research in British primary care practices, where antibiotic prescribing is generally much more restrained than in the United States, still indicates that between 8 and 23 percent of antibiotic prescriptions are inappropriate and could be avoided with better diagnostics (Smieszek et al., 2018).

The well-founded fear of failing to treat a serious infection is reflected in formal treatment guidelines. For example, surveillance of gonococcal isolates in the United States since 2009 has shown an alarming trend in resistance to azithromycin, with elevated minimum inhibitory concentrations of azithromycin seen in almost 5 percent of isolates by 2018 (St Cyr et al., 2020). These data prompted the CDC to revise first-line treatment guidelines for gonorrhea to ceftriaxone, a WHO Watch Group medicine, in 2020 (St Cyr et al., 2020; WHO, 2021). This is a prudent revision and one needed in response to rising levels of azithromycin resistance. If there were a fast, reliable way to distinguish azithromycin-susceptible cases from the azithromycin-

resistant ones, then more targeted use of the second-tier treatment would be possible. Molecular assays to rule out fluoroquinolone-resistant gonococci by detecting *gyrA* gene would allow for prediction of ciprofloxacin susceptibility (Hemarajata et al., 2016). Such tests would, in turn, slow the spread of resistance and preserve the useful life of antimicrobial medicines.

Despite wide agreement that rapid diagnostic tests could reduce unnecessary reliance on antimicrobials, their uptake has been slow and uneven (PCAST, 2020; Review on Antimicrobial Resistance, 2015). Some of the barriers relate to the product development pipeline (e.g., regulatory hurdles, clinical trials, and data validation) and will be discussed in the next chapter. There are also useful diagnostic tests already on the market that are not used widely enough to drive better stewardship.

Rapid, point-of-care diagnostic tests, when used appropriately, could have considerable benefit for antimicrobial use and patient outcomes. At the same time, these tests can also lead to an overuse of testing that may have the opposite effect on antimicrobial use than was intended. Diagnostic stewardship helps ensure that the right test and the most clinically relevant results are being reported on the right patient, avoiding unnecessary therapeutics and inappropriate management (Messacar et al., 2017). Testing for bacterial pharyngitis caused by *Streptococcus pyogenes* is often rapid and performed at the point of care, but in the absence of defined bacterial pharyngitis symptoms, a positive test (due to colonization rather than infection) may lead to a misdiagnosis of bacterial pharyngitis, in turn leading to overuse of antibiotics (Thompson et al., 2021a). Another example are urine cultures, which are notoriously overused and overinterpreted, leading to the overdiagnosis of urinary tract infections in patients with no symptoms, who happen to have bacteria in the urine (asymptomatic bacteriuria) a syndrome which does not warrant treatment (Chan-Tack et al., 2020). In using or developing rapid diagnostics for urinary tract infections, speeding the time to results is important, but it is also important to consider the target patient population for the test. Understanding the test performance and clinical interpretation in specific populations, such as patients in long-term care facilities, pregnant women, and children, will be critical in optimizing the use of these novel diagnostics for urinary tract infections (Patel et al., 2021).

Clinical microbiologists are important stewards of these diagnostic tests, particularly as molecular developments yield more complex tests that put more interpretative demands on laboratory staff. Communication between clinical microbiologists and prescribers helps ensure that rapid diagnostic tests are used at the right time on the right patient for optimal patient care.

One rapid diagnostic test that would optimize patient care would be a point-of-care test to distinguish viral from bacterial infection. A blood test that can make this distinction in 12 hours, rapid only in comparison to traditional culture and disk susceptibility testing methods, is projected to hasten de-escalation is hospitals with the potential to reduce antimicrobial use by 14 percent (Yui et al., 2020). In a trial at a large teaching hospital, multiplex PCR on positive blood cultures, along with antimicrobial stewardship, reduced use of broad-spectrum antimicrobials (Banerjee et al., 2015). The same technology can be used at point of care to assist in identifying viral infections (i.e., respiratory virus infections) in outpatient medicine and have performed better than antigen tests in terms of targeting treatment and improving workflow in the clinic (Beal et al., 2020). Nevertheless, at a cost of more than $100 a test for consumables alone, the diagnostic is considerably more expensive than an antibacterial medicine (Genome Web, 2012). Recent CMS reimbursement guidelines clarify that such tests will not be covered unless certain additional patient criteria are met, such as the patient's serious or critical illness and underlying conditions (e.g., cystic fibrosis, chronic obstructive pulmonary disease) (CMS, 2021e).

Point-of-care tests for infections account for some of the highest volume of diagnostic tests performed (Bonislawski, 2019). These tests also have very low profit margins for their manufacturers; there is no advantage to a high test volume when every test is individually run (Bonislawski, 2019). Recent reductions in the CMS reimbursement for diagnostics could discourage use of point-of-care tests (Sears, 2018).

Furthermore, the problem of diagnostic stewardship is not just a lack of tests. Sometimes tests are available and not used (Pulcini et al., 2012). The clinical decision to prescribe an antimicrobial is influenced by the test performance and indication, reimbursement for it, and provider attitudes. The rapid antigen test for streptococcal infection, for example, is a cheap test that is widely used to direct antimicrobial treatment for pharyngitis (Barakat et al., 2019; NLM, 2020). At least with adult patients, a negative antigen test provides a reason to deny antimicrobials to a patient who may be asking for them. (In children, the strep antigen test performance is not sufficiently reliable and confirmatory culture is necessary [Barakat et al., 2019; Cohen et al., 2016]). Nevertheless, these tests are thought to decrease antimicrobial treatment relatively little (Cohen et al., 2016). At the same time, novel point-of-care diagnostic tests may be improving this picture. Nucleic acid amplification tests for group A streptococcal pharyngitis have gained use in recent years and show diagnostic accuracy comparable to that of gold-standard culture methods (Luo et al., 2019).

Tools to diagnose a viral infection in outpatient medicine could, if used widely, avert even more unnecessary treatment as empirical treatment is usually the default in these settings (Cooke et al., 2020). But most rapid tests are expensive, and they carry cost implications in terms of diverted staff time (Okeke et al., 2011). Coupled with a pressure on clinical laboratories to save money, additional spending on testing is hard to justify without solid evidence of its value (Caliendo, 2015).

The limited use of rapid diagnostics has downstream negative consequences for antimicrobial resistance (Roope et al., 2019). It is unlikely that any diagnostic test can undercut first- or even second-line antimicrobial treatments on direct cost alone. Yet society has an urgent need for wider use of these tests to allow for antimicrobial stewardship.

Reimbursing the full value of diagnostic tests would be a meaningful step toward better stewardship, but determining this value is not straightforward. Diagnostic testing is one early step on a path of treatment decisions, wherein later decisions are partially predetermined by earlier ones (Ferrante di Ruffano et al., 2012). Rapid, accurate results are valuable only if they change treatment decisions early on this path, as there is plausible reason to assume that rapid molecular drug susceptibility test results would do. Prescribers have no incentive to use a broad-spectrum antibiotic against clear indication of the narrow-spectrum drug indicated. At the same time the value of these tests, especially in terms of changes in patient outcomes such as morbidity and length of hospital stay, or financial outcomes such as cost of treatment or repeated office visits, are not usually readily apparent to doctors or administrators.

Furthermore, the switch to wider reliance on microbiological diagnostics depends on provider behavior, something that is influenced by practice guidelines that emphasize diagnostic use. For example, concerns about multidrug-resistant tuberculosis prompted the CDC to call for more research on molecular testing for drug resistance in (CDC, 2009). This research informed the 2017 revision to practice guidelines, including a recommendation to use rapid, molecular drug susceptibility tests on certain patients (Lewinsohn et al., 2017). When formal treatment guidelines reference diagnostic use, providers have clear reason to use them, although lag time to change practice can be lengthy (Morris et al., 2011).

There is wide agreement that antimicrobial stewardship should include patient and provider education as well as technological tools such as better diagnostics (O'Neill, 2018; PCAST, 2020). A lack of compelling evidence on the value of diagnostic testing, however, prevents its inclusion in practice guidelines. The Department of Health and Human Services (HHS) could help remove that barrier by supporting the outcomes research on diagnostic testing that the CDC, the Infectious Diseases Society of America (IDSA), and other societies use to inform their practice guidelines.

**Recommendation 5-4: The Department of Health and Human Services agencies, including the Centers for Disease Control and Prevention, the Food and Drug Administration, and the Centers for Medicare & Medicaid Services, and the Patient-Centered Outcomes Research Institute should support outcomes research in diagnostic testing to drive an iterative process of guidelines development and to influence reimbursement for diagnostic testing.**

The problem of widespread empiric therapy is at the center of antimicrobial resistance. Generic antibiotics will almost always be cheaper than even inexpensive diagnostic tests, discouraging providers from curtailing inappropriate antimicrobial use. Reliance on diagnostic testing has the potential to alter this pattern, but the use of these tests is limited (Trevas et al., 2021). The failure of diagnostic stewardship is a thorny and circular problem, driven by cost and human behavior as much as evidence. When confronted by a problem with multiple competing causes it can be difficult to identify the root cause, a dilemma that can lead to inaction. The committee recognizes that generating evidence on the value of diagnostic testing will not in itself alter clinicians' behavior or bring down the cost of test kits. But without explicit attention to this evidence base it is difficult to encourage clinicians to use the tests or to justify subsidizing their cost. The first step in compensating tests based on their value is establishing that value with evidence.

This recommendation echoes IDSA's recent call for, "improved study designs to better capture the clinical and economic benefits of diagnostics" (Trevas et al., 2021). Large multi-center studies evaluating the value of diagnostics tests are done mostly for regulatory approval, and are therefore focused on the tests accuracy, not on its economic or clinical value, outcomes delineated in Box 5-4 (Trevas et al., 2021). As this box shows, the cost savings associated with diagnostic testing are often accrued downstream, not in the departments closest to testing. For example, a rapid test for methicillin-resistant *Staphylococcus aureus* eventually saved $1.5 million in less than 2 years on the avoided costs of contact precautions (extra protective gowns and gloves, isolating the patients in private rooms, etc.) (Shenoy et al., 2013).

**BOX 5-4**
**Study Design Considerations for Assessing the Value of Diagnostics**

- Clearly define the unmet need, issues of concern, problems, and barriers (according to the clinical setting). Describe the limitations of the current diagnostics available.
- Clearly define the clinical settings and patient populations to be engaged.
- Apply the correct study design, control groups, study power, and statistical analyses to achieve or refute expected outcomes.

- Define outcomes measures, such as the following:

**Clinical Value**
  - Improvement in disease detection
  - Improvement in time to actionable results
  - Improvement in time to optimal antimicrobial therapy (e.g., initiate or cease antimicrobial use, increase or decrease dosage, switch to narrow-spectrum antibiotic or targeted therapy)
  - Reduction in adverse events (e.g., drug reactions, nephrotoxicity, *Clostridioides difficile* infection)
  - Reduction in morbidity and mortality (note: ideal outcome measure, but difficult to demonstrate)
  - Faster time to isolation for infection control when indicated; reduction of isolation time when not indicated
  - Identification of patient populations or subsets who would receive maximum benefit

**Direct economic value**
  - Overall cost savings in patient management
  - Reduced costs associated with antimicrobial treatments
  - Reduced hospitalization costs (e.g., length of stay, days in intensive care unit, days of ventilator use)
  - Avoidance of missed admissions or inappropriate discharges
  - Reduced costs for additional diagnostic testing (e.g., laboratory and radiologic testing)
  - Reduced health care-associated infections (note: costs not reimbursed for Medicare beneficiaries)
  - Reduced cost of unneeded infection-control measures (e.g., unnecessary isolation)

SOURCE: Reprinted with permission from Trevas et al., 2021.

The evidence needed will be challenging to generate, as it must include both clinical trials and clinical laboratories in its design. Health records and claims data, sometimes called real-world data, can also be important sources of data for outcomes research (FDA, 2021c). The participation of multiple clinical sites is also essential as the inferences made from aggregate data are more generalizable and better able to detect small but meaningful treatment differences (Kahn et al., 2012). A lack of statistical power to detect differences can also be a serious problem in diagnostics research, something that can be avoided with multisite studies. Previous research at a large teaching hospital found that rapid diagnostics cause doctors to use antimicrobials more judiciously, but was not powered to detect difference on other outcomes (Banerjee et al., 2015). Multisite studies are also more expensive to run (Lovegreen et al., 2018). There is also a need for industry participation across sites that sometimes requires the involvement of a coordinating center (Smith et al., 2019).

The Antibiotic Resistance Leadership Group has a research framework in place that would lend itself to the type of outcome research envisioned in this recommendation. The National Institute of Allergy and Infectious Diseases funds the group to design and execute clinical research related to antibiotic-resistant bacteria, including research related to improving

diagnosis (ARLG, 2021b). The group's scientific agenda emphasizes "practice-changing guidelines" and has identified diagnostics as a broad research priority (ARLG, 2021a,b). This diagnostic research portfolio is weighted toward assessment of new diagnostic tools and biomarkers, but does mention strategies to make best use of diagnostic tests (ARLG, 2021a). Although this group is not funded to do diagnostic outcome studies, its existing research and laboratory network could be a starting point for pursuing these questions.

Cost is still a major barrier to conducting outcomes research on diagnostic tests, however. HHS agencies could reduce this barrier by making such studies an explicit priority and mobilizing funding for them. Though not a major research funder, CMS does sponsor research relating to new payment policies and the effect of the agency's policies on its customers and beneficiaries (CMS, 2012). The CDC also funds research that feeds into the iterative process of guidelines development. As the national leader in developing public health guidelines, the CDC has an interest in supporting the evidence base that informs them and directing attention to serious gaps (CDC, 2012). The Patient-Centered Outcomes Research Institute (PCORI), a large public research funder, is also in a good position to investigate the relationship between antimicrobial diagnostic test use and health outcomes. PCORI's mandate is to improve the quality of evidence informing clinical and health policy decisions (PCORI, 2014).

Even with sufficient evidence to inform treatment guidelines, rapid diagnostic tests still face an uphill battle, with many clinicians choosing to wait for traditional culture and susceptibility testing before de-escalating or changing treatment. For example, genotypic assays that screen for the *mecA* gene can accurately determine resistance or susceptibility to methicillin in staphylococci, including *Staphylococcus aureus* (Bakthavatchalam et al., 2017). Use of these rapid tests are referenced in multiple treatment guidelines (Hanson et al., 2020; Uyeki et al., 2019). Yet there was a lag time of several years before the tests gained wide acceptance (Banerjee et al., 2015; Ehren et al., 2020). Though aware of these barriers, the committee encourages more attention to the evidence linking diagnostic testing with patient outcomes. Without this evidence in hand, it will be that much harder to start the process of changing clinical behavior or test reimbursement.

## STRATEGIES TO PREVENT THE EMERGENCE OF RESISTANCE ESPECIALLY IN LOW- AND MIDDLE-INCOME COUNTRIES

As Chapter 2 explained, the need for effective, good-quality antimicrobials is greater in low- and middle-income countries than in the United States, and access is a serious problem. The burden of infectious disease is higher in these parts of the world, requiring more justifiable courses of antimicrobials but also prompting more unjustified use. Governments have less to spend on health and patients have less to spend on medicines, putting even relatively inexpensive generic antimicrobials out of reach for many (Craig, 2019). Rational selection of antimicrobials is also complicated when newer treatments are not available. Of the 21 new antibiotics to come to market between 1999 and 2014, 90 percent of countries registered 10 or fewer (Craig, 2019). See Figure 5-3.

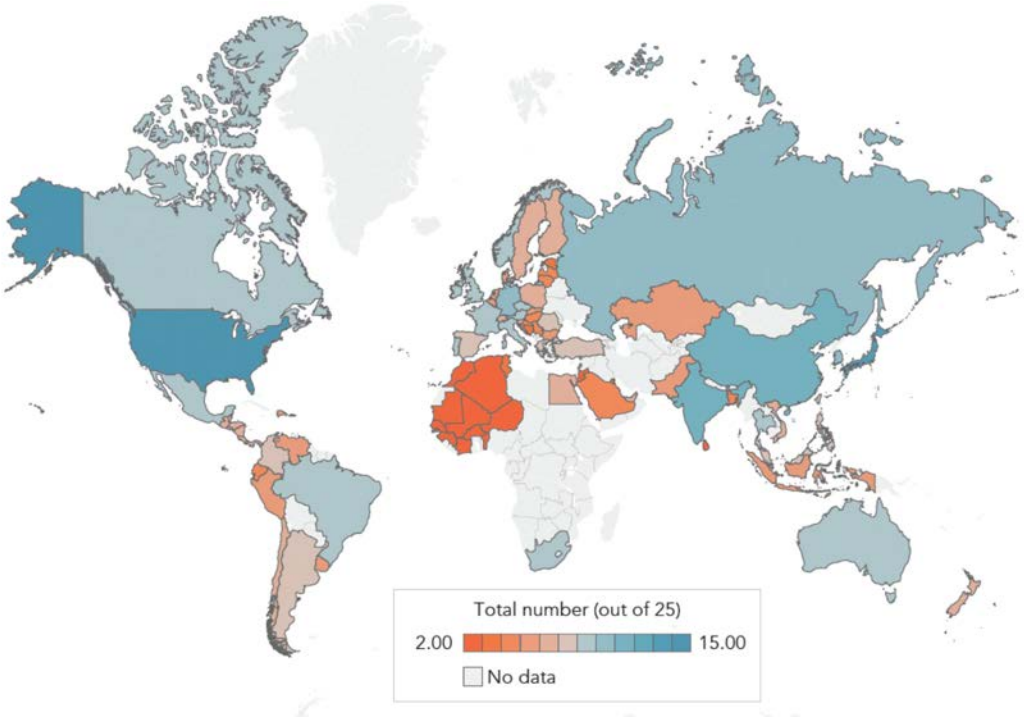



**FIGURE 5-3** New antibiotics introduced into country markets, 1999–2014.
NOTE: Countries in Central American and Francophone West Africa reported at regional levels.
SOURCE: Frost et al., 2019.

Given the greater need for antimicrobials and problems with access to medicines, interventions to curb the unnecessary use of antimicrobials are harder to implement in low- and middle-income countries. The lack of diagnostic testing and microbiology laboratories is a serious barrier to stewardship (Okeke et al., 2011; Pierce et al., 2020). Without better, rapid diagnostics coming to the market, a point discussed more in the next chapter, it is difficult to encourage more judicious antimicrobial use in low- and middle-income countries. Sales restrictions would be unwise when access to medicines is a problem, nor are they likely to be effective. The sale of antimicrobials without a prescription may be banned in some low- and middle-income countries but is still common practice (Horumpende et al., 2018; Jacobs et al., 2019; Muri-Gama et al., 2018; Sulis et al., 2020). Despite formal requirements for a prescription, more than half of antimicrobials are dispensed without one in Vietnam, about 46 percent in Bangladesh, and 36 percent in Ghana (Do et al., 2021). Even if sales restrictions were enforceable, they are not likely to be effective when only a relatively small share of the population is able to see a licensed prescriber in the first place (Bebell and Muiru, 2014; Craig, 2019; Tattevin et al., 2020). Broad targets to reduce consumption are also not appropriate given the burden of disease (Tattevin et al., 2020). In many low- and middle-income countries good antimicrobial stewardship could mean more, appropriate use, not less.

Much antibiotic use in low- and middle-income countries is for diarrheal disease and respiratory tract infections (Bielicki and Fink, 2020). Antibiotics are also often given to patients with fever against the chance that they have a life-threatening bacterial bloodstream infection like typhoid or bacteremia, but in fact more tropical fevers are caused by vector-borne diseases such as malaria and dengue (Adrizain et al., 2019; Batwala et al., 2011). Vector control, safe

drinking water, and improved sanitation could all do much to reduce the need for antimicrobials, a topic discussed more in Chapter 8.

Especially in developing countries, antimicrobial stewardship plans need to take a broad view, with an eye on reducing the need for antimicrobials. The WHO has put considerable emphasis on infection prevention in its toolkits for antimicrobial stewardship programs in low- and middle-income countries, though these toolkits are intended for use in clinical medicine, where concepts like infection prevention are necessarily somewhat narrow in scope (Pierce et al., 2020; WHO, 2019a). Action against the more distal determinants of infection has the potential to elicit a more meaningful reduction in use.

## Establishing the Value of Prevention Through Vaccination

Vaccines have the potential to reduce the need for antimicrobials and control the spread of resistance in the parts of the world where the problem is worst (Lipsitch and Siber, 2016). Though not a substitute for essential infrastructure or a functional health system, vaccines can prevent common respiratory and diarrheal diseases, something all the more valuable when improved sanitation and clean water are missing. Although many studies have assessed efficacy of vaccines in reducing infections, few high-quality studies evaluate their effect on antibiotic use and antimicrobial resistance.

Figure 5-4 shows several possible pathways through which use of vaccines could reduce antimicrobial resistance. The most obvious is by reducing the selective pressure from antimicrobials used to prevent and treat bacterial infections. Table 5-1 reviews other pathways and examples of the relationship between vaccines and antimicrobial use.

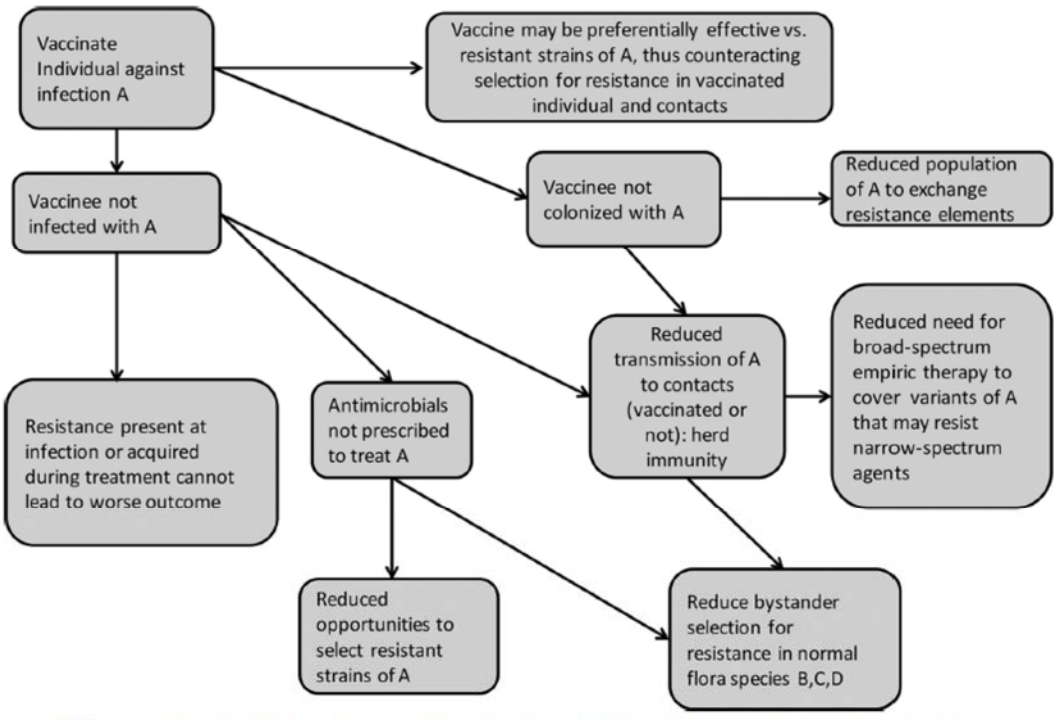



FIG 1 Mechanisms by which vaccines can contribute to reducing the prevalence and impact of antimicrobial resistance.

**FIGURE 5-4** Mechanisms through which vaccines can contribute to reducing antimicrobial resistance. SOURCE: Lipsitch and Siber, 2016.

**TABLE 5-1** Vaccines Can Work Through Many Pathways to Reduce Bacterial Infections

| Pathway Through Which Vaccines Can Reduce Antimicrobial Resistance | Examples | Evidence |
|---|---|---|
| Preventing common community acquired bacterial infections | Hib, TCV, cholera, PCV, COVID-19, as well as *Shigella*, enterotoxigenic *E. coli*, *N. gonorrhoeae*, and group B strep vaccines in development | Some, particularly for Hib and PCV |
| Preferentially targeting antimicrobial-resistant lineages of infectious bacteria | PCV | Some, PCV |
| Preventing hospital-acquired infections | MRSA, CRE, and *Acinetobacter* vaccines in development | No population study data yet, vaccines still in pipeline |
| Protecting against diseases that make patients prone to secondary bacterial infection | Influenza, measles, COVID-19 | Little, and mostly concerning antimicrobial use |
| Preventing nonbacterial infections that produce syndromes that prompt antimicrobial use or misuse | Influenza, rotavirus, COVID-19, malaria, and dengue, as well as RSV vaccine in development | |

NOTE: CRE = carbapenem-resistant *Enterobacteriaceae*; Hib = *Haemophilus influenzae* type b; MRSA = Methicillin-resistant *Staphylococcus aureus*; PCV = pneumococcal conjugate vaccine; RSV = respiratory syncytial virus; TCV = typhoid conjugate vaccine.

### *Vaccines for Bacterial Infections*

Especially in children, there is good evidence that pneumococcal and influenza vaccines predict less antimicrobial use and fewer courses initiated (Buckley et al., 2019). A recent study drawing on data from 18 low- or middle-income countries found that at current coverage levels, pneumococcal conjugate vaccine averted almost 24 million courses of antibacterials among children under 5 (Lewnard et al., 2020).

It follows that by reducing use of antibiotics, immunization would in turn slow the emergence of resistance. It is also plausible that vaccines act against resistance indirectly, by reducing the need for hospitalization and thereby reducing contact with amplifying reservoirs of resistant pathogens. For example, in the United States, before the *Haemophilus influenzae* type B vaccine (called Hib) was licensed for infants, there was increasing evidence of ampicillin resistance in meningitis, bacterial pneumonia, and epiglottitis, all diseases caused by invasive Hib (Jansen et al., 2018). The widespread use of Hib vaccine virtually eliminated invasive Hib, including infections caused by resistant strains in the United States and in low- and middle-income countries (Agrawal and Murphy, 2011).

Pneumococcal conjugate vaccines have a similar effect,[1] protecting against *Streptococcus pneumoniae*, a common bacterial pathogen that can cause meningitis, pneumonia, septicemia, and otitis media and is the worldwide leading cause of pneumonia among children under 5

[1] So called because of their outer coating or capsule from the target bacterial serotypes conjugated to a carrier.

(CDC, 2020f; WHO, 2019b). There are many types of *S. pneumoniae*, and vaccines are designed to protect against the serotypes that cause the most disease, which are also the serotypes most associated with resistant infections (Klugman and Black, 2018). For this reason, serotypes used in the vaccine are occasionally changed in response to epidemiological surveillance.

Since their introduction, multiple studies, mostly in high-income countries, have shown an association between pneumococcal conjugate vaccines and reduced antibiotic use, reduced use of second-line antibiotics, and reduced incidence of resistant infections (Klugman and Black, 2018). In the United States, rates of invasive pneumococcal disease not susceptible to penicillin dropped 64 percent among children under 5 and 45 percent among adults older than 65 following the first introduction of pneumococcal conjugate vaccine in the United States (Hampton et al., 2012). The same pattern held after the vaccine's expanded serotype coverage was introduced in 2010 (Tomczyk et al., 2016). Pneumococcal isolates collected from children with invasive infections have shown decreases in resistance to penicillin, cephalosporins, and trimethoprim-sulfamethoxazole after the introduction of a 13-serotype pneumococcal conjugate vaccine, though this research is mainly from the United States and Europe (Tin Tin Htar et al., 2019). As the technology for producing conjugate vaccines improves, the number of serotypes included is set to expand (Lochen et al., 2020). Some evidence suggests that these expanded vaccines could be used to target the bacterial linages that evolve low-level penicillin resistance (Chaguza et al., 2020).

Furthermore, pneumococcal vaccine, like many vaccines, protects against *transmissible* infection, thereby providing protection that extends beyond the vaccinated population. Vaccinated people harbor less asymptomatic *S. pneumoniae* in the upper throat and nose, also the site of most exchange of pneumococcal resistance genes (Dagan et al., 2015; Hammitt et al., 2014). By limiting the reservoir of bacteria in this resistance hotspot, the vaccine has the potential to reduce emergence of resistance. Research in Kenyan children (one of few studies of this sort in a low- or middle-income country) found that a 10-serotype conjugate vaccine reduced bacteremic pneumococcal pneumonia by 85 percent and pneumococcal meningitis by 69 percent (Dagan et al., 2015; Hammitt et al., 2014). In this study both vaccinated and unvaccinated people both carried less *S. pneumoniae* in their nose and throat. This reduction in community-wide disease burden might have been responsible for a decrease in invasive pneumococcal disease among infants too young to be vaccinated and in older age groups (Hammitt et al., 2014).

Immunization against the bacteria that cause cholera and typhoid fever can also decrease antibiotic consumption, have the potential to curb antimicrobial resistance, and may reduce transmission (Gibani et al., 2019). Cholera vaccination has proven especially valuable in humanitarian emergencies and other settings where access to clean water and sanitation is limited (Hsueh and Waters, 2019). Cholera vaccine can also reduce antimicrobial use in the outbreak, which rapidly selects resistant strains (Okeke, 2009). Two-dose, oral cholera vaccines have been shown to reduce population vulnerability outbreaks for up to 4 years, something that treatment obviously cannot do (Franke et al., 2018). While cholera vaccine is advised for travelers to areas of active cholera transmission, problems with cold chain and other logistical barriers limit the vaccines' use in the parts of the world where it is most needed (CDC, 2020c; Shaikh et al., 2020). A more serious barrier is cost; the vaccines are expensive, and population-level benefit is unlikely in anything short of a complex humanitarian emergency (Gupta et al., 2016; Teshome et al., 2018). A similar pattern holds with typhoid conjugate vaccines, which are underused in endemic areas, but preventing multidrug-resistant infections is an important reason for adoption (Khan et al., 2017).

*Vaccines for Viral Infections*

Influenza and other viral respiratory infections are important drivers of antibiotic use, which tends to rise during the influenza season (Martinez et al., 2019; Morris et al., 2017). By disrupting normal protective barriers in the respiratory tract, the influenza virus increases bacterial colonization and predisposes to secondary bacterial infection (MacIntyre et al., 2018; Morris et al., 2017). Influenza vaccines can reduce antibiotic use by preventing these secondary bacterial infections and by avoiding the febrile respiratory infections for which antibiotics are frequently (often inappropriately) prescribed.

Some real-world evidence bears out this effect. Universal influenza vaccination became policy in Ontario, Canada, when policy in the rest of the country was to vaccinate only certain high-risk groups (Kwong et al., 2009). In the years following this policy influenza vaccine coverage rose from 18 to 38 percent, and antimicrobial prescriptions for infections associated with influenza were 64 percent lower in Ontario relative to the rest of the country (Kwong et al., 2009). A similar pattern has been seen in the United States, where a 10-percentage point increase in the statewide influenza vaccination rate is associated with between 6 and 23 percent less antibiotic use after controlling for multiple confounders (Klein et al., 2020). Survey data from low- and middle-income countries show the same trend after introduction of the rotavirus vaccine; by recent estimates this vaccine avoided 13.6 million courses of antibiotics among children under 5 (Lewnard et al., 2020).

There is some trial data, mostly from Europe and North America, on the effect of influenza vaccine on antimicrobial use (Buckley et al., 2019). A recent systematic review concluded with high certainty that the vaccine has reduced antibiotic use among healthy adults by 28 percent (95% confidence interval: 16.0, 38.4); the same review found evidence of moderate certainty of a reduction in antibiotic use among vaccinated children and in children more broadly, regardless of whether they were vaccinated (Buckley et al., 2019). Nevertheless, the review ultimately concluded that the evidence tying vaccines to reductions in antibiotic use is poor, emphasizing the need for more attention to these outcomes in vaccine trials (Buckley et al., 2019).

In short, the logical argument in favor of wider vaccination as a tool to reduce antimicrobial use is clear and there is plausible evidence that vaccines control the emergence and spread of resistant bacteria. But the relationship is not well studied or understood (Buckley et al., 2019; Lewnard et al., 2020; Malarski et al., 2019). As with outcomes research on diagnostic tests, the data showing the effect of vaccines on antimicrobial use or emergence of resistance would come from large, multidisciplinary, and long-term studies, which are costly to run and difficult to manage. At the same time, incorporating questions about antimicrobial use or resistance into *ongoing* vaccine trials could be done with relatively little additional effort or expense. As research and development for vaccines, including vaccines that target antimicrobial-resistant pathogens, are going on all over the world there is considerable opportunity to study this relationship (BCG, 2018). Adding measures of resistance to immunization trials would be a relatively minor additional effort that could yield a disproportionate payoff in terms of understanding this tool for infection prevention.

**Recommendation 5-5: The National Institutes of Health and the Centers for Disease Control and Prevention should provide supplemental research funding to track antimicrobial use and antimicrobial resistance in immunization trials and large cohort studies to measure the indirect benefits**

**vaccines provide and to provide evidence to enhance vaccine deployment as a tool to mitigate antimicrobial resistance.**

Given the plausible logical argument and promising epidemiological evidence presented in this chapter, it is likely that vaccines for a number of bacterial and viral infections will reduce antibiotic use and curb the escalation of resistance in low- and middle-income countries. A recent WHO framework has called for the same, emphasizing expanding access to vaccines shown to reduce antimicrobial resistance (Vekemans et al., 2021). It is likely that there are many vaccines that meet this criteria, and further research could establish which ones those are. It is also likely that vaccines for animals would have the same preventative effects on the emergence of resistance, a topic discussed more in Chapters 6 and 8.

Nevertheless, there are multiple, often complex pathways by which vaccines influence the emergence of resistance, making it difficult to measure the full value of investment in a vaccine (Kingwell, 2018; Malarski et al., 2019). Better quality evidence, ideally from randomized, controlled trials would clarify these benefits and provide estimates of their magnitude. The size of the potential reduction in antibiotic use will be influenced by the incidence of infection and the uptake and efficacy of the vaccine. Potential benefits may be accrued only to specific demographic groups or in certain geographic areas (e.g., typhoid or cholera vaccines) or could affect the global population if infections are widespread (e.g., pneumococcal, Hib, and influenza vaccines).

This information would be valuable in considering what immunizations countries should recommend for their national immunization programs. These decisions are made by national or regional technical advisory groups charged with weighing the potential benefit of a vaccine against its cost and the ease of deployment (NITAG, 2019; WHO, 2014). The ability of vaccines to control resistance is not a criterium that enters into their review (WHO, 2014). But if better evidence were available regarding such indirect benefits of vaccines, these review criteria could change. Cost is an important consideration in evaluating a vaccine, especially in middle-income countries transitioning away from international support for their immunization programs (Wellcome, 2020). Capturing the full public health and economic value of vaccines is imperative for decision makers in these countries. Evidence that a vaccine could prolong the useful life of inexpensive antimicrobial medicines would be a strong financial argument in its favor.

In low- and middle-income countries, febrile illness is often treated with broad-spectrum antibiotics because the cause of the infection can be difficult to confirm. Empiric treatment for potential typhoid fever is common, especially among children in typhoid-endemic areas (Gibani et al., 2018; Veeraraghavan et al., 2018). Partly for this reason, resistant strains of *Salmonella* Typhi are becoming more common, especially in South and Southeast Asia (Gibani et al., 2018). These resistant bacteria no longer respond to oral antibiotics and require expensive parenteral antibiotic treatments, not readily available or affordable in typhoid-endemic countries (Gibani et al., 2018). Increasing azithromycin-resistant *Salmonella* Typhi in South Asia has prompted calls for wider use of a new typhoid conjugate vaccine (Bhutta, 2020; Carter et al., 2020). Nevertheless, country adoption of the vaccine has been slow (Jamka et al., 2019). More information on its ability to control resistance might help persuade relevant immunization councils of its value and give a needed support for coverage.

In general, the decision to introduce or expand immunization in low- and middle-income countries is based on evidence that the vaccine in question prevents severe disease and the cost to deploy it would be manageable (Ott et al., 2013). Wider cost savings and indirect benefits are not

necessarily part of this evaluation. Partly for this reason, global coverage of influenza, pneumococcal conjugate, and rotavirus vaccines are low. In the 149 WHO member states that have introduced pneumococcal conjugate vaccine, coverage is less than half (WHO, 2020). Fewer countries (101) have introduced rotavirus vaccine, and coverage in these countries was around 35 percent in 2018 (Peck et al., 2019). Influenza vaccines are particularly seldom used in low- and middle-income countries; industry data indicate that over 95 percent of influenza vaccines are deployed in Europe, the Americas, and the Western Pacific (Ortiz and Neuzil, 2019). Closing these coverage gaps could have far-reaching benefits, including curbing resistance. By 2016 estimates, universal coverage with pneumococcal conjugate vaccine would avoid 11.4 million days of antibiotic therapy in children under 5 (Laxminarayan et al., 2016).

The Wellcome Trust has recently supported research investigating the effect of vaccines on measures of antimicrobial resistance and use (Wellcome, 2021). The Bill and Melinda Gates Foundation has recently called for more evidence linking antimicrobial endpoints to vaccine use, ideally taking account of differences in local medicines markets and health systems (Srikantiah, 2018). A 2017 Chatham House publication called for the same (Clift, 2017). A recent Wellcome Trust publication pointed to barriers to vaccine uptake in low- and middle-income countries, something better clarity regarding the full public health value of immunization would help overcome (Wellcome, 2020).

There is also a certain urgency to implementing this recommendation now. There are multiple dengue vaccines currently in clinical development (WHO, 2018). The addition of antimicrobial use or resistance measures to these trials could yield invaluable information that could influence countries' use of the vaccine.

## REFERENCES

AACTING. 2021. *VetStat*. https://aacting.org/matrix/vetstat/?lid=1447 (accessed May 4, 2021).

Adibuzzaman, M., P. DeLaurentis, J. Hill, and B. D. Benneyworth. 2017. Big data in healthcare - the promises, challenges and opportunities from a research perspective: A case study with a model database. *AMIA Annual Symposium Proceedings* 2017:384-392.

Adrizain, R., D. Setiabudi, and A. Chairulfatah. 2019. The inappropriate use of antibiotics in hospitalized dengue virus-infected children with presumed concurrent bacterial infection in teaching and private hospitals in bandung, indonesia. *PLoS Neglected Tropical Diseases* 13(6):e0007438.

Agrawal, A., and T. F. Murphy. 2011. Haemophilus influenzae infections in the H. Influenzae type b conjugate vaccine era. *Journal of Clinical Microbiology* 49(11):3728-3732.

AHCA/NCAL (American Health Care Association/National Center for Assisted Living). 2020. *Five-star quality rating system*. https://www.ahcancal.org/Survey-Regulatory-Legal/Pages/FiveStar.aspx (accessed June 24, 2021).

AHRQ (Agency for Healthcare Research and Quality). 2016a. *Tool 1. Gather a team.* Agency for Healthcare Research and Quality.

AHRQ. 2016b. *Tool 2. Roles and responsibilities for antimicrobial stewardship.* Agency for Healthcare Research and Quality.

Apata, I. W., S. Kabbani, A. M. Neu, T. M. Kear, E. M. C. D'Agata, D. J. Levenson, A. S. Kliger, L. A. Hicks, and P. R. Patel. 2021. Opportunities to improve antibiotic prescribing in outpatient hemodialysis facilities: A report from the american society of nephrology and centers for disease control and prevention antibiotic stewardship white paper writing group. *American Journal of Kidney Diseases* 77(5):757-768.

Arensman, K., J. L. Miller, A. Chiang, N. Mai, J. Levato, E. LaChance, M. Anderson, M. Beganovic, and J. Dela Pena. 2020. Clinical outcomes of patients treated for candida auris infections in a multisite health system, Illinois, USA. *Emerging Infectious Diseases* 26(5):876-880.

ARLG (Antibacterial Resistance Leadership Group). 2021a. *ARLG scientific agenda*. https://arlg.org/about-the-arlg/arlg-scientific-agenda/ (accessed May 24, 2021).

ARLG. 2021b. *Who we are*. https://arlg.org/ (accessed May 24, 2021).

ASHA (American Speech-Language-Hearing Association). 2021. *Long-term acute care hospitals.* https://www.asha.org/slp/healthcare/ltac (accessed May 3, 2021).

ASM (American Society for Microbiology). 2019. CMS. final rule on antibiotic stewardship programs. American Society for Microbiology.

Augie, B. M., J. Miot, R. L. van Zyl, and P. A. McInerney. 2021. Educational antimicrobial stewardship programs in medical schools: A scoping review. *JBI Evidence Synthesis*.

AVMA (American Veterinary Medical Association). 2020. Antimicrobial resistant pathogens affecting animal health in the United States American Veterinary Medical Association.

AVMA. 2021a. *Antimicrobial stewardship definition and core principles*. https://www.avma.org/resources-tools/avma-policies/antimicrobial-stewardship-definition-and-core-principles (accessed May 4, 2021).

AVMA. 2021b. *Prescriptions and pharmacies: Faqs for veterinarians*. https://www.avma.org/prescriptions-and-pharmacies-faqs-veterinarians (accessed July 13, 2021).

AVMA. 2021c. *Veterinary prescription orders*. https://www.avma.org/advocacy/state-local-issues/veterinary-prescription-orders (accessed May 4, 2021).

AVMA. 2021d. *Veterinary telehealth: The basics* (accessed May 4, 2021).

Bakthavatchalam, Y. D., L. E. Nabarro, and B. Veeraraghavan. 2017. Evolving rapid methicillin-resistant staphylococcus aureus detection: Cover all the bases. *Journal of Global Infectious Diseases* 9(1):18-22.

Banerjee, R., C. B. Teng, S. A. Cunningham, S. M. Ihde, J. M. Steckelberg, J. P. Moriarty, N. D. Shah, J. N. Mandrekar, and R. Patel. 2015. Randomized trial of rapid multiplex polymerase chain reaction-based blood culture identification and susceptibility testing. *Clinical Infectious Diseases* 61(7):1071-1080.

Barakat, A. J., C. Evans, M. Gill, and D. Nelson. 2019. Rapid strep testing in children with recently treated streptococcal pharyngitis. *Pediatric Investigation* 3(1):27-30.

Batwala, V., P. Magnussen, and F. Nuwaha. 2011. Antibiotic use among patients with febrile illness in a low malaria endemicity setting in uganda. *Malaria Journal* 10(1):377.

Baudoin, F., H. Hogeveen, and E. Wauters. 2021. Reducing antimicrobial use and dependence in livestock production systems: A social and economic sciences perspective on an interdisciplinary approach. *Frontiers in Veterinary Science* 8:584593.

BCG (Boston Consulting Group). 2018. *Vaccines to tackle drug resistant infections: An evaluation of R&D opportunities.* Boston Consulting Group.

Beal, S. G., M. Posa, M. Gaffar, J. Reppucci, J. A. Mack, M. J. Gurka, K. Rand, H. Houck, and M. N. Kelly. 2020. Performance and impact of a clia-waived, point-of-care respiratory pcr panel in a pediatric clinic. *Pediatric Infectious Disease Journal* 39(3):188-191.

Beaulac, K., S. Corcione, L. Epstein, L. E. Davidson, and S. Doron. 2016. Antimicrobial stewardship in a long-term acute care hospital using offsite electronic medical record audit. *Infection Control and Hospital Epidemiology* 37(4):433-439.

Bebell, L. M., and A. N. Muiru. 2014. Antibiotic use and emerging resistance: How can resource-limited countries turn the tide? *Global Heart* 9(3):347-358.

Bhutta, Z. A. 2020. International travel and the risk of extensively drug-resistant (xdr) typhoid: Issues and potential solutions. *Clinical Infectious Diseases*.

Bielicki, J. A., and G. Fink. 2020. Measuring antibiotic use in children: Piecing together the puzzle. *The Lancet Global Health* 8(6):e742-e743.

Bjarnadottir, R. I., C. T. A. Herzig, J. L. Travers, N. G. Castle, and P. W. Stone. 2017. Implementation of electronic health records in us nursing homes. *Computers, Informatics, Nursing* 35(8):417-424.

Bonislawski, A. 2019. *Point-of-care testing hit hard by pama cuts*. https://www.360dx.com/clinical-lab-management/point-care-testing-hit-hard-pama-cuts#.YUjnQLhKiUl (accessed September 16, 2021).

Bright-Ponte, S. J. 2020. Antimicrobial use data collection in animal agriculture. *Zoonoses and Public Health* 67:1-5.

Buckley, B. S., N. Henschke, H. Bergman, B. Skidmore, E. J. Klemm, G. Villanueva, C. Garritty, and M. Paul. 2019. Impact of vaccination on antibiotic usage: A systematic review and meta-analysis. *Clinical Microbiology and Infection* 25(10):1213-1225.

Caliendo, A. M. 2015. Editorial commentary: Rapid blood culture identification: The value of a randomized trial. *Clinical Infectious Diseases* 61(7):1081-1083.

CARB (National Action Plan for Combating Antibiotic-Resistant Bacteria). 2020. National action plan for combating antibiotic resistant bacteria. *Federal Task Force on Combating Antibiotic-Resistant Bacteria*.

Carter, A. S., S. P. Luby, and D. O. Garrett. 2020. Introducing typhoid conjugate vaccine in south asia: Lessons from the surveillance for enteric fever in asia project. *Clinical Infectious Diseases* 71(Suppl 3):S191-S195.

CDC (Centers for Disease Control and Prevention). 2009. Report of expert consultations on rapid molecular testing to detect drug-resistant tuberculosis in the United States. Atlanta, GA: Centers for Disease Control and Prevention.

CDC. 2012. Guidelines and recommendations: A CDC primer. *Atlanta: Office of the Associate Director for Science Centers for Disease Control and Prevention*.

CDC. 2015a. *Antibiotic prescribing and use in hospitals and long-term care: Costs*. https://www.cdc.gov/antibiotic-use/healthcare/evidence/asp-int-costs.htm (accessed May 4, 2021).

CDC. 2015b. *The core elements of antibiotic stewardship for nursing homes.* Atlanta, GA.

CDC. 2018. Implementation of antibiotic stewardship core elements at small and critical access hospitals. Atlanta, GA: U.S. Department of Health and Human Services, CDC.

CDC. 2019a. *Antibiotic resistance threats in the United States, 2019.* Atlanta, GA: http://dx.doi.org/10.15620/cdc:82532.

CDC. 2019b. *Antibiotic use in the United States, 2018 update: Progress and opportunities.* Atlanta, GA.

CDC. 2019c. *Core elements of hospital antibiotic stewardship programs.* Atlanta, GA.

CDC. 2020a. Antibiotic stewardship in nursing homes: Centers for Disease Control and Prevention National Center for Emerging Zoonoti.

CDC. 2020b. Antibiotic use in the united states, 2020 update: Progress and opportunities Atlanta, GA: U.S. Department of Health and Human Services, CDC.

CDC. 2020c. *Cholera - vibrio cholerae infection*. https://www.cdc.gov/cholera/travelers.html (accessed May 24, 2021).

CDC. 2020d. *Current report: Antibiotic prescribing and use in the U.S.* https://www.cdc.gov/antibiotic-use/stewardship-report/current.html (accessed May 3, 2021).

CDC. 2020e. *Dialysis safety*. https://www.cdc.gov/dialysis/index.html (accessed May 3, 2021).

CDC. 2020f. *Pneumococcal disease (streptococcus pneumoniae)*. https://wwwnc.cdc.gov/travel/diseases/pneumococcal-disease-streptococcus-pneumoniae (accessed May 19, 2021).

CDC. 2020g. *Small and critical access facilities*. https://www.cdc.gov/antibiotic-use/core-elements/small-critical.html (accessed May 3, 2021).

CDC. 2021a. *Antibiotic prescribing and use: Nursing home facilities*. https://www.cdc.gov/antibiotic-use/core-elements/nursing-homes.html (accessed May 4, 2021).

CDC. 2021b. *Antibiotic use data and research*. https://www.cdc.gov/antibiotic-use/data/index.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fantibiotic-use%2Fhealthcare%2Fevidence.html (accessed May 3, 2021).
CDC. 2021c. CDC to invest $2.1 billion to protect patients and healthcare workers from covid-19 and future infectious diseases.
CDC. 2021d. A complex web: Everything is connected food, farms, & animals.
CDC. 2021e. *Core elements of antibiotic stewardship*. https://www.cdc.gov/antibiotic-use/core-elements/index.html (accessed May 3, 2021).
CDC. 2021f. *National Center for Health Statistics: Nursing home care*. https://www.cdc.gov/nchs/fastats/nursing-home-care.htm (accessed May 3, 2021).
Chaguza, C., E. Heinsbroek, R. A. Gladstone, T. Tafatatha, M. Alaerts, C. Peno, J. E. Cornick, P. Musicha, N. Bar-Zeev, A. Kamng'ona, A. Kadioglu, L. McGee, W. P. Hanage, R. F. Breiman, R. S. Heyderman, N. French, D. B. Everett, and S. D. Bentley. 2020. Early signals of vaccine-driven perturbation seen in pneumococcal carriage population genomic data. *Clinical Infectious Diseases* 70(7):1294-1303.
Chambers, A., S. MacFarlane, R. Zvonar, G. Evans, J. E. Moore, B. J. Langford, A. Augustin, S. Cooper, J. Quirk, L. McCreight, and G. Garber. 2019. A recipe for antimicrobial stewardship success: Using intervention mapping to develop a program to reduce antibiotic overuse in long-term care. *Infection Control and Hospital Epidemiology* 40(1):24-31.
Chan-Tack, K. M., B. W. Trautner, and D. J. Morgan. 2020. The varying specificity of urine cultures in different populations. *Infection Control and Hospital Epidemiology* 41(4):489-491.
Chandler, C. I. R., E. Hutchinson, and C. Hutchison. 2016. *Addressing antimicrobial resistance through social theory: An anthropologically oriented report.* London School of Hygiene & Tropical Medicine.
Childers, C. P., J. Q. Dworsky, G. Kominski, and M. Maggard-Gibbons. 2019. A comparison of payments to a for-profit dialysis firm from government and commercial insurers. *JAMA Internal Medicine* 179(8):1136-1138.
Chirollo, C., F. P. Nocera, D. Piantedosi, G. Fatone, G. Della Valle, L. De Martino, and L. Cortese. 2021. Data on before and after the traceability system of veterinary antimicrobial prescriptions in small animals at the university veterinary teaching hospital of naples. *Animals (Basel)* 11(3):913.
Chitnis, A. S., J. R. Edwards, P. M. Ricks, D. M. Sievert, S. K. Fridkin, and C. V. Gould. 2012. Device-associated infection rates, device utilization, and antimicrobial resistance in long-term acute care hospitals reporting to the national healthcare safety network, 2010. *Infection Control and Hospital Epidemiology* 33(10):993-1000.
Clark, C. 2017. *Veterinary feed directive: What small farming operations need to know*. https://www.extension.iastate.edu/smallfarms/veterinary-feed-directive-what-small-farming-operations-need-know-0 (accessed May 4, 2021).
Clark, S., R. Daly, E. Jordan, J. Lee, A. Mathew, and P. Ebner. 2012. Extension education symposium: The future of biosecurity and antimicrobial use in livestock production in the united states and the role of extension. *Journal of Animal Science* 90(8):2861-2872.
Clift, C. 2017. The value of vaccines in the avoidance of antimicrobial resistance: Chatham House.
CMS (Centers for Medicare & Medicaid Services). 2012. *Research & demonstration grant options*. https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ResearchDemoGrantsOpt (accessed May 24, 2021).
CMS. 2015. Nursing home data compendium 2015 edition. U.S. Department of Health and Human Services, CMS.
CMS. 2016. Medicare and Medicaid programs; reform of requirements for longterm care facilities. U.S. Department of Health and Human Services, CMS.
CMS. 2019a. Medicare and Medicaid programs; regulatory provisions to promote program efficiency, transparency, and burden reduction; fire safety requirements for certain dialysis facilities; hospital

and critical access hospital (CAH) changes to promote innovation, flexibility, and improvement in patient care. U.S. Department of Health and Human Services, CMS.
CMS. 2019b. What are long-term care hospitals? U.S. Department of Health and Human Services.
CMS. 2020. *Quality measures*. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/NursingHomeQualityInits/NHQIQualityMeasures (accessed June 25, 2021).
CMS. 2021a. *Fact sheet: Nursing home compare five-star quality rating system.* https://www.cms.gov/medicare/provider-enrollment-and-certification/certificationandcomplianc/downloads/consumerfactsheet.pdf (accessed July 13, 2021)
CMS. 2021b. *Find & compare nursing homes, hospitals & other providers near you*. https://www.medicare.gov/care-compare/ (accessed June 25, 2021).
CMS. 2021c. *Five-star quality rating system*. https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandComplianc/FSQRS (accessed June 25, 2021).
CMS. 2021d. *Medicare program - general information*. https://www.cms.gov/Medicare/Medicare-General-Information/MedicareGenInfo. (accessed May 19, 2021).
CMS. 2021e. *Proposed local coverage determination (LCD): Moldx: Multiplex nucleic acid amplification test (NAAT) panels for infectious disease testing (dl38988).*
CMS. 2021f. *Successful return to home & community*. https://www.medicare.gov/care-compare/details/long-term-care/092002?city=Washington&state=DC&zipcode=20001 (accessed June 25, 2021).
CMS. 2021g. *Your rights and protections as a nursing home resident*. https://downloads.cms.gov/medicare/your_resident_rights_and_protections_section.pdf (accessed September 15, 2021).
CMS News and Media Group. 2020. Cms care compare empowers patients when making important health care decisions.
Cohen, C. C., M. Pogorzelska-Maziarz, C. T. Herzig, E. J. Carter, R. Bjarnadottir, P. Semeraro, J. L. Travers, and P. W. Stone. 2015. Infection prevention and control in nursing homes: A qualitative study of decision-making regarding isolation-based practices. *BMJ Quality & Safety* 24(10):630-636.
Cohen, J. F., N. Bertille, R. Cohen, and M. Chalumeau. 2016. Rapid antigen detection test for group a streptococcus in children with pharyngitis. *Cochrane Database of Systematic Reviews* 7:CD010502.
Collier, P., and L. J. O'Neill. 2018. Two years on: An update on achievement towards the recommendations of the antimicrobial resistance report. *Journal of Applied Microbiology* 125(2):308-312.
Cooke, J., C. Llor, R. Hopstaken, M. Dryden, and C. Butler. 2020. Respiratory tract infections (RTIs) in primary care: Narrative review of c reactive protein (CRP) point-of-care testing (POCT) and antibacterial use in patients who present with symptoms of RTI. *BMJ Open Respiratory Research* 7(1).
Cooper, S. J. 2020. Overview of CMS rule changes to promote antimicrobial stewardship programs. Paper read at HHS Listening Session on Combating Antibiotic-Resistant Bacteria Washington, DC.
Craig, J. 2019. Weekly digest: XDR typhoid fever in pakistan; flu activity rising in northern hemisphere and south asia; antibiotic use on pennsylvania dairy farms. *Center for Disease Dynamics, Economics & Policy*.
Dagan, R., C. Juergens, J. Trammel, S. Patterson, D. Greenberg, N. Givon-Lavi, N. Porat, A. Gurtman, W. C. Gruber, and D. A. Scott. 2015. Efficacy of 13-valent pneumococcal conjugate vaccine (PCV13) versus that of 7-valent PCV (PCV7) against nasopharyngeal colonization of antibiotic-nonsusceptible streptococcus pneumoniae. *Journal of Infectious Diseases* 211(7):1144-1153.

D'Agata, E. M. C., D. Tran, J. Bautista, D. Shemin, and D. Grima. 2018. Clinical and economic benefits of antimicrobial stewardship programs in hemodialysis facilities: A decision analytic model. *Clinical Journal of the American Society of Nephrology* 13(9):1389-1397.

Damborg, P. 2021. Vetcast susceptibility test breakpoints. Paper read at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 3, Webinar.

Dargatz, D. A., M. M. Erdman, and B. Harris. 2017. A survey of methods used for antimicrobial susceptibility testing in veterinary diagnostic laboratories in the united states. *Journal of Veterinary Diagnostic Investigation* 29(5):669-675.

Denyer Willis, L., and C. Chandler. 2019. Quick fix for care, productivity, hygiene and inequality: Reframing the entrenched problem of antibiotic overuse. *BMJ Global Health* 4(4):e001590.

Do, N. T. T., H. T. L. Vu, C. T. K. Nguyen, S. Punpuing, W. A. Khan, M. Gyapong, K. P. Asante, K. Munguambe, F. X. Gómez-Olivé, J. John-Langba, T. K. Tran, M. Sunpuwan, E. Sevene, H. H. Nguyen, P. D. Ho, M. A. Matin, S. Ahmed, M. M. Karim, O. Cambaco, S. Afari-Asiedu, E. Boamah-Kaali, M. A. Abdulai, J. Williams, S. Asiamah, G. Amankwah, M. P. Agyekum, F. Wagner, P. Ariana, B. Sigauque, S. Tollman, H. R. van Doorn, O. Sankoh, J. Kinsman, and H. F. L. Wertheim. 2021. Community-based antibiotic access and use in six low-income and middle-income countries: A mixed-method approach. *The Lancet Global Health* 9(5):e610-e619.

Doron, S., and L. E. Davidson. 2011. Antimicrobial stewardship. *Mayo Clinic Proceedings* 86(11):1113-1123.

DVFA (Danish Veterinary and Food Administration). 2017. *The yellow card initiative on antibiotics*. https://www.foedevarestyrelsen.dk/english/Animal/AnimalHealth/Pages/The-Yellow-Card-Initiative-on-Antibiotics.aspx (accessed May 4, 2021).

Ehren, K., A. Meissner, N. Jazmati, J. Wille, N. Jung, J. J. Vehreschild, M. Hellmich, and H. Seifert. 2020. Clinical impact of rapid species identification from positive blood cultures with same-day phenotypic antimicrobial susceptibility testing on the management and outcome of bloodstream infections. *Clinical Infectious Diseases* 70(7):1285-1293.

Ekakoro, J. E., M. Caldwell, E. B. Strand, and C. C. Okafor. 2019. Drivers, alternatives, knowledge, and perceptions towards antimicrobial use among tennessee beef cattle producers: A qualitative study. *BMC Veterinary Research* 15(1):16.

Eljaaly, K., S. Elarabi, S. Alshehri, and D. E. Nix. 2018. Impact of requiring re-authorization of restricted antibiotics on day 3 of therapy. *Journal of Antimicrobial Chemotherapy* 73(2):527-530.

EMA (European Medicines Agency). 2020. Advice on implementing measures under article 57(4) of regulation (EU) 2019/6 on veterinary medicinal products – report on the format of the data to be collected on antimicrobial medicinal products used in animals: Committee for Medicinal Products for Veterinary Use.

Espinosa-Gongora, C., L. R. Jessen, O. J. Dyar, A. Bousquet-Melou, B. Gonzalez-Zorn, C. Pulcini, G. Re, S. Schwarz, D. Timofte, P. L. Toutain, L. Guardabassi, The PREPARE-VET Working Group, ESCMID Study Group for Veterinary Microbiology (ESGVM), and ESCMID Study Group for Antimicrobial Stewardship (ESGAP). 2021. Towards a better and harmonized education in antimicrobial stewardship in european veterinary curricula. *Antibiotics (Basel)* 10(4).

EUCAST (European Committee on Antimicrobial Susceptibility Testing). 2021. *The EUCAST veterinary subcommittee on antimicrobial susceptibility testing (VETCAST).* https://www.eucast.org/organization/subcommittees/vetcast/ (accessed May 19, 2021).

Eyler, R. F., and K. Shvets. 2019. Clinical pharmacology of antibiotics. *Clinical Journal of the American Society of Nephrology* 14(7):1080-1090.

FAO (Food and Agriculture Organization of the United Nations). 2019. *Monitoring and surveillance of antimicrobial resistance in bacteria from healthy food animals intended for consumption.* Bangkok: Food and Agriculture Organization of the United Nations.

FAO and Denmark Ministry of Environment and Food. 2019. *Tackling antimicrobial use and resistance in pig production: Lessons learned from denmark.* Rome: FAO and Denmark Ministry of Environment and Food – Danish Veterinary and Food Administration.

FDA (U.S. Food and Drug Administration). 2020a. *Antibacterial susceptibility test interpretive criteria*. https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria (accessed May 19, 2021).

FDA. 2020b. *Center for Veterinary Medicine*. https://www.fda.gov/about-fda/fda-organization/center-veterinary-medicine (accessed May 24, 2021).

FDA. 2020c. *FDA announces 2020 funding opportunity to help define durations of use for certain medically important antimicrobial drugs for food animals*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-2020-funding-opportunity-help-define-durations-use-certain-medically-important (accessed September 20, 2021).

FDA. 2020d. *FDA announces FY 2020 funding opportunity for collection of antimicrobial use data in dogs and cats*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-fy-2020-funding-opportunity-collection-antimicrobial-use-data-dogs-and-cats (accessed May 4, 2021).

FDA. 2020e. *FDA releases annual summary report on antimicrobials sold or distributed in 2019 for use in food-producing animals*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing (accessed May 4, 2021).

FDA. 2020f. *Learn about FDA advisory committees*. https://www.fda.gov/patients/about-office-patient-affairs/learn-about-fda-advisory-committees (accessed May 19, 2021).

FDA. 2021a. *Extralabel use and antimicrobials*. https://www.fda.gov/animal-veterinary/antimicrobial-resistance/extralabel-use-and-antimicrobials (accessed May 4, 2021).

FDA. 2021b. *FDA seeks public comment on potential approach for defining durations of use for certain medically important antimicrobial drugs for food animals*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-seeks-public-comment-potential-approach-defining-durations-use-certain-medically-important (accessed September 20, 2021).

FDA. 2021c. *Real-world evidence*. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence (accessed August 11, 2021).

FDA Center for Veterinary Medicine. 2018. Supporting antimicrobial stewardship in veterinary settings: Goals for fiscal years 2019 – 2023

Feldstein, D., P. D. Sloane, and C. Feltner. 2018. Antibiotic stewardship programs in nursing homes: A systematic review. *Journal of the American Medical Directors Association* 19(2):110-116.

Ferrante di Ruffano, L., C. J. Hyde, K. J. McCaffery, P. M. Bossuyt, and J. J. Deeks. 2012. Assessing the value of diagnostic tests: A framework for designing and evaluating trials. *BMJ* 344:e686.

Franke, M. F., R. Ternier, J. G. Jerome, W. R. Matias, J. B. Harris, and L. C. Ivers. 2018. Long-term effectiveness of one and two doses of a killed, bivalent, whole-cell oral cholera vaccine in haiti: An extended case-control study. *The Lancet Global Health* 6(9):e1028-e1035.

Frost, I., J. Craig, J. Joshi, K. Faure, and R. Laxminarayan. 2019. *Access barriers to antibiotics.* Washington, DC: Center for Disease Dynamics, Economics & Policy.

Fu, C. J., E. Mantell, P. W. Stone, and M. Agarwal. 2020. Characteristics of nursing homes with comprehensive antibiotic stewardship programs: Results of a national survey. *American Journal of Infection Control* 48(1):13-18.

Genome Web. 2012. *Update: Biofire ramping up filmarray adoption, test development*. https://www.genomeweb.com/pcr/update-biofire-ramping-filmarray-adoption-test-development#.YNNAjuhKiUl (accessed June 25, 2021).

Gerding, D. N. 2001. The search for good antimicrobial stewardship. *Joint Commission Journal on Quality Improvement* 27(8):403-404.

Gibani, M. M., C. Britto, and A. J. Pollard. 2018. Typhoid and paratyphoid fever: A call to action. *Current Opinion in Infectious Diseases* 31(5):440-448.

Gibani, M. M., M. Voysey, C. Jin, C. Jones, H. Thomaides-Brears, E. Jones, P. Baker, M. Morgan, A. Simmons, M. A. Gordon, V. Cerundolo, V. E. Pitzer, B. Angus, M. M. Levine, T. C. Darton, and A. J. Pollard. 2019. The impact of vaccination and prior exposure on stool shedding of salmonella

typhi and salmonella paratyphi in 6 controlled human infection studies. *Clinical Infectious Diseases* 68(8):1265-1273.

Gliklich, R. E., N. A. Dreyer, and M. B. Leavy. 2014. Registries for evaluating patient outcomes: A user's guide.

Goebel, M. C., B. W. Trautner, and L. Grigoryan. 2021. The five ds of outpatient antibiotic stewardship for urinary tract infections. *Clinical Microbiology Reviews* 0(0):e0000320.

Goggs, R., J. M. Menard, C. Altier, K. J. Cummings, M. E. Jacob, D. F. Lalonde-Paul, M. G. Papich, K. N. Norman, V. R. Fajt, H. M. Scott, and S. D. Lawhon. 2021. Patterns of antimicrobial drug use in veterinary primary care and specialty practice: A 6-year multi-institution study. *Journal of Veterinary Internal Medicine* 35(3):1496-1508.

Gotterson, F., K. Buising, and E. Manias. 2021. Nurse role and contribution to antimicrobial stewardship: An integrative review. *International Journal of Nursing Studies* 117:103787.

Gould, C. V., R. Rothenberg, and J. P. Steinberg. 2006. Antibiotic resistance in long-term acute care hospitals: The perfect storm. *Infection Control and Hospital Epidemiology* 27(9):920-925.

Government of Ireland. 2021. *Webinar series for EU regulations on veterinary medicinal products, 2019/6, and the manufacture, placing on the market and use of medicated feed, 2019/4.* https://www.gov.ie/en/publication/2dffa-webinar-series-for-eu-regulation-on-veterinary-medicinal-products-20196-and-the-manufacture-of-medicated-feed-20194/#the-future-of-prescribing-eu-regulations-and-what-they-mean-for-you (accessed May 4, 2021).

Gupta, S. S., K. Bharati, D. Sur, A. Khera, N. K. Ganguly, and G. B. Nair. 2016. Why is the oral cholera vaccine not considered an option for prevention of cholera in india? Analysis of possible reasons. *Indian Journal of Medical Research* 143(5):545-551.

Hammitt, L. L., D. O. Akech, S. C. Morpeth, A. Karani, N. Kihuha, S. Nyongesa, T. Bwanaali, E. Mumbo, T. Kamau, S. K. Sharif, and J. A. Scott. 2014. Population effect of 10-valent pneumococcal conjugate vaccine on nasopharyngeal carriage of streptococcus pneumoniae and non-typeable haemophilus influenzae in kilifi, kenya: Findings from cross-sectional carriage studies. *The Lancet Global Health* 2(7):e397-e405.

Hampton, L. M., M. M. Farley, W. Schaffner, A. Thomas, A. Reingold, L. H. Harrison, R. Lynfield, N. M. Bennett, S. Petit, K. Gershman, J. Baumbach, B. Beall, J. Jorgensen, A. Glennen, E. R. Zell, and M. Moore. 2012. Prevention of antibiotic-nonsusceptible streptococcus pneumoniae with conjugate vaccines. *Journal of Infectious Diseases* 205(3):401-411.

Hanson, K. E., M. M. Azar, R. Banerjee, A. Chou, R. C. Colgrove, C. C. Ginocchio, M. K. Hayden, M. Holodiny, S. Jain, S. Koo, J. Levy, T. T. Timbrook, and A. M. Caliendo. 2020. Molecular testing for acute respiratory tract infections: Clinical and diagnostic recommendations from the idsa's diagnostics committee. *Clinical Infectious Diseases* 71(10):2744-2751.

Harris-Kojetin, L. D., M. Sengupta, J. P. Lendon, V. Rome, R. Valverde, and C. Caffrey. 2019. Long-term care providers and services users in the united states, 2015-2016. *National Center for Health Statistics* 3(43).

Haverkate, M. R., S. Weiner, K. Lolans, N. M. Moore, R. A. Weinstein, M. J. Bonten, M. K. Hayden, and M. C. Bootsma. 2016. Duration of colonization with klebsiella pneumoniae carbapenemase-producing bacteria at long-term acute care hospitals in chicago, illinois. *Open Forum Infectious Diseases* 3(4):ofw178.

Hemarajata, P., S. Yang, O. O. Soge, R. M. Humphries, and J. D. Klausner. 2016. Performance and verification of a real-time pcr assay targeting the gyra gene for prediction of ciprofloxacin resistance in neisseria gonorrhoeae. *Journal of Clinical Microbiology* 54(3):805-808.

Henriksson, P. J. G., A. Rico, M. Troell, D. H. Klinger, A. H. Buschmann, S. Saksida, M. V. Chadag, and W. Zhang. 2018. Unpacking factors influencing antimicrobial use in global aquaculture and their implication for management: A review from a systems perspective. *Sustainibility Science* 13(4):1105-1120.

Holz, M., S. Naavaal, S. Stilianoudakis, C. Carrico, B. E. Byrne, and G. L. Myers. 2021. Antibiotics and antimicrobial resistance: Evaluation of the knowledge, attitude, and perception among students and faculty within us dental schools. *Journal of Dental Education* 85(3):383-391.

Horton, G., J. Roach, and S. Scheffler. 2020 (unpublished). *Understanding measures, star ratings, and quality outcomes*. Centers for Medicare & Medicaid Services.

Horumpende, P. G., T. B. Sonda, M. van Zwetselaar, M. L. Antony, F. F. Tenu, C. E. Mwanziva, E. R. Shao, S. E. Mshana, B. T. Mmbaga, and J. O. Chilongola. 2018. Prescription and non-prescription antibiotic dispensing practices in part I and part II pharmacies in Moshi municipality, Kilimanjaro region in Tanzania: A simulated clients approach. *PloS One* 13(11):e0207465.

Hsueh, B. Y., and C. M. Waters. 2019. Combating cholera. *F1000Res* 8:F1000 Faculty Rev-1589.

Humphries, R. M., A. N. Abbott, and J. A. Hindler. 2019. Understanding and addressing clsi breakpoint revisions: A primer for clinical laboratories. *Journal of Clinical Microbiology* 57(6).

ISU (Iowa State University). 2021. *Diagnostic tests*. https://vetmed.iastate.edu/vdl/diagnostic-tests/ (accessed May 19, 2021).

Jacob, J., A. Morace, J. Park, and N. Renzi. 2019. 1169. Preventing central line-associated bloodstream infections in long-term acute care. *Open Forum Infectious Diseases* 6(Suppl 2):S418-S419.

Jacobs, T. G., J. Robertson, H. A. van den Ham, K. Iwamoto, H. Bak Pedersen, and A. K. Mantel-Teeuwisse. 2019. Assessing the impact of law enforcement to reduce over-the-counter (otc) sales of antibiotics in low- and middle-income countries; a systematic literature review. *BMC Health Services Research* 19(1):536.

Jamka, L. P., K. W. Simiyu, A. D. Bentsi-Enchill, A. J. Mwisongo, H. Matzger, A. A. Marfin, A. J. Pollard, and K. M. Neuzil. 2019. Accelerating typhoid conjugate vaccine introduction: What can be learned from prior new vaccine introduction initiatives? *Clinical Infectious Diseases* 68(Suppl 2):S171-S176.

Jansen, K. U., C. Knirsch, and A. S. Anderson. 2018. The role of vaccines in preventing bacterial antimicrobial resistance. *Nature Medicine* 24(1):10-19.

Joint Commission. 2016. Approved: New antimicrobial stewardship standard. *Joint Commission Perspectives* 36(7):1-3.

Kadri, S. S. 2020. Key takeaways from the u.S. CDC's 2019 antibiotic resistance threats report for frontline providers. *Critical Care Medicine* 48(7):939-945.

Kahlmeter, G., C. G. Giske, T. J. Kirn, and S. E. Sharp. 2019. Point-counterpoint: Differences between the european committee on antimicrobial susceptibility testing and clinical and laboratory standards institute recommendations for reporting antimicrobial susceptibility results. *Journal of Clinical Microbiology* 57(9):e01129-01119.

Kahn, M. G., M. A. Raebel, J. M. Glanz, K. Riedlinger, and J. F. Steiner. 2012. A pragmatic framework for single-site and multisite data quality assessment in electronic health record-based clinical research. *Medical Care* 50 Suppl(0):S21-29.

Kapadia, S. N., E. L. Abramson, E. J. Carter, A. S. Loo, R. Kaushal, D. P. Calfee, and M. S. Simon. 2018. The expanding role of antimicrobial stewardship programs in hospitals in the united states: Lessons learned from a multisite qualitative study. *Joint Commission Journal on Quality and Patient Safety* 44(2):68-74.

Kasabova, S., M. Hartmann, N. Werner, A. Kasbohrer, and L. Kreienbrock. 2019. Used daily dose vs. Defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Frontiers in Veterinary Science* 6:116.

Katz, M. J., A. P. Gurses, P. D. Tamma, S. E. Cosgrove, M. A. Miller, and R. L. P. Jump. 2017. Implementing antimicrobial stewardship in long-term care settings: An integrative review using a human factors approach. *Clinical Infectious Diseases* 65(11):1943-1951.

Kelloway, C. 2018. Mars buys another veterinary network, as a candy-company turned pet care giant furthers its influence over animal health. *Food & Power*, https://www.foodandpower.net/latest/2018/06/21/mars-buys-another-veterinary-network-as-a-

candy-company-turned-pet-care-giant-furthers-its-influence-over-animal-health (accessed May 19, 2021).

Khan, M. I., C. Franco-Paredes, S. Sahastrabuddhe, R. L. Ochiai, V. Mogasale, and B. D. Gessner. 2017. Barriers to typhoid fever vaccine access in endemic countries. *Research and Reports in Tropical Medicine* 8:37-44.

Kingwell, K. 2018. Vaccines take a shot at antimicrobial resistance. *Nature Reviews Drug Discovery* 17(4):229-231.

Klein, E. Y., E. Schueller, K. K. Tseng, D. J. Morgan, R. Laxminarayan, and A. Nandi. 2020. The impact of influenza vaccination on antibiotic use in the united states, 2010-2017. *Open Forum Infectious Diseases* 7(7):ofaa223.

Klugman, K. P., and S. Black. 2018. Impact of existing vaccines in reducing antibiotic resistance: Primary and secondary effects. *Proceedings of the National Academy of Sciences of the United States of America* 115(51):12896-12901.

Koper, L. M., C. Bode, A. Bender, I. Reimer, T. Heberer, and J. Wallmann. 2020. Eight years of sales surveillance of antimicrobials for veterinary use in germany-what are the perceptions? *PloS One* 15(8):e0237459.

Kwong, K. L., D. Lung, S. N. Wong, T. L. Que, and N. S. Kwong. 2009. Influenza-related hospitalisations in children. *Journal of Paediatrics and Child Health* 45(11):660-664.

LaBore, K. 2014. *Minnesota nursing home abuse and neglect attorney: Residents have free choice to determine physician*. https://www.mnnursinghomelaw.com/physician-2/ (accessed September 15, 2021).

Laxminarayan, R., P. Matsoso, S. Pant, C. Brower, J. A. Rottingen, K. Klugman, and S. Davies. 2016. Access to effective antimicrobials: A worldwide challenge. *Lancet* 387(10014):168-175.

Levin, D. I., T. Lingam, and N. J. Janiga. 2020. *2020 outlook: Dialysis clinics and esrd*. https://healthcareappraisers.com/2020-outlook-dialysis-clinics-and-esrd/ (accessed May 4, 2020).

Lewinsohn, D. M., M. K. Leonard, P. A. LoBue, D. L. Cohn, C. L. Daley, E. Desmond, J. Keane, D. A. Lewinsohn, A. M. Loeffler, G. H. Mazurek, R. J. O'Brien, M. Pai, L. Richeldi, M. Salfinger, T. M. Shinnick, T. R. Sterling, D. M. Warshauer, and G. L. Woods. 2017. Official american thoracic society/infectious diseases society of america/centers for disease control and prevention clinical practice guidelines: Diagnosis of tuberculosis in adults and children. *Clinical Infectious Diseases* 64(2):e1-e33.

Lewnard, J. A., N. C. Lo, N. Arinaminpathy, I. Frost, and R. Laxminarayan. 2020. Childhood vaccines and antibiotic use in low- and middle-income countries. *Nature* 581(7806):94-99.

Lin, M. Y., R. D. Lyles-Banks, K. Lolans, D. W. Hines, J. B. Spear, R. Petrak, W. E. Trick, R. A. Weinstein, M. K. Hayden, Centers for Disease Control, and Prevention Epicenters Program. 2013. The importance of long-term acute care hospitals in the regional epidemiology of klebsiella pneumoniae carbapenemase-producing enterobacteriaceae. *Clinical Infectious Diseases* 57(9):1246-1252.

Lipsitch, M., and G. R. Siber. 2016. How can vaccines contribute to solving the antimicrobial resistance problem? *mBio* 7(3):e00428-00416.

Livorsi, D. J., R. Nair, B. C. Lund, B. Alexander, B. F. Beck, M. Goto, M. Ohl, M. S. Vaughan-Sarrazin, M. B. Goetz, and E. N. Perencevich. 2021. Antibiotic stewardship implementation and antibiotic use at hospitals with and without on-site infectious disease specialists. *Clinical Infectious Diseases* 72(10):1810-1817.

Lochen, A., N. J. Croucher, and R. M. Anderson. 2020. Divergent serotype replacement trends and increasing diversity in pneumococcal disease in high income settings reduce the benefit of expanding vaccine valency. *Scientific Reports* 10(1):18977.

Lovegreen, O., D. Riggs, M. A. Staten, P. Sheehan, and A. G. Pittas. 2018. Financial management of large, multi-center trials in a challenging funding milieu. *Trials* 19(1):267.

Lubbers, B. 2021. Addressing challenges in veterinary diagnostics. Paper read at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 3, Webinar.

Luo, R., J. Sickler, F. Vahidnia, Y. C. Lee, B. Frogner, and M. Thompson. 2019. Diagnosis and management of group a streptococcal pharyngitis in the united states, 2011-2015. *BMC Infectious Diseases* 19(1):193.

Lynch, J. 2021. *Telehealth and antimicrobial stewarship*. Paper presented at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 3, Webinar.

MacIntyre, C. R., A. A. Chughtai, M. Barnes, I. Ridda, H. Seale, R. Toms, and A. Heywood. 2018. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(h1n1)pdm09. *BMC Infectious Diseases* 18(1):637.

Makam, A. N., T. Tran, M. E. Miller, L. Xuan, O. K. Nguyen, and E. A. Halm. 2019. The clinical course after long-term acute care hospital admission among older medicare beneficiaries. *Journal of the American Geriatrics Society* 67(11):2282-2288.

Malarski, M., M. Hasso-Agopsowicz, A. Soble, W. Mok, S. Mathewson, and J. Vekemans. 2019. Vaccine impact on antimicrobial resistance to inform gavi, the vaccine alliance's 2018 vaccine investment strategy: Report from an expert survey. *F1000Res* 8:1685.

Martinez, E. P., M. Cepeda, M. Jovanoska, W. M. Bramer, J. Schoufour, M. Glisic, A. Verbon, and O. H. Franco. 2019. Seasonality of antimicrobial resistance rates in respiratory bacteria: A systematic review and meta-analysis. *PloS One* 14(8):e0221133.

MayoClinic. 2020. *C. Difficile infection* (accessed 2021).

MedPAC (Medicare Payment Advisory Commission). 2020. Long-term care hospital services. In *Report to the Congress: Medicare Payment Policy*. Medicare Payment Advisory Commission.

Meeker, D., J. A. Linder, C. R. Fox, M. W. Friedberg, S. D. Persell, N. J. Goldstein, T. K. Knight, J. W. Hay, and J. N. Doctor. 2016. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: A randomized clinical trial. *JAMA* 315(6):562-570.

Mendelson, M., and M. P. Matsoso. 2015. The world health organization global action plan for antimicrobial resistance. *South African Medical Journal* 105(5):325.

Messacar, K., S. K. Parker, J. K. Todd, and S. R. Dominguez. 2017. Implementation of rapid molecular infectious disease diagnostics: The role of diagnostic and antimicrobial stewardship. *Journal of Clinical Microbiology* 55(3):715-723.

Moeller, G., S. Buchsbaum, P. Wilson, A. Shepherd, P. Kaspar, M. Giovanni, L. Penny, M. Urdea, P. Vickerman, C. Dye, J. Cunningham, S. Reed, C. Hanson, P. Small, M. Perkins, R. Allan, A. Magill, T. Taylor, R. Guerrant, J. Agosti, L. von Seidlein, J. Hughes, M. Miller, C. Mason, P. Tarr, C. Wilfert, K. Holmes, P. Mwaba, N. Hellmann, R. Peeling, et al. 2007. *Estimating the global health impact of improved diagnostic tools for the developing world*. RAND Corporation.

Morley, P. S., M. D. Apley, T. E. Besser, D. P. Burney, P. J. Fedorka-Cray, M. G. Papich, J. L. Traub-Dargatz, J. S. Weese, and American College of Veterinary Internal Medicine. 2005. Antimicrobial drug use in veterinary medicine. *Journal of Veterinary Internal Medicine* 19(4):617-629.

Morris, D. E., D. W. Cleary, and S. C. Clarke. 2017. Secondary bacterial infections associated with influenza pandemics. *Frontiers in Microbiology* 8:1041.

Morris, Z. S., S. Wooding, and J. Grant. 2011. The answer is 17 years, what is the question: Understanding time lags in translational research. *Journal of the Royal Society of Medicine* 104(12):510-520.

Munoz-Price, L. S. 2009. Long-term acute care hospitals. *Clinical Infectious Diseases* 49(3):438-443.

Muri-Gama, A. S., A. Figueras, and S. R. Secoli. 2018. Inappropriately prescribed and over-the-counter antimicrobials in the brazilian amazon basin: We need to promote more rational use even in remote places. *PloS One* 13(8):e0201579.

Mushtaq, A., R. A. Awali, S. Chandramohan, A. Krishna, C. Biedron, O. Jegede, and T. Chopra. 2017. Implementing an antibiotic stewardship program at a long-term acute care hospital in detroit, michigan. *American Journal of Infection Control* 45(12):e157-e160.

Nasr, Z. G., D. M. Abbara, and K. J. Wilby. 2021. A scoping review of antimicrobial stewardship teaching in pharmacy education curricula. *American Journal of Pharmaceutical Education* 85(6):8415.

NIA (National Institute on Aging). 2017a. *Residential facilities, assisted living, and nursing homes*. https://www.nia.nih.gov/health/residential-facilities-assisted-living-and-nursing-homes (accessed May 19, 2021).

NIA. 2017b. *What is long-term care?* https://www.nia.nih.gov/health/what-long-term-care (accessed May 19, 2021).

NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases). 2012. *Livertox: Clinical and research information on drug-induced liver injury, vancomycin*. https://www.ncbi.nlm.nih.gov/books/NBK548881/ (accessed May 4, 2021).

NIMSS (National Information Management & Support System). 2017. *NC1206: Antimicrobial resistance*. https://www.nimss.org/projects/view/mrp/outline/18361 (accessed 2021).

NITAG (National Immunization Technical Advisory Groups). 2019. *Network*. https://www.nitag-resource.org/network/vision-mission (accessed May 19, 2021).

NLM (National Library of Medicine). 2020. *Strep a test*. https://medlineplus.gov/lab-tests/strep-a-test/ (accessed July 13, 2021).

O'Fallon, E., S. Gautam, and E. M. D'Agata. 2009. Colonization with multidrug-resistant gram-negative bacteria: Prolonged duration and frequent cocolonization. *Clinical Infectious Diseases* 48(10):1375-1381.

Okeke, I. N. 2009. Cholera vaccine will reduce antibiotic use. *Science* 325(5941):674.

Okeke, I. N., R. W. Peeling, H. Goossens, R. Auckenthaler, S. S. Olmsted, J. F. de Lavison, B. L. Zimmer, M. D. Perkins, and K. Nordqvist. 2011. Diagnostics as essential tools for containing antibacterial resistance. *Drug Resistance Updates* 14(2):95-106.

O'Neill, J. 2018. Tackling drug-resistant infections globally: Final report and recommendations. 2016. *HM Government and Welcome Trust: UK*.

Ortiz, J. R., and K. M. Neuzil. 2019. Influenza immunization in low- and middle-income countries: Preparing for next-generation influenza vaccines. *Journal of Infectious Diseases* 219(Suppl 1):S97-S106.

Ott, J. J., J. Klein Breteler, J. S. Tam, R. C. Hutubessy, M. Jit, and M. R. de Boer. 2013. Influenza vaccines in low and middle income countries: A systematic review of economic evaluations. *Human Vaccines & Immunotherapeutics* 9(7):1500-1511.

Ouedraogo, F., M. Salois, B. Bain, C. Hansen, and B. Dutton. 2018. 2018 AVMA report on the market for veterinary services, Colorado State University. Libraries.

Papich, M. 2020. *Antibiotic use in companion animals*. Paper presented at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 2, Webinar.

Patel, R., C. R. Polage, J. D. Bard, L. May, F. M. Lee, V. Fabre, M. K. Hayden, S. D. B. Doernberg, D. A. Haake, B. W. Trautner, L. Grigoryan, E. L. Tsalik, and K. E. Hanson. 2021. Envisioning future uti diagnostics. *Clinical Infectious Diseases*.

PCAST (President's Council of Advisors on Science and Technology). 2020. *National action plan for combating antibiotic-resistant bacteria, 2020-2025.* Washington, DC: White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

PCORI (Patient-Centered Outcomes Research Institute). 2014. *Our story*. https://www.pcori.org/about-us/our-story (accessed July 23, 2021).

Peck, M., M. Gacic-Dobo, M. S. Diallo, Y. Nedelec, S. V. Sodha, and A. S. Wallace. 2019. Global routine vaccination coverage, 2018. *Morbidity and Mortality Weekly Report* 68(42):937-942.

Petrak, R. M. 2014. *Infectious diseases specialists vital in ltc facilities*. https://www.mcknights.com/blogs/guest-columns/infectious-diseases-specialists-vital-in-ltc-facilities/ (accessed May 3, 2021).

Pierce, J., A. Apisarnthanarak, N. Schellack, W. Cornistein, A. A. Maani, S. Adnan, and M. P. Stevens. 2020. Global antimicrobial stewardship with a focus on low- and middle-income countries. *International Journal of Infectious Diseases* 96:621-629.

Pinto Ferreira, J. 2017. Why antibiotic use data in animals needs to be collected and how this can be facilitated. *Frontiers in Veterinary Science* 4:213.

Pollack, L. A., K. L. van Santen, L. M. Weiner, M. A. Dudeck, J. R. Edwards, and A. Srinivasan. 2016. Antibiotic stewardship programs in u.S. Acute care hospitals: Findings from the 2014 national healthcare safety network annual hospital survey. *Clinical Infectious Diseases* 63(4):443-449.

Prestel, C., E. Anderson, K. Forsberg, M. Lyman, M. A. de Perio, D. Kuhar, K. Edwards, M. Rivera, A. Shugart, M. Walters, and N. Q. Dotson. 2021. Candida auris outbreak in a covid-19 specialty care unit - florida, july-august 2020. *Morbidity and Mortality Weekly Report* 70(2):56-57.

Pulcini, C., L. Pauvif, A. Paraponaris, P. Verger, and B. Ventelou. 2012. Perceptions and attitudes of french general practitioners towards rapid antigen diagnostic tests in acute pharyngitis using a randomized case vignette study. *Journal of Antimicrobial Chemotherapy* 67(6):1540-1546.

Resman, F. 2020. Antimicrobial stewardship programs; a two-part narrative review of step-wise design and issues of controversy part i: Step-wise design of an antimicrobial stewardship program. *Therapeutic Advances in Infectious Disease* 7:2049936120933187.

Review on Antimicrobial. 2015. *Rapid diagnostics: Stopping unnecessary use of antibiotics*. Review on Antimicrobial Resistance.

Roope, L. S. J., R. D. Smith, K. B. Pouwels, J. Buchanan, L. Abel, P. Eibich, C. C. Butler, P. S. Tan, A. S. Walker, J. V. Robotham, and S. Wordsworth. 2019. The challenge of antimicrobial resistance: What economics can contribute. *Science* 364(6435).

Sanchez, G. V., K. E. Fleming-Dutra, R. M. Roberts, and L. A. Hicks. 2016. *Core elements of outpatient antibiotic stewardship.*

Sanders, P., W. Vanderhaeghen, M. Fertner, K. Fuchs, W. Obritzhauser, A. Agunos, C. Carson, B. Borck Hog, V. Dalhoff Andersen, C. Chauvin, A. Hemonic, A. Kasbohrer, R. Merle, G. L. Alborali, F. Scali, K. D. C. Stark, C. Muentener, I. van Geijlswijk, F. Broadfoot, L. Pokludova, C. L. Firth, L. P. Carmo, E. G. Manzanilla, L. Jensen, M. Sjolund, J. Pinto Ferreira, S. Brown, D. Heederik, and J. Dewulf. 2020. Monitoring of farm-level antimicrobial use to guide stewardship: Overview of existing systems and analysis of key components and processes. *Frontiers in Veterinary Science* 7:540.

Sarnak, M. J., and B. L. Jaber. 2000. Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney International* 58(4):1758-1764.

Sears, C. 2018. *IDSA comments to cms re pama implementation and diagnostics reimbursement*. https://www.idsociety.org/globalassets/idsa/policy--advocacy/current_topics_and_issues/diagnostics/agency-efforts/110718-idsa-comments-to-cms-re-pama-implementation-and-diagnostics-reimbursement.pdf (accessed September 16, 2021).

Shaikh, H., J. Lynch, J. Kim, and J. L. Excler. 2020. Current and future cholera vaccines. *Vaccine* 38 Suppl 1:A118-A126.

Shenoy, E. S., J. Kim, E. S. Rosenberg, J. A. Cotter, H. Lee, R. P. Walensky, and D. C. Hooper. 2013. Discontinuation of contact precautions for methicillin-resistant staphylococcus aureus: A randomized controlled trial comparing passive and active screening with culture and polymerase chain reaction. *Clinical Infectious Diseases* 57(2):176-184.

Shively, N. R., M. A. Moffa, K. T. Paul, E. J. Wodusky, B. A. Schipani, S. L. Cuccaro, M. S. Harmanos, M. S. Cratty, B. N. Chamovitz, and T. L. Walsh. 2020. Impact of a telehealth-based antimicrobial stewardship program in a community hospital health system. *Clinical Infectious Diseases* 71(3):539-545.

Singh, A. K., and A. K. Bhunia. 2019. Animal-use antibiotics induce cross-resistance in bacterial pathogens to human therapeutic antibiotics. *Current Microbiology* 76(10):1112-1117.

Singleton, D. A., A. Rayner, B. Brant, S. Smyth, P. M. Noble, A. D. Radford, and G. L. Pinchbeck. 2021. A randomised controlled trial to reduce highest priority critically important antimicrobial prescription in companion animals. *Nature Communications* 12(1):1593.

Sloane, P. D., K. Huslage, C. E. Kistler, and S. Zimmerman. 2016. Optimizing antibiotic use in nursing homes through antibiotic stewardship. *North Carolina Medical Journal* 77(5):324-329.

Smieszek, T., K. B. Pouwels, F. C. K. Dolk, D. R. M. Smith, S. Hopkins, M. Sharland, A. D. Hay, M. V. Moore, and J. V. Robotham. 2018. Potential for reducing inappropriate antibiotic prescribing in english primary care. *Journal of Antimicrobial Chemotherapy* 73(suppl_2):ii36-ii43.

Smith, L., A. Tan, J. D. Stephens, D. Hibler, and S. A. Duffy. 2019. Overcoming challenges in multisite trials. *Nursing Research* 68(3):227-236.

Srikantiah, P. 2018. The potential of vaccines to prevent AMR. Paper read at PDVAC Meeting.

St Cyr, S., L. Barbee, K. A. Workowski, L. H. Bachmann, C. Pham, K. Schlanger, E. Torrone, H. Weinstock, E. N. Kersh, and P. Thorpe. 2020. Update to cdc's treatment guidelines for gonococcal infection, 2020. *Morbidity and Mortality Weekly Report* 69(50):1911-1916.

StratisHealth. 2020. Antibiotic stewardship implementation: Suggested strategies from high performing cahs. *Natural Rural Health Resource Center*.

Strich, J. R., and S. S. Kadri. 2019. Difficult-to-treat antibiotic-resistant gram-negative pathogens in the intensive care unit: Epidemiology, outcomes, and treatment. Paper read at Seminars in Respiratory and Critical Care Medicine.

Sulis, G., P. Adam, V. Nafade, G. Gore, B. Daniels, A. Daftary, J. Das, S. Gandra, and M. Pai. 2020. Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and meta-analysis. *PLoS Medicine* 17(6):e1003139.

Tattevin, P., G. Levy Hara, A. Toumi, M. Enani, G. Coombs, A. Voss, H. Wertheim, A. Poda, Z. Daoud, and R. Laxminarayan. 2020. Advocacy for increased international efforts for antimicrobial stewardship actions in low-and middle-income countries on behalf of alliance for the prudent use of antimicrobials (apua), under the auspices of the international society of antimicrobial chemotherapy (isac). *Frontiers in Medicine* 7:503.

Teshome, S., S. Desai, J. H. Kim, D. Belay, and V. Mogasale. 2018. Feasibility and costs of a targeted cholera vaccination campaign in ethiopia. *Human Vaccines & Immunotherapeutics* 14(10):2427-2433.

The Pew Charitable Trusts. 2016. Judicious animal antibiotic use requires drug label refinements.

Thompson, J. M., A. L. Zagel, A. B. Spaulding, E. A. Krause, and J. L. Arms. 2021a. Streptococcal pharyngitis: Compliance with national testing guidelines in a pediatric emergency department. *Pediatric Emergency Care*.

Thompson, N. D., A. Penna, T. R. Eure, W. M. Bamberg, G. Barney, D. Barter, P. Clogher, M. B. DeSilva, G. Dumyati, E. Epson, L. Frank, D. Godine, L. Irizarry, M. A. Kainer, L. Li, R. Lynfield, J. P. Mahoehney, J. Nadle, V. Ocampo, L. Perry, S. M. Ray, S. S. Davis, M. Sievers, L. E. Wilson, A. Y. Zhang, N. D. Stone, and S. S. Magill. 2020. Epidemiology of antibiotic use for urinary tract infection in nursing home residents. *Journal of the American Medical Directors Association* 21(1):91-96.

Thompson, N. D., N. D. Stone, C. J. Brown, A. R. Penna, T. R. Eure, W. M. Bamberg, G. R. Barney, D. Barter, P. Clogher, M. B. DeSilva, G. Dumyati, L. Frank, C. B. Felsen, D. Godine, L. Irizarry, M. A. Kainer, L. Li, R. Lynfield, J. P. Mahoehney, M. Maloney, J. Nadle, V. L. S. Ocampo, R. Pierce, S. M. Ray, S. S. Davis, M. Sievers, K. Srinivasan, L. E. Wilson, A. Y. Zhang, and S. S. Magill. 2021b. Antimicrobial use in a cohort of us nursing homes, 2017. *JAMA* 325(13):1286-1295.

Tin Tin Htar, M., A. H. J. van Den Biggelaar, H. Sings, G. Ferreira, M. Moffatt, C. Hall-Murray, T. Verstraeten, B. D. Gessner, H. J. Schmitt, and L. Jodar. 2019. The impact of routine childhood immunization with higher-valent pneumococcal conjugate vaccines on antimicrobial-resistant pneumococcal diseases and carriage: A systematic literature review. *Expert Review of Vaccines* 18(10):1069-1089.

Tomczyk, S., R. Lynfield, W. Schaffner, A. Reingold, L. Miller, S. Petit, C. Holtzman, S. M. Zansky, A. Thomas, J. Baumbach, L. H. Harrison, M. M. Farley, B. Beall, L. McGee, R. Gierke, T. Pondo, and L. Kim. 2016. Prevention of antibiotic-nonsusceptible invasive pneumococcal disease with the 13-valent pneumococcal conjugate vaccine. *Clinical Infectious Diseases* 62(9):1119-1125.

Toutain, P. L., A. Bousquet-Melou, P. Damborg, A. A. Ferran, D. Mevius, L. Pelligand, K. T. Veldman, and P. Lees. 2017. En route towards european clinical breakpoints for veterinary antimicrobial susceptibility testing: A position paper explaining the vetcast approach. *Frontiers in Microbiology* 8:2344.

Trevas, D., A. M. Caliendo, K. Hanson, J. Levy, and C. C. Ginocchio. 2021. Diagnostic tests can stem the threat of antimicrobial resistance: Infectious disease professionals can help. *Clinical Infectious Diseases* 72(11):e893-e900.

University of Michigan Kidney Epidemiology and Cost Center. 2018. *Technical notes on the dialysis facility compare quality of patient care star rating methodology for the October 2018 release.* Ann Arbor, MI: Centers for Medicare & Medicaid Services.

USDA (U.S. Department of Agriculture). 2014. *Antimicrobial resistance: Action plan.* U.S. Department of Agriculture.

USDA. 2017. Antimicrobial use and stewardship on u.S. Swine operations, 2017. Fort Collins, CO: USDA–APHIS–VS−CEAH–NAHMS.

USDA. 2018. Supporting antimicrobial stewardship in veterinary settings: Goals for fiscal years 2019–2023. Washington, DC: FDA Center for Veterinary Medicine.

USDA. 2019. Antimicrobial use and stewardship on us feedlots, 2017. Fort Collins, CO: USDA–APHIS–VS–CEAH–NAHMS

UWTASP (University of Washington Tele-Antimicrobial Stewardship Program). 2018. *The challenge of antibiotic resistance is here*. https://www.uwtasp.org/about (accessed May 3, 2021).

Uyeki, T. M., H. H. Bernstein, J. S. Bradley, J. A. Englund, T. M. File, A. M. Fry, S. Gravenstein, F. G. Hayden, S. A. Harper, J. M. Hirshon, M. G. Ison, B. L. Johnston, S. L. Knight, A. McGeer, L. E. Riley, C. R. Wolfe, P. E. Alexander, and A. T. Pavia. 2019. Clinical practice guidelines by the infectious diseases society of america: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. *Clinical Infectious Diseases* 68(6):e1-e47.

Van Katwyk, S. R., S. L. Jones, and S. J. Hoffman. 2018. Mapping educational opportunities for healthcare workers on antimicrobial resistance and stewardship around the world. *Human Resources for Health* 16(1):9.

Veeraraghavan, B., A. K. Pragasam, Y. D. Bakthavatchalam, and R. Ralph. 2018. Typhoid fever: Issues in laboratory detection, treatment options & concerns in management in developing countries. *Future Science OA* 4(6):FSO312.

Vekemans, J., M. Hasso-Agopsowicz, G. Kang, W. P. Hausdorff, A. Fiore, E. Tayler, E. J. Klemm, R. Laxminarayan, P. Srikantiah, M. Friede, and M. Lipsitch. 2021. Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: A world health organization action framework. *Clinical Infectious Diseases* 73(4):e1011-e1017.

Veterinary Practice News Editors. 2017. Mars to buy vca clinics, labs in $9.1 billion deal. *Veterinary Practice News* https://www.veterinarypracticenews.com/mars-to-buy-vca-clinics-labs-in-9-1-billion-deal/ (accessed May 19, 2021).

Wang, T. Z., R. P. L. Kodiyanplakkal, and D. P. Calfee. 2019. Antimicrobial resistance in nephrology. *Nature Reviews Nephrology* 15(8):463-481.

Watts, J. L., M. T. Sweeney, and B. V. Lubbers. 2018. Antimicrobial susceptibility testing of bacteria of veterinary origin. *Microbiology Spectrum* 6(2).

Weinstein, M. P., and J. S. Lewis, 2nd. 2020. The clinical and laboratory standards institute subcommittee on antimicrobial susceptibility testing: Background, organization, functions, and processes. *Journal of Clinical Microbiology* 58(3).

Wellcome. 2020. The global response to AMR: Momentum, success, and critical gaps: Wellcome.

Wellcome. 2021. *Impact of vaccines on antimicrobial resistance (closed)*. https://wellcome.org/grant-funding/schemes/impact-vaccines-antimicrobial-resistance-closed (accessed May 24, 2021).

Wemette, M., A. G. Safi, W. Beauvais, K. Ceres, M. Shapiro, P. Moroni, F. L. Welcome, and R. Ivanek. 2020. New york state dairy farmers' perceptions of antibiotic use and resistance: A qualitative interview study. *PloS One* 15(5):e0232937.

WHO (World Health Organization). 2014. Principles and considerations for adding a vaccine to a national immunization programme: From decision to implementation and monitoring.

WHO. 2018. *Vaccines and immunization: Dengue*. https://www.who.int/news-room/q-a-detail/dengue-vaccines (accessed June 30, 2021).

WHO. 2019a. Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: A who practical toolkit.

WHO. 2019b. *Pneumonia*. https://www.who.int/news-room/fact-sheets/detail/pneumonia (accessed May 19, 2021).

WHO. 2020. *Immunization coverage*. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage (accessed May 24, 2021).

WHO. 2021. *Aware*. https://aware.essentialmeds.org/list (accessed September 22, 2021).

Yu, H., O. Baser, and L. Wang. 2016. Burden of clostridium difficile-associated disease among patients residing in nursing homes: A population-based cohort study. *BMC Geriatrics* 16(1):1-7.

Yui, S., G. Bercades, M. Muzslay, E. Blackburn, S. Ali, D. Smyth, A. Macklin, J. H. Ryu, P. Bassett, N. MacCallum, D. Brealey, and P. Wilson. 2020. Assessment of a rapid diagnostic test to exclude bacteraemia and effect on clinical decision-making for antimicrobial therapy. *Scientific Reports* 10(1):3122.

Zacharioudakis, I. M., F. N. Zervou, P. D. Ziakas, and E. Mylonakis. 2014. Meta-analysis of methicillin-resistant staphylococcus aureus colonization and risk of infection in dialysis patients. *Journal of the American Society of Nephrology* 25(9):2131-2141.

Zacharioudakis, I. M., F. N. Zervou, P. D. Ziakas, L. B. Rice, and E. Mylonakis. 2015. Vancomycin-resistant enterococci colonization among dialysis patients: A meta-analysis of prevalence, risk factors, and significance. *American Journal of Kidney Diseases* 65(1):88-97.

Zhou, Y., J. B. Lynch, P. S. Pottinger, J. Scott, L. A. S. Quilter, M. D'Angeli, Z. Kassamali, R. Jain, R. J. Cybulski, and N. Martinez-Paz. 2017. University of Washington Tele-Antimicrobial Stewardship program (UW-TASP/ECHO): Collaboration across Washington State to improve antimicrobial use. *Open Forum Infectious Diseases* 4(Suppl 1):S271-S271.

Zvonar, R., S. Natarajan, C. Edwards, and V. Roth. 2008. Assessment of vancomycin use in chronic haemodialysis patients: Room for improvement. *Nephrology, Dialysis, Transplantation* 23(11):3690-3695.

# 6

# Bringing New Products to Market and Ensuring Their Reach

Antimicrobial medicines are miracle drugs: highly effective (at least in the absence of resistance), relatively inexpensive, easy to use, and often with a broad spectrum of activity. The goal of the antimicrobial stewardship and preventive measures described in the previous chapter is to minimize the need for these medicines, prolonging the useful life of those already on the market. But the nature of resistance means that new antimicrobials will always be needed, as will diagnostic tools to correctly target therapy. There are also a range of promising nontraditional therapies "ways to influence disease beyond inhibiting or killing pathogens through small molecules" (Theuretzbacher and Piddock, 2019). Examples include chemicals that act by reducing bacterial virulence instead of bacterial growth, and bacteriophages, the viruses that infect bacteria (Czaplewski et al., 2016; Kirienko et al., 2019).

The market for new medical products needed to combat antimicrobial resistance includes novel antimicrobials. While these products are at the center of much of the public discourse on antimicrobial resistance, new antimicrobials are not the only innovative products needed. Recognizing that there are finite resources to direct to this problem, the committee acknowledges that some trade-offs will be necessary. There is a need for an integrated investment across different product types, some preventive and some therapeutic—including, but not limited to, new antimicrobial medicines.

This chapter discusses some of the barriers to bringing new medical products to market and ensuring their reach. Challenges unique to human medicine and diagnostic markets in the United States are presented first. The last section describes problems that cut across multiple product lines and countries. The recommendations in this chapter reflect the committee's judgement that some special programs are needed to bring new antimicrobials to market and to ease the burden they place on diagnostic laboratories. At the same time, there is a need for a more explicit discussion of a balance of investments in a range of products that decrease use and preserve the life of antimicrobials. The concluding section describes a One Health portfolio of preventive and therapeutic products for both humans and animals and the importance of a holistic strategy for making these investments.

## MEDICINES

At the center of the problem of the antimicrobials market is that the medicines are complicated and costly to develop and manufacture and have a relatively small market both in

terms of duration of use, usually only a few days, and need (Chapman, 2020). Demand for these drugs is further constrained by the public health imperative to hold new antimicrobials in reserve (Ardal et al., 2020; McKenna, 2020). Given these constraints, it can more than 10 years of on-patent sales for a new antimicrobial to achieve profitability (McKenna, 2020). There is also a chance, depending on the pace of resistance in the target pathogen that by this time the drug may no longer be an effective treatment. Although these medicines are essential to the *future* of clinical medicine, the *present* demand for them complicates their market viability.

For example, although there are over 2.8 million resistant infections every year in the United States, causing 35,000 deaths, infections with any particular resistant pathogen are rare (CDC, 2019a). A recent study of resistant gram-negative infections at 134 U.S. hospitals found that difficult-to-treat, gram-negative infections with no or poor treatment options were relatively rare (Strich et al., 2020). Across almost 3 million patient encounters, only 39 to 138 would be candidates for a novel antimicrobial against gram-negative infections (Strich et al., 2020). As long as the prevalence of gram-negative infections *not* susceptible to available treatments is substantially lower than the prevalence of infections susceptible to them, the market incentive alone is not likely to motivate new drug development (provided the prices are constrained) (Fitzpatrick, 2020).

The same pattern holds with more common resistant infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the more common, serious resistant infections. By 2019 estimates, there are about 323,700 MRSA cases a year, causing 10,600 deaths, exceeding the National Institutes of Health (NIH) threshold for a rare disease by about 30 percent (CDC, 2019a; NCATS GARD, 2021). As with difficult-to-treat, gram-negative infections, there are still several effective treatment options available for MRSA (CDC, 2019a). While new treatments for MRSA, as for all resistant pathogens, are needed and valuable, good stewardship would require older drugs be used first, even if there were no difference in price. When multiple antimicrobials can treat the same pathogen with similar effectiveness, the new medicine has more in common, economically, with a commodity, meaning it is largely interchangeable with similar products, than with a branded, niche product (Spellberg et al., 2013).

But unlike other commodities, the cost, time, and expertise needed to bring a new antimicrobial to market is extremely high. Estimates of the median development price for antimicrobials are between $673 million and $1.86 billion (Towse et al., 2017; Wouters et al., 2020).[1] These estimates do not account for significant postmarket expenses. After the drug is approved, there are regulatory requirements such as pharmacokinetic studies in children and special adult populations (e.g., overweight or obese patients), routine pharmacovigilance and postmarket surveillance, susceptibility testing for diagnostic devices (discussed in the next section), and manufacturing (Krause, 2021a). As with most pharmaceuticals, manufacturing antimicrobials is complicated. Sourcing raw materials for them can take 8 months and manufacturing another 14 months, so some manufacturing expense is incurred more than a year before the drug is sold (Krause, 2021a).

Against all these expenses is the reality that new antimicrobials will not sell well. There are public health reasons to use them sparingly and even in the absence of a public health reason, the drugs have to compete on price with older, cheaper medicines, often of comparable clinical value. Furthermore, regardless of the drug's activity in vitro against various pathogens, its use is largely, practically limited to those indications the regulatory agency approved based on clinical trial data. Finding trial participants with suspected resistant infections is challenging in the

[1] After accounting for the cost of failures and the cost of capital.

United States, where these infections are relatively rare, a topic discussed later in the chapter. Box 6-1 discusses how the limited approved indications for the drug plazomicin contributed to its commercial failure.

The bankruptcy of Achaogen described in Box 6-1 and those of several other similar small antibiotic developers led to widespread calls of a market failure for antimicrobials (Daniel et al., 2013; Gotham et al., 2021; Jacobs, 2019; Jit et al., 2020; O'Brien and Chu, 2020). Others have argued that, strictly speaking, this is not a market failure because, "drugs with limited clinical benefit over existing treatments (which plazomicin was for urinary tract infections in the United States) provide smaller financial return. As such, Achaogen's bankruptcy is not necessarily a good example of a broken market for antibiotics, nor should the company's collapse serve as a justification to pressure governments to establish large-scale pull incentives for the multinational pharmaceutical industry" (Aagaard et al., 2021).

Furthermore, although Achaogen's bankruptcy might deter other firms from entering the market, plazomicin is still available to patients. The key public health goal of making a new antimicrobial medicine available was met.

**BOX 6-1**
**Plazomicin and Achaogen**

Carbapenem-resistant Enterobacterales (CRE) is a Centers for Disease Control and Prevention (CDC) urgent threat and a World Health Organization (WHO) level one priority pathogen, classified by both organizations as the highest threat to public health. In 2018, when the Food and Drug Administration (FDA) approved plazomicin, a new aminoglycoside targeting these pathogens, there was considerable enthusiasm and projections that the drug would bring in $500 million a year in its peak year sales. (For reference, all branded antibiotics combined sold only $535 million in 2018). Although only licensed in the United States, the WHO promptly added plazomicin to the Essential Medicines List as a reserve group antibiotic.

Projected sales never materialized, however. In its first year on the market, plazomicin sold only about $1 million. Before its initial public offering in 2014, Achaogen had substantial venture capital funding, notwithstanding at least $136 million from the Biomedical Advanced Research and Development Authority, $80 million from the National Institutes of Health and the Defense Threat Reduction Agency, and contributions from the Wellcome Trust. Its stock value declined around the time of plazomicin's launch, as often does for antibiotic companies because of uncertainty in the approvals process or speculation that the company might be bought. Faced with few options to raise money in the face of considerable postmarket and manufacturing expenses, Achaogen filed for bankruptcy in 2019.

Plazomicin's sales were held back by the fact that the drug was only approved to treat complicated urinary tract infections, meaning those caused by drug-resistant bacteria in patients with no other treatment options. Achaogen had sought FDA-approval for CRE bloodstream infections, but this indication was denied, partly because of the small sample enrolled in the clinical trial. The inability to recruit trial participants with CRE bloodstream infections, in turn, stems at least in part from the fact that these infections are extremely rare in the United States.

Plazomicin is a striking example of the gap between need and availability for new antimicrobials. This example prompted the ReACT network to call for changes to design and conduct of clinical trials, allowing for greater participation in low- and middle-income countries and a global registration to ensure the drugs would be available in the parts of the world where they are most needed.

SOURCES: Aagaard et al., 2021; Brozak, 2018; Carroll, 2019; Crunchbase; GSA, 2020; Keane, 2018; Krause, 2021a.

It is possible that while the *global* market for antimicrobials is failed, national markets in the high-income countries responsible for most new drug development are, ironically, performing. At the same time, the U.S. government, like other governments and international organizations, recognizes that, market failure or not, there is a serious mismatch in the need for new antimicrobials and the willingness of industry to invest in them. To this end, the government encourages antimicrobial development with assistance to reduce the cost of research and development (i.e., push incentive) and to transition the products to market and sustain them (i.e., pull incentives) (Simpkin et al., 2017). Figure 6-1 shows how these various incentives work on the drug development timeline, showing also where push and pull incentives can overlap.

Because the different types of incentive programs work at different stages of the development timeline, some quite distal, it is difficult to estimate the effectiveness, let alone the relative cost-effectiveness, of any one incentive program. Furthermore, the different incentives tend to work together as bundles of initiatives. The committee recognizes that the success of an incentive program is partly predetermined by earlier success of different programs or incentives. With this in mind, the next sections review the ways different push and pull incentives contribute to the antimicrobial drug pipeline. This is not an exhaustive discussion of the hundreds of incentive programs working around the world to stimulate the antimicrobials market and is heavily, though not exclusively, weighted to programs in the United States.

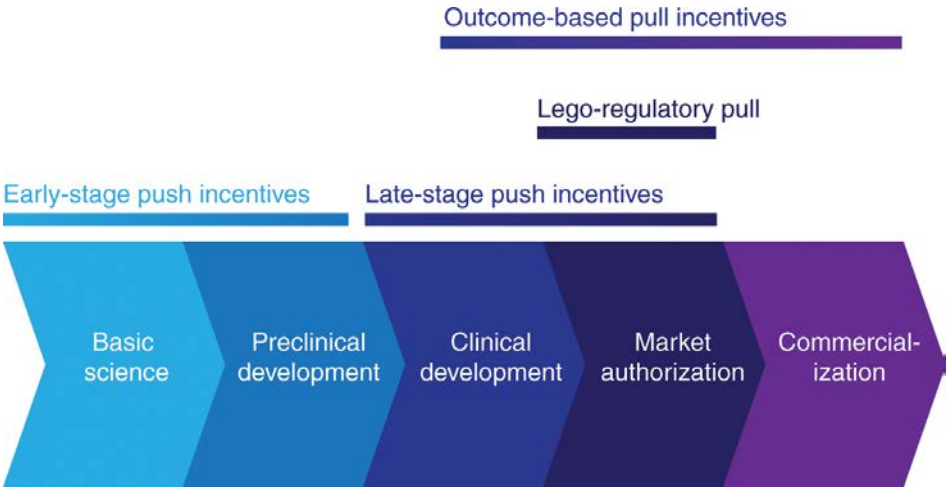



**FIGURE 6-1** Push and pull incentives operate at different stages of antimicrobial development.
SOURCE: Renwick and Mossialos, 2020.

## Push Incentives

Push incentives work early in the drug development timeline. They aim to reduce the costs of research and development to any one entity by spreading these costs across a range of interested parties (Renwick et al., 2016). As Figure 6-2 shows, these early costs are high and the risk of failure is great. As a product moves into later development stages the risk of failure declines (see Figure 6-3). This high-risk, preclinical research is funded almost entirely by taxpayers (Aagaard et al., 2021).

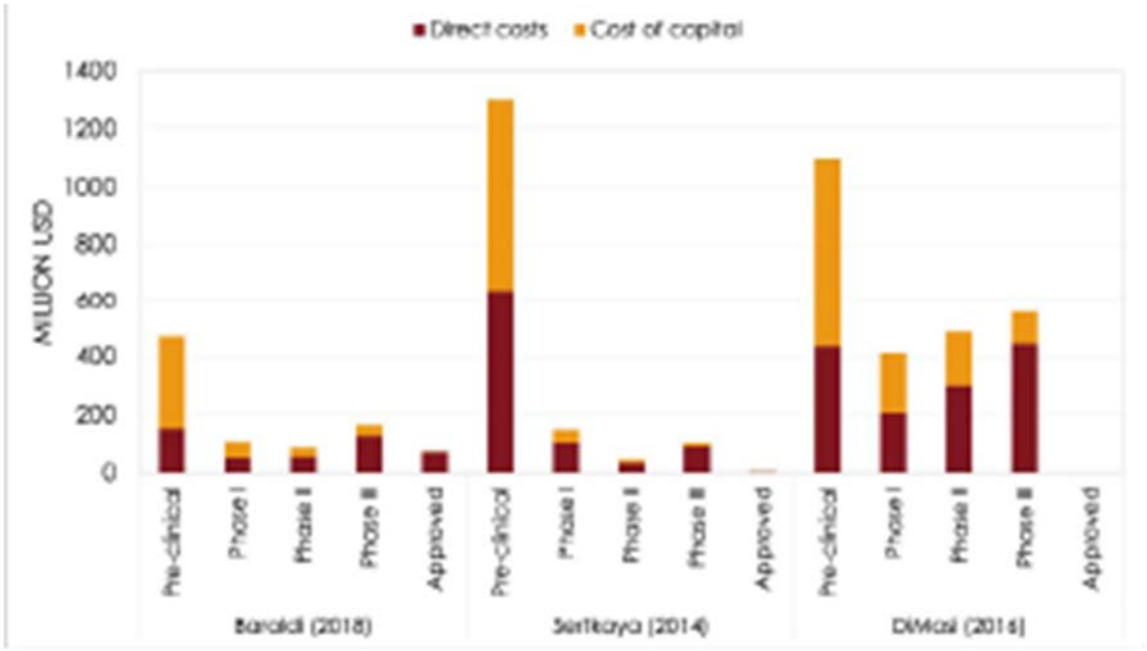



**FIGURE 6-2** Research and development cost, both direct and cost of capital, by clinical trial phases.
SOURCE: Aagaard et al., 2021.

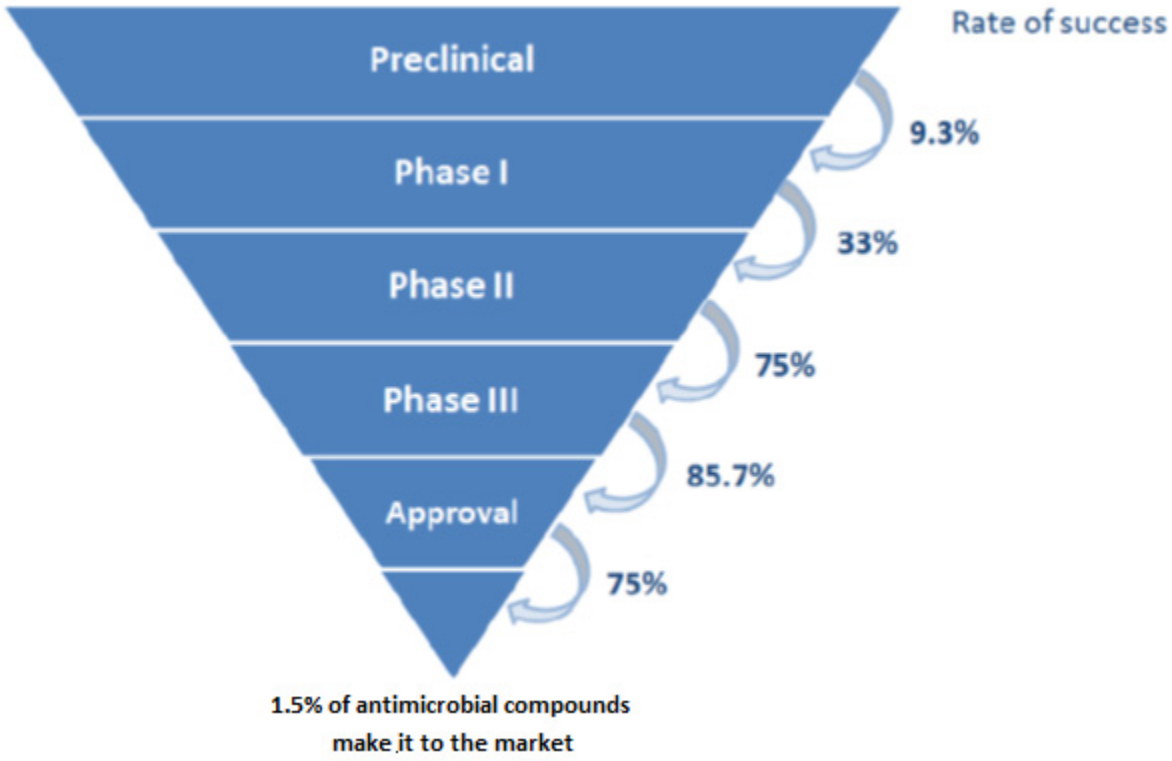



**FIGURE 6-3** Failure is increasingly less likely as drug candidates move to later stages of development.
SOURCE: OECD et al., 2017.

The goal of push incentives is to make drug development more attractive to firms by minimizing early costs, encouraging cooperation of a diverse pool of experts from academia and research institutes, nongovernmental organizations, and private industry. Push incentives work through three main pathways: increasing access to research by putting more tools and information in the public domain, investing in scientific training needed for antimicrobial development, and direct research funding (Mossialos et al., 2010; Renwick et al., 2016).

The first two of these strategies are not specific to antimicrobial development, but are sometimes forgotten in considering the mix of government tools encouraging new antimicrobials. For example, the Community for Open Antimicrobial Drug Discovery, launched in 2015, uses high-throughput screening to test drug compounds for antimicrobial activity (CO-ADD; Desselle et al., 2017).[2] The service is free and aims to include academic chemists in the drug discovery process. The CDC and Food and Drug Administration (FDA) Antibiotic Resistance Isolate Bank also works to increase access to research by making resistant organisms available to researchers; the National Database of Antibiotic-Resistant Organisms discussed in Chapter 4 works at a similar, early stage in the pipeline through increasing access to standardized data on resistance genes, bacterial genomes, and antibiotic susceptibility (CDC, 2020a; NLM, 2021). The Pew Charitable Trust's Shared Platform for Antibiotic Research and Knowledge works at a similar point in drug discovery, providing a consolidated, publicly available database of results (some previously unpublished) and insights garnered from scientists studying gram-negative bacteria (Pew, 2021; Thomas et al., 2018).

Grant funding for basic and applied scientific research is part of the earliest phase of push incentives (Årdal et al., 2018). Grants for training young scientists and other support to academia and research institutes would all fall into this category of early-stage push incentive (Ardal et al., 2020). Figure 6-4 shows how NIH's National Institute for Allergy and Infectious Diseases (NIAID) extensive portfolio of basic science research informs understanding of host–pathogen interactions, virulence, resistance mechanisms, and novel drug targets, for example.

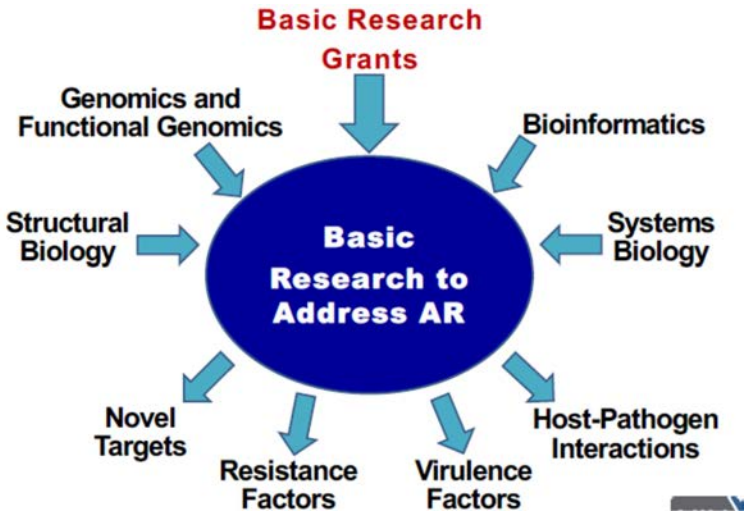



**FIGURE 6-4** NIAID's research grants in basic science inform a broad understanding of antimicrobial resistance.
SOURCE: Knisely, 2020.

[2] High-throughput screening is a drug discovery tool that relies on robotics and advanced computing to test a sample for a pathway or activity against an organism in millions of combinations in a short time (ScienceDirect, 2021b).

While it is not always counted as part of the investment in developing medical products, this early-stage research can be some of the most helpful in the long run. Resistance can emerge rapidly and in unpredictable ways. The multidrug-resistant fungal pathogen *Candida auris,* for example, was unheard of before 2009 (CDC, 2019b). In a span of just a few years, it has become a CDC urgent threat, with cases increasing over 300 percent between 2015 and 2018 (CDC, 2019a; Chiller, 2017). Though information about this pathogen is limited, there is reason to suspect a case-fatality rate of 30 to 60 percent for patients with invasive infection (CDC, 2019b). *C. auris* is a valuable reminder that it will be difficult to predict what pathogen will be of greatest public health threat even 5 or 10 years in the future. The strong, adaptable research base described in Figure 6-4 is an investment in the response to future threats.

*Preclinical and Early Clinical Development*

There are also many push incentives providing direct funding for preclinical research and early clinical trials, sometimes called the midstage of antimicrobial development (Årdal et al., 2018). A recent review found that, as of mid-2019, there were 314 institutions around the world active in discovery and preclinical development of antibacterials, supporting a combined 407 projects (Theuretzbacher et al., 2020). Most institutions working at these stages (81 percent) are small and medium-sized firms in North America and Europe (Theuretzbacher et al., 2020). As Figure 6-5 shows, this research is heavily weighted to direct-acting, small molecule antibiotics.

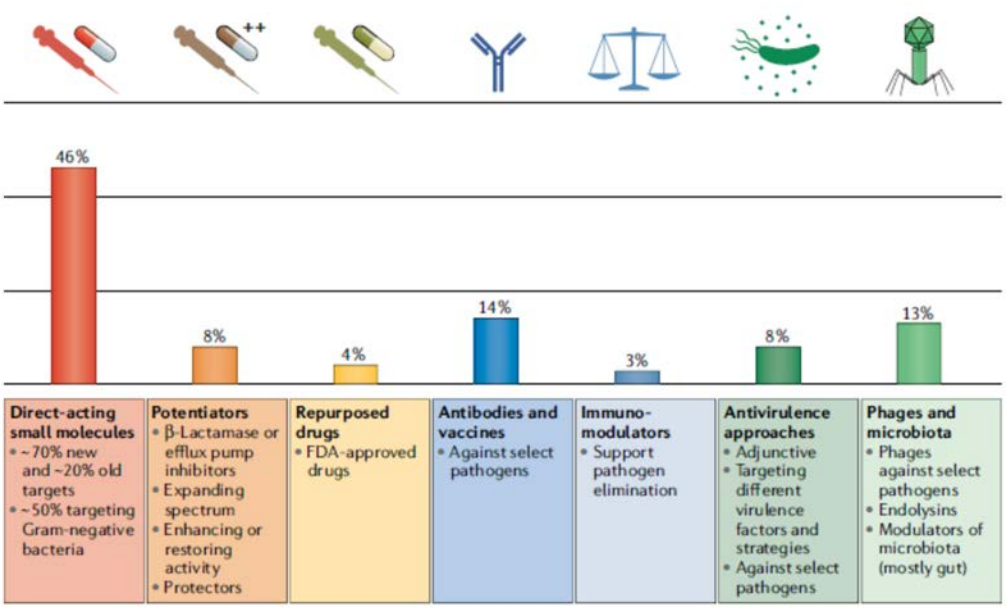



**FIGURE 6-5** Overview of the preclinical pipeline for antimicrobials and related products.
SOURCE: Adapted from Theuretzbacher et al., 2020.

In the United States, the NIH and the Biomedical Advanced Research and Development Authority (BARDA) provide multiple grants and awards to support research and development into new antimicrobials (GAO, 2020; Simpkin et al., 2017). The Joint Programming Initiative on Antimicrobial Resistance provides similar research funding in Europe (JPIAMR). Private foundations including the Wellcome Trust and the Bill & Melinda Gates Foundation also support development of new antimicrobials, either individually, or through public–private partnerships

such as the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), (CARB-X, 2021b; Knox, 2020). Many of these programs work at the preclinical stage and earlier, though the lines are not always clear. NIH grants can provide funding up to the point of regulatory approval, and BARDA's activity is more concentrated in middle- and late-stage clinical trials (Årdal et al., 2018; Simpkin et al., 2017). The nonprofit Global Antibiotic Research and Development Partnership (GARDP), described in Box 6-2, works across all phases of drug development, though most heavily in clinical development and postmarket stages (Balasegaram, 2021).

**BOX 6-2**
**The Global Antibiotic Research and Development Partnership (GARDP)**

In 2016 the WHO and the nonprofit Drugs for Neglected Diseases Initiative (DNDi), in consultation with various organizations working on antimicrobial resistance, founded the Global Antibiotic Research and Development Partnership (GARDP). After several years as a working group within DNDi, GARDP became an independent, nonprofit organization in 2019. GARDP works with public- and private-sector partners to develop new antibacterial medicines. Their focus is on treatment for the WHO priority pathogens list, late-stage clinical trials, and access to these medicines in low- and middle-income countries.

As a nonprofit, GARDP is able to take more risks, doing research in countries and patient groups where the commercial returns might be expected to be low, but the need is high (i.e., in low- and middle-income countries, among neonates). It can work with local partners to set up trial networks and expand licensing in the places of greatest need for new medicines. To this end GARDP has invested €500 million to develop and deploy five new antibacterial medicines that work on WHO priority pathogens by 2025. Its special priorities are serious bacterial infections that strike in hospitals, drug-resistant infections in children, neonatal sepsis, and sexually transmitted infections. The figure shows a rough breakdown of the GARDP portfolio, not including cost-sharing agreements that account for a quarter to half of new projects.

GARDP works at all stages of the drug development timeline, but its primary emphasis is on late-stage development and ensuring access. This includes working with regulators to ensure the authorization of new medicines and with contract manufacturers to ensure stable supply of the new drug.


**FIGURE** Breakdown of the GARDP €500 million portfolio.

SOURCES: Balasegaram, 2021; GARDP, 2021a.

### Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator

One of BARDA's main contributions to the research and development of new antimicrobials, as well as other therapeutics, diagnostics, and preventive products, was the 2016 creation of the nonprofit CARB-X partnership (CARB-X, 2021a). Other CARB-X contributors, either financially or in-kind, include the Wellcome Trust, the German government (via the Federal Ministry for Education and Research), the Bill & Melinda Gates Foundation, the British government's Global Antimicrobial Resistance Fund, and NIAID (CARB-X, 2021a). The program aims to speed the development of a range of antimicrobial products providing product developers with technical support and non-dilutive funding (meaning the funding is added to other revenue streams but is not contingent on the owner selling a piece of the company) (CARB-X, 2020). CARB-X works mainly in preclinical development and early clinical trials for WHO and CDC priority pathogens (CARB-X, 2020).[3] With $500 million of funding for its first 5 years, CARB-X is the world's largest early development investor in new antimicrobials and related products (Alm and Gallant, 2020).

Figure 6-6 shows how, across its three funding cycles to date, CARB-X has invested heavily in the riskiest stages of product development. For therapeutic and preventive products this includes the process of refining an active compound (i.e., a hit) to a chemical prototype (i.e., a lead) and establishing the compound's in vitro activity as well as other important chemical properties such as solubility, stability, and permeability through structure-activity relationship studies (lead optimization), steps that occur before preclinical development (Bleicher et al., 2003). (To give a sense of the CARB-X scope of work, Figure 6-6 also shows investments across the analogous stages in diagnostics development.)

[3] CDC urgent threat pathogens are *Clostridioides difficile*, carbapenem-resistant *Acinetobacter*, carbapenem-resistant Enterobacterales, *Candida auris*, and drug-resistant *Neisseria gonorrhoeae* (CDC, 2019a). The WHO critical threat pathogens are carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, carbapenem-resistant extended spectrum beta-lactamase-producing Enterobacterales (OECD et al., 2017).

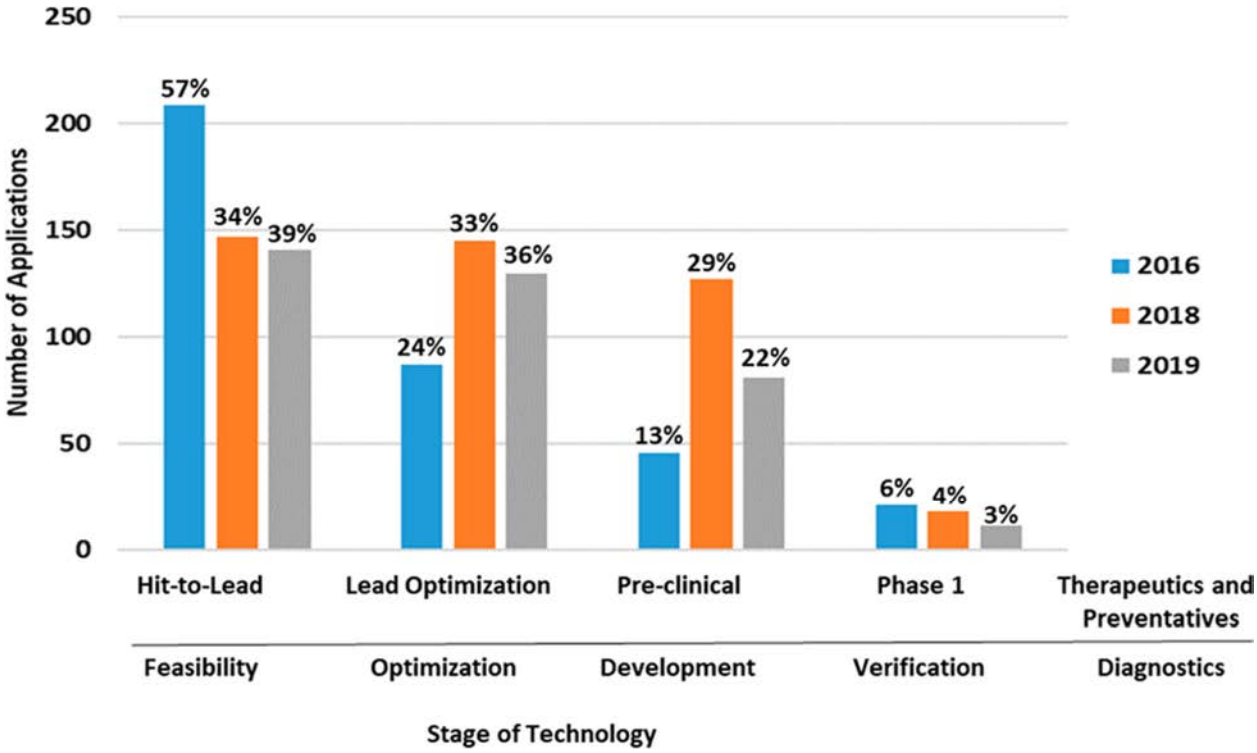



**FIGURE 6-6** Distribution of CARB-X applications based on stage of technology in development. SOURCE: Alm and Gallant, 2020.

CARB-X funds product development all over the world, but most of its funding goes to small firms in Europe and North America (Alm and Gallant, 2020; CARB-X, 2020). As a condition of receiving funding, product developers are required to develop plans for stewardships and access to their products within 3 months of entering phase 3 trials (CARB-X, 2021e). At this point, however, most products would no longer be part of the CARB-X portfolio, but possibly handed-off to BARDA for phase 2 and 3 clinical trials (Singer et al., 2020).

*Mid- and Late-Stage Clinical Development*

While preclinical stages of antimicrobial research are the most financially risky, later-stage trials have increasing technical and regulatory demands (Ardal et al., 2020; Ventola, 2015). Even effective drugs can sometimes fail to demonstrate their value at these stages because of problems with trial design, its cited endpoints, or a lack of statistical power (Fogel, 2018). As projects advance from the preclinical and early clinical trials stages, different funding and technical support may be needed. In the United States, BARDA funding supports this stage of research and development (Buckmon, 2020). Through partnership with various private companies, BARDA supports the largest portfolio of antibacterial drug development in the world (Buckmon, 2020).

## BARDA's Project BioShield and the Broad Spectrum Antimicrobials Program

Project BioShield Act was signed into law in 2004 with the objective of accelerating the research, development, acquisition, and availability of medical countermeasures, those medical tools that the government would need to respond to biological or chemical weapons (HHS, 2019;

Russell, 2007). The act created a special reserve fund from which the secretary of health can, with presidential approval, access up to $5.6 billion over 10 years to develop and procure medical countermeasures for which the government is the main market (MedicalCountermeasures.gov, 2019b; Parker, 2006). Through its provisions for emergency use, it allows the FDA to give temporary authorization to unapproved medicines or unapproved use of approved ones (ASTHO, 2021). BARDA manages the development and purchasing of countermeasure products under Project BioShield (Houchens and Larsen, 2017). To this end, BARDA provides advanced research and development contracts as well as market commitments to qualified pharmaceutical and biotechnology companies (Larsen and Disbrow, 2017). These contacts are intended to reduce the risk of developing products and improve their return on investment (Larsen and Disbrow, 2017).

In 2010, BARDA established the Broad Spectrum Antimicrobials Program to encourage research and development of novel antimicrobial drugs with broad-spectrum activity against pathogens that threaten national or global security (MedicalCountermeasures.gov, 2019a). The program funding, like CARB-X funding, is nondilutive (Merkeley, 2014). Should the product gain FDA approval the company would be free to sell it on the commercial market (Merkeley, 2014).

Initially, the Broad Spectrum Antimicrobials Program had to employ a so-called dual utility approach, meaning that drug candidates had to treat a clinically prevalent infection *and* be useful against one or more of the biodefense threats listed in the Department of Homeland Security (DHS) material threat list (Billington, 2015; Eichberg, 2015). The DHS material threat list did not, however, overlap with the CDC list of antimicrobial resistance threats (see Table 6-1**Error! Reference source not found.**) (Billington, 2015; Eichberg, 2015). The 2014 executive order Combating Antibiotic Resistant Bacteria gave BARDA the ability to target CDC priority pathogens (Billington, 2015). Further, the first *National Action Plan for Combating Antibiotic-Resistant Bacteria*, released in March 2015, called for BARDA to partner with at least one drug or biotechnology company to speed the development of antibacterial medicines (Billington, 2015; PCAST, 2015). By 2018 the agency was to have 12 candidate antibiotics in development, with at least two of these products submitted for FDA approval by 2020 (Billington, 2015; PCAST, 2015).

**TABLE 6-1** Comparison of CDC and BSA Priority Bacterial Threats

| CDC Urgent or Serious Antibiotic Resistance Threats | DHS High-Priority Bacterial Threats |
|---|---|
| *Clostridioides difficile* | *Burkholderia mallei* (glanders) |
| Carbapenem-resistant Enterobacterales | *Burkholderia pseudomallei* (melioidosis) |
| Drug-resistant *Neisseria gonorrhoeae* | *Francisella tularensis* (tularemia) |
| Multidrug-resistant *Acinetobacter* | *Rickettsia prowazekii* (typhus) |
| Drug-resistant *Campylobacter* | *Yersinia pestis* (plague) |
| Fluconazole-resistant *Candida* (a fungus) | *Bacillus anthracis* (anthrax) |
| Extended spectrum β-lactamase-producing Enterobacterales (ESBLs) | |
| Vancomycin-resistant *Enterococcus* (VRE) | |
| Multidrug-resistant *Pseudomonas aeruginosa* | |
| Drug-resistant nontyphoidal *Salmonella* | |
| Drug-resistant *Salmonella* Typhi | |
| Drug-resistant *Shigella* | |

| CDC Urgent or Serious Antibiotic Resistance Threats | DHS High-Priority Bacterial Threats |
|---|---|
| Methicillin-resistant *Staphylococcus aureus* (MRSA) | |
| Drug-resistant *Streptococcus pneumoniae* | |
| Drug-resistant tuberculosis | |

SOURCE: Adapted from Billington, 2015.

Figure 6-7 presents BARDA's antimicrobial drug candidate portfolio as of fall 2021. Along with supporting development of medicines for priority biothreats, such as plague and anthrax, the agency supports the development of treatment for CDC priority pathogens (Kadlec, 2019). Four of its antimicrobial candidates received FDA approval (Albrecht, 2020; Kadlec, 2019).[4] As Figure 6-7 shows another seven are in phase 3 clinical trials (Kadlec, 2019).

| STAGE OF DEVELOPMENT | ROUTE OF ADMINISTRATION | SPONSOR | COMPOUND | TYPE | TARGET PATHOGENS AMR | TARGET PATHOGENS BIOTHREATS | TARGET INDICATION |
|---|---|---|---|---|---|---|---|
| Approved | | Paratek (PBS) | Nuzyra | Tetracycline | Broad Spectrum | 1º anthrax 2º plague, tularemia | ABSSSI, CABP |
| Phase 3 | | Basilea | Ceftobiprole | Cephalosporin | *S. aureus* | 1º tularemia | ABSSSI, SAB |
| Phase 3 | | GSK (OTA) | Gepotidacin | Topo II Inhibitor | MDR GCI, CR-*E. coli* | 1º plague 2º tularemia, anthrax | GC, uUTI |
| Phase 3 | | Pfizer (OTA) | Aztreonam-Avibactam | BL/BLI Combo | MDR G- | 1º plague | cIAI, HABP/VABP |
| Phase 3 | | Spero | Tebipenem | BL | Enterobacteriaceae | 1º anthrax, plague | cUTI |
| Phase 3 | | ContraFect | Exebacase | Novel Class | *S. aureus* | | SAB |
| Phase 3 | | Summit | Ridinilazole | Novel Class | *C. difficile* | | CDI |
| Phase 3 | | VenatoRx | VNRX-5133 | BL/BLI Combo | MDR G- | 1º meliodosis | cUTI, HABP/VABP |
| Phase 2 | | Vedanta | VE-303 | Microbiome | *C. difficile* | | rCDI |
| Phase 1 | | Locus Biosciences | LBP-EC01 | Bacteriophage | *E.coli* | | rUTI |
| Phase 1 | | Qpex/MDCO (OTA) | OMNIvance | BL/BLI Combo | CRE, CRAB, ESBLs, MDR *P. aeruginosa* | | cUTI, HABP/VABP |
| Phase 1 | | Qpex/MDCO (OTA) | ORIvance | BL/BLI Combo | CRE, ESBL | | cUTI |
| Phase 1 | | Qpex/MDCO (OTA) | QPX9003 | Novel Polymyxin | CRAB, MDR *P. aeruginosa* | | HABP/VABP |
| Phase 1 | | Hoffman-LaRoche (OTA) | RO7223280 | Peptide | *A. baumannii* | | |
| Preclinical | | Genentech (OTA) | GDC-5780 | Novel Arylomycin | CRE, ESBL | | cUTI |
| Preclinical | | Genentech (OTA) | GDC-0829 | Novel Class | *CRE, ESBL, P. aeruginosa, A. baumannii* | | cUTI, HABP/VABP |
| Preclinical | | DARPA/AstraZeneca (IAA) | RNA-encoded Antibodies | RNA | *S. aureus* | | DFU, bacteremia |
| Preclinical | | Hoffman-LaRoche (OTA) | Diagnostic | IL-6 | Sepsis | | Sepsis, COVID-19 |
| Preclinical →P1 | | CARB-X | Portfolio | Multiple | Multiple | | Multiple |

For Public Use

**FIGURE 6-7** BARDA's antimicrobial portfolio, fall 2021.

Figure Legend: Injection, Intravenous, topical, Inhaled, oral

[4] Vabomere® (a combination of meropenem and vaborbactam) by Melinta Therapeutics, Zemdri® (plazomicin by Achaogen [now Cipla]), Xerava® (eravacycline) by Tetraphase Pharmaceuticals, and Nuzyra® (omadacycline by Paratek Pharmaceuticals) (Albrecht, 2020).

NOTE: ABSSSI = acute bacterial skin and skin structure infections; BL = beta-lactam; BL/BLI = beta-lactam/beta-lactamase inhibitor; CABP = community-acquired bacterial pneumonia; CDI = *Clostridioides difficile* infection; cIAI = complicated intra-abdominal infection; CRAB = carbapenem-resistant *Acinetobacter baumannii*; CRE = carbapenem-resistant Enterobacterales; cUTI = complicated urinary tract infection; DFUI = diabetic foot ulcer infections; ESBL(s) = extended spectrum beta-lactamase(s); GCI = gonococcal infection; HABP/VABP = hospital-associated bacterial pneumonia/ventilator-associated bacterial pneumonia; MDR = multidrug resistant; MDR G- = multidrug-resistant gram-negative bacteria; rCDI = recurrent *Clostridioides difficile* infection; rUTI = recurrent urinary tract infection; SAB = *Staphylococcus aureus* bacteremia; uUTI = uncomplicated urinary tract infection.
SOURCE: Images were provided courtesy of the Biomedical Advanced Research and Development Authority (BARDA) a division within the Assistant Secretary for Preparedness and Response of the Department of Health and Human Services.

Broad Spectrum Antibacterial program contracts end when the sponsoring company receives new drug approval from the FDA (Larsen and Disbrow, 2017). While other types of BARDA contracts include advance market commitments, there are no such provisions for broad-spectrum antimicrobials (Kadlec, 2019). BARDA can, however, arrange advance market commitments for qualified products needed for the national stockpile (Albrecht, 2018).

*Increasing Attention to Push Funding*

While push incentives are helpful and necessary for antimicrobial development, they are not tied to results, so there is less of a direct relationship between the incentive and its intended goals (Dutescu and Hillier, 2021). For example, early-stage research funding cannot be readily contingent on ensuring access to new medicines or antimicrobial stewardship. Individual companies and scientists benefit from push incentives, but they are also seen to have broad, indirect value to society. These indirect benefits and the relatively straightforward implementation make push incentives attractive tools for governments and other funders (Dutescu and Hillier, 2021). For these reasons, government and private incentive programs may be proportionately overinvested in early-stage and preclinical research (Simpkin et al., 2017). At the same time, the high-risk early stages may be the most appropriate place for public spending on drug development as it is the riskiest. Especially with antimicrobial medicines, the later stages of drug development have far less risk of failure.

In 2017 the Organisation for Economic Co-operation and Development (OECD) estimated that governments spent over $546 million a year on push funding for antimicrobial research and development (OECD et al., 2017). At the time, this amounted to 64 percent of research and development funding and 95 percent of the total incentive funding for antimicrobial development (OECD et al., 2017). The mix of incentives for antimicrobial development has changed more recently. There may be relatively less venture capital available today for small and medium-sized biotechnology firms (Dall, 2020; Nielsen et al., 2019). On the other hand, growing international attention to the problem has brought new funders to early stage development. The Novo Nordisk Foundation's REPAIR Impact Fund, for example, has a $165 million budget to invest in about 20 different therapies for antimicrobial resistance (Novo Nordisk Foundation, 2018). The AMR Action Fund, announced in 2020, will supply about $1 billion in funding, as well as technical support, from a group of innovator pharmaceutical companies via their trade association to small biotechnology companies developing treatments for CDC or WHO priority pathogens (AMR Action Fund, 2021). This push funding will be available "across all stages of clinical development" (AMR Action Fund, 2020, 2021). Though financed mainly by

pharmaceutical companies, private foundations are also involved and the fund's groundwork was set by the European Investment Bank, the Wellcome Trust, and the WHO (Beyer et al., 2020).

There is some imprecision in estimating the effects of push incentives, partly because some early-stage incentives work so broadly that they could not be reliably counted against any research and development funding total (Årdal et al., 2018). While push funding will be invaluable to maintaining a strong pipeline for antimicrobials and other products needed to fight resistance, there is growing consensus that they need to be paired with pull and hybrid incentives to maximize their usefulness and to compensate for the lack of a vigorous market for new antimicrobials (Årdal et al., 2018; Dutescu and Hillier, 2021; WHO, 2021).

## Pull Incentives

While push incentives are geared toward reducing the cost of research and development, pull incentives are designed to facilitate higher market returns for product developers (Bhavnani et al., 2020; Renwick et al., 2016). Pull incentives can be divided into two categories: ones that provide direct monetary reward, sometimes called outcome-based incentives, or ones that act through legal and regulatory channels to indirectly increase a company's returns (called lego-regulatory incentives) (Renwick and Mossialos, 2020). Outcome-based pull incentives include lump-sum payments and cash rewards for sales and regulatory milestones. Advanced commitment to buy a certain amount of a drug or to license the patent for a set sum are also considered outcome-based pull incentives. Box 6-3 describes one such advance commitment program recently introduced in Congress.

### BOX 6-3
### The Onshoring Essential Antibiotics Act

The COVID-19 pandemic brought new attention to vulnerabilities in the global supply chain for medical products. But as early as 2016 an explosion at the Chinese factory—the world's single producer of active ingredients for the combination antibiotic piperacillin-tazobactam—and Hurricane Maria's disruption to Puerto Rican manufacturing of medical products had heightened federal interest in maintaining a stable supply of essential medicines. This interest is reflected in the Onshoring Essential Antibiotics Act introduced before the Senate Health, Education, Labor, and Pensions committee in April 2021.

The act proposes grant awards to the manufacturers of up to three essential, generic antimicrobial drugs. These awards, of up to $500 million, would be used for both direct manufacturing of antimicrobials and for building or recommissioning antimicrobial factories in the United States. The funds would also be available to purchase the antimicrobials made in these factories for the national stockpile. The act also sets aside an additional $2 million towards research determining what essential medicines are most vulnerable to supply chain disruptions.

The Onshoring Essential Antibiotics Act is not intended to stimulate the antimicrobial pipeline or the viability of new antimicrobials. But it is an example of how pull incentives can be used for generic antimicrobials. Long after the initial approvals cycle, antimicrobials and other essential medicines can face difficulties in reaching their target patient population.

SOURCES: Mereish, 2018; Oehler and Gompf, 2020; Suzuki, 2021.[5]

[5] *Onshoring Essential Antibiotics Act, S. 1176*, 117th Cong., 1st sess. (April 15, 2021).

In contrast, legal and regulatory pulls are designed to increase financial returns indirectly using strategies such as extension on market exclusivity or accelerated regulatory review (thereby reducing the time to bring a drug to market). By only rewarding successful development, both types of pull incentives aim to shift the risk associated with bringing a medicine to market from the developer to the payer.

France and Germany have instituted a number of legal and regulatory pull incentives that allow for more flexible pricing and accelerate regulatory review process for antimicrobial drugs. Both programs work through attention to list price and sales incentives, though the French one puts more emphasis on rewarding added therapeutic value (Gotham et al., 2021). These incentives have been in effect since 2015 in France and 2017 in Germany (Gotham et al., 2021).[6] Formal outcome evaluations for these programs are not yet available, but it is reasonable to expect that they have increased company revenues from sales of their qualified antimicrobial drugs in those markets. The United States also uses several legal and regulatory pull incentives, Box 6-4 describes some of the more common ones employed as of midyear 2021. Box 6-4 does not include some outcome-based pull incentives such as the purchase of a new antimicrobial for the national stockpile or an advanced purchase commitment. Since new antimicrobials have relatively small patient populations, it is difficult to envision such purchases being of sufficient volume to be a meaningful incentive.

**BOX 6-4**
**Legal and Regulatory Pull Incentives in the United States**

- Generating Antibiotic Incentives Now (GAIN) Act enacted in 2012 as part of the Food and Drug Administration Safety and Innovation Act provides additional years of marketing exclusivity to new antimicrobial drugs that meet the definition of a qualified infectious disease product, a designation that makes these drugs eligible for expedited regulatory review and approval.
- Limited Population Pathway for Antibacterial and Antifungal Drugs enacted in 2016 as part of the 21st Century Cures Act, allows for a more streamlined clinical development (i.e., smaller, shorter, or fewer clinical trials) for those drugs "intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs."
- Revisions to the Centers for Medicare & Medicaid Services' (CMS's) New Technology Add-On Payments: as of 2019, the Inpatient Prospective Payment System (IPPS) final rule increased reimbursement from 50 to 75 percent for all antimicrobial drugs designated as qualified infectious disease products. The rule also changed the severity level designations for a total of 18 resistant infections thereby increasing reimbursement rates for care related to any of those infections. Further changes to CMS's inpatient payment are set for 2021; this will allow antimicrobials designated as qualified infectious disease products approved via the Limited Population Pathway to be eligible for additional reimbursement within the first 3 months of market authorization as opposed to waiting for the next fiscal year.

[6] There is an additional law that was passed in 2020 in Germany that exempts certain antimicrobials from the health technology assessment process used for making reimbursement decisions. The exemption is similar to that granted to orphan drugs, meaning those drugs aimed to treat rare diseases and conditions (Gotham et al., 2021).

SOURCES: Dall, 2019; Schneider, 2020.

There are also two bills pending in Congress that include additional legal and regulatory incentives for antimicrobial manufacturers. First is the 2018 Re-Valuing Anti-Microbial Products Act (REVAMP). This act amends the Food, Drug, and Cosmetic Act to enable developers of priority antimicrobial medicines designated as "qualified infectious disease products" to receive transferable extensions on market exclusivity for up to a year.[7] The act's provisions include a committee of FDA, CDC, and BARDA representatives as well as other experts from medicine, public health, economics, and related fields of research.[8] The fact that Congress has taken no action on REVAMP since 2018 suggests it is not a priority and may not be revisited.

The 2019 Congress saw proposed changes to Medicare's system of bundled payments, the paying of hospitals or other providers for multiple, related services for a predetermined flat fee (Hardin et al., 2017). Bundled payments are meant to make medicine more efficient and remove the incentive to over-treat inherent in a fee-for-service system (Hardin et al., 2017). One of the earliest forms of bundled payment, in places since the 1980s, are "fixed payments for inpatient services associated with specific diagnoses and procedures" or Diagnosis Related Groups (Cortese et al., 2018). By paying a flat fee for related services and medicines, the rule creates a disincentive for hospitals to use newer, expensive antimicrobials and related diagnostics (Gotham et al., 2021). Revisions to the Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM) Act would allow the Centers for Medicare & Medicaid Services (CMS) to reimburse antimicrobials qualified by FDA separately, in addition to the bundled payments determined by diagnosis.[9] Supporters of this change point to the limited patient pool and short treatment duration for novel antimicrobials. By reimbursing more for these medicines in hospitals, they maintain, CMS would improve outcomes for patients with resistant infections, slow the emergence of resistance, and contribute to the market viability of companies making these drugs (Coukell, 2019; IDSA, 2019; Segerman, 2019).

At the same time, research has shown that, however well-intentioned, recent pull incentives have not brought about the changes intended. To start, eligibility as a qualified infectious disease product, a determination on which many of the proposed incentives hinge, appear to be overly broad (Darrow and Kesselheim, 2020). Many serious, life-threatening infections already have good treatments on the market, yet the qualification process, "disproportionately rewards modifications to existing drugs rather than the creation of novel drugs" (Darrow and Kesselheim, 2020). To put it another way, new antimicrobials that do not necessarily satisfy an unmet need can qualify for fast track approval and extended exclusivity protections afforded as a qualified infectious disease product.

Ironically, uniform extensions on market exclusivity are most valuable to the least innovative products. At the heart of the questions is the time value of money, the idea that money is worth more in the present than the same amount in the future because of forgone investments it could have been used for. In deciding whether to invest in a given drug development project, an investor calculates the net present value of that project in which future revenues are discounted by the cost of capital. (Due to this discounting, revenues in out-years are worth less

[7] The authorizing legislation of the modern FDA (FDA, 2018a).
[8] REVAMP Act, HR 6294, 115th Cong., 2nd sess., Congressional Record 164, no. 109, daily ed. (June 28, 2018): H 5977.
[9] DISARM Act of 2019, S 1712, 116th Cong., 1st sess. (June 4, 2018).

than those realized in the shorter term.) Therefore, as Figure 6-8 shows, a 5-year extension to exclusivity is worth more than half the net present value of a drug's revenue for modification to an existing drug, something otherwise determined to warrant a 3-year period of market exclusivity, but only about a quarter of the present value for an orphan drug product guaranteed 7-year market exclusivity. Baseline differences in market exclusivity reflect the relative value different new medical products bring society. Blanket extension on market exclusivity undermines that calculation, disproportionately rewarding the least valuable products (Darrow and Kesselheim, 2020).

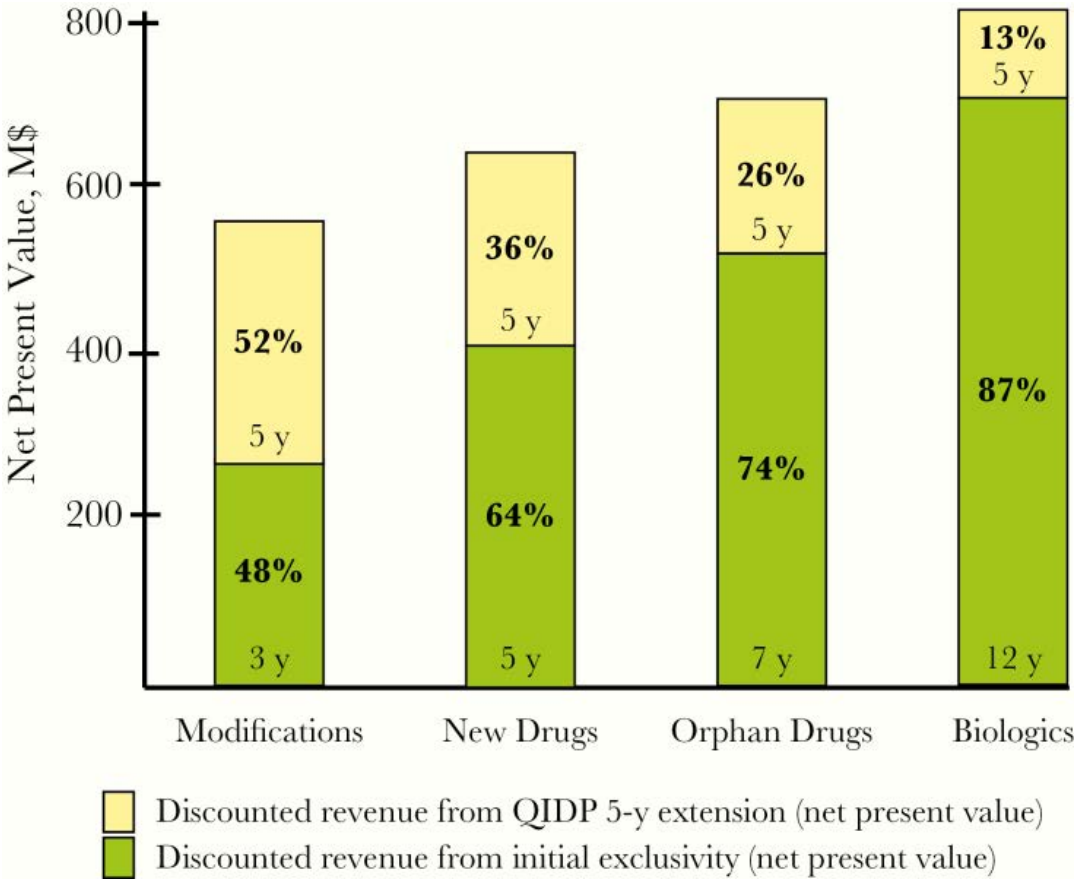



**FIGURE 6-8** Estimated contributions of the Generating New Antibiotic Incentives Now Act's 5-year extensions on market exclusivity. The hypothetical value of the extension at time of market entry, assuming $100 million a year in revenue paid on the last day of the year and no revenue thereafter.
NOTE: Biologics are not eligible for exclusivity under the act and are included for illustrative purposes only.
SOURCE: Darrow and Kesselheim, 2020.

CMS' attempts to increase payment for novel antimicrobials have also met with roadblocks. To qualify for New Technology Add-On Payments staff in the hospital pharmacy have to apply to CMS for reimbursement, expending significant, unbillable time and effort on the application (Bhavnani et al., 2020). To complicate the matter, although the expense of the new medicine and the staff time to file for an add-on payment are incurred at the pharmacy level, CMS reimburses the highest organizational level, the hospital (Bhavnani et al., 2020). This lump-sum payment is not broken out with details about what technologies are being reimbursed,

information that could at least give the hospital executives a sense of which divisions' work had contributed to the reimbursement (Bhavnani et al., 2020). Furthermore, even after reimbursement of 75 percent of a new antimicrobial's launch price (what the CMS New Technology Add-On Payment would allow) the new drugs are still considerably more expensive than generics (Bhavnani et al., 2020).

Nevertheless, the add-on payments do offer hospitals additional payment for expensive, new antimicrobials. While there are problems with the tracking of these payments and with the administrative burden they put on staff, especially on pharmacy staff, these are not strictly speaking, problems with the incentive, but rather with the way it is managed.

It is difficult to gauge the effect of the 2016 Limited Population Pathway for Antibacterial and Antifungal drugs on stimulating the market, as only two drugs have been approved under it to date (FDA, 2020d). One treats lung disease caused by *Mycobacterium avium* complex, the other a type of highly resistant tuberculosis (FDA, 2020d). Unlike the other pull incentives described in Box 6-4, this pathway does not hinge on qualification as an infectious disease product but on FDA's judgment that the medicine will effect, "such factors as survival, day-to-day functioning, or the likelihood that the condition, if left untreated, will progress from a less severe condition to a more serious one" (FDA, 2020d).

## The Strength of the Pipeline

Overall, the push and pull incentives in effect modestly improved the number of products in the antimicrobial drug pipeline. After a drop in the 1990s and early 2000s, the number of new antimicrobials the FDA approves every year has risen recently (Spellberg, 2021; Spellberg et al., 2013). In a 2019 paper, Cunha and colleagues estimated that the number of drug candidates in the pipeline has increased more than 10 percent between 2014 and 2019 (Cunha et al., 2019) (see Figure 6-9). Moreover, during the same period, the FDA approved a total of 20 new antimicrobial drugs, 17 of which had activity against the so-called ESKAPE pathogens, pathogens designated as urgent threats by the CDC or the WHO.[10] Of these 17 new antimicrobials, 12 qualified as infectious disease products, thereby earning priority regulatory review and extended exclusivity protections (Berger et al., 2021; FDA, 2021c).[11]

[10] ESKAPE pathogens include *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species (CDC, 2019a).

[11] The FDA aims to take action within 6 months on an accepted new drug application that is designated as Priority Review rather than the 10 months under standard review (OECD et al., 2017).

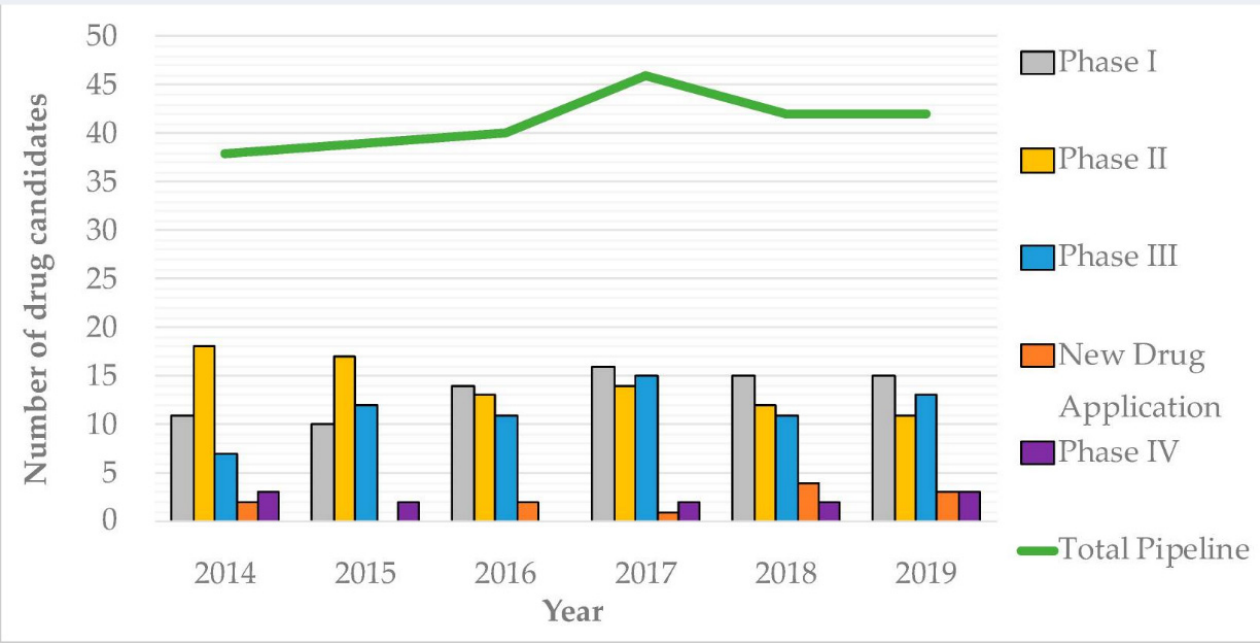



**FIGURE 6-9** Antimicrobial drug pipeline, by stage of development over time.
SOURCE: Cunha et al., 2019.

However, these figures only tell a partial story about the antimicrobial drug pipeline. Of the 43 new antimicrobials currently in clinical development, only 10 are of a novel class or target (Pew, 2014). Of the 15 new antimicrobials in phase 3 trials or granted new drug approval in the last quarter of 2020, only 4 had expected activity against CDC urgent threats or WHO critical, priority pathogens (Pew, 2014). In short, the majority of the pipeline drugs are not very different from existing antimicrobial medicines, nor do they have activity against those pathogens that are the most worrisome, mainly multidrug-resistant, gram-negative bacteria (WHO, 2019b). Only 6 of the 50 antibiotics currently in the pipeline meet even one WHO criteria for being innovative,[12] only two target multidrug-resistant, gram-negative pathogens (WHO, 2019a).

Further, most of the recently approved drugs appear to offer little to no added clinical value over existing treatments (Schulz et al., 2019; WHO, 2019b). A 2019 WHO review commented on "a visible mismatch between the few newly approved antibiotics and the WHO priority pathogen list" (WHO, 2019a). The review concluded that overall the newly approved products "lack of differentiation against existing treatments, their non-inclusion in clinical guidelines, and their higher prices in comparison to existing generic treatments make it difficult to predict their place in the treatment landscape" (WHO, 2019a). While the existing incentives have helped revitalize research and development in antimicrobials and increased the number of antimicrobial drugs in the pipeline and on the market, they have not succeeded in bringing to market innovative new antimicrobial drugs for serious and life-threatening infections caused by pathogens of concern.

It is difficult to say how many drug candidates or other products in development constitutes a strong pipeline. As Figure 6-9 showed, many candidates fall away in clinical trials

[12] These criteria are no known cross-resistance with existing medicines, a new drug class, a new target, or a new mode of action (WHO, 2019b).

before reaching the New Drug Application phase. Market entry rewards that fully or partially delink product revenues from quantity sold are one promising strategy. Such additional incentives could improve the expected net present value of antimicrobial drug projects compared to other therapeutic areas and entice large pharmaceutical companies to reenter the antimicrobial market, goals that existing mechanisms have not yet achieved (Daniel et al., 2018; PACCARB, 2019; WHO, 2019b).

Participation of large, multinational companies in antibiotic development would also help ensure the viability of new antimicrobials. These companies are immensely profitable, with cumulative profits of over $8 trillion between 2000 and 2018 (Ledley et al., 2020). Their diverse product lines generate sufficient revenue to offset the manufacturing and postmarket expenses associated with new antimicrobials during the roughly 2 decades before the drugs become profitable (McKenna, 2020). But the same economic factors that drive small antimicrobial manufacturers to bankruptcy apply to large pharmaceutical companies as well. Publicly traded companies are not supposed to lose money on purpose, even if they have a lot of money to cover the losses. This is why 15 of the 18 largest pharmaceutical companies have quit antimicrobial development in the last 20 years (Council of Canadian Academies, 2019; Talbot et al., 2019). In their place are small and medium-sized biotechnology firms, which account for over 95 percent of the antimicrobials in development today (The Pew Charitable Trusts, 2020b). These companies do not have the capital reserves to withstand the time between launch and profitability, nor do they have comparable infrastructure, laboratories, or depth of staffing (Talbot et al., 2019; The Pew Charitable Trusts, 2020b; WHO, 2019b).

## Optimal Incentives for Antimicrobial Development

The optimal incentives for antibiotic development would improve the drug's net present value and facilitate cooperation of both large pharmaceutical companies and small biotechnology firms (Renwick et al., 2016). Market entry rewards are one promising tool to this end. A recent systematic review found market entry rewards to be the most frequently suggested incentive for antimicrobial development (Dutescu and Hillier, 2021). There is, however, no consensus on the appropriate size of the reward, eligibility criteria, or the implementation method.

It is also difficult to judge the success of some incentives discussed in this chapter simply because they are so new. For example, the widely criticized 2019 revisions to the Inpatient Prospective Payment System may, in some ways, be seen as a failure (Outterson, 2019; The Pew Charitable Trusts, 2020a). At the same time, most impact evaluations for economic programs give longer than a year between program implementation and evaluation. Hospital administrations can move slowly, but it may be rash to conclude that they will not move at all to adjust to a new incentive.

### *The Amount of Market Entry Reward*

The Infectious Diseases Society of America (IDSA) has proposed a reward of "at least $500 million" for new antibiotics that address unmet needs (Talbot et al., 2019). The O'Neill report and the European public–private partnership Drive-AB have suggested that a market entry payment of $1 billion for each new antibiotic approved may be appropriate (Årdal et al., 2018; O'Neill, 2018). After the British government announced a plan to pay over $140 million for each new antibiotic approved, proposals for a similar, proportionate payment from G20 countries led to calls for a pooled payment of $4 billion for each new drug (Mullard, 2020; Rex and Outterson,

2020). Given the United States accounts for almost half of global pharmaceutical sales, it is safe to conclude that the U.S. share of a $4 billion payment would be close to $2 billion per drug (Mikulic, 2021). In its 2017 recommendations on this question, the President's Advisory Council on Combating Antibiotic-Resistant Bacteria recommended the use of market entry rewards, pointing to recent analyses suggesting $1 to $2 billion or more may be needed (HHS, 2017). This represents a significant outlay of taxpayers' money. To put it in perspective, $1 billion is comparable to the FDA's entire 2020 budget for food safety; the CDC's total budget request for fiscal year 2020 was $6.6 billion (CDC, 2020b; FDA, 2020c).

The amount of the reward should be sufficiently large to entice entry but not so large that it results in what economists describe as rent seeking, the practice of companies asking the government for financial protections not proportionate to their value (Henderson, 2019). The reward amounts cited in the literature are often based on economic models with high parameter uncertainty. The O'Neill report's $1 billion figure, for example, was based on a "broad estimate" of a $40 billion cost of inaction over 10 years (O'Neill, 2018). This estimate was in turn influenced by the report's predictions of the future burden of resistance, a prediction of questionable reliability and based on uncertain methods (de Kraker et al., 2016; Harbarth, 2018). Drive-AB's similar estimate was derived from economic modeling, though with more clearly stated assumptions (Årdal et al., 2018). One such explicit assumption of this model was that large pharmaceutical companies would not enter the market for profitability below a $50 to $500 million threshold (Årdal et al., 2018). This may reflect company expectations based on highly successful product launches.

However, across the pharmaceutical market as a whole, both launch year and peak year sales for most drugs have been on the decline (Berndt et al., 2015). For example, from 2011 through 2015, 64 percent of all new drug launches garnered less than $100 million in annual sales within the first 5 years and 23 percent earned less than $10 million per year (Aitken and Kleinrock, 2017). The average peak-year sales for new drugs have decreased by more than 50 percent from 2010 through 2018, from $816 million to $316 million per annum (Steedman and Taylor, 2019). Given these trends, it may be more prudent to benchmark the market entry reward to independently reported industry averages, thereby reducing the likelihood of under- or over-incentivizing the market.

### *Full or Partial Delinking of Sales and Revenues*

One of the main questions in offering a market entry reward for novel antimicrobials is the delinking of the drug's revenues from sales. Originally proposed as a way to encourage development of medicines for neglected diseases, delinking essentially pays the development costs of a new drug up front, rather than gradually through sales (Aagaard et al., 2021). Antimicrobials are well suited to some delinking of revenues, as the best interests of society are served not by selling the drug but by holding it in reserve to use only when needed.

The delinking of sales and revenues is not necessarily an all or nothing proposal, however. In some models the market entry reward is paid *in addition* to sales revenue, meaning that the link between sales and revenues is partially delinked. The Duke-Margolis Center and Drive-AB consortium have both proposed partially delinked rewards, seeing them as more flexible, responsive to unpredictable changes in demand for the drug, more adaptable to different countries' national reimbursement models, and easier to pilot (Årdal et al., 2018; Schneider et al., 2020a). The Duke-Margolis model specifically pointed to an impartial antibiotic manager that would adjust payments (in this case annual subscription fees) in response to ebbs and flows

in demand, or to reflect its relative value to public health (Schneider et al., 2020a,b). The partially delinked model can also make payments contingent on meeting goals for stewardship or investments in the drug supply chain (Hillock et al., 2020).

Other models advocate for full delinking of drug revenues from sales, citing concerns that, should manufacturers earn any sales revenues, their incentive to oversell remains (Aagaard et al., 2021). The full delinking of sales from revenues also allows for better controls on the drug's price, assuring its affordability (Aagaard et al., 2021). Full delinkage requires the drug company to refrain from marketing or promoting the drug in any way (Sciarretta et al., 2016). In short, fully delinked reward payments are an alternative to sales revenues, partially delinked payments are a supplement to them (Okhravi et al., 2018).

Especially when applying rewards internationally, partial delinking might seem more fair; high-income countries can and arguably should pay more for medicines than low- or middle-income ones. Some scholars have argued, however, that when the manufacturer's incentive to sell in lucrative markets remains, it can aggravate inequities in access, giving companies an incentive to concentrate on rich-country markets, regardless of their relative need (Outterson et al., 2016).

*Payment Eligibility*

Suggested eligibility for a reward payment also varies. Some guidelines emphasize rewarding only novel antimicrobials that target the highest-priority pathogens (WEF, 2018). Others allow additional rewards for products with a novel mechanism of action, but do not make these criteria strict eligibility requirements for the payment (Talbot et al., 2019). A sizable group, including the President's Advisory Council on Combating Antibiotic-Resistant Bacteria and the Duke-Margolis Center have advocated for a reward payment benchmarked to objective determination of the drug's value to public health (Daniel et al., 2019; HHS, 2017).

Despite good consensus that rewarding added clinical value is the best use of a market entry reward, this is something that is difficult to discern. FDA approval indicates that a new drug provides benefits that outweigh its known and potential risks for specific indications. Regulatory approval is not, however, an endorsement of meaningful or added clinical value over existing treatments. This distinction is informed, in part, by late-stage clinical trials, trials that are classified, depending on the regulatory agency, as noninferiority (establishing the new drug is no worse than old drugs), equivalence (neither better nor worse than existing treatment), or superiority (establishing added clinical value over the old drug) (CPMP, 2000). This classification is based on criteria that are not always clear and are influenced by sample size and statistical power (Dunn et al., 2018). In some situations, companies may go in to the trial intending to establish superiority, but give an a priori margin for noninferiority if that result would be sufficient for licensing (CPMP, 2000).

Superiority in clinical trials is a clear indicator of added clinical value, but such trials are not often feasible for antimicrobial medicines. Since the use of a placebo control would be unethical, only patients suspected to have an infection caused by a pathogen susceptible to both the conventional and test drug are eligible (IDSA, 2012; Rex et al., 2017). There are also logistical challenges to recruiting patients with a specific, resistant pathogen within hours of their presentation for treatment especially without rapid diagnostics (IDSA, 2012; Rex et al., 2017). These patients, especially those suffering from serious infections with resistant, gram-negative pathogens, may be too mentally or physically deteriorated at intake to give informed consent (IDSA, 2012). Given these constraints on trial design, it is unsurprising that antimicrobial drugs

approved by the FDA between 2014 and 2019 used noninferiority pivotal trial designs (FDA, 2021c).

Superiority trials cannot replace the current system by which new antimicrobials are evaluated. Such trials are neither feasible nor necessary for new antimicrobial agents against resistant pathogens with limited or no treatment options (Rex et al., 2017). Furthermore, patients can have multiple infections with different pathogens; it is not always clear which one is the primary cause of disease, making it difficult to judge a patient's suitability for a trial. In other cases, the diagnosis of infection may be based on clinical presentation rather than culture results, leading to a situation where the more seriously ill patients are more likely to be considered for the new treatment, making the treatment's superiority hard to judge (Stafford et al., 2014).

At the same time, superiority trials can be useful. Additional therapeutic value can be hard to discern in noninferiority trials, which are intended to show that the difference, if any, between the new treatment and its comparator is small (Gotham et al., 2021; HHS et al., 2016). A recent study of antimicrobial prescription guidelines from 70 hospitals in 12 countries and regional standards from seven academic societies found that preferred antimicrobial treatment classes for the same infections varied widely, concluding "the lack of consensus seemed to emanate from a dearth of studies designed to determine superior treatment options, leaving the possibility for standards to vary when interpreting the same literature base" (Rost et al., 2021). Evidence of clinical superiority could do much to harmonize clinical guidelines.

Emerging approaches, such as data exchange and adaptive clinical trial designs, may enable conduct of superiority trials for antimicrobial drugs (Gatti et al., 2020; Lanini et al., 2019; Paul et al., 2021; Rubin, 2016; Trusheim et al., 2016). An adaptive clinical trial design allows for prospective modifications to the trial design based on the accumulated data (HHS et al., 2019). As Figure 6-10 shows, adaptive randomized controlled trials require fewer participants, largely because stopping criteria are revisited at multiple points; the risk difference between groups calculated in interim analyses can influence the statistical power and needed sample sizes for later stages (Lanini et al., 2019). In other words, study parameters are carefully modified while the adaptive trial is in progress on the basis of a review of interim data (Lanini et al., 2019). Such trials are better indicators of added clinical utility and should not be abandoned during pre- or postapproval evaluations. The amount of any market entry payment should be proportionate to the quality of evidence provided in the clinical data submitted for regulatory approval.

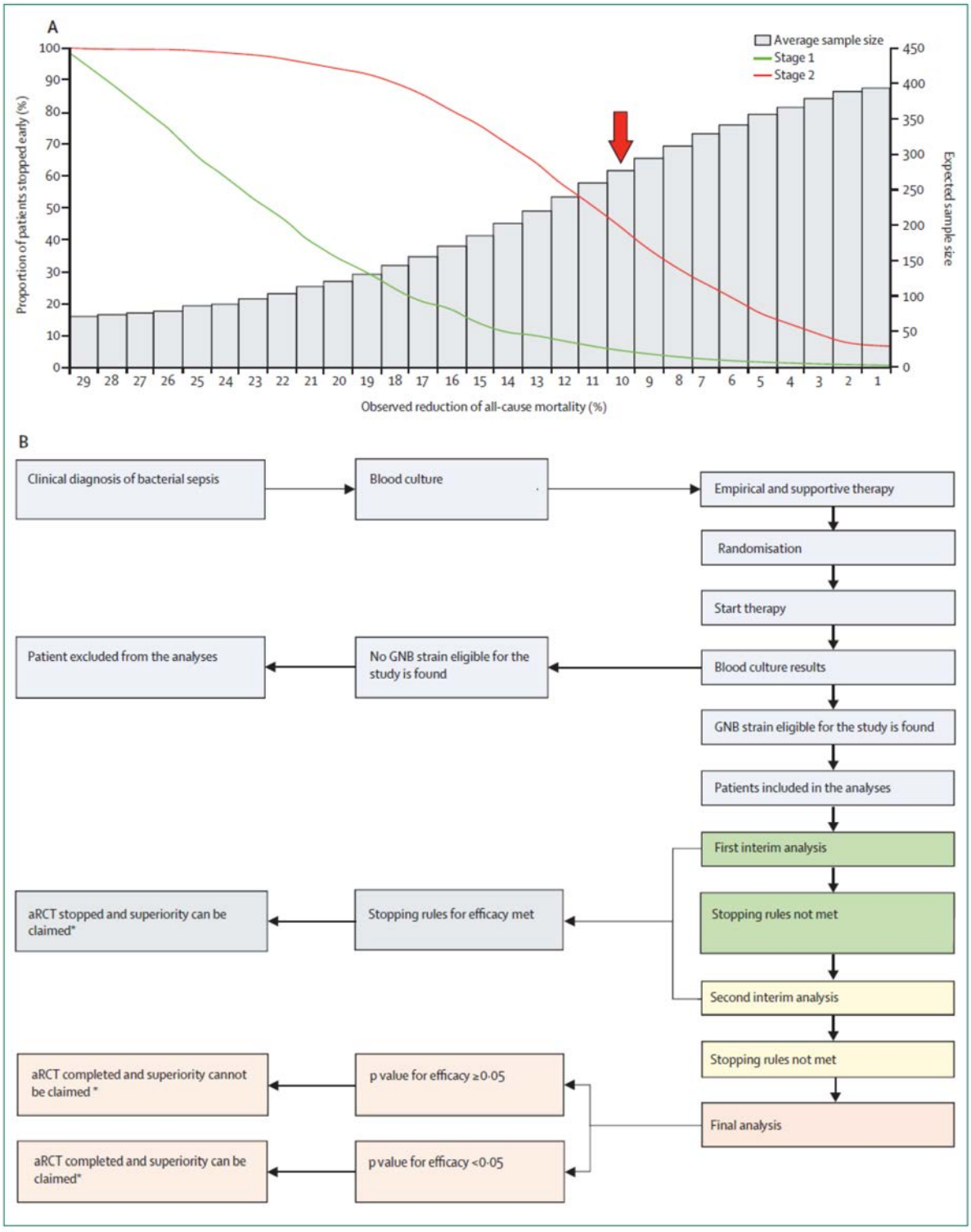



**FIGURE 6-10** Simulation of an adaptive randomized controlled trial for gram-negative bloodstream infections.

(A) The probability of early stopping of the aRCT (lines) and expected sample size (bars) for observed reduction in all mortality between the control (assumed at 30 percent) and experimental group (variable between 1 percent and 29 percent). Red arrow represents sample size (n = 278)

for the main aRCT assumption, including power 80 percent, α = 0.05, and efficacy (risk difference) of 10 percent.

(B) Different phases of the aRCT, including participant enrollment and selection (blue), first interim analysis (green), second interim analysis (yellow), binding decision on early aRCT termination (grey), and final analysis (red). aRCT-adaptive, post marketing randomized clinical trial. GNB-Gram negative bacteria. * As one or multiple aRCTs are completed, their results can be added to the results of other existing trials in cumulative meta-analyses that provide new, comprehensive views of the developing evidence.

SOURCE: Lanini et al., 2019.

*A Deliberative Process for Establishing Added Value*

The amount of market entry rewards, options for delinking revenues, and eligibility criteria all stand to affect the programs' viability and its effects—both intentional and unintentional—on the global antimicrobials market. The varied experiences with legal and regulatory pull incentives described here point to a need for deliberation and piloting of possible market entry reward programs, as both Sweden and the United Kingdom are currently doing (Gotham et al., 2021). The Swedish program combines partially delinked rewards and a minimum guaranteed annual revenue amount for a qualifying drug that has efficacy against a WHO critical, priority pathogen and an acceptable safety profile (Gotham et al., 2021). The British program uses fully delinked fixed annual payments in the range of $40 to $140 million regardless of volume (Gotham et al., 2021).[13] Participation in both pilot programs is voluntary and requires companies to apply for consideration. The Swedish pilot program will run through 2022 (Gotham et al., 2021). The British program launched, after some delays, in June 2020 (Mahase, 2020). Later that year, NHS England announced the selection of Fetroja®, a treatment for drug-resistant, gram-negative bacteria in patients with limited treatment options, and Zavicefta® a combination antibacterial used against serious, gram-negative infections (Bassetti et al., 2021; Perkins and Glover, 2020; Pfizer, 2017). Fetroja® is made by Shionogi and Zavicefta® by Pfizer, both products should be available to patients in late 2022 (Perkins and Glover, 2020).

Market entry rewards require significant investment of taxpayer dollars. While the threat of antimicrobial resistance is real and more antimicrobial drugs are needed in our arsenal, it is important to ensure the best possible design and execution of reward payments to minimize the risk to taxpayers. Before funding any market entry reward, the government needs to be clear that it is rewarding a truly novel and useful antimicrobial.

**Recommendation 6-1: A Department of Health and Human Services (HHS) interagency committee should establish well-targeted, objective criteria to identify novel antimicrobials with high potential for filling a critical, unmet need. HHS should then support trials to establish the additional clinical benefit and optimal use of these drugs.**

The importance of independent, objective criteria for determining eligibility for payment cannot be overstated. The success of any future market entry reward program depends on these

[13] The amount represents 2 percent of the $2 to $4 billion valuation for a new antimicrobial. The percentage is based on the UK share of global pharmaceutical sales (Gotham et al., 2021).

criteria against which a product's true value would be assessed. For this reason, the committee recommends such criteria be set by an independent panel (Daniel et al., 2018). Recognizing that there will be differences of opinion as to what constitutes a product of meaningful value to public health, the deliberative process for setting criteria should be open and the relative weight given to competing criteria made public (Schneider et al., 2020b).

**An arbiter on what constitutes critical unmet need** Pending legislation in Congress makes attention to the eligibility criteria for market entry rewards especially urgent. One of the main criticisms of the GAIN Act is its reliance on overly broad criteria to qualify as an infectious disease product (i.e., products for which there is an effective alternative are not excluded) (Gatti et al., 2020; Rubin, 2016). What is more, the designation as a qualified infectious disease product may be misunderstood to be a reflection of value, something that could justify excessive spending on a drug with limited to no added benefit to the public health (Darrow and Kesselheim, 2020). The DISARM Act, currently introduced in the Senate, carries forward GAIN's flawed eligibility criteria in its plan to raise CMS reimbursement on qualified antimicrobials. Therefore, the pending DISARM legislation gives some urgency to the need to narrow the eligibility criteria for market entry rewards. One important role for the proposed committee would be to identify those products with greatest potential for clinical value to avoid continued reliance on the GAIN Act's criteria.

The Pioneering Antimicrobial Subscriptions to End Up-surging Resistance (PASTEUR) Act proposes that governments pay for new antimicrobials by subscription, similar to the model NHS England is currently piloting.[14] Antimicrobials determined to meet a critical need would earn annual contracts of between $750 million and $3 billion a year, paid out over a period of up to 10 years or length of patent exclusivity.[15] This model would fully delink drug sales from revenues, as the award would be independent of quantity of drug sold. Eligibility for payments includes, but is not limited to "treating infections for which there is unmet need; improving clinical outcomes for patients with multidrug-resistant infections; being a first-approved drug that treats certain multidrug-resistant infections, and, to a lesser extent, second and third drugs that treat such infections; addressing an infection located in an organ or other location that is challenging to treat; or addressing a multidrug-resistant infection through a novel chemical scaffold or mechanism of action, especially through oral administration."[16] It also calls for regulatory measures to establish the relative weight assigned to each of these desired characteristics.[17] Recent revisions to the PASTEUR Act make it clear that the subscription payments would end if the drug developer fails to submit a plan for registering it in low- and middle-income countries. Purchased drugs would also be available to Medicare, Medicaid, and Veterans Health Administration beneficiaries in the United States; the revisions also allow for smaller contracts with new developers and a requirement that the list of high-priority microbes for which medicines are needed be updated every other year.[18]

The PASTEUR Act aims to reward drugs that improve clinical outcomes in drug-resistant infections. It contains similar provisions for the establishment of an interagency Committee on

[14] The PASTEUR Act, HR 8920, 116th Cong., 2nd sess., Congressional Record 166, no. 208, daily ed. (December 9, 2020): H 7111.
[15] The PASTEUR Act, S 4760, 116th Cong., 2nd sess. (September 30, 2020).
[16] The PASTEUR Act, S 4760, 116th Cong., 2nd sess. (September 30, 2020).
[17] The PASTEUR Act, S 4760, 116th Cong., 2nd sess. (September 30, 2020).
[18] The PASTEUR Act, S 4760, 116th Cong., 2nd sess. (September 30, 2020).

Critical Need Antimicrobials to identify products that meet a real clinical need.[19] This group is an essential feature not just of the PASTEUR Act, but of any public effort to reward novel antimicrobials. For this reason, the committee recommends HHS convene this panel regardless of how or when Congress votes on the PASTEUR Act.

A new antimicrobial's real clinical value is not usually obvious at the time it is approved, however. The key challenge is to keep the drug on the market and used sparingly for long enough to establish its value and extend its label indications (Clift et al., 2015). It may be possible to use a drug's early postmarket years, traditionally intended for surveillance of infrequent side-effects and assessment of cost-effectiveness, for adaptive trials to this end (Lanini et al., 2019). These trials could be integrated into infection control programs in places that see considerable incidence of drug-resistant infections, including the long-term acute care hospitals and dialysis centers described in the previous chapter (Lanini et al., 2019).

**Public funding for trials that establish value** One of the main advantages the proposed strategy would bring to the discussion of incentives for antimicrobial development is the public funding for late-stage trials. This would be a major incentive for drug developers as clinical trials are costly to run. It would also benefit prescribers, who may be reluctant to use a drug outside of its approved indications. Even those who are willing to authorize such use, infectious disease specialists, for example, have difficulty using new medicines off-label because of lack of clarity on the dose or duration of treatment. By identifying the most promising antimicrobials and supporting their late-stage trials, HHS could help bridge a crucial gap preventing use of new antimicrobials.

Having the government support the label extension and clinical value trials for promising antimicrobials has several advantages. The first is cost. The exact costs of clinical trials are confidential, and industry estimates may be padded to justify high drug prices (Aagaard et al., 2021). In any case, roughly half the expense of the trial is driven by the cost of capital; the company's lost opportunity to invest money used in the trial (Aagaard et al., 2021). The cost of capital is not an expense that would apply to a government funder, making the total cost of trials considerably lower.

There would also be logistical advantages. As this chapter has explained, finding trial participants for antimicrobial studies is difficult. However, as COVID-19 has shown, trials working across multicenter consortiums can quickly enroll the patients they need and report trials results (Li Bassi et al., 2020). As with COVID-19, it may be wise to include international centers in the network both to ease the licensure of novel antimicrobials abroad and to speed the process of establishing added clinical value (Trusheim et al., 2016).

The HHS interagency committee would select antimicrobials for which HHS would fund the additional studies on clinical value. At this time, the drug sponsor could also receive a milestone payment, which may be necessary to keep the company in business. This split approach to market entry rewards also controls the risk to the taxpayer, as the payment would be smaller than the single, lump-sum payments that have been proposed as market-entry rewards. It is also possible that the proposed interagency committee could conclude that, in certain cases, some kind of fully delinked lump sum reward would be warranted.

This strategy is deliberative, and critics may find it too time consuming in a market where new antimicrobial developers routinely go bankrupt in their drug's first year on the market

[19] The PASTEUR Act, S 4760, 116th Cong., 2nd sess. (September 30, 2020).

(Jacobs, 2019; Lepore and Kim, 2021; Plackett, 2020). At the same time, it is not financially or politically feasible for Congress to authorize payments of a billion dollars or more without significant deliberation on the value of the investment. HHS is well positioned to advise on this value, so Congress can properly target the taxpayers' investment in novel antimicrobials.

*A Nonprofit Model*

By providing trial funding and identifying candidate medicines that need it, the recommended strategy is essentially a public–private partnership for drug development. There is precedent for this kind of partnership in antimicrobial development, including CARB-X and the BARDA partnerships discussed earlier in this chapter, as well as many similar partnerships in Europe (Desselle et al., 2017). It is also possible, however, that drugs with a very small market may be natural nonprofits, (i.e., it is not possible to profit from their sale). If so, one alternative to public spending in the form of market entry rewards is to invest the same amount of money (or less) in a nonprofit drug development institute.

A nonprofit model may be better suited to development of medicines with small markets and low peak sales (Nielsen et al., 2019). It would also be in a better position to promote judicious use of the drug if the developer were a nonprofit as the imperative to sell the drug, often at odds with good stewardship, would be removed (Nielsen et al., 2019). New compounds could be introduced sequentially and over fairly long intervals, promoting good drug stewardship (Spellberg, 2021). For reference, four new antimicrobials targeting extremely drug-resistant, gram-negative bacilli have been introduced since 2015; they compete for a small market of carbapenem-resistant *Enterobacterales* infections (Nielsen et al., 2019).

Another point in favor of a nonprofit model is that it may require less financial support from the taxpayer than the other incentive programs suggested. A $1 billion investment has been suggested as sufficient seed capital to create such an institute, and this money would be invested only once, making it more sustainable than long-term subsidies for drug companies (Nielsen et al., 2019; Spellberg, 2021). This type of institute might also be able to draw from expertise in government and academia (Desselle et al., 2017). It would likely use the same contract manufacturers and contract research organizations as the biotechnology firms engage today to manage the trial and manufacturing steps in the drug development process. One major difference however, is that a nonprofit developer would not have the same expectation to recoup the costs of development with sales (Aagaard et al., 2021). This is an advantage with antimicrobial development as society benefits from the drugs being held in reserve. It is also not clear that the cost of developing a new antimicrobial even could be recouped through sales. Recent research indicates that the majority of new antimicrobials approved in the 2010s were accessible in only three countries (the United States, the United Kingdom, and Sweden) (Outterson et al., 2021). It is possible that the expected sales of these medicines are not sufficient incentive for companies to outweigh the costs of seeking authorization in other markets (Outterson et al., 2021).

At the same time, entry of a nonprofit antimicrobial drug developer could alter antimicrobial market dynamics and has the potential to crowd out private investment. In the committee's judgment there is too much uncertainty to accurately assess whether this change would result in a net societal benefit to recommend this strategy. Such a change may be necessary in the future, however, and is an important topic for ongoing public discussion.

**Ensuring the global reach of new products** Some of the precedent for nonprofit drug development comes from products intended largely for low- and middle-income country

markets. The GARD-P and DNDi examples discussed in Box 6-2 are evidence that nonprofit drug development is valuable especially in developing products for patients who will not be able to pay for them. GARD-P and DNDi give considerable attention to the registration of new medicines in low- and middle-income countries, as does the nonprofit Medicines for Malaria Venture (DNDi, 2021; GARDP, 2021b; MMV, 2021).

The push and pull incentives described earlier in this chapter are evidence of the considerable sums of money the United States and other high-income countries are willing to spend to fight antimicrobial resistance. When the taxpayer spends a billion dollars or more to bring a new product to market, the government may rightly have a say in how and where that product is deployed. This logic underlies a condition of accepting certain CARB-X funds. Those projects supported by British government's development assistance must produce a stewardship and access plan detailing how the product will be made available and affordable in low- and middle-income countries (CARB-X, 2021d). CARB-X stewardship and access guidelines clarify that this condition applies only to products developed with Global Antimicrobial Resistance Innovation Funds that are intended to "primarily and directly benefit" patients in low- and middle-income countries (CARB-X, 2021d).[20]

The emphasis on a primary and direct benefit to patients in low- and middle-income countries may be somewhat arbitrary, however. Given the vastly higher burden of antimicrobial resistance in these parts of the world and problems with access to safe, affordable medicines, it would seem that almost any product, at least any novel antimicrobial, rapid point-of-care diagnostic, or preventive product would be disproportionately beneficial in low- and middle-income country markets, markets these products do not currently reach. For this reason, the ReACT network, an international group dedicated to mitigating antimicrobial resistance, has proposed that any product developer that takes government money for product development should enter into a patent pool facilitating global procurement (Aagaard et al., 2021).

## DIAGNOSTICS

The process of culturing bacteria does not provide susceptibility information fast enough to inform the first choice of medicine (Okeke et al., 2011). For this reason, diagnostic testing is a rate-limiting step in the optimal use of antimicrobials. Slow or expensive diagnostic tests influence providers to use empiric treatment and contribute to considerable misuse in human and animal health. A lack of rapid diagnostic tests also holds back the development of new antimicrobial medicines. With rapid diagnostics, researchers could identify participants for narrow-spectrum drug trials faster, removing a serious logistical hurdle in the new drug approval process (Okeke et al., 2011).

Antimicrobials are underpriced because the price does not include the future cost of resistance (Okeke et al., 2011). One option to adjust the value calculation for using antimicrobials might lie with subsidizing the cost of the diagnostic tests that inform the decision to use antimicrobials in the first place. Making up-to-date diagnostic testing easier would advance the goal of antimicrobial stewardship and the correct use of new medicines. New drugs pose challenges to diagnostic laboratories, however.

[20] The same stewardship and access guidelines ask all product developers to describe any plans for sublicensing the product in low- and middle-income countries via the Global Antibiotic Research and Development Partnership (GARDP), and well as compassionate use or equitable pricing plans (CARB-X, 2021d). Such plans are not, however, a general condition of CARB-X sponsorship.

### Barriers to Keeping Diagnostic Tests Up to Date[21]

As the previous chapter discussed, antibiotic susceptibility testing is one of the mainstays of diagnostic microbiology. Susceptibility results allow providers to tailor antimicrobial treatment. These results can also prompt de-escalation from the broader-spectrum antibiotics often selected for empiric therapy to a narrower, more targeted antibiotic thereby curtailing the selection pressure that drives emergence of resistant pathogens (van Belkum et al., 2020). When resistant pathogens are involved, susceptibility testing gives insight into the mechanism of resistance. It can also identify asymptomatic patients infected with resistant pathogens, allowing for them to be isolated if necessary to control a resistant outbreak (Burnham et al., 2017). In cases of multi- and pan-resistant bacteria, there are generally few treatment options, and a newer antibiotic with activity against the target pathogen will be indicated. For this reason, susceptibility testing for novel antibiotics is necessary. These tests ensure the drug can be used and establish the dosage appropriate to treat the infection.

When clinical microbiology laboratories cannot test a pathogen's susceptibility to a new antimicrobial, then clinicians will not feel comfortable using it, seriously limiting the use of the new medicine. Another possibility is that the drug would be misused, triggering the development of resistance before the new antimicrobial even sees wide, appropriate clinical use (Burnham et al., 2017). But there are multiple barriers to susceptibility testing for new antimicrobials. First is the inclusion of the microbe–drug combination in automated testing device panels (Krause, 2021b). As the previous chapter described, these are essentially flat test plates holding wells, or microtubes, each containing different concentrations of medicines. The test plates are read by machine, breakpoint changes are automatically updated as part of routine software updates. The number of wells the plates can hold is fixed, so adding a new medicine to the plate usually means removing something else and forfeiting the associated diagnostic information. Removing an old medicine in favor of a new one is not something most device companies are inclined to do, particularly when there is no strong demand for new antibiotics since these medicines are meant to be used only infrequently.

In the absence of an automated testing option, the susceptibility of a pathogen to a new drug can be established with manual testing methods. The drug manufacturer will, for example, supply discs or strips (i.e., E-tests®) saturated with the drug, which diffuses onto a culture plate inoculated with the target pathogen (ScienceDirect, 2021a). The drug's potency against the target pathogen can be inferred from the diameter of growth it inhibits in the culture (ScienceDirect, 2021a). Using such manual methods is difficult for most clinical laboratories in the United States because they use automated methods. First of all, these methods are extremely time-consuming (Benkova et al., 2020). Culturing pathogens requires an incubation of at least 16 hours, sometimes several days while automated tests usually yield results in 6 to 12 hours (Benkova et al., 2020). Manual testing requires more staff time, the redirection of staff disrupts routine workflow, and test results do not automatically integrate with the hospital information system (Humphries et al., 2018c). These methods are used less frequently so fewer technicians practice them regularly enough to remain proficient (Humphries et al., 2018c; van Belkum et al., 2020).

The disks and test strips manufacturers provide with new antibiotics are often designated as "research use only" until they receive regulatory clearance, a process that can take months or

[21] This section deals with the challenges of susceptibility testing in human medicine. Veterinary antimicrobial susceptibility testing is done with broth micro dilution; disk diffusion is less common (Bowden and Burbick, 2020). Challenges relating to the need for animal-specific test breakpoints were discussed in Chapter 5.

years. The FDA does not authorize the use of research-only tests to inform clinical care as the manufacturer's tests have not been through regulatory clearance to establish their clinical performance (Humphries and Hindler, 2016). Research-only tests are meant to inform surveillance and to give clinical microbiologists better information about patterns of susceptibility in the organisms they are seeing (Humphries and Hindler, 2016). As a condition of requesting reagents for research-only tests, the requesting scientist has to attest in writing that the results will not be reported to a physician or used to guide treatment; the clinical laboratory cannot bill for the tests (Humphries and Hindler, 2016). The associated liability concerns are enough to prompt many hospitals to prohibit the use of research-only diagnostics (Humphries and Hindler, 2016).

Most clinical laboratories in the United States today use *only* automated methods for susceptibility testing (Humphries et al., 2018b; Humphries et al., 2018c). Therefore, the inclusion of new antimicrobials on automated testing systems is a practical requirement for use, but is not, strictly speaking, essential for the safe and effective use of the medicine. If it were, the FDA would require the medicine and diagnostic be developed and reviewed simultaneously, eliminating any lag time between the availability of the drug and associated diagnostics (FDA, 2018c). Since the regulatory approval for the medicine and diagnostic are separate, but related, the drug and device companies have to cooperate on the development of the automated test. This involves significant expense on both sides.

The device company, for its part, must be regularly reevaluating the time needed to bring a new test through regulatory review against obligations to support testing changes for drugs already in wide use. The volume of breakpoint changes alone creates an overwhelming amount of work when incorporating them into automated susceptibility testing devices (Brasso, 2017). Emerging resistance to a medicine that is heavily used has, after all, more immediate implications for public health than the introduction of a new one (Krause, 2021b).

Developing tests for new antimicrobials can be slowed when actual breakpoints are lower than what the manufacturer predicted, as often happens when the wild-type pathogens' resistance mechanisms render it less susceptible to the drug than was initially assumed (Carpenter and Brasso, 2016). Changes in the indications for use can also present a barrier. Indications for a new antimicrobial are usually narrow during drug development (Theuretzbacher et al., 2020). Early on, the range of pathogens the new molecule has activity against is not always clear or maybe described only generally (e.g., active against gram-negative bacteria) (Theuretzbacher et al., 2020). Because of the demands of clinical trials and participant recruitment, the drug developers usually apply for approval using only one indication. Many pathogens against which the drug shows activity, especially rare ones or uncommon clinical presentations, are not included on the FDA approved drug label (Boucher et al., 2017). Such regulatory changes make it impossible for the device manufacturer to start developing the susceptibility test before the drug company has at least filed a new drug application containing the proposed drug label and indication with the FDA (Carpenter and Brasso, 2016). Even then, only those pathogens and indications included in the *final* FDA-approved drug label can be included in the regulatory application for the device (Shawar, 2016).

After any changes to automated susceptibility tests, either the addition of new drugs or updating of breakpoints, the testing device and software all need to be updated (Humphries et al., 2018c). This has long presented a challenge to clinical microbiology labs. Even after the Clinical and Laboratory Standards Institute (CLSI) had gone through the research to revise a breakpoint, it could take years for these standards to be included in automated devices. A 2016 survey of

California clinical laboratories found that only 72 percent of the state's 128 clinical microbiology laboratories used the most recent carbapenem breakpoints for *Enterobacterales* and that implementing the new breakpoint took a median of 4.5 half years (Humphries et al., 2018b). The use of an outdated breakpoint can cause clinicians to make incorrect treatment decisions, to say nothing of downstream effects such as failing to implement contact precautions and allowing an outbreak to spread.

The mismatch of regulatory timelines for drug and diagnostic developers contributes to the delay in bringing new antimicrobials into automated test panels. More recent changes in the FDA review for automated susceptibility test devices has brought the timelines into better alignment, but there is still a lag time of up to several years between an antimicrobial being introduced into clinical practice and routine diagnostic testing of pathogens' susceptibility to it gaining regulatory clearance (Burnham et al., 2017). This delay limits the market viability of the medicine.

The validation and trials necessary to bring a new automated susceptibility test to market are time consuming and costly (van Belkum et al., 2020). Regulatory approvals are separate for each new antimicrobial and each new indication (Carpenter and Brasso, 2016). Still, much has improved in the last 5 years, especially for manual test methods such as disk diffusion, which can be included in the data the company submits with the new drug application. For example, because of close and early collaboration among the drug developer, device company, and the FDA three manual susceptibility tests for the new drug delafloxacin gained regulatory clearance in only 44 days (compared to the more typical lag time of several years) (FDA, 2019a; Humphries et al., 2018a).

The FDA's 2016 draft guidance publication, *Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices,* encouraged collaboration between drug and device companies in relatively early stages of drug development (FDA, 2019a). Collecting clinical isolates, previously a major bottleneck in test development, improved with the creation of the FDA and the CDC antibiotic resistance isolate bank, which provides isolates to companies developing diagnostic tools and for validation studies (CDC, 2020a; Shawar, 2016).

The 21st Century Cures Act, signed into law in 2016, also helped by ensuring a more efficient process for updating breakpoints. Rather than having FDA-recognized breakpoint criteria on drug labels, the act moves this information online (FDA, 2020a; Humphries et al., 2018a). Two websites, one for antifungals and one for antibacterials, lists all the current FDA-recognized breakpoints from drug labels (FDA, 2017, 2020a). Every 6 months, FDA has to update the breakpoint websites, ensuring more timely addition of new or revised breakpoints into clinical practice; the agency can also recognize any new or updated breakpoints *not* included on a drug's label. Therefore, the automated device companies can use any breakpoints from these websites in their applications for regulatory clearance. Removing breakpoints from drug labels also decouples the drug's label indications from susceptibility testing, allowing device manufacturers to use breakpoints for microbe–drug combinations with demonstrated in vitro activity, even if there are not necessarily in vivo studies establishing the same (FDA, 2020a; Humphries et al., 2018a). The act also recognizes some but not all CLSI breakpoints (Humphries et al., 2018a).

Despite significant recent progress, driven in large part by the 21st Century Cures Act, there are still regulatory restrictions that stand in the way of prompt regulatory clearance of antimicrobial susceptibility test devices (see Table 6-2). One important limitation is that automated test devices are still limited to only the microbe–drug combinations approved by the

FDA (Humphries et al., 2018a). The FDA strongly discourages testing or interpretation of pathogens not included in the approved drug label, even if, as sometimes happens with antimicrobials, the off-label indication is widely used (Humphries et al., 2018a).

**TABLE 6-2** Antimicrobial Susceptibility Testing Challenges Addressed by the 21st Century Cures Act and Remaining Needs

| Challenge | Addressed by 21st Century Cures Act? | Comments |
|---|---|---|
| Test devices cleared after 2007 can only test antimicrobials against organisms for which there are clinical indications listed in drug label | Yes | Progress:<br>- 21st Century Cures Act removes breakpoints from the drug label, decoupling prescribing indications from susceptibility testing<br>- CLSI breakpoints for some off-label organisms are now recognized by the FDA and listed on the breakpoints website (e.g., cefepime for *Citrobacter* spp; daptomycin for *Enterococcus faecium*)<br>- Diagnostic manufacturers may now submit to the FDA for clearance of test devices for these organisms recognized by the FDA and listed on the breakpoints website<br>- CLSI will present rationale for including some additional breakpoints for off-label organisms recognized by CLSI but not yet recognized by the FDA for review and approval by the FDA (e.g., meropenem for *Acinetobacter* spp)<br>Ongoing risk:<br>- The data required by the FDA CDER to approve older CLSI breakpoints that are not listed in drug labels are unknown<br>- The FDA CDRH has no current pathway for how to address the scenario where no clinical breakpoint exists, but an epidemiological cutoff is published by CLSI |
| Current breakpoints are not available on all test devices used by clinical laboratories | Partially | Progress:<br>- Recognition of many CLSI breakpoints by the FDA allows test devices manufacturers to use these breakpoints for FDA clearance of their test devices<br>Ongoing risk:<br>- Diagnostic manufacturers are not required to update test devices with current breakpoints under existing regulations; updates are voluntary and may not be a priority for the manufacturer |
| Lack of test devices for new drugs | No | Progress outside 21st Century Cures Act:<br>- Streamlined process coordinated by CDRH for clearance of test devices for new drugs has resulted in quicker timelines for some drugs<br>Ongoing risk:<br>- Development of tests for new drugs on automated test devices remains slow and is costly |

| | | |
|---|---|---|
| | | - Implementation of tests for new drugs in clinical laboratories is slowed by verification requirements |

NOTE: CDER = Center for Drug Evaluation and Research; CDRH = Center for Devices and Radiological Health; CLSI = Clinical and Laboratory Standards Institute; FDA = Food and Drug Administration.
SOURCE: Adapted from Humphries et al., 2018a.

Furthermore, the FDA still retains full authority to accept or reject breakpoints proposed by CLSI. There are still many CLSI breakpoints not recognized by the FDA, sometimes because the agency recognizes an older or higher breakpoint (FDA, 2021a). The FDA's willingness to recognize some CLSI breakpoints is related to the agency's formal recognition of CLSI as a standards development organization (FDA, 2021a). This recognition hinges on CLSI meeting statutory requirements for transparency, scientific rigor, vetting its volunteers for conflicts of interest, and for soliciting public input on technical decisions (FDA, 2021a). Because automated susceptibility test manufacturers can use the recognized breakpoints from the FDA websites in their test development, it streamlines the manufacturer's process to keep the devices up to date (FDA, 2021a).

As antimicrobial resistance continues to emerge and more data are available, breakpoint changes will only be needed more frequently. Every investment in keeping automated testing devices up to date is an investment in keeping clinical practice more responsive to antimicrobial resistance and protecting public health (Humphries, 2018). By recognizing all CLSI breakpoints, the FDA could allow for more widespread use of breakpoint criteria for many additional microbe–drug combinations. This in turn would allow susceptibility test manufacturers to report minimum inhibitory concentrations for the antibiotics that currently do not have FDA recognized breakpoints. This would speed the regulatory clearance by widening the number of recognized breakpoints without putting a burden on the manufacturer to develop them. This process would also lessen some burden on clinical laboratories to resort to manual testing to report these susceptibility results.

**Recommendation 6-2: To reduce regulatory hurdles in bringing automated susceptibility tests to market, the Food and Drug Administration should coordinate the review of new antimicrobials with the review of their automated susceptibility tests and work with the Clinical Laboratories Standards Institute to issue and update breakpoints for microbe–drug combinations.**

Ideally, automated susceptibility testing devices would include new antimicrobials immediately upon market entry and revised breakpoints for older drugs as they are approved. This would mean the new drug and device approvals work simultaneously, not sequentially as they currently do (i.e., the device application begins after the new drug approval). Since 2012, FDA has expedited the review process for novel antimicrobials (FDA, 2018d). A similar fast track approval option is necessary for automated susceptibility testing devices. This process would be akin to Operation Warp Speed for vaccine development and emergency use authorization granted to diagnostic tests during the COVID-19 pandemic (FDA, 2021b).

To this end, the FDA and the susceptibility test device manufacturers should work together to define a less restrictive pathway for validation studies and new ways to assess device performance. This accelerated review would not compromise the quality of the devices cleared

for diagnostic use, as recent experience with COVID-19 has shown. For example, allowing multiple antimicrobials or multiple indications to be included in one submission (called bundling) could ease the application burden and fees for industry. Current FDA policy allows for "one drug, one method of reading, and one method of inoculation" in susceptibility test submissions although the manufacturer is able to bundle gram-positive and gram-negative claims provided the same procedure is followed (FDA, 2018b).

Furthermore, the label indications for new antimicrobials are usually restrictive. If CLSI has established breakpoints for other microbe–drug combinations, it would greatly ease clinical practice to recognize them. But the FDA's process for assessing CLSI breakpoints and their timeline for doing so is not clear (Humphries et al., 2018a). Antimicrobial drug labels are not all encompassing. The nature of the drug's biological activity against microbes means that there will be demonstrable in vivo activity against organisms not included in the initial regulatory review.

A consequence of the FDA not recognizing all CLSI breakpoints is that automated test device manufacturers are not allowed to report out the minimum inhibitory concentration for any drug without breakpoints recognized by the FDA (Zimmer, 2021). Device companies should also be able to share the minimum inhibitory concentrations for microbe–drug combinations, even when the breakpoint interpretation is not recognized by the FDA. Including minimum inhibitory concentrations in the automated test would allow clinical laboratories to interpret the susceptibility pattern for organisms even when only non-FDA recognized breakpoints exists. For example, currently the FDA only recognizes meropenem breakpoints for gram-negative bacteria such as Enterobacterales, *Pseudomonas aeruginosa*, and *Acinetobacter* species. Despite existing meropenem breakpoints established by CLSI years ago, FDA still does not recognize breakpoints for *Burkholderia cepacia* complex and non-Enterobacterales. In the absence of FDA acceptance for these other organisms, manufacturers are prohibited from reporting meropenem inhibitory concentrations for the latter two organism groups (CLSI, 2021; FDA, 2020e). If clinical laboratories had this information, they could avoid the need for manual test methods that few labs can support, thereby broadening drugs' usefulness in clinical practice.

Successful implementation of this recommendation will remove some of the barriers automated susceptibility test manufacturers face in developing tests for new antimicrobials and updated breakpoints. This updating is a voluntary process for the companies. Even with the assistance that the Antibiotic Resistance Isolate Bank and streamlining of breakpoint recognition has provided, the trials and validation involved are expensive and time consuming. The companies have little incentive to go through this process, except the moral incentive to protect public health.

The Reinvigorating Antibiotic and Diagnostic Innovation (READI) Act introduced to Congress in 2015, aimed to encourage research and development on new antibiotics and rapid diagnostics for antimicrobial-resistant pathogens by providing a 50 percent tax credit against clinical testing expenses to companies that create these products.[22] This tax credit might be an even more meaningful incentive for the manufacturers of automated susceptibility devices to offset their clinical trial expenses incurred accommodating breakpoint revisions (Humphries et al., 2018a).[23]

[22] Reinvigorating Antibiotic and Diagnostic Innovation Act of 2017, HR 1840, 115th Cong., 1st sess., Congressional Record 163, no. 56, daily ed. (March 30, 2017): H 2601.
[23] Reinvigorating Antibiotic and Diagnostic Innovation Act of 2015, HR 3539, 114th Cong., 1st sess., Congressional Record 161, no. 134, daily ed. (September 17, 2015): H 6137.

**Recommendation 6-3: Congress should make automated susceptibility test manufacturers eligible for tax incentives to bring new automated susceptibility tests to market.**

Tax incentives and streamlining regulatory processes could do much to reduce the lag time in bringing automated susceptibility tests to market, but there are some drugs for which there will simply never be sufficient demand to warrant inclusion in an automated susceptibility panel. The decision to add a new drug to these panels is influenced by local and national epidemiology of resistance patterns as well as customer demand for the test. For those drugs that will not be included in the automated test panel, manual diagnostic testing will be necessary. Such tests pose challenges to clinical labs. The next section discusses a strategy to mitigate these challenges.

## The Antibiotic Resistance Laboratory Network

New antimicrobials and breakpoint changes also pose significant challenges to clinical laboratories. The logistics of manual testing make it unrealistic for most clinical labs. While clearance of automated susceptibility test panels would remove a major hurdle, it is still likely that the testing for new antimicrobials will not be a priority if the drug is not commonly used or not on the hospital formulary. The CDC Antibiotic Resistance Laboratory Network (ARLN) aims to fill this gap by funding 55 public health laboratories, as well as seven regional labs, and the National Tuberculosis Molecular Surveillance Center to test pathogens that are beyond the capacity of clinical microbiology laboratories (CDC, 2021d). The committee commends the CDC for this valuable service. At the same time, there is room to improve the network's ability to support public health and clinical labs.

The ARLN offers expanded susceptibility testing for hard-to-treat infections with Enterobacterales that carry metallo-beta-lactamases, enzymes that make bacteria resistant to beta-lactam antibacterials, including the carbapenems (CDC, 2021d; Palzkill, 2013). This service is free of charge, but all samples must be sent with confirmation that they are not susceptible to all the beta-lactam medicines tested, "including either ceftazidime/avibactam or meropenem/vaborbactam" and send confirmatory molecular testing that the isolate has at least one metallo-beta-lactamase gene (CDC, 2021a). These inclusion criteria are difficult for some hospital laboratories to meet, especially if they do not have the means to test these broad-spectrum medicines. The other services the network provides (colonization screening, whole genome sequencing, molecular testing for resistance genes, culturing for carbapenemase, and identification of pathogens) have similar requirements for submission that can be challenging for clinical laboratories (CDC, 2021d).

Between 2017 and 2019, 42,423 carbapenem-resistant Enterobacterales and nearly 15,000 carbapenem-resistant *Pseudomonas aeruginosa* isolates were tested through the ARLN (CDC, 2021c; Vallabhaneni et al., 2021). This represents a significant investment in public health laboratories, but one that has not necessarily reached clinical laboratories or other microbiology labs. For example, in fiscal year 2020 the CDC invested over $6.9 million in resistance programming in California alone, much of through the ARLN, only $609,000 of which went to universities or health care partners, and that to only two universities (CDC, 2021b). This investment stands to grow: the CDC's fiscal year 2022 budget included $672 million for expanding the ARLN domestically and internationally (IDSA, 2021).

Expanding the ARLN would be helpful, but this expansion would ideally be done in a way that extends the reach of the services offered in the most efficient and economical way possible. To this end, inclusion of all broad-spectrum drugs in the expanded susceptibility testing service would be helpful, including cefiderocol and others not yet offered. In a larger sense, it would help to have the network put at least as much of an emphasis on clinical diagnostics as on surveillance. The ARLN emphasis on surveillance means that many of the results are reported to the CDC but not back to the clinical laboratories sending the samples (Vallabhaneni et al., 2021). There is a difference between the public health laboratories' responsibility for surveillance and the need for support for challenging clinical testing. Relative to the emphasis on surveillance, the ARLN's support for clinical testing is less.

**Recommendation 6-4: The Centers for Disease Control and Prevention (CDC) should expand the capacity of the Antibiotic Resistance Laboratory Network by offering expedited, expanded susceptibility testing of all broad-spectrum antibiotics via certain CLIA–certified laboratories.[24] The CDC should also promote this service to clinical laboratories.**

It is not reasonable to expect hospital clinical microbiology laboratories to be able to test microbe–drug combinations they see only once or twice a year. Laboratories need a backstop for these tests. The ARLN provides this service to clinical laboratories struggling with diagnostic testing and test interpretation for resistant bacteria. At the same time, there is room to improve the efficiency of the service, the turnaround time on results, and the amount of testing offered. Currently, the ARLN's extended susceptibility testing offers results within 3 business days (CDC, 2021a). Clinical laboratories may be able to turn these results around more quickly; 48 hours would be the ideal response time for most cases, allowing that some microbes are slow growing and may take longer.

The Clinical Laboratory Improvement Amendments of 1988 (CLIA) are a set of federal regulations for laboratories that work with human specimens for the diagnosis, treatment, or prevention of disease (CDC, 2018). Before any laboratory can accept human samples for diagnostic testing the Centers for Medicare and Medicaid Services have to certify that the lab meets CLIA regulations (FDA, 2020b). CLIA certification would be a minimum criteria for supporting the expanded susceptibility testing program recommended.

CDC could take advantage of CLIA-certified laboratories to expand susceptibility testing. Academic medical centers, for example, have laboratory technologists and clinical microbiologists with expertise in diagnostic testing. These laboratory scientists routinely use these skills and may even be available for consulting on challenging cases.

Most of the CLIA-certified laboratories best placed to offer expanded susceptibility testing will be at tertiary care, teaching hospitals. Major medical centers often have an infrastructure in place to do broad-spectrum antimicrobial susceptibility testing. Many of these laboratories are already offering in-house testing similar to the ARLN extended panel. It would generally be less of a burden on staff in academic laboratories to do these tests than it might be for the public health system. Furthermore, some academic medical centers already serve as reference laboratories, so they have systems in place to receive and process isolates from external laboratories. The challenge would be ensuring they have protected time to do them,

[24] The Clinical Laboratory Improvement Amendments (CLIA) regulate testing and are required for laboratories handling human samples.

which a formal contract with the CDC could provide. Furthermore, many of these laboratories already have community support programs in place, sometimes necessitated by a surge in demand for diagnostic testing because of COVID-19 (Tsai et al., 2021; Warrington et al., 2021).

It is not enough for the CDC to expand the ARLN's capacity for susceptibility testing if the service is not thoroughly communicated to the clinical laboratory managers who would need to use it. The CDC could promote the service through state and local health offices and with regular targeted outreach in clinical laboratories.

## INVESTING IN ONE HEALTH SOLUTIONS

As this chapter has discussed, there are serious difficulties bringing needed antimicrobial medicines to market in the United States and other high-income countries. There are also barriers to product development that cut across countries as well as some that are far more pronounced in low- and middle-income countries. In general, less attention is paid to products for animal health. No drug developer will bring a new antimicrobial to market specifically for use in animals, for example. A One Health approach to product development takes a broader view of the need for new products—both therapeutic and preventive. A One Health model is helpful in guiding countries' support for products intended for crop and animal agriculture, aquaculture, and the environment, and as such is called out, at least in principle, in many countries' national action plans for antimicrobial resistance (GCOA and IDSA, 2021).

While not ignoring the pressing need for improving the market for small-molecule antimicrobials and diagnostics, proper management of antimicrobial resistance in humans, animals, and the environment will require attention to a larger range of products. Given the global transmission of resistance and a shared, global vulnerability to resistant pathogens, some product development initiatives would be most valuable if undertaken with a goal of shared global access to novel products.

### Need for Innovative Products

This section discusses how international cooperation could stimulate development of some important tools for fighting resistance. New antimicrobial medicines are obviously one type of essential and needed product. It is also possible that attention to novel delivery mechanisms could do much to improve the antimicrobial activity of existing or repurposed medicines. Nanostructured materials, for example, can be used to deliver antimicrobials, and some nanoparticles have antimicrobial activity on their own (Baptista et al., 2018). Advances in materials science have brought about new biomaterials to deliver antimicrobials and antibacterial polymers with preventive uses such as catheters that resist infection (Kalelkar et al., 2021).

There is a need for a variety of new and innovative products to combat antimicrobial resistance. Factors unique to the development of novel small molecule medicines is discussed earlier in this chapter; this section will give more attention to the need for new diagnostics and preventive tools for human and animal health. This is not an exhaustive discussion of all preventive products needed, however. Promising anti-virulence and phage therapies, for example, are not discussed in detail, neither are nanostructures. Rather, this section will highlight some important needs and challenges in the market for point-of-care diagnostics and some widely used preventive products.

*Point-of-Care Diagnostics*

The diagnostic tests currently considered rapid are those feasible in one microbiologist's 8-hour shift (van Belkum et al., 2019). Especially with gram-negative infections, starting antibiotic treatment with a properly targeted treatment in the first 6 to 12 hours is crucial for the patient's recovery prospects (Burnham et al., 2017). There is good evidence that antibiotic use declines with increasing use of rapid diagnostics (Goossens et al., 2005; van de Sande-Bruinsma et al., 2008). Rapid tests are also essential to support clinical trials for new antimicrobial medicines. Such tests enable the identification of the appropriate patients, thereby reducing the total number of enrolled patients in a trial (Okeke et al., 2011).

As this chapter has discussed, the true value of diagnostics can be difficult to determine. The problem of lack of funding and low return on investment (real or perceived) is a special barrier to bringing rapid diagnostics to market, especially in the low- and middle-income countries that bear the highest burden of resistant infections (Okeke et al., 2011). For the tests to achieve the needed reach in these settings, they need to be easily usable and not dependent on clean water, electricity, or specialty training (Moeller et al., 2007). Models suggest that rapid diagnostics for respiratory tract infections alone could avert over 150,000 child deaths a year and far more unnecessary courses of antimicrobial (Okeke et al., 2011). Yet the diagnostic tests needed for respiratory infections shown in Table 6-3, and published as part of a 2014 *Lancet* series, are, for the most part, still needed today.[25]

**TABLE 6-3** Clinical Needs for Rapid Point-of-Care Diagnostics for Respiratory Tract Infections

| | Technology requirements | Purpose | Desired characteristics | Technological innovation and current stage of development |
|---|---|---|---|---|
| Viral respiratory infections | Point-of-care (eg, primary care office, outpatient clinics, accident and emergency) | To distinguish viral and bacterial infections and inform antiviral therapy. Infection control and bed management allowing patients with diferent viruses to be separated; outbreak tracing | Rapid <1 h<br>Able to be operated by front-line clinical staff (eg, nurse or family practitioner)<br>Ability to process multiple samples simultaneously<br>Low cost | Multiplexed NAAT based tests for high-throughput test platforms requring minimum user skill and hands-on time (currently available in low-thoughput format)<br>Breath-based tests for key viral pathogens such as influenza (in development)<br>Simple tests on a non-invasive sample able to distinguish viral and bacterial infections (conceptual) |
| Community acquired pneumonia | Near-patient, rapid response (eg, in larger outpatient clinic or laboratory adjacent to accident and emergency) | To diagnose cause of infection and recommend effective and proportionate antimicrobial therapy, to asses whether patient should be admitted | Rapid <1 h<br>Ability to detect pathogen and distinguish pathogen from colonisers<br>Ability to detect drug resistance<br>Low to medium cost, operation by front-line staff<br>Adaptation for resource limited settings | Multiplex NAAT based tests for a variety of pathogens and resistance determinants requiring minimal user skill and hands-on time (already available but with minimal data regarding performance and clinical utility)<br>Quantitative NAAT-based tests allowing pathogens and colonisers to be distinguished (in concept)<br>Simple tests on a non-invasive sample able to distinguish viral and bacterial infections (conceptual) |
| Hospital acquired pneumonia and ventilator associated pneumonia | Rapid response (near intensive care unit/in clinical microbiology laboratory with good transport and communication systems) | To diagnose cause of infection and recommend effective and proportionate antimicrobial therapy | Rapid <2 h, round-the-clock service<br>Ability to detect pathogens and distinguish them from colonisers.<br>Ability to detect drug resistance<br>Low to medium cost, operation by trained personnel capable of complex interpretation of results | Rapid, highly multiplexed NAAT based tests and platforms incorporating a wide variety of pahogens and resisance deteminants requiring minimum user skill and hands-on time (currently in development)<br>Quantitative NAAT-based tests allowing pathogens and colonisers to be distinguished (in concept)<br>Next-generation sequencing based diagnostics allowing the identification of rare and unusual pathogens and the rapid generation of antibiotic suscpetibility profiles (in concept) |
| Tuberculosis | Point of care (eg, doctors office, tuberculosis clinic) | To identify those with acute tuberculosis and needing therapy | Rapid <1 h<br>Reliable detection of drug-resistance<br>Suitable for resource limited setting (eg, requiring minimum operator training, low cost, limited power requirements, room temperature storage) | NAAT based tests for "sample-in answer out" platforms (already available)<br>Hand-held NAAT based tests that can be operated by battery or solar power (in development)<br>Breath-based tests |

NAAT= nucleic acid amplification techniques.

SOURCE: Reprinted with permission from Zumla et al., 2014.

[25] The committee recognizes some changes since this table's publication, including the introduction of rapid, highly multiplexed nucleic acid amplification tests.

*Products for Human Health*

The purpose of antimicrobial chemotherapy is to treat infection. Antimicrobials are also used injudiciously when infections are suspected but not actually present. Therefore tools that can prevent infections or lower the burden of viral illness have the potential to reduce both judicious and inappropriate antimicrobial use. Vaccines can do this. They can also prevent healthy, vaccinated people from being colonized by resistant bacteria (Anderson et al., 2018; Bloom et al., 2018; Lipsitch and Siber, 2016). As the previous chapter discussed, these benefits can extend beyond those who receive the vaccine by way of population effects.

More infectious diseases today are vaccine-preventable than in any other time in history. Vaccines that prevent human infections caused by bacteria, particularly those bacteria that are resistance prone, such as pneumococci, *Haemophilus influenzae*, cholera, and typhoid fever, may also prevent the emergence of resistance (Kaufhold et al., 2019; Lewnard et al., 2020; Lipsitch and Siber, 2016; Moore et al., 2015; Okeke, 2009). Viral vaccines such as influenza vaccine, rotavirus and, more recently, respiratory syncytial virus, and COVID-19 vaccines, prevent syndromes for which antimicrobials are commonly misused, and can therefore also lower selective pressure for antimicrobial resistance (Buckley et al., 2019; Lewnard et al., 2020; Vekemans et al., 2021). The formidable net effect that vaccines could have on antimicrobial resistance in humans is generally under-appreciated and grossly under-exploited (Vekemans et al., 2021).

Vaccines specifically targeted at resistant bacteria, particularly those that have been highlighted as urgent or serious threats by the CDC, and as critical or high-priority resistant pathogens by the WHO, remain to be approved. Some promising candidates are in development; there are four in the CARB-X portfolio, for example (CARB-X). But it could take years before they are available to prevent resistant infections (Vekemans et al., 2021). Such “anti-resistance” vaccines would be valuable for high-risk groups such as residents in nursing homes or women with recurrent urinary tract infections. They could also be used to vaccinate patients upon hospital admission to protect them against antimicrobial-resistant nosocomial pathogens. Outside hospitals and other care facilities there is also a pressing need for *Neisseria gonorrhoeae* and *Shigella* vaccines as multiple drug-resistant pathogens belonging to these species are spreading worrisomely.

When resistant bacterial infections cannot be prevented through hygiene or contact precautions or with the use of specific vaccines, resistant organisms and the resistance genes they carry can spread. Therefore vaccination is one area where inadequate deployment in other parts of the world contributes to the burden of resistance in the United States (as does inadequate deployment in the United States). Global travel is easy, and most travel vaccines are not required even when good options exist (McAteer et al., 2020). Therefore antibiotic-resistant organisms and resistance genes can be imported into via travel and trade (D’Souza et al., 2021; Frost et al., 2019).

*Preventive Products for Animal Health*

Intensive agriculture in high-income countries depended on antimicrobials well before developments in biosecurity and selective breeding made these interventions less necessary. Farmers in low- and middle-income countries need not repeat this pattern. Preventive tools will be essential to reducing agricultural use of antimicrobials. Even if new antimicrobial medicines were coming to market frequently, none would likely be authorized for veterinary use (Laxminarayan et al., 2015). It is therefore important to look to preventive measures to control

the emergence of resistance and reduce the need for antimicrobials in agriculture and aquaculture.

Infection prevention strategies for animals, as for humans, include access to safe water, improved sanitation and biosecurity, selective breeding, and vaccines. They also include therapeutic alternatives to antimicrobials such as antibodies, probiotics and fecal transplant therapy, bacteriophages, and antimicrobial peptides, among many others (Czaplewski et al., 2016; Ghosh et al., 2019). Another promising alternative tool to directly fight antimicrobial resistance is the use of oligonucleotides for silencing resistance genes or other approaches still in research stages (Czaplewski et al., 2016). Many of these strategies show great promise but will require further experimental and translational expertise to bring them to market if they are to deliver clinical benefit (Czaplewski et al., 2016).

While new antimicrobial medicines are sorely needed, in the long term, preventive tools and alternative therapies may do more to break the cycle of resistance (Roope et al., 2019). The next sections discuss two commonly used tools to avoid antimicrobial use in agriculture: vaccines and probiotics.

**Agricultural vaccines** Reducing the use of antimicrobials in animal production demands alternatives that can be used to maintain animal health and welfare and sustain the productivity of animal agriculture. Vaccines have been successfully used for the prevention and control of infectious diseases and represent promising alternatives for antibiotics (Hoelzer et al., 2018). In Norway, for example, aggressive vaccination, in conjunction with good management, has eliminated the need for antibiotics in salmon production (WHO, 2015). Vaccination has also successfully resulted in less use of antibiotics in terrestrial animal species such as swine and poultry (Hoelzer et al., 2018). Despite the demonstrated benefits of vaccination, there is still a significant shortage of efficacious and economically affordable vaccines for animal agriculture (Hoelzer et al., 2018). There are too few vaccines, and those that are approved tend to be less affective against polymicrobial infections, which often occur under natural conditions (Chae, 2016; Chamorro and Palomares, 2020). The cost of vaccine production and difficulty in administration further limit their use (Hoelzer et al., 2018).

Vaccines and other innovative products for preventing infection in animals are especially needed in low- and middle-income countries. This need motivated the World Organiation for Animal Health (known by the historical acronym OIE), to convene two expert groups to set priorities for agricultural vaccine development (Erlacher-Vindel, 2019). Their choices highlighted diseases for which there is no available vaccine or the existing vaccine is impractical to use (e.g., every fish in a pond has to be individually vaccinated) or cost prohibitive (OIE, 2015, 2018). In response, animal medicines producers, through their industry association Health for Animals, committed $10 billion to research and development for these vaccines and other preventive products to reduce the need for antimicrobials in animals (Health for Animals, 2020). To this end, the industry committed to developing 100 new animal vaccines, 20 new diagnostic tools, and at least 50 other nutritional or immune-boosting products (Health for Animals, 2020). This is valuable work and an area where government support at relatively modest levels could help ensure the products reach their intended markets. Cooperative regulatory review, for example, would facilitate prompt licensing of the new vaccines. International cooperation, harmonized review, and a common application form could also do much to improve the reach of new animal vaccines, much as the regulatory cooperation via the International Council for

Harmonization of Technical Requirements for Pharmaceuticals for Human Use has done for human medicine.

In promoting livestock and finfish vaccines for use in low- and middle-income countries, it will be important to ensure the products are affordable and can be easily administered on farms. Without an economic reason, producers are unlikely to consider the use of vaccines in lieu of antimicrobials, thus losing the benefits of vaccines as an alternative to antimicrobials.

New vaccines could control considerable antimicrobial use in agriculture. The committee recognizes that it is not possible to produce vaccines against every pathogen in every animal species. Nevertheless, an OIE ad hoc group looking at this topic developed a list of priority diseases and pathogens in poultry, swine, and finfish (OIE, 2015). Similarly, the American Veterinary Medical Association's Committee on Antimicrobials has identified host and species-specific pathogens of concern in both food-producing and companion animals (Scheftel et al., 2020). These lists are a good starting point for research and development efforts in animal vaccines.

**Microbiome strategies** Probiotics are "live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host" (FAO and WHO, 2002). Bacteria, yeast, and microalgae can all act as probiotics. Prebiotics are feed ingredients, such as complex carbohydrates, that modulate the microbiome of the host, promoting the growth of beneficial organisms (Davani-Davari et al., 2019).

Pre- and probiotics are relatively inexpensive, easy to use, accessible, and an environmentally friendly option for disease management. When used in animal feeds, they have an FDA designation of "Generally Recognized as Safe," meaning they are not subject to premarket review, given a recognition among qualified experts that the product has been shown to be safe under its intended condition of use (FAO, 2016; FDA, 2019b). But, as Table 6-4 shows, there are different regulatory requirements if the probiotic is intended as a treatment or preventive product for disease.

**TABLE 6-4** Regulation of Directly Fed Micro-Organisms (Probiotics) by FDA

| Intended use/Claim | Legal Status | Regulated As | Regulated By |
|---|---|---|---|
| Cure, mitigate, treatment, or prevention of disease | New animal drug | Drug | FDA |
| Affect the structure and function of the body | New animal drug | Drug | FDA |
| Without any therapeutic or structure/function claim (micro-organisms listed in AAFCO official publication) | Food | Food | State government |
| Without any therapeutic or structure/function claim (micro-organisms not listed in AAFCO official publication | Food additives | Food additives | FDA |

SOURCE: FAO, 2016, reprinted with permission.

Probiotics can work as immune modulators to enhance growth and prevent disease (FAO, 2016). For animals, these are mainly enteric diseases, but for aquatic species there is evidence that probiotics work against a variety of diseases and enhance reproduction, maintain water

quality, inhibit pathogenic bacterial growth, and aid in nutrient metabolism (FAO, 2016; Martinez Cruz et al., 2012). Most probiotics need to be used daily to be beneficial to the host (Chauhan and Singh, 2018).

Probiotics can be a powerful tool to manage the risks of antimicrobial treatment on the gut microbiota that can lead to secondary infections (Ghosh et al., 2019; Schmidt et al., 2017). They have also been shown to improve animal growth, meat yield, and quality; to decrease zoonotic pathogens; and to increase survival to bacterial and viral challenge in a variety of animals used in agriculture, from chickens to shellfish (FAO, 2016; Hasan and Banerjee, 2020; Hoseinifar et al., 2018). Though the mechanism through which probiotics work is not always clear, there is evidence that they can alter stress and inflammatory response; reduce the permability of the gut walls; change the microbial flora of the gut or other tissues; promote the production of digestive enzymes and their metabolites; compete for space and nutrients with pathogenic bacteria; and, in aquaculture, improve water quality (FAO, 2016; Hasan and Banerjee, 2020; Hoseinifar et al., 2018). The relative contribution of any one of these mechanisms may differ between probiotic strains (even between those closely related), so there is an advantage to mixing probiotics with complementary mechanisms of action (FAO, 2016; Hasan and Banerjee, 2020; Hoseinifar et al., 2018).

Despite extensive research on the benefits of probiotics in animal agriculture, there are relatively few commercially available probiotic and prebiotic products consistently used in clinical practice or animal husbandry (FAO, 2016; Hasan and Banerjee, 2020). One challenge lies with screening candidate probiotic strains, a technique that relies heavily on in vitro identification of bacterial strains with antimicrobial activity, especially activity against the most common target pathogens. Figure 6-11 shows the main questions in safety screening of these products. The next step is an evaluation of activity in small-scale cultures. This approach does not account for other potential mechanisms of action, nor does it capture the complex microbe, host, and ecosystem interactions (de Souza Vandenberghe et al., 2017). Therefore, many probiotic candidates with good laboratory potential show inconsistent performance in the field (Day et al., 2019; Terpou et al., 2019). There are also barriers related to cost. Some micro-organisms that show promise in laboratory and small-scale commercial trials cannot be easily and cheaply grown at large scales (e.g., through fermentation) or formulated into stable products that can be easily transported, stored, and delivered (Cunningham et al., 2021; Fenster et al., 2019).

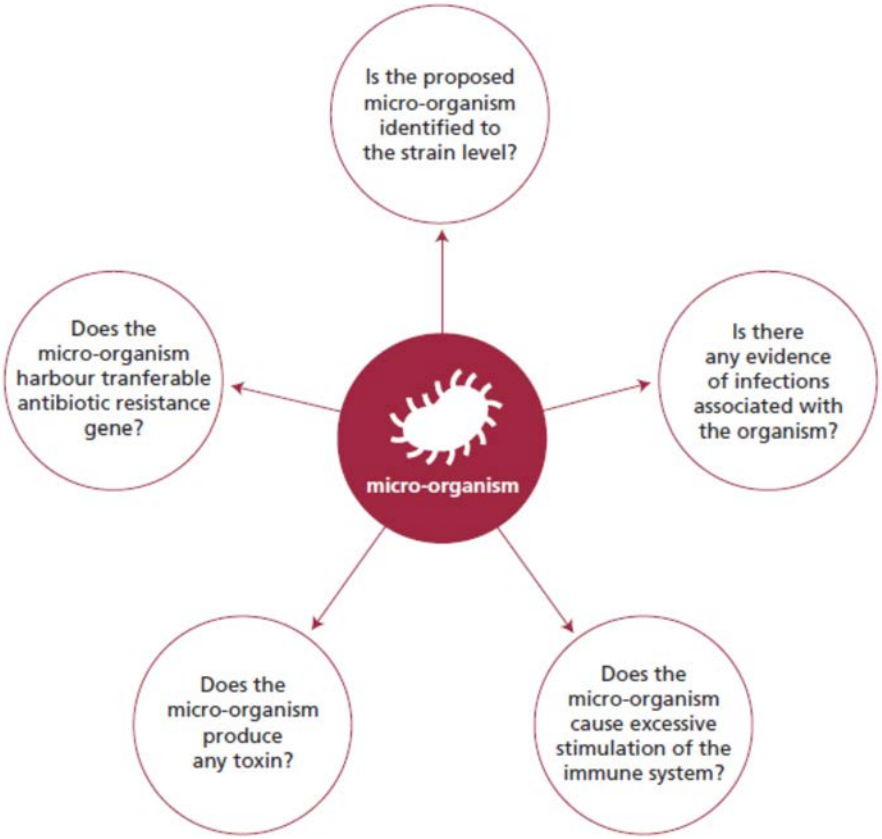



**FIGURE 6-11** Major questions in assessing the safety of micro-organisms being considered for use in animal feed.
SOURCE: FAO, 2016.

These are not unsurmountable obstacles. Research to develop high throughput screening for probiotics could allow for investigation of the mechanisms of action in the target environmental conditions, facilitating discovery of effective probiotics. The same tools are already being used in antimicrobial development and animal breeding. The challenge is directing more attention to this problem in industry, academia, and nonprofits and establishing a product development and regulatory environment conducive to research and commercial development in the field.

As Table 6-4 showed, probiotics that avoid therapeutic label claims face considerably less regulatory scrutiny. Reports of uneven quality are common, especially among probiotics for human use (Drago et al., 2010; Jackson et al., 2019). Supplements not containing the labelled organisms are common; a 2013 study found less than a third of commercial, human probiotics tested met label claims for micro-organisms listed and their viability (Drago et al., 2010). Increasing research and industry interest in probiotics would need to be mindful of this potential pitfall, possibly contributing to third-party certification to ensure product quality and confidence in the market (Jackson et al., 2019).

*Facilitating Cooperation on Product Development*

Insufficient exchange of information between the public and private sectors holds back the development of new medicines, diagnostics, and preventive products for antimicrobial

resistance (van Belkum et al., 2019). The recent success of the product development partnerships for COVID-19 vaccines, diagnostics, and therapeutics depended on steady funding and collaboration among industry, government, and academia. The NIH Rapid Acceleration of Diagnostics program, for example, worked to speed the development of point-of-care and laboratory diagnostics for COVID-19 (NIH, 2021). Such partnerships can make faster action possible and limit redundancy of effort, especially when political will for action is high.

There is some indication that political will for action against antimicrobial resistance has reached a tipping point. A recent statement from finance ministers and central bank governors of the G7 countries pledged to "work together with our health colleagues … including with industry, to explore proposals for strengthening market incentives for antibiotic drug development" (USDT, 2021). The analogous meeting for health ministers produced a statement about cooperation in the implementation of clinical trials for therapeutics and vaccines (G7 Research Group, 2021). The health ministers commented on the need for internationally coordinated testing and the sharing of test materials in response to "pandemic threats" (G7 Research Group, 2021). Their statements are evidence of growing global commitment to cooperation on product development.

The international product development partnerships put in place for COVID-19 have transferrable elements especially relevant to product development for other infectious threats. This is the ideal framework upon which to build a coordinated product development partnership for antimicrobial resistance. A partnership of this scale could help make the U.S. investment in antimicrobial resistance more of a One Health effort, with coordinated action on the human, animal, and environmental fronts.

**Recommendation 6-5: The Department of Health and Human Services should establish a public–private partnership similar to ACTIV for antimicrobial resistance, bringing together the Biomedical Advanced Research and Development Authority, the National Institutes of Health, the U.S. Department of Agriculture, the Environmental Protection Agency, and the Department of Defense and interested academic, industry, and nonprofit organizations. The partnership would have working groups on diagnostics, alternatives to antibiotics, and prevention, with a goal of supporting a diversified and balanced portfolio of tools to reduce antimicrobial resistance using a One Health approach.**

Public–private partnerships are well suited to medical product development, as Figure 6-12 illustrates. Such partnerships are able to draw on a range of needed expertise and have the benefit of a relatively long time-horizon. These types of collaborations are well known in antimicrobial resistance. The CARB-X public–private partnership discussed earlier in this chapter is clearly important to development and market shaping for new medical products. A public–private partnership was able to bring the Xpert MTB/Rif assay, a rapid diagnostic for rifampicin-resistant tuberculosis, to 116 countries with a high burden of tuberculosis (Albert et al., 2016; Bill & Melinda Gates Foundation, 2012; CDC, 2016). Another public–private partnership, the Foundation for Innovative Diagnostics, works with various governments and private-sector partners to develop diagnostic tests and bring them to market in low- and middle-income countries (FIND, 2021b). The foundation's road map emphasizes developing diagnostics

for resistant infections, particularly those that cause gonorrhea and chlamydia, as well as neonatal sepsis and severe infections in hospitals (FIND, 2021a).


**FIGURE 6-12** Main participants in a public–private partnership and their core strengths for medical product development.
SOURCE: Davis et al., 2021.

The committee is not suggesting that the government replicate these efforts. Rather, the needed partnership would complement these and other programs from development banks, multilaterals, and various regional cooperatives (Okeke et al., 2011). As with ACTIV, this would require multisite, multi-arm trials of different medical products simultaneously in different countries (Murray et al., 2021). This kind of coordinated global attention will be essential in trials on resistant pathogens, as the major burden of these infections in in low- and middle-income countries.

There is also already good evidence that the private sector would be amenable to joining the type of partnership suggested. The AMR Industry Alliance, for example, is a 5-year old coalition of private-sector partners working on solutions to prevent and mitigate antimicrobial resistance (AMR Industry Alliance, 2019). This coalition includes generic and innovator pharmaceutical companies as well as diagnostics companies and small biotechnology firms (AMR Industry Alliance, 2019). Such collaboration is essential to One Health progress. For example, reducing manufacturing discharge has been an AMR Industry Alliance priority, and something its members have collaborated on to identify best practices (AMR Industry Alliance, 2019). The AMR Industry Alliance progress report gives attention to access, especially access to affordable medicines and diagnostics in low- and middle-income countries, as well as access to vaccines and preventive products (AMR Industry Alliance, 2020). The Health for Animals industry coalition has a similar commitment to the development of animal health vaccines, medicines, immune boosters, and development of best practices (Health for Animals, 2017).

These industry coalitions would be good targets for inclusion among the proposed partnership's private-sector contributors.

The ACTIV model, with its collaborative working groups and strategies for streamlined trials is the best model to coordinate our national investment in antimicrobial resistance (Collins and Stoffels, 2020). The model is also helpful in avoiding duplication of effort both within the United States and internationally. It is easier for one large collaborative body to work in close connection with counterpart organizations in other parts of the world, including multilaterals and foundations (Collins and Stoffels, 2020). This is an area where the NIH and BARDA have developed considerable expertise over the last 18 months, and one that could be adapted to speed the development of needed medical products to fight antimicrobial resistance. The NIH and BARDA also have valuable relationships with foreign research efforts, including the European Commission's Joint Programming Initiative on Antimicrobial Resistance (JPIAMR, 2021a,b). JPIAMR aims to coordinate research and encourage collaborative action against antimicrobial resistance among its member countries, mostly in Europe, and internationally (JPIAMR, 2021a,b). Continuing and building on such collaborative relationships would be an important role for the partnership envisioned in this recommendation.

There is also a need to balance investments in antimicrobial resistance across new medicines, diagnostics, and preventive products. Some products have considerable market potential that the private sector will recognize; not all products need the same level of government investment in development. Determining the right balance of investments across product types is challenging and would benefit from explicit public discussion of the sort a prominent public–private partnership could engender. BARDA and the NIH have experience managing this discussion as they have perspective on what society's relative investment is in small-molecule therapeutics. The Department of Defense (DOD) would also provide valuable perspective, drawing from its experience in medicines, diagnostics, and vaccines to treat infectious diseases (USAMRIID, 2021). DOD has experience with some of the nontraditional therapies for resistant infections. Phage therapy, for example, has received relatively greater attention in military medicine than in other practice settings, including recent funding for clinical trials of phage therapy (Clevenger, 2020; Gelman et al., 2018; Trudil, 2015).

It will also be important to the One Health orientation of this strategy to include the Environmental Protection Agency (EPA) and the U.S. Department of Agriculture (USDA) among the partnership's convening agencies. The EPA has programs to fund small business to produce innovative technologies for use in environmental monitoring, water remediation, and viral decontamination; it also provides for cooperative research and development agreements and technology transfer (EPA, 2021). It would also be important to involve the EPA in the development of any product that might be used on crops or in water. Similarly, USDA has an agency action plan on antimicrobial resistance that calls for the development of alternatives to antimicrobials and other mitigating technologies (USDA, 2014). When the discussion turns to the optimal balance of spending across a range of innovative products, the involvement of government experts from the range of One Health disciplines will be crucial.

Global, coordinated efforts were helpful in streamlining supply chains and procurement for COVID-19 diagnostics (Peplow, 2020; The Rockefeller Foundation, 2020). There were transferable lessons learned in responding to COVID-19 that would apply to the problem of antimicrobial resistance. For example, rapid portable tests that do not rely on laboratory infrastructure similar to those developed for COVID-19 would be essential for fighting infections in low- and middle-income countries (WHO, 2020).

A global, cooperative approach to product development could also have the advantage of easing regulatory review. This could be important for animal preventive products for which the regulatory barriers among countries can vary widely, and for alternative therapies (e.g., bacteriophages) that may require novel regulatory review (Czaplewski et al., 2016; Hauser et al., 2016; Nwokoro et al., 2016; Rex et al., 2014). Licensing and deploying new diagnostics are also serious challenges in low- and middle-income countries, where the regulatory systems and product distribution chains are not necessarily designed to handle these products (Peeling and Mabey, 2010). The ACTIV partnership had strategies to speed regulatory review across its international collaborating centers, mainly by sharing regulator's questions and coordinating regulatory submissions (Murray et al., 2021). The experience with COVID-19 prompted a statement from the International Coalition of Medicines Regulatory Authorities stating its commitment to aligning regulatory requirements and collaborating on accelerated approvals, taking advantage of the opportunity "to advance regulatory understanding and convergence" (ICMRA, 2020).

## REFERENCES


Aagaard, H., R. Malpani, and A. Zorzet. 2021. *Ensuring sustainable access to effective antibiotics for everyone, everywhere – how to address the global crisis in antibiotic research and development."* ReAct - Action on Antibiotic Resistance.

Aitken, M., and M. Kleinrock. 2017. *Lifetime trends in biopharmaceutical innovation - recent evidence and implications.* Parsippany, NJ: QuintilesIMS Institute.

Albert, H., R. R. Nathavitharana, C. Isaacs, M. Pai, C. M. Denkinger, and C. C. Boehme. 2016. Development, roll-out and impact of xpert mtb/rif for tuberculosis: What lessons have we learnt and how can we do better? *European Respiratory Journal* 48(2):516-525.

Albrecht, M. 2018. Incentivizing antibacterial research and development. https://www.medicalcountermeasures.gov/BARDA/Documents/BID2018_Presentations/Albrecht_BID18_Antibacterials.pdf (accessed October 29, 2020).

Albrecht, M. 2020. BARDA's achievements under the national action plan. Paper read at Committee on the Long-Term Health and Economic Effects of Antimicrobial Resistance in the United States, Webinar.

Alm, R. A., and K. Gallant. 2020. Innovation in antimicrobial resistance: The CARB-X perspective. *ACS Infectious Diseases* 6(6):1317-1322.

AMR Action Fund. 2020. New AMR Action Fund worldwide launch – press release. AMR Action Fund.

AMR Action Fund. 2021. *Our investments*. https://amractionfund.com/our-investments/#page-section-0 (accessed September 22, 2021).

AMR Industry Alliance. 2019. *Introducing the amr industry alliance*. https://www.amrindustryalliance.org/wp-content/uploads/2019/03/AMR_Alliance_Membership_Brochure.pdf (accessed September 22, 2021).

AMR Industry Alliance. 2020. *2020 progress report executive summary.* AMR Industry Alliance.

Anderson, E. J., M. A. Daugherty, L. K. Pickering, W. A. Orenstein, and R. Yogev. 2018. Protecting the community through child vaccination. *Clinical Infectious Diseases* 67(3):464-471.

Ardal, C., M. Balasegaram, R. Laxminarayan, D. McAdams, K. Outterson, J. H. Rex, and N. Sumpradit. 2020. Antibiotic development - economic, regulatory and societal challenges. *Nature Reviews: Microbiology* 18(5):267-274.

Årdal, C., D. Findlay, M. Savic, Y. Carmeli, I. Gyssens, R. Laxminarayan, K. Outterson, and J. H. Rex. 2018. *Revitalizing the antibiotic pipeline - stimulating innovation while driving sustainable use and global access.* Drive-AB.

ASTHO (Association of State and Territorial Health Officials). 2021. *Project bioshield act fact sheet*. https://www.astho.org/Programs/Preparedness/Public-Health-Emergency-Law/Emergency-Use-Authorization-Toolkit/Project-BioShield-Act-Fact-Sheet/ (accessed June 11, 2021).

Balasegaram, M. 2021. Global antibiotic research and development partnership (GARDP): A model for public-health driven R&D and access. Paper read at Committee on the Long-Term Health and Economic Effects of Antimirobial Resistance in the United States, March 16, 2021, Webinar.

Baptista, P. V., M. P. McCusker, A. Carvalho, D. A. Ferreira, N. M. Mohan, M. Martins, and A. R. Fernandes. 2018. Nano-strategies to fight multidrug resistant bacteria-"a battle of the titans." *Frontiers in Microbiology* 9:1441.

Bassetti, M., R. Echols, Y. Matsunaga, M. Ariyasu, Y. Doi, R. Ferrer, T. P. Lodise, T. Naas, Y. Niki, D. L. Paterson, S. Portsmouth, J. Torre-Cisneros, K. Toyoizumi, R. G. Wunderink, and T. D. Nagata. 2021. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant gram-negative bacteria (credible-cr): A randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infectious Diseases* 21(2):226-240.

Benkova, M., O. Soukup, and J. Marek. 2020. Antimicrobial susceptibility testing: Currently used methods and devices and the near future in clinical practice. *Journal of Applied Microbiology* 129(4):806-822.

Berger, C., A. Sertkaya, A. Jessup, C. Sullivan, A. Kolbe, Eastern Research Group Inc., and HHS Office of Inspector General. 2021. Integrating existing metrics to assess comparative real-world clinical effectiveness of recently approved antimicrobial drugs.

Berndt, E. R., D. Nass, M. Kleinrock, and M. Aitken. 2015. Decline in economic returns from new drugs raises questions about sustaining innovations. *Health Affairs* 34(2):245-252.

Beyer, P., T. B. Cueni, J. Knox, and F. Riedl. 2020. A research and development fund for new treatments for bacterial infections. *Bulletin of the World Health Organization* 98(12):822-822A.

Bhavnani, S. M., K. M. Krause, and P. G. Ambrose. 2020. A broken antibiotic market: Review of strategies to incentivize drug development. *Open Forum Infectious Diseases* 7(7):ofaa083.

Bill & Melinda Gates Foundation. 2012. *Public-private partnership announces immediate 40 percent cost reduction for rapid TB test | Bill & Melinda Gates Foundation*. https://www.gatesfoundation.org/ideas/media-center/press-releases/2012/08/publicprivate-partnership-announces-immediate-40-percent-cost-reduction-for-rapid-tb-test (accessed September 15, 2021).

Billington, J. K. 2015. The ABCs of the us broad spectrum antimicrobials program: Antibiotics, biosecurity, and congress. *Health Security* 13(6):349-354.

Bleicher, K. H., H. J. Bohm, K. Muller, and A. I. Alanine. 2003. Hit and lead generation: Beyond high-throughput screening. *Nature Reviews Drug Discovery* 2(5):369-378.

Bloom, D. E., S. Black, D. Salisbury, and R. Rappuoli. 2018. Antimicrobial resistance and the role of vaccines. *Proceedings of the National Academy of Sciences of the United States of America* 115(51):12868-12871.

Boucher, H. W., P. G. Ambrose, H. F. Chambers, R. H. Ebright, A. Jezek, B. E. Murray, J. G. Newland, B. Ostrowsky, J. H. Rex, and A. Infectious Diseases Society of. 2017. White paper: Developing antimicrobial drugs for resistant pathogens, narrow-spectrum indications, and unmet needs. *Journal of Infectious Diseases* 216(2):228-236.

Bowden, R., and C. Burbick. 2020. *Learning about veterinary ast from lady glittersparkles*. https://clsi.org/about/blog/learning-about-veterinary-ast-from-lady-glittersparkles (accessed September 16, 2021).

Brasso, B. 2017. Industry perspective on the challenges of ast methods and the role of stma. Paper read at Public Workshop - Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices, September 13, 2017, Silver Spring, MD.

Brozak, S. 2018. *An unlikely biotech investor: The government*. https://www.forbes.com/sites/stephenbrozak/2018/06/08/merck-and-achaogen-two-companies-working-with-barda-to-fight-emerging-health-threats/?sh=3b5762e64fd0 (accessed June 10, 2021).

Buckley, B. S., N. Henschke, H. Bergman, B. Skidmore, E. J. Klemm, G. Villanueva, C. Garritty, and M. Paul. 2019. Impact of vaccination on antibiotic usage: A systematic review and meta-analysis. *Clinical Microbiology and Infection* 25(10):1213-1225.

Buckmon, K. 2020. BARDA's reflections on antibiotic resistance and the path forward. In *ASPR Blog*: Medical Countermeasures.

Burnham, C. D., J. Leeds, P. Nordmann, J. O'Grady, and J. Patel. 2017. Diagnosing antimicrobial resistance. *Nature Reviews: Microbiology* 15(11):697-703.

CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator). 2020. Antibiotic resistance: A global health preparedness crisis: CARB-X.

CARB-X. 2021a. *About CARB-X*. https://carb-x.org/about/overview/ (accessed June 10, 2021).

CARB-X. 2021b. *Funding partners*. https://carb-x.org/partners/funding-partners/#; (accessed June 10, 2021).

CARB-X. 2021c. *Portfolio-product developers*. https://carb-x.org/portfolio/portfolio-companies/ (accessed June 28, 2021).

CARB-X. 2021d. *Stewardship & access plan (sap) development guide.*

CARB-X. 2021e. *Stewardship and access*. https://carb-x.org/about/stewardship-and-access/ (accessed June 10, 2021).

Carpenter, D., and B. Brasso. 2016. How to develop & obtain regulatory approval of commercial antimicrobial susceptibility tests in a timely manner. Paper read at Public Workshop--Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices, September 29, 2016, Silver Spring, MD.

Carroll, J. 2019. *Once picked as a $500m winner, bankrupt achaogen auctions off its antibiotic for a fraction of that*. https://endpts.com/once-picked-as-a-500m-winner-bankrupt-achaogen-auctions-off-its-antibiotic-for-a-fraction-of-that/ (accessed Jun 10, 2021).

CDC (Centers for Disease Control and Prevention). 2016. *A new tool to diagnose tuberculosis: The xpert MTB/RIF assay*. https://www.cdc.gov/tb/publications/factsheets/testing/xpert_mtb-rif.htm (accessed September 22, 2021).

CDC. 2018. *Clinical Laboratory Improvement Amendments (CLIA)*. https://www.cdc.gov/clia/about.html (accessed July 1, 2021).

CDC. 2019a. *Antibiotic resistance threats in the united states, 2019.* U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

CDC. 2019b. *General information about candida auris*. https://www.cdc.gov/fungal/candida-auris/candida-auris-qanda.html (accessed June 10, 2021).

CDC. 2020a. *Antibiotic resistance isolate bank*. https://www.cdc.gov/drugresistance/resistance-bank/index.html (accessed July 1, 2021).

CDC. 2020b. *CDC—budget request overview: FY20 president's budget request | $6.594 billion* Centers for Disease Control and Prevention

CDC. 2021a. *About exast*. https://www.cdc.gov/drugresistance/laboratories/AR-lab-network-testing-details/expanded-ast.html (accessed June 29, 2021).

CDC. 2021b. *Antibiotic resistance investment map*. https://arinvestments.cdc.gov/ (accessed June 29, 2021).

CDC. 2021c. *Carbapenem-resistant enterobacteriaceae (CRE): An urgent public health threat*. https://arpsp.cdc.gov/story/cre-urgent-public-health-threat (accessed June 29, 2021).

CDC. 2021d. *Expanded antimicrobial susceptibility testing for hard-to-treat infections (exast)*. https://www.cdc.gov/drugresistance/laboratories/AR-lab-network-testing-details/expanded-ast.html (accessed June 28, 2021).

Chae, C. 2016. Porcine respiratory disease complex: Interaction of vaccination and porcine circovirus type 2, porcine reproductive and respiratory syndrome virus, and mycoplasma hyopneumoniae. *Veterinary Journal* 212:1-6.

Chamorro, M. F., and R. A. Palomares. 2020. Bovine respiratory disease vaccination against viral pathogens: Modified-live versus inactivated antigen vaccines, intranasal versus parenteral, what is the evidence? *Veterinary Clinics of North America: Food Animal Practice* 36(2):461-472.

Chapman, R. 2020. *It's time to fix the antibiotic market*. https://wellcome.org/what-we-do/our-work/drug-resistant-infections/its-time-fix-broken-antibiotics-market (accessed June 10, 2021).

Chauhan, A., and R. Singh. 2018. Probiotics in aquaculture: A promising emerging alternative approach. *Symbiosis* 77(2):99-113.

Chiller, T. 2017. *The unexpected and troubling rise of candida auris*. https://www.medscape.com/viewarticle/884470 (accessed June 10, 2021).

Clevenger, T. 2020. *Adaptive phage therapeutics awarded initial contract with Department of Defense* (accessed September 21, 2021).

Clift, C., U. Gopinathan, C. M. Morel, K. Outterson, J.-A. Røttingen, and A. So. 2015. *Towards a new global business model for antibiotics: Delinking revenues from sales*: Chatham House.

CLSI (Clinical and Laboratory Standards Institute). 2021. *Performance standards for antimicrobial susceptibility testing.*

CO-ADD (Community for Open Antimicrobial Drug Discovery). *Sending compound library for high throughput screening*. https://co-add.org/content/sending-compound-library-for-high-throughput-screening (accessed June 10, 2021).

Collins, F. S., and P. Stoffels. 2020. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): An unprecedented partnership for unprecedented times. *JAMA* 323(24):2455-2457.

Cortese, D. A., N. Landman, and R. K. Smoldt. 2018. Making bundled payments work: Leveraging the cms drg experience. *NEJM Catalyst*. https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0179 (accessed June 3, 2021).

Coukell, A. 2019. *(DISARM) act of 2019 letter - The Pew Charitable Trusts*. https://www.pewtrusts.org/-/media/assets/2019/08/08-01-19-disarm-support-letter.pdf (accessed June 11, 2021).

Council of Canadian Academies. 2019. When antibiotics fail. Ottawa (ON): The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada, Council of Canadian Academies.

CPMP (Committee for Proprietary Medicinal Products). 2000. Points to consider on switching between superiority and non-inferiority: The European Agency for the Evaluation of Medicial Products.

Crunchbase. *List of achaogen's 2 lead investors*. https://www.crunchbase.com/search/principal.investors/field/organizations/num_lead_investors/achaogen (accessed June 10, 2021).

Cunha, B. R. d., L. Fonseca, and C. Calado. 2019. Antibiotic discovery: Where have we come from, where do we go? *Antibiotics (Basel)* 8(2):45. doi:10.3390/antibiotics8020045.

Cunningham, M., M. A. Azcarate-Peril, A. Barnard, V. Benoit, R. Grimaldi, D. Guyonnet, H. D. Holscher, K. Hunter, S. Manurung, D. Obis, M. I. Petrova, R. E. Steinert, K. S. Swanson, D. van Sinderen, J. Vulevic, and G. R. Gibson. 2021. Shaping the future of probiotics and prebiotics. *Trends in Microbiology* 29(8):667-685.

Czaplewski, L., R. Bax, M. Clokie, M. Dawson, H. Fairhead, V. A. Fischetti, S. Foster, B. F. Gilmore, R. E. Hancock, D. Harper, I. R. Henderson, K. Hilpert, B. V. Jones, A. Kadioglu, D. Knowles, S. Olafsdottir, D. Payne, S. Projan, S. Shaunak, J. Silverman, C. M. Thomas, T. J. Trust, P. Warn, and J. H. Rex. 2016. Alternatives to antibiotics-a pipeline portfolio review. *Lancet Infectious Diseases* 16(2):239-251.

Dall, C. 2019. Medicare payment changes aim to boost antibiotic development. https://www.cidrap.umn.edu/news-perspective/2019/08/medicare-payment-changes-aim-boost-antibiotic-development (accessed August 5, 2020).

Dall, C. 2020. New pharma-led fund aims to boost antibiotic development. https://www.cidrap.umn.edu/news-perspective/2020/07/new-pharma-led-fund-aims-boost-antibiotic-development (accessed June 11, 2021).

Daniel, G. W., H. Colvin, and S. Mayer. 2013. *Antibiotic development and market failure: No quick fix*. https://www.brookings.edu/blog/up-front/2013/09/20/antibiotic-development-and-market-failure-no-quick-fix/ (accessed June 3, 2021).

Daniel, G. W., M. Schneider, M. H. Lopez, and M. B. McClellan. 2018. Implementation of a market entry reward within the United States. *Journal of Law, Medicine and Ethics* 46(1 Suppl):50-58.

Daniel, G. W., M. B. McClellan, M. Schneider, J. Qian, G. Lavezzari, and E. d. Graffenreid. 2019. Value-based strategies for encouraging new development of antimicrobial drugs: Duke Margolis Center for Health Policy.

Darrow, J. J., and A. S. Kesselheim. 2020. Incentivizing antibiotic development: Why isn't the generating antibiotic incentives now (GAIN) act working? *Open Forum Infectious Diseases* 7(1):ofaa001.

Davani-Davari, D., M. Negahdaripour, I. Karimzadeh, M. Seifan, M. Mohkam, S. J. Masoumi, A. Berenjian, and Y. Ghasemi. 2019. Prebiotics: Definition, types, sources, mechanisms, and clinical applications. *Foods* 8(3).

Davis, A. M., O. Engkvist, R. J. Fairclough, I. Feierberg, A. Freeman, and P. Iyer. 2021. Public-private partnerships: Compound and data sharing in drug discovery and development. *SLAS Discov* 26(5):604-619.

Day, R. L., A. J. Harper, R. M. Woods, O. G. Davies, and L. M. Heaney. 2019. Probiotics: Current landscape and future horizons. *Future Science OA* 5(4):FSO391.

de Kraker, M. E., A. J. Stewardson, and S. Harbarth. 2016. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Medicine* 13(11):e1002184.

de Souza Vandenberghe, L. P., L. M. B. Garcia, C. Rodrigues, M. C. Camara, G. V. de Melo Pereira, J. de Oliveira, and C. R. Soccol. 2017. Potential applications of plant probiotic microorganisms in agriculture and forestry. *AIMS Microbiol* 3(3):629-648.

Desselle, M. R., R. Neale, K. A. Hansford, J. Zuegg, A. G. Elliott, M. A. Cooper, and M. A. Blaskovich. 2017. Institutional profile: Community for open antimicrobial drug discovery - crowdsourcing new antibiotics and antifungals. *Future Science OA* 3(2):FSO171.

DNDi (Drugs for Neglected Diseases Initiative). 2021. *Registration & access*. https://dndi.org/research-development/registration-and-access (accessed July 13, 2021).

Drago, L., V. Rodighiero, T. Celeste, L. Rovetto, and E. De Vecchi. 2010. Microbiological evaluation of commercial probiotic products available in the USA in 2009. *Journal of Chemotherapy* 22(6):373-377.

D'Souza, A. W., M. Boolchandani, S. Patel, G. Galazzo, J. M. van Hattem, M. S. Arcilla, D. C. Melles, M. D. de Jong, C. Schultsz, C. Consortium, G. Dantas, and J. Penders. 2021. Destination shapes antibiotic resistance gene acquisitions, abundance increases, and diversity changes in dutch travelers. *Genome Medicine* 13(1):79.

Dunn, D. T., A. J. Copas, and P. Brocklehurst. 2018. Superiority and non-inferiority: Two sides of the same coin? *Trials* 19(1):499.

Dutescu, I. A., and S. A. Hillier. 2021. Encouraging the development of new antibiotics: Are financial incentives the right way forward? A systematic review and case study. *Infection and Drug Resistance* 14:415-434.

Eichberg, M. J. 2015. Public funding of clinical-stage antibiotic development in the united states and european union. *Health Security* 13(3):156-165.

EPA (U.S. Environmental Protection Agency). 2021. *EPA's SBIR and homeland security programs: A decade of success* (accessed July 13, 2021).

Erlacher-Vindel, E. 2019. Prioritization of vaccines to reduce antibiotic use in animals. Paper read at PACCARB Meeting, Washington, DC.

FAO (Food and Agriculture Organization of the United Nations). 2016. *Probiotics in animal nutrition - production, impact and regulation.* FAO.

FAO and WHO (World Health Organization). 2002. *Guidelines for the evaluation of probiotics in food.* World Health Organization.

FDA (U.S. Food and Drug Administration). 2017. *Antifungal susceptibility test interpretive criteria*. https://www.fda.gov/drugs/development-resources/antifungal-susceptibility-test-interpretive-criteria (accessed June 4, 2021).

FDA. 2018a. *80 years of the Federal Food, Drug, and Cosmetic Act*. https://www.fda.gov/about-fda/fda-history-exhibits/80-years-federal-food-drug-and-cosmetic-act (accessed June 4, 2021).

FDA. 2018b. *Antimicrobial susceptibility test (AST) systems - class ii special controls guidance for industry and FDA*. https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/antimicrobial-susceptibility-test-ast-systems-class-ii-special-controls-guidance-industry-and-fda (accessed June 4, 2021).

FDA. 2018c. *Companion diagnostics*. https://www.fda.gov/medical-devices/in-vitro-diagnostics/companion-diagnostics (accessed June 4, 2021).

FDA. 2018d. *FDA in brief: FDA reports on its progress advancing policies for developing next generation antibiotics*. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-reports-its-progress-advancing-policies-developing-next-generation-antibiotics (accessed June 4, 2021).

FDA. 2019a. Coordinated development of antimicrobial drugs and antimicrobial susceptibility test devices: Guidance for industry and food and drug administration staff: U.S. Department of Health and Human Services, U.S. Food and Drug Administration, and Center for Devices and Radiological Health and Center for Drug Evaluation and Research.

FDA. 2019b. *Generally recognized as safe (GRAS)*. https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras (accessed.

FDA. 2020a. *21st Century Cures Act*. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act (accessed June 4, 2021).

FDA. 2020b. *Clinical Laboratory Improvement Amendments (CLIA)*. https://www.fda.gov/medical-devices/ivd-regulatory-assistance/clinical-laboratory-improvement-amendments-clia (accessed July 1, 2021).

FDA. 2020c. *Fact sheet: FDA at a glance*. https://www.fda.gov/about-fda/fda-basics/fact-sheet-fda-glance (accessed June 3, 2021).

FDA. 2020d. *Limited population pathway for antibacterial and antifungal drugs – the LPAD pathway*. https://www.fda.gov/drugs/development-resources/limited-population-pathway-antibacterial-and-antifungal-drugs-lpad-pathway (accessed June 11, 2020).

FDA. 2020e. *Meropenem - injection products*. https://www.fda.gov/drugs/development-resources/meropenem-injection-products (accessed June 4, 2021).

FDA. 2021a. *FDA-recognized antimicrobial susceptibility test interpretive criteria*. https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria (accessed June 4, 2021).

FDA. 2021b. *In vitro diagnostics EUAs*. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas (accessed June 4, 2021).

FDA. 2021c. *Orange book: Approved drug products with therapeutic equivalence evaluations*. https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm (accessed June 29, 2021).

Fenster, K., B. Freeburg, C. Hollard, C. Wong, R. Ronhave Laursen, and A. C. Ouwehand. 2019. The production and delivery of probiotics: A review of a practical approach. *Microorganisms* 7(3):83.

FIND. 2021a. *Antimicrobial resistance*. https://www.finddx.org/amr/ (accessed June 28, 2021).

FIND. 2021b. *Partners & donors*. https://www.finddx.org/partners-donors/ (accessed June 28, 2021).

Fitzpatrick, M. A. 2020. Real-world antibiotic needs for resistant gram-negative infections. *Lancet Infectious Diseases* 20(10):1108-1109.

Fogel, D. B. 2018. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. *Contemporary clinical trials communications* 11:156-164.

Frost, I., T. P. Van Boeckel, J. Pires, J. Craig, and R. Laxminarayan. 2019. Global geographic trends in antimicrobial resistance: The role of international travel. *Journal of Travel Medicine* 26(8).

G7 Research Group. 2021. G7 therapeutics and vaccines clinical trials charter.

GAO (U.S. Government Accountability Office). 2020. Antibiotic resistance: Additional federal actions needed to better determine magnitude and reduce impact. Washington, DC: U.S. Government Accountability Office.

GARDP (Global Antibiotic Research and Development Partnership). 2021a. *About GARDP*. https://gardp.org/who-we-are/about-gardp/ (accessed July 13, 2021).

GARDP. 2021b. *Access & stewardship*. https://dndi.org/research-development/registration-and-access (accessed July 13, 2021).

Gatti, M., M. Giannella, L. Scudeller, and P. Viale. 2020. Adaptive trials of new antimicrobials for infections with carbapenem-resistant, gram-negative bacteria. *Lancet Infectious Diseases* 20(1):24.

GCOA and IDSA (Global Coalition on Aging and Infectious Diseases Society of America). 2021. 2021 AMR preparedness index.

Gelman, D., A. Eisenkraft, N. Chanishvili, D. Nachman, S. Coppenhagem Glazer, and R. Hazan. 2018. The history and promising future of phage therapy in the military service. *Journal of Trauma and Acute Care Surgery* 85(1S Suppl 2):S18-S26.

Ghosh, C., P. Sarkar, R. Issa, and J. Haldar. 2019. Alternatives to conventional antibiotics in the era of antimicrobial resistance. *Trends in Microbiology* 27(4):323-338.

Goossens, H., M. Ferech, R. Vander Stichele, M. Elseviers, and ESAC Project Group. 2005. Outpatient antibiotic use in europe and association with resistance: A cross-national database study. *The Lancet* 365(9459):579-587.

Gotham, D., L. Moja, M. van der Heijden, S. Paulin, I. Smith, and P. Beyer. 2021. Reimbursement models to tackle market failures for antimicrobials: Approaches taken in France, Germany, Sweden, the United Kingdom, and the United States. *Health Policy* 125(3):296-306.

GSA (U.S. General Services Administration). 2020. *Federal procurement data system - next generation*. https://www.fpds.gov/fpdsng_cms/index.php/en/ (accessed July 1, 2021).

Harbarth, S. 2018. Will 10 million people die a year due to antimicrobial resistance by 2050? Paper read at Risk talk on antibiotic resistance, Rüschlikon, Zurich, Switzerland.

Hardin, L., A. Kilian, and E. Murphy. 2017. Bundled payments for care improvement: Preparing for the medical diagnosis-related groups. *Journal of Nursing Administration* 47(6):313-319.

Hasan, K. N., and G. Banerjee. 2020. Recent studies on probiotics as beneficial mediator in aquaculture: A review. *The Journal of Basic and Applied Zoology* 81(1).

Hauser, A. R., J. Mecsas, and D. T. Moir. 2016. Beyond antibiotics: New therapeutic approaches for bacterial infections. *Clinical Infectious Diseases* 63(1):89-95.

Health for Animals. 2017. Responsible antibiotic use: Five ways the animal health industry is tackling amr. *Health for Animals Newsletter*, https://www.healthforanimals.org/resources-and-events/newsletter-repository/6-responsible-antibiotic-use.html?q=20 (accessed July 13, 2021).

Health for Animals. 2020. *Our contribution*. https://healthforanimals.org/roadmap/contribution.html (accessed July 13, 2021).

Henderson, D. R. 2019. Rent seeking. https://www.econlib.org/library/Enc/RentSeeking.html (accessed June 11, 2021).

HHS (U.S. Department of Health and Human Services). 2017. Recommendations for incentivizing the development of vaccines, diagnostics, and therapeutics to combat antibiotic-resistance. *Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria*.

HHS. 2019. Project bioshield overview. https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/ (accessed June 11, 2021).

HHS, FDA (U.S. Food and Drug Administration), CDER (Center for Drug Evaluation and Research), and CBER (Center for Biologics Evaluation and Research). 2016. Non-inferiority clinical trials to establish effectiveness guidance for industry: U.S. Food and Drug Administration.

HHS, FDA, CDER, and CBER. 2019. *Adaptive designs for clinical trials of drugs and biologics.* HHS, FDA, CDER, and CBER.

Hillock, N. T., T. L. Merlin, J. Karnon, J. Turnidge, and J. Eliott. 2020. Feasibility of de-linking reimbursement of antimicrobials from sales: The Australian perspective as a qualitative case study. *JAC Antimicrob Resist* 2(2):dlaa023.

Hoelzer, K., L. Bielke, D. P. Blake, E. Cox, S. M. Cutting, B. Devriendt, E. Erlacher-Vindel, E. Goossens, K. Karaca, S. Lemiere, M. Metzner, M. Raicek, M. Collell Surinach, N. M. Wong, C. Gay, and F. Van Immerseel. 2018. Vaccines as alternatives to antibiotics for food producing animals. Part 1: Challenges and needs. *Veterinary Research* 49(1):64.

Hoseinifar, S. H., Y. Z. Sun, A. Wang, and Z. Zhou. 2018. Probiotics as means of diseases control in aquaculture, a review of current knowledge and future perspectives. *Frontiers in Microbiology* 9:2429.

Houchens, C., and J. Larsen. 2017. The role of the biomedical advanced research and development authority (BARDA) in promoting innovation in antibacterial product development. *AMR Control* August 2.

Humphries, R. M. 2018. Implementation of the 21st Century Cures Act for for breakpoints and interpretive categories, 06/02/2018, San Diego, California.

Humphries, R. M., and J. A. Hindler. 2016. Emerging resistance, new antimicrobial agents ... But no tests! The challenge of antimicrobial susceptibility testing in the current us regulatory landscape. *Clinical Infectious Diseases* 63(1):83-88.

Humphries, R. M., J. Hindler, M. Jane Ferraro, and A. Mathers. 2018a. Twenty-first century cures act and antimicrobial susceptibility testing: Clinical implications in the era of multidrug resistance. *Clinical Infectious Diseases* 67(7):1132-1138.

Humphries, R. M., J. A. Hindler, E. Epson, S. Horwich-Scholefield, L. G. Miller, J. Mendez, J. B. Martinez, J. Sinkowitz, D. Sinkowtiz, C. Hershey, P. Marquez, S. Bhaurla, M. Moran, L. Pandes, D. Terashita, and J. A. McKinnell. 2018b. Carbapenem-resistant enterobacteriaceae detection practices in California: What are we missing? *Clinical Infectious Diseases* 66(7):1061-1067.

Humphries, R. M., S. Kircher, A. Ferrell, K. M. Krause, R. Malherbe, A. Hsiung, and C. A. Burnham. 2018c. The continued value of disk diffusion for assessing antimicrobial susceptibility in clinical laboratories: Report from the Clinical and Laboratory Standards Institute methods development and standardization working group. *Journal of Clinical Microbiology* 56(8).

ICMRA (International Coalition of Medicines Regulatory Authorities). 2020. ICMRA statement on COVID-19.

IDSA (Infectious Diseases Society of America). 2012. White paper: Recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. *Clinical Infectious Diseases* 55(8):1031-1046.

IDSA. 2019. *Disarm act provides framework needed to spur antibiotic R&D, protect existing drugs*. https://www.idsociety.org/news--publications-new/articles/2019/disarm-act-provides-framework-needed-to-spur-antibiotic-rd-protect-existing-drugs/ (accessed June 3, 2021).

IDSA. 2021. FY 2022 budget recommendations for antimicrobial resistance programs.

Jackson, S. A., J. L. Schoeni, C. Vegge, M. Pane, B. Stahl, M. Bradley, V. S. Goldman, P. Burguiere, J. B. Atwater, and M. E. Sanders. 2019. Improving end-user trust in the quality of commercial probiotic products. *Frontiers in Microbiology* 10(739):739.

Jacobs, A. 2019. *Crisis looms in antibiotics as drug makers go bankrupt*. https://www.nytimes.com/2019/12/25/health/antibiotics-new-resistance.html (accessed July 13, 2021).

Jit, M., D. H. L. Ng, N. Luangasanatip, F. Sandmann, K. E. Atkins, J. V. Robotham, and K. B. Pouwels. 2020. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: Rapid methodological review, conceptual framework and recommendations for future studies. *BMC Medicine* 18(1):38.

JPIAMR (Joint Programming Initiative on Antimicrobial Resistance). *About* https://www.jpiamr.eu/about/ (accessed June 10, 2021).

JPIAMR. 2021. *JPIAMR activity report 2020.* Stockholm: JPIAMR.

Kadlec, R. 2019. Committee on Energy and Commerce Subcommittee on Oversight and Investigations - hearing on flu season: U.S. public health preparedness and response. https://docs.house.gov/meetings/IF/IF02/20191204/110278/HHRG-116-IF02-Wstate-KadlecMDMTMHMSR-20191204-SD002.pdf (accessed December 4, 2020).

Kalelkar, P. P., M. Riddick, and A. J. García. 2021. Biomaterial-based antimicrobial therapies for the treatment of bacterial infections. *Nature Reviews Materials*.

Kaufhold, S., R. Yaesoubi, and V. E. Pitzer. 2019. Predicting the impact of typhoid conjugate vaccines on antimicrobial resistance. *Clinical Infectious Diseases* 68(Suppl 2):S96-S104.

Keane, A. 2018. Plazomicin. Paper read at Antimicrobial Drugs Advisory Committee Meeting, May 2, 2018, Washington, D.C.

Kirienko, N. V., L. Rahme, and Y. H. Cho. 2019. Editorial: Beyond antimicrobials: Non-traditional approaches to combating multidrug-resistant bacteria. *Frontiers in Cellular and Infection Microbiology* 9:343.

Knisely, J. 2020. NIAID support to meet the carb challenge. Paper read at Committee on the Long-Term Health and Economic Effects of Antimicrobial Resistance, 09/23/2020, Webinar.

Knox, J. 2020. *A lifeline for antibiotic development*. https://wellcome.org/news/lifeline-antibiotic-development (accessed June 10, 2021).

Krause, K. 2021a. The post-approval challenges of antimicrobial development. Paper read at Committee on the Long-Term Medical And Economic Effects Of Antimicrobial Resistance: Meeting 3, 01/05/2021, Webinar.

Krause, K. 2021b. The relationship between antimicrobial susceptibility testing devices and antibiotic markets. Paper read at Committee on the Long-Term Medical And Economic Effects Of Antimicrobial Resistance: Meeting 3, 01/06/2021, Webinar.

Lanini, S., J. P. A. Ioannidis, F. Vairo, M. Pletschette, G. Portella, V. Di Bari, A. Mammone, R. Pisapia, S. Merler, B. Nguhuni, M. Langer, A. Di Caro, S. J. L. Edwards, N. Petrosillo, A. Zumla, and G. Ippolito. 2019. Non-inferiority versus superiority trial design for new antibiotics in an era of high antimicrobial resistance: The case for post-marketing, adaptive randomised controlled trials. *Lancet Infectious Diseases* 19(12):e444-e451.

Larsen, J., and G. Disbrow. 2017. Project bioshield and the biomedical advanced research development authority: A 10-year progress report on meeting us preparedness objectives for threat agents. *Clinical Infectious Diseases* 64(10):1430–1434, doi: /1410.1093/cid/cix1097.

Laxminarayan, R., T. Van Boeckel, and A. Teillant. 2015. The economic costs of withdrawing antimicrobial growth promoters from the livestock sector.

Ledley, F. D., S. S. McCoy, G. Vaughan, and E. G. Cleary. 2020. Profitability of large pharmaceutical companies compared with other large public companies. *JAMA* 323(9):834-843.

Lepore, C., and W. Kim. 2021. *Opportunities in 2021 to fix the broken antibiotics market*. https://globalforum.diaglobal.org/issue/january-2021/opportunities-in-2021-to-fix-the-broken-antibiotics-market/ (accessed June 11, 2021).

Lewnard, J. A., N. C. Lo, N. Arinaminpathy, I. Frost, and R. Laxminarayan. 2020. Childhood vaccines and antibiotic use in low- and middle-income countries. *Nature* 581(7806):94-99.

Li Bassi, G., J. Suen, A. G. Barnett, A. Corley, J. Millar, J. Fanning, I. Lye, S. Colombo, K. Wildi, S. Livingstone, G. Abbate, S. Hinton, B. Liquet, S. Shrapnel, H. Dalton, J. F. Fraser, and COVID-19 Critical Care Consortium Investigators. 2020. Design and rationale of the covid-19 critical care consortium international, multicentre, observational study. *BMJ Open* 10(12):e041417.

Lipsitch, M., and G. R. Siber. 2016. How can vaccines contribute to solving the antimicrobial resistance problem? *mBio* 7(3):e00428-00416.

Mahase, E. 2020. UK launches subscription style model for antibiotics to encourage new development. *BMJ* 369:m2468.

Martinez Cruz, P., A. L. Ibanez, O. A. Monroy Hermosillo, and H. C. Ramirez Saad. 2012. Use of probiotics in aquaculture. *ISRN Microbiology* 2012:916845.

McAteer, J., G. Derado, M. Hughes, A. Bhatnagar, F. Medalla, K. Chatham-Stevens, G. D. Appiah, and E. Mintz. 2020. Typhoid fever in the us pediatric population, 1999-2015: Opportunities for improvement. *Clinical Infectious Diseases*.

McKenna, M. 2020. The antibiotic paradox: Why companies can't afford to create life-saving drugs. *Nature* 584(7821):338-341.

MedicalCountermeasures.gov. 2019a. Broad spectrum antimicrobials. https://www.medicalcountermeasures.gov/barda/cbrn/broad-spectrum-antimicrobials/ (accessed June 11, 2021).

MedicalCountermeasures.gov. 2019b. *Project bioshield overview*. https://www.medicalcountermeasures.gov/barda/cbrn/project-bioshield-overview/ (accessed June 11, 2021).

Mereish, K. 2018. *Threats to pharmaceutical supply chains.* U.S. Department of Homeland Security.

Merkeley, T. 2014. BARDA broad spectrum antimicrobials (BSA) program. https://www.phe.gov/ASPRBlog/pages/BlogArticlePage.aspx?PostID=97 (accessed June 24, 2021).

Mikulic, M. 2021. World pharmaceutical market distribution by submarket 2014-2020. https://www.statista.com/statistics/266547/total-value-of-world-pharmaceutical-market-by-submarket-since-2006/ (accessed June 11, 2021).

MMV (Medicines for Malaria Venture). 2021. *Working with regulators to advance access to quality medicines*. https://www.mmv.org/research-development/working-regulators-advance-access-quality-medicines (accessed July 13, 2021).

Moeller, G., S. Buchsbaum, P. Wilson, A. Shepherd, P. Kaspar, M. Giovanni, L. Penny, M. Urdea, P. Vickerman, C. Dye, J. Cunningham, S. Reed, C. Hanson, P. Small, M. Perkins, R. Allan, A. Magill, T. Taylor, R. Guerrant, J. Agosti, L. von Seidlein, J. Hughes, M. Miller, C. Mason, P. Tarr, C. Wilfert, K. Holmes, P. Mwaba, N. Hellmann, R. Peeling, et al. 2007. *Estimating the global health impact of improved diagnostic tools for the developing world*. RAND Corporation.

Moore, M. R., R. Link-Gelles, W. Schaffner, R. Lynfield, C. Lexau, N. M. Bennett, S. Petit, S. M. Zansky, L. H. Harrison, A. Reingold, L. Miller, K. Scherzinger, A. Thomas, M. M. Farley, E. R. Zell, T. H. Taylor, T. Pondo, L. Rodgers, L. McGee, B. Beall, J. H. Jorgensen, and C. G. Whitney. 2015. Effect of use of 13-valent pneumococcal conjugate vaccine in children on invasive pneumococcal disease in children and adults in the USA: Analysis of multisite, population-based surveillance. *The Lancet Infectious Diseases* 15(3):301-309.

Mossialos, E., C. M. Morel, S. Edwards, J. Berenson, M. Gemmill-Toyama, D. Brogan, and W. H. Organization. 2010. *Policies and incentives for promoting innovation in antibiotic research*: World Health Organization. Regional Office for Europe.

Mullard, A. 2020. UK outlines its antibiotic pull incentive plan. *Nature Reviews Drug Discovery* 19(5):298.

Murray, D. D., A. G. Babiker, J. V. Baker, C. E. Barkauskas, S. M. Brown, C. C. Chang, V. J. Davey, A. C. Gelijns, A. A. Ginde, B. Grund, E. Higgs, F. Hudson, V. L. Kan, H. C. Lane, T. A. Murray, R. Paredes, M. K. B. Parmar, S. Pett, A. N. Phillips, M. N. Polizzotto, C. Reilly, U. Sandkovsky, S. Sharma, M. Teitelbaum, B. T. Thompson, B. E. Young, J. D. Neaton, and J. D. Lundgren. 2021.

Design and implementation of an international, multi-arm, multi-stage platform master protocol for trials of novel SARS-CoV-2 antiviral agents: Therapeutics for inpatients with COVID-19 (tico/activ-3). *medRxiv*.

NCATS GARD (National Center for Advancing Translational Sciences Genetic and Rare Diseases Information Center). 2021. *FAQs about rare diseases*. https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (accessed June 10, 2021).

Nielsen, T. B., E. P. Brass, D. N. Gilbert, J. G. Bartlett, and B. Spellberg. 2019. Sustainable discovery and development of antibiotics—is a nonprofit approach the future? *The New England Journal of Medicine* 381(6):503.

NIH (National Institutes of Health). 2021. *Radx programs*. https://www.nih.gov/research-training/medical-research-initiatives/radx/radx-programs (accessed September 24, 2021).

NLM (National Library of Medicine). *National Database of Antibiotic Resistant Organisms (NDARO)*. 2021. https://www.ncbi.nlm.nih.gov/pathogens/antimicrobial-resistance/ (accessed June 10, 2021).

Novo Nordisk Foundation. 2018. *Repair impact fund*. https://www.repair-impact-fund.com/about/ (accessed June 11, 2021).

Nwokoro, E., R. Leach, C. Ardal, E. Baraldi, K. Ryan, and J. Plahte. 2016. An assessment of the future impact of alternative technologies on antibiotics markets. *J Pharm Policy Pract* 9:34.

O'Brien, M. K., and P. Chu. 2020. *A market failure for antimicrobial resistant medicines* (accessed October 12, 2021).

O'Neill, J. 2018. Tackling drug-resistant infections globally: Final report and recommendations. 2016. *HM Government and Welcome Trust: UK*.

OECD (Organisation for Economic Co-operation and Development), WHO (World Health Organization), FAO (Food and Agriculture Organization of the United Nations), and OIE (World Organisation for Animal Health). 2017. Tackling antimicrobial resistance: Ensuring sustainable R&D: OECD, WHO, FAO, OIE.

Oehler, R. L., and S. G. Gompf. 2020. Shortcomings in the us pharmaceutical supply chain: Potential risks associated with international manufacturing and trade-related tariffs. *JAMA* 324(2):143-144.

OIE (World Organisation for Animal Health). 2015. Report of the meeting of the OIE *ad hoc* group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals, 21-23 April 2015, Paris, France.

OIE. 2018. Report of the meeting of the OIE *ad hoc* group on prioritisation of diseases for which vaccines could reduce antimicrobial use in animals, 7-9 May 2018, Paris, France.

Okeke, I. N. 2009. Cholera vaccine will reduce antibiotic use. *Science* 325(5941):674.

Okeke, I. N., R. W. Peeling, H. Goossens, R. Auckenthaler, S. S. Olmsted, J. F. de Lavison, B. L. Zimmer, M. D. Perkins, and K. Nordqvist. 2011. Diagnostics as essential tools for containing antibacterial resistance. *Drug Resistance Updates* 14(2):95-106.

Okhravi, C., S. Callegari, S. McKeever, C. Kronlid, E. Baraldi, O. Lindahl, and F. Ciabuschi. 2018. Simulating market entry rewards for antibiotics development. *Journal of Law, Medicine and Ethics* 46(1 Suppl):32-42.

Outterson, K. 2019. A shot in the arm for new antibiotics. *Nature Biotechnology* 37(10):1110-1112.

Outterson, K., U. Gopinathan, C. Clift, A. D. So, C. M. Morel, and J. A. Rottingen. 2016. Delinking investment in antibiotic research and development from sales revenues: The challenges of transforming a promising idea into reality. *PLoS Medicine* 13(6):e1002043.

Outterson, K., E. S. F. Orubu, J. Rex, C. Ardal, and M. H. Zaman. 2021. Patient access in fourteen high-income countries to new antibacterials approved by the FDA, EMA, PMDA, or Health Canada, 2010-2020. *Clinical Infectious Diseases*.

PACCARB (Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria). 2019. Priorities for the national action plan on combating antibiotic-resistant bacteria: 2020–2025 U.S. Department of Health and Human Services.

Palzkill, T. 2013. Metallo-beta-lactamase structure and function. *Annals of the New York Academy of Sciences* 1277:91-104.

Parker, G. 2006. Office of public health emergency preparedness; draft HHS public health emergency medical countermeasures enterprise (PHEMCE) strategy for chemical, biological, radiological and nuclear (CBRN) threats Department of Health and Human Services

Paul, M., S. Harbarth, A. Huttner, G. E. Thwaites, U. Theuretzbacher, M. J. M. Bonten, and L. Leibovici. 2021. Investigator-initiated randomized controlled trials in infectious diseases: Better value for money for registration trials of new antimicrobials. *Clinical Infectious Diseases* 72(7):1259-1264.

PCAST (President's Council of Advisors on Science and Technology). 2015. National action plan for combating antibiotic-resistant bacteria. Washington, DC: The White House.

Peeling, R. W., and D. Mabey. 2010. Point-of-care tests for diagnosing infections in the developing world. *Clinical Microbiology and Infection* 16(8):1062-1069.

Peplow, M. 2020. Developing countries face diagnostic challenges as the COVID-19 pandemic surges. *Chemical and Engineering News*.

Perkins, M., and D. Glover. 2020. How the "NHS model" to tackle antimicrobial resistance (amr) can set a global standard: NHS.

Pew. 2014. *Antibiotics currently in global clinical development* (accessed June 11, 2021).

Pew. 2021. *The shared platform for antibiotic research and knowledge (SPARK)*. https://www.pewtrusts.org/en/research-and-analysis/articles/2018/09/21/the-shared-platform-for-antibiotic-research-and-knowledge (accessed June 10, 2021).

Pfizer. 2017. Pfizer launches zavicefta™ (ceftazidime-avibactam) in the U.K. and Germany, a new antibiotic to treat complicated infections caused by gram-negative bacteria: Pfizer.

Plackett, B. 2020. Why big pharma has abandoned antibiotics. *Nature* 586(7830):S50-S52.

Renwick, M., and E. Mossialos. 2020. Fostering R&D of novel antibiotics and other technologies to prevent and treat infection. *European Journal of Public Health* 30(Suppl 5):ckaa165. 1203.

Renwick, M. J., D. M. Brogan, and E. Mossialos. 2016. A systematic review and critical assessment of incentive strategies for discovery and development of novel antibiotics. *Journal of Antibiotics* 69(2):73-88.

Rex, J., and K. Outterson. 2020. *UK antibiotic subscription pilot implies pull incentive of up to $4b across the G20*. https://amr.solutions/2020/03/29/uk-antibiotic-subscription-pilot-implies-pull-incentive-of-up-to-4b-across-the-g20/ (accessed June 3, 2021).

Rex, J. H., M. Goldberger, B. I. Eisenstein, and C. Harney. 2014. The evolution of the regulatory framework for antibacterial agents. *Annals of the New York Academy of Sciences* 1323:11-21.

Rex, J. H., G. H. Talbot, M. J. Goldberger, B. I. Eisenstein, R. M. Echols, J. F. Tomayko, M. N. Dudley, and A. Dane. 2017. Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern noninferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. *Clinical Infectious Diseases* 65(1):141-146.

Roope, L. S. J., R. D. Smith, K. B. Pouwels, J. Buchanan, L. Abel, P. Eibich, C. C. Butler, P. S. Tan, A. S. Walker, J. V. Robotham, and S. Wordsworth. 2019. The challenge of antimicrobial resistance: What economics can contribute. *Science* 364(6435).

Rost, L. M., M. H. Nguyen, C. J. Clancy, R. K. Shields, and E. S. Wright. 2021. Discordance among antibiotic prescription guidelines reflects a lack of clear best practices. *Open Forum Infectious Diseases* 8(1):ofaa571.

Rubin, D. 2016. Evaluating antibacterial drugs in unmet need settings. https://www.fda.gov/files/drugs/published/Evaluating-antibacterial-drugs-in-unmet-need-settings.pdf (accessed July 18, 2021).

Russell, P. 2007. Project bioshield: What it is, why it is needed, and its accomplishments so far. *Clinical Infectious Diseases* 45(Supplement 1):S68–S72. doi: 10.1086/518151.

Scheftel, J., M. T. Jay-Russell, T. W. Lehenbauer, D. R. Smith, M. Papich, L. Schnabel, T. M. Parker, C. Brookshire, R. Singer, H. Cervantes, J. E. Whaley, P. S. Gaunt, A. Canon, and P. Davies. 2020.

Antimicrobial resistant pathogens affecting animal health in the united states: Americal Veterinary Medical Association.

Schmidt, V., M. Gomez-Chiarri, C. Roy, K. Smith, and L. Amaral-Zettler. 2017. Subtle microbiome manipulation using probiotics reduces antibiotic-associated mortality in fish. *mSystems* 2(6):e00133-00117.

Schneider, M. 2020. New rules expand application of the NTAP program for innovative antibiotics. https://www.contagionlive.com/view/new-rules-expand-application-of-the-ntap-program-for-innovative-antibiotics (accessed April 7, 2021).

Schneider, M., G. W. Daniel, N. R. Harrison, and M. B. McClellan. 2020a. Delinking us antibiotic payments through a subscription model in medicare: Duke-Margolis Center For Health Policy.

Schneider, M., N. R. Harrison, and M. B. McClellan. 2020b. *Recommended post-market incentive strategies to support the development of innovative antibiotics.* Duke-Margolis Center for Health Policy.

Schulz, L. T., S. Y. Kim, A. Hartsell, and W. E. Rose. 2019. Antimicrobial stewardship during a time of rapid antimicrobial development: Potential impact on industry for future investment. *Diagnostic Microbiology and Infectious Disease* 95(3):114857.

Sciarretta, K., A. Opalska, A. Van-Hengel, and J. Larsen. Economic incentives for antimicrobial therapy development: Summary from the transatlantic task force on antimicrobial resistance.

ScienceDirect. 2021a. *Disk diffusion*. https://www.sciencedirect.com/topics/immunology-and-microbiology/disk-diffusion (accessed June 4, 2021).

ScienceDirect. 2021b. *High throughput screening*. https://www.sciencedirect.com/topics/medicine-and-dentistry/high-throughput-screening (accessed June 10, 2021).

Segerman, A. 2019. The disarm act can help fix the broken antibiotics market. In *BIOtechNOW*: Biotechnology Innovation Organization.

Shawar, R. 2016. Overview of AST device clearance process: CDRH perspective. Paper read at Public Workshop--Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices, Silver Spring, MD.

Simpkin, V. L., M. J. Renwick, R. Kelly, and E. Mossialos. 2017. Incentivising innovation in antibiotic drug discovery and development: Progress, challenges and next steps. *Journal of Antibiotics* 70(12):1087-1096.

Singer, A. C., C. Kirchhelle, and A. P. Roberts. 2020. (inter)nationalising the antibiotic research and development pipeline. *Lancet Infectious Diseases* 20(2):e54-e62.

Spellberg, B. 2021. A new sustainable model of antibiotic R&D. Paper read at Committee on the Long-Term Health and Economic Effects on Antimicrobial Resistance in the United States: Meeting 3, 01/05/2021, Webinar.

Spellberg, B., J. G. Bartlett, and D. N. Gilbert. 2013. The future of antibiotics and resistance. *New England Journal of Medicine* 368(4):299-302.

Stafford, K. A., M. Boutin, S. R. Evans, and A. D. Harris. 2014. Difficulties in demonstrating superiority of an antibiotic for multidrug-resistant bacteria in nonrandomized studies. *Clinical Infectious Diseases* 59(8):1142-1147.

Steedman, M., and K. Taylor. 2019. *Ten years on measuring the return from pharamceutical innovation.* London, UK: Deloitte LLP.

Strich, J. R., S. Warner, Y. L. Lai, C. Y. Demirkale, J. H. Powers, 3rd, R. L. Danner, and S. S. Kadri. 2020. Needs assessment for novel gram-negative antibiotics in us hospitals: A retrospective cohort study. *Lancet Infectious Diseases* 20(10):1172-1181.

Suzuki, H. 2021. *Building resilient global supply chains--the geopolitics of the indo-pacific region.* Center for Strategic and International Studies (CSIS).

Talbot, G. H., A. Jezek, B. E. Murray, R. N. Jones, R. H. Ebright, G. J. Nau, K. A. Rodvold, J. G. Newland, H. W. Boucher, and A. Infectious Diseases Society of. 2019. The Infectious Diseases Society of America's 10 x '20 initiative (10 new systemic antibacterial agents U.S. Food and

Drug Administration approved by 2020): Is 20 x '20 a possibility? *Clinical Infectious Diseases* 69(1):1-11.

Terpou, A., A. Papadaki, I. K. Lappa, V. Kachrimanidou, L. A. Bosnea, and N. Kopsahelis. 2019. Probiotics in food systems: Significance and emerging strategies towards improved viability and delivery of enhanced beneficial value. *Nutrients* 11(7).

The Pew Charitable Trusts. 2020a. Correspondence re: Cms-1735-p: Medicare program; hospital inpatient prospective payment systems for acute care hospitals and the long term care hospital prospective payment system and proposed policy changes and fiscal year 2021 rates; quality reporting and medicare and medicaid promoting interoperability programs requirements for eligible hospitals and critical access hospitals proposed rule.

The Pew Charitable Trusts. 2020b. Tracking the global pipeline of antibiotics in development, April 2020: The Pew Charitable Trusts Washington, DC.

The Rockefeller Foundation. 2020. *A landscape analysis of laboratory technologies for COVID-19.*

Theuretzbacher, U., and L. J. V. Piddock. 2019. Non-traditional antibacterial therapeutic options and challenges. *Cell Host & Microbe* 26(1):61-72.

Theuretzbacher, U., K. Outterson, A. Engel, and A. Karlen. 2020. The global preclinical antibacterial pipeline. *Nature Reviews: Microbiology* 18(5):275-285.

Thomas, J., M. Navre, A. Rubio, and A. Coukell. 2018. Shared platform for antibiotic research and knowledge: A collaborative tool to spark antibiotic discovery. *ACS Infectious Diseases* 4(11):1536-1539.

Towse, A., C. K. Hoyle, J. Goodall, M. Hirsch, J. Mestre-Ferrandiz, and J. H. Rex. 2017. Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation. *Health Policy* 121(10):1025-1030.

Trudil, D. 2015. Phage lytic enzymes: A history. *Virologica Sinica* 30(1):26-32.

Trusheim, M. R., A. A. Shrier, Z. Antonijevic, R. A. Beckman, R. K. Campbell, C. Chen, K. T. Flaherty, J. Loewy, D. Lacombe, S. Madhavan, H. P. Selker, and L. J. Esserman. 2016. Pipelines: Creating comparable clinical knowledge efficiently by linking trial platforms. *Clinical Pharmacology and Therapeutics* 100(6):713-729.

Tsai, J. M., N. V. Tolan, A. K. Petrides, S. Kanjilal, M. Brigl, N. I. Lindeman, Y. D. Li, M. J. Tanasijevic, S. S. Basu, and S. E. F. Melanson. 2021. How SARS-CoV-2 transformed the clinical laboratory: Challenges and lessons learned. *J Appl Lab Med* 6(5):1338-1354.

USAMRIID (United States Army Medical Research Institute of Infectious Diseases). 2021. *USAMRIID: Biodefense solutions to protect our nation*. https://www.usamriid.army.mil/ (accessed September 21, 2021).

USDA (U.S. Department of Agriculture). 2014. Antimicrobial resistance action plan: U.S. Department of Agriculture.

USDT (U.S. Department of the Treasury). 2021. G7 finance ministers & central bank governors communiqué. London, United Kingdom.

Vallabhaneni, S., J. Y. Huang, J. E. Grass, A. Bhatnagar, S. Sabour, J. D. Lutgring, D. Campbell, M. Karlsson, A. J. Kallen, E. Nazarian, E. A. Snavely, S. Morris, C. Wang, R. Lee, M. Koag, R. Lewis, B. Garcia, E. I. P. W. Group, A. C. Brown, and M. S. Walters. 2021. Antimicrobial susceptibility profiles to predict the presence of carbapenemase genes among carbapenem-resistant pseudomonas aeruginosa isolates. *Journal of Clinical Microbiology* 59(6):e02874-02820.

van Belkum, A., T. T. Bachmann, G. Ludke, J. G. Lisby, G. Kahlmeter, A. Mohess, K. Becker, J. P. Hays, N. Woodford, K. Mitsakakis, J. Moran-Gilad, J. Vila, H. Peter, J. H. Rex, W. M. Dunne, Jr., and the JPIAMR AMR-RDT Working Group on Antimicrobial Resistance and Rapid Diagnostic Testing. 2019. Developmental roadmap for antimicrobial susceptibility testing systems. *Nature Reviews: Microbiology* 17(1):51-62.

van Belkum, A., C. D. Burnham, J. W. A. Rossen, F. Mallard, O. Rochas, and W. M. Dunne, Jr. 2020. Innovative and rapid antimicrobial susceptibility testing systems. *Nature Reviews: Microbiology* 18(5):299-311.

van de Sande-Bruinsma, N., H. Grundmann, D. Verloo, E. Tiemersma, J. Monen, H. Goossens, M. Ferech, European Antimicrobial Resistance Surveillance System Group, and European Surveillance of Antimicrobial Consumption Project Group. 2008. Antimicrobial drug use and resistance in Europe. *Emerging Infectious Diseases* 14(11):1722-1730.

Vekemans, J., M. Hasso-Agopsowicz, G. Kang, W. P. Hausdorff, A. Fiore, E. Tayler, E. J. Klemm, R. Laxminarayan, P. Srikantiah, M. Friede, and M. Lipsitch. 2021. Leveraging vaccines to reduce antibiotic use and prevent antimicrobial resistance: A world health organization action framework. *Clinical Infectious Diseases* 73(4):e1011-e1017.

Ventola, C. L. 2015. The antibiotic resistance crisis: Part 1: Causes and threats. *P T* 40(4):277-283.

Warrington, J. S., J. W. Crothers, A. Goodwin, L. Coulombe, T. Hong, L. Bryan, C. Wojewoda, M. Fung, G. Warrington, V. Clark, L. Risley, and M. Lewis. 2021. All hands-on deck and all decks on hand: Surmounting supply chain limitations during the COVID-19 pandemic. *Academic Pathology* 8:23742895211011928.

WEF (World Economic Forum). 2018. Antimicrobial resistance tackling the gap in R&D resources with pull incentives, edited by Wellcome. Geneva.

WHO (World Health Organization). 2015. Vaccinating salmon: How Norway avoids antibiotics in fish farming. 10/29/2015.

WHO. 2019a. Antibacterial agents in clinical development: An analysis of the antibacterial clinical development pipeline. Geneva, Switzerland: World Health Organization.

WHO. 2019b. *Antibacterial agents in preclinical development: An open access database.* Geneva, Switzerland: World Health Organization.

WHO. 2020. Global partnership to make available 120 million affordable, quality COVID-19 rapid tests for low- and middle-income countries.

WHO. 2021. *2020 antibacterial agents in clinical and preclinical development: An overview and analysis.* Geneva, Switzerland: World Health Organization.

Wouters, O. J., M. McKee, and J. Luyten. 2020. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA* 323(9):844-853.

Zimmer, B. 2021. Regulatory challenges in antimicrobial diagnostics. Paper read at Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance: Meeting 3, Webinar.

Zumla, A., J. A. Al-Tawfiq, V. I. Enne, M. Kidd, C. Drosten, J. Breuer, M. A. Muller, D. Hui, M. Maeurer, M. Bates, P. Mwaba, R. Al-Hakeem, G. Gray, P. Gautret, A. A. Al-Rabeeah, Z. A. Memish, and V. Gant. 2014. Rapid point of care diagnostic tests for viral and bacterial respiratory tract infections—needs, advances, and future prospects. *The Lancet Infectious Diseases* 14(11):1123-113.

# 7

# The National Action Plan for Combating Antibiotic-Resistant Bacteria

The need for a coordinated and cohesive approach to preventing, detecting, and controlling infections related to antimicrobial-resistant pathogens is a national and international concern. The need was the basis of the 2015 World Health Assembly resolution on antimicrobial resistance, which encouraged countries to develop national action plans and to collaborate with other countries in their implementation (Shallcross and Davies, 2014). This chapter describes the U.S. government's work since 2015 to combat antimicrobial resistance in the United States and internationally. To advance this analysis, the committee commissioned the Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota to review agencies' progress against the *National Action Plan for Combating Antibiotic-Resistant Bacteria 2015–2020.* This chapter will first review this action plan, its goals, and implementation. Next, it will review the Government Accountability Office (GAO) report on progress made with regard to antibiotic resistance and human health. The following section reviews the CIDRAP commissioned analysis. The last section of the chapter discusses the recently released *National Action Plan for Combating Antibiotic-Resistant Bacteria 2020–2025*, including the new objectives and milestones set for the federal government over the next 5 years. The chapter concludes with a brief assessment of progress made by the federal government in preventing, controlling, and treating antimicrobial resistance in the United States and around the world and identifies the major challenges the agencies have encountered in this work.

## THE 2015 NATIONAL ACTION PLAN

In September 2014, the White House released a National Strategy for Combating Antibiotic-Resistant Bacteria (The White House, 2014). This document identified the federal government's priorities to prevent, detect, and control outbreaks of resistant pathogens recognized by the Centers for Disease Control and Prevention (CDC) as urgent or serious threats (The White House, 2014). The strategy also put considerable emphasis on the continued availability of effective therapies for the treatment of bacterial infections and the ability to detect and control emerging resistant pathogens in humans and animals (The White House, 2014). Box

7-1 lists the goals and objectives set out in the first national strategy document, goals that were further divided into subobjectives and milestones for the first, third, and fifth years of the plan.

**BOX 7-1**
**Five Goals and Objectives of the National Strategy for Combating Antibiotic-Resistant Bacteria**

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections.
   - 1.1 Implement public health programs and reporting policies that advance antibiotic-resistance prevention and foster antibiotic stewardship in health care settings and the community.
   - 1.2 Eliminate the use of medically important antibiotics for growth promotion in food-producing animals, and bring other agricultural uses of antibiotics, for treatment, control, and prevention of disease, under veterinary oversight.
   - 1.3 Identify and implement measures to foster stewardship of antibiotics in animals.
2. Strengthen national One Health surveillance efforts to combat resistance.
   - 2.1 Create a regional public health laboratory network to strengthen national capacity to detect resistant bacterial strains and a specimen repository to facilitate development and evaluation of diagnostic tests and treatments.
   - 2.2 Expand and strengthen the national infrastructure for public health surveillance and data reporting, and provide incentives for timely reporting of antibiotic resistance and antibiotic use in all health care settings.
   - 2.3 Develop, expand, and maintain capacity in state and federal veterinary and food safety laboratories to conduct antibiotic susceptibility testing and characterize select zoonotic and animal pathogens.
   - 2.4 Enhance monitoring of antibiotic-resistance patterns, as well as antibiotic sales, usage, and management practices, at multiple points in the production chain for food animals and retail meat.
3. Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria.
   - 3.1 Develop and validate new diagnostics—including tests that rapidly distinguish between viral and bacterial pathogens and tests that detect antibiotic resistance—that can be implemented easily in a wide range of settings.
   - 3.2 Expand availability and use of diagnostics to improve treatment of antibiotic-resistant infections, enhance infection control, and facilitate outbreak detection and response in health care and community settings.
4. Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines.
   - 4.1 Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic resistance and the spread of resistance genes that are common to animals and humans.
   - 4.2 Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
   - 4.3 Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
   - 4.4 Develop nontraditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
   - 4.5 Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.

5. Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control, and antibiotic research and development.
   - 5.1 Promote laboratory capability to identify at least three of the seven WHO priority antimicrobial-resistant pathogens using standardized, reliable detection assays.
   - 5.2 Collaborate with WHO, OIE, and other international efforts focused on the development of integrated, laboratory-based surveillance to detect and monitor antibiotic-resistance in relevant animal and human foodborne pathogens.
   - 5.3 Develop a mechanism for international communication of critical events that may signify new resistance trends with global public and animal health implications.
   - 5.4 Promote the generation and dissemination of information needed to effectively address antibiotic resistance.
   - 5.5 Establish and promote international collaboration and public–private partnerships to incentivize development of new therapeutics to counter antibiotic resistance including new, next-generation, and other alternatives to antibiotics, vaccines, and affordable, rapidly deployable, point-of-need diagnostics.
   - 5.6 Support countries to develop and implement national plans to combat antibiotic resistance and strategies to enhance antimicrobial stewardship.
   - 5.7 Partner with other nations to promote quality, safety, and efficacy of antibiotics and strengthen their pharmaceutical supply chains.
   - 5.8 Coordinate regulatory approaches by collaborating with international organizations such as FAO and OIE to harmonize international data submission requirements and risk assessment.

SOURCE: The White House, 2014, reprinted with permission.

*The National Action Plan for Combating Antibiotic-Resistant Bacteria 2015–2020* (hereafter, the 2015 action plan), provided agencies with a roadmap to achieve the goals shown in Box 7-1 (The White House, 2015). The 2015 action plan also included national targets, as determined by the CDC, that the plan aimed to achieve by 2020. These targets were categorized as responding to CDC-recognized urgent threats and CDC-recognized serious threats (see Box 7-2). These quantitative targets were intended to reduce the incidence of threats to both human and animal health, particularly for carbapenem-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, and *Clostridioides difficile*. For each goal in the action plan, there are several (two to six) expected outcomes that might reasonably follow the achievement of the cited milestones. Several of these outcomes are quantitative, such as a percentage reduction in inappropriate antibacterial prescriptions (The White House, 2015). But most of the expected outcomes listed are processes outcomes, such as developing a global database to collect information on antimicrobial use in animals (The White House, 2015)

The 2015 action plan also created a federal government task force, co-chaired by the secretaries of defense, agriculture, and health and human services, charged with monitoring progress against cited goals and objectives and updating the president on their progress every year (The White House, 2015). The action plan also set out 230 milestones, spread among each of the five goals to be achieved in the first, third, or last year of the plan (Moore, 2021).

**BOX 7-2**
**National Targets to Combat Antimicrobial-Resistant Bacteria**

CDC-Recognized Urgent Threats

- Reduce by 50 percent the incidence of overall *Clostridioides difficile* infection compared to estimates from 2011.
- Reduce by 60 percent carbapenem-resistant Enterobacterales infections acquired during hospitalization compared to estimates.
- Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2 percent compared to estimates from 2013.

CDC Recognized Serious Threats

- Reduce by 35 percent multidrug-resistant *Pseudomonas* spp. infections acquired during hospitalization compared to estimates from 2011.
- Reduce by at least 50 percent overall methicillin-resistant *Staphylococcus aureus* bloodstream infections by 2020 as compared to 2011.
- Reduce by 25 percent multidrug-resistant nontyphoidal *Salmonella* infections compared to estimates from 2010–2012.
- Reduce by 15 percent the number of multidrug-resistant tuberculosis infections.
- Reduce by at least 25 percent the rate of antibiotic-resistant invasive pneumococcal disease among < 5-year-olds compared to estimates from 2008.
- Reduce by at least 25 percent the rate of antibiotic-resistant invasive pneumococcal disease among > 65-year-olds compared to estimates from 2008.

SOURCE: The White House, 2015.

Federal agencies identified in the action plan include the Department of Health and Human Services (HHS) and its agencies,[1] the Department of Defense (DOD), the Department of Veterans Affairs (VA), the U.S. Department of Agriculture (USDA),[2] the Environmental Protection Agency (EPA), the U.S. Agency for International Development (USAID), and the Department of State (The White House, 2015). Many of the milestones in the 2015 action plan require collaboration among agencies or departments. For example, sub-objective 4.1.2 states that within 1 year "FDA, USDA, CDC, and NIH will bring together experts in food production, agriculture, and public health to encourage collaborative research—from basic research to clinical testing—on antibiotic resistance" (The White House, 2015, p. 42). However, such milestones are vague, subject to interpretation, and lack a defined or measurable outcome against which to determine success. Furthermore, for many of the targets outlined in Box 7-2, it is not evident that there are baseline measures against which the targets could be measured.

Some of the cited goals and milestones require input and dissemination from professional associations such as the American Veterinary Medical Association and various state and regional organizations. The 2015 action plan also sets specific milestones for some states, as well as Puerto Rico and the District of Columbia (The White House, 2015). Finally, many of the federal agencies are called on to work with multilaterals such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations, and the World Organisation for

[1] Including the Centers for Medicare & Medicaid Services (CMS), the Centers for Disease Prevention and Control (CDC), the Agency for Healthcare Research and Quality (AHRQ), the U.S. Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA).

[2] Including the Animal and Plant Health Inspection Service, the Agricultural Research Service, and the Food Safety Inspection Service.

Animal Health to develop a variety of databases, systems, and capacities to meet the action plan goals (The White House, 2015).

Many of the milestones in the 2015 action plan involve data tracking and sharing and laboratory surveillance or goals that depend on coordinated effort across government agencies and at various levels (i.e., federal, state, county) (The White House, 2015). This need for coordination is reflected across the 2015 action plan. For example, under the goal of strengthening One Health surveillance, there were milestones on integrating data from the National Healthcare Safety Network, the Emerging Infections Program, the National Antimicrobial Resistance Monitoring System, the National Animal Health Monitoring System, the National Animal Health Laboratory Network, and the Veterinary Laboratory Investigation and Response Network. The advancing of One Health surveillance was also tied to the creation of a regional network of public health laboratories with standardized methods for testing, and monitoring of antimicrobial sales, use, and emerging resistance across the food production system (The White House, 2015).

The agencies implementing the 2015 action plan published regular progress reports (USTFCARB, 2017, 2018, 2019). These progress reports summarize the major activities advancing the 2015 action plan, but not information on specific milestones.

## GAO REPORTS

Between 2017 and 2020, GAO reviewed the progress of federal agencies against the 2015 action plan. The 2020 report looked closely at CDC's surveillance work, as well as federal efforts to encourage diagnostic testing, and the development of new treatments for resistant infections, and the promotion of antimicrobial stewardship (GAO, 2020). GAO reviewed the use of medically important antimicrobials in animal agriculture in a 2017 report (GAO, 2017).

### Key Findings from the GAO 2020 Report

After reviewing relevant literature and interviewing involved officials, the GAO report summarized the progress the various agencies had made against their milestones. The report noted four important challenges the agencies faced in implementing the action plan. First, despite expanded surveillance, the CDC still faces an uphill battle in measuring the magnitude of the problem (GAO, 2020). Despite expanding surveillance for its priority bacteria via collaborative systems with state and local health partners, the report concluded, "the precise magnitude and trend in antibiotic resistance are unknown" (GAO, 2020). A lack of a central surveillance system is part of the problem, as various divisions at the CDC are responsible for tracking different infections and diseases. In response to the 2015 action plan, the CDC has established several new networks to assess the scope of antimicrobial resistance such as the Antibiotic Resistance Laboratory Network in 2016, the Emerging Infections Program, and the Enhanced Gonococcal Isolate Surveillance Program. Nevertheless, hospital participation in the National Healthcare Safety Network was found to be low and the resistant gonorrhea surveillance system perhaps not representative of the general population (GAO, 2020). GAO also found that testing for resistance in clinical practice is often not up to date and laboratories may report only the interpretation of a test (e.g., pathogen susceptible or resistant to antimicrobial) rather than the more useful quantitative test results (GAO, 2020). The report also commented on the difficulties the CDC faces in assembling accurate data for prompt inclusion in its *Threats Reports* (GAO, 2020).

The report also commented on the challenges associated with diagnostic testing, emphasizing the need for rapid, point-of-care tests especially for resistant gonorrhea and resistant *Campylobacter* (GAO, 2020). Rapid tests to distinguish viral from bacterial infections are also urgently needed and called for in the 2015 action plan. To this end, both HHS and DOD are investing in diagnostics development (GAO, 2020). Many of HHS's efforts, via NIH and BARDA, are focused on supporting the federal biopharmaceutical accelerator program, CARB-X (officially, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) (GAO, 2020). GAO found that despite supporting important research and reducing duplicative research funding, HHS had not given sufficient attention to the managing of clinical outcomes research, something "important for encouraging the use of diagnostic tests for antibiotic resistance, among other things, because such studies can demonstrate the benefits of those tests" (GAO, 2020, p. 38). The FDA also has a role in advancing diagnostic testing. GAO commended the FDA on its efforts to recognize the Clinical and Laboratory Standards Institute's interpretive criteria for antimicrobial susceptibility testing (information that companies rely on it to bring new tests to market), a topic discussed further in Chapter 5 (GAO, 2020). The FDA has also made some gains in determining whether laboratories are using up-to-date criteria for susceptibility testing (GAO, 2020).

The GAO report commented on the dearth of antibacterial classes available to treat resistant infections, finding the current drug pipeline to be insufficient, possibly because of the cost of antimicrobial development and regulatory barriers (GAO, 2020). The relatively low cost of many antibiotics, their use for short periods of time, and the often small number of patients who require them are all disincentives for companies to invest in the field. The FDA commented on the additional challenges of conducting clinical trials, demonstrating clinical value, and gaining approval for multiple indications, all topics discussed in Chapter 6. Overall, GAO found these incentives to be inadequate. HHS did not agree, however that post-market financial rewards should be paid for the development of new antimicrobials (GAO, 2020).

The GAO report also gave some attention to antimicrobial stewardship programs. It found the Centers for Medicare & Medicaid Services (CMS), DOD, and the VA had strengthened stewardship in hospitals and nursing homes. CMS incentives for appropriate clinical use of antimicrobials were also well received, as were Agency for Healthcare Research and Quality (AHRQ) and CDC stewardship guidance documents (GAO, 2020). Based on its analysis, GAO made eight recommendations on how to improve progress against the goals and objectives of the 2015 action plan, shown in Box 7-3 (GAO, 2020).

**BOX 7-3**
**GAO Recommendations for Improving Progress on the National Action Plan**

1. CDC should determine participation rates and distribution needed in the Antibiotic Resistance Option of the National Healthcare Safety Network for conducting regional and national assessments of antibiotic resistance of public health importance.
2. CDC should ensure its evaluation of its surveillance system for antibiotic-resistant gonorrhea includes measures of its representativeness, using specially designed studies if needed.
3. CDC should provide information on uncertainties for antibiotic resistance estimates in its consolidated Threats Reports, including standard errors or confidence intervals, as appropriate.

4. CDC should plan for timely, consolidated reports of antibiotic resistance in priority pathogens at regular intervals.
5. HHS should identify leadership and clarify roles and responsibilities among HHS agencies to assess the clinical outcomes of diagnostic testing for identifying antibiotic-resistant bacteria.
6. The FDA Center for Devices and Radiological Health should conduct additional monitoring and evaluation of the status of FDA-authorized tests that rely on breakpoints, on a regular basis, to determine whether test manufacturers are updating breakpoints.
7. HHS should develop a strategic framework to further incentivize the development of new treatments for antibiotic-resistant infections, including the use of postmarket financial incentives, and make recommendations to Congress for necessary authority.
8. The CARB Task Force should include in its annual updates plans for addressing any barriers preventing full implementation of the national action plan and, as appropriate, make recommendations for new or modified actions.

SOURCE: Adapted from GAO, 2020, reprinted with permission.

## Key Findings from the GAO 2017 Report

The 2017 GAO report on the use of pharmaceuticals in animals found that since the agency's previous report in 2011 the FDA had increased veterinary oversight of antimicrobials and was engaged in promising work on label changes for veterinary antimicrobials, though these changes were not fully implemented in 2017 (GAO, 2017). The report also described joint efforts by the FDA and USDA to improve data collection on antimicrobial use and resistant infections in food-producing animals. To a similar end, the report reiterated a 2011 recommendation that HHS and USDA monitor antimicrobial use and resistance on farms, noting that neither the FDA nor the USDA's Animal and Plant Health Inspection Service "have metrics to assess the impact of actions they have taken, which is inconsistent with leading practices for performance measurement" (GAO, 2017).

The GAO report commented on a lack of a clear framework to determine when farm-level investigations of foodborne illnesses would be necessary, suggesting that the CDC, USDA, and other stakeholders coordinate to develop such guidance and identify factors that contribute to or cause foodborne illness including illnesses caused by resistant pathogens (GAO, 2017). Box 7-4 shows the recommendations from the 2017 GAO report.

**BOX 7-4**
**GAO Recommendations on the Use of Medically Important Drugs in Food Animals**

The Secretary of Health and Human Services should direct the commissioner of the FDA to take the following three actions:

- Develop a process, which may include time frames, to establish appropriate durations of use on labels of all medically important antibiotics used in food animals.
- Establish steps to increase veterinary oversight of medically important antibiotics administered in routes other than feed and water, such as injections and tablets.
- Develop performance measures and targets for actions to manage the use of antibiotics such as revising the veterinary feed directive and developing guidance documents on judicious use.

The Secretary of Agriculture should take the following three actions:

- Direct the administrator of the Animal and Plant Health Inspection Service (APHIS) to develop performance measures and targets for collecting farm-specific data on antibiotic use in food animals and antibiotic-resistant bacteria in food animals.
- Direct the administrator of APHIS and the administrator of the Food Safety Inspection Service (FSIS) to work with the director of the CDC to develop a framework for deciding when on-farm investigations are warranted during outbreaks.

SOURCE: GAO, 2017, reprinted with permission.

## FEDERAL GOVERNMENT IMPLEMENTATION OF THE 2015 NATIONAL ACTION PLAN

To better understand agencies' successes and failures in implementing the 2015 national action plan, the committee commissioned an independent analysis from CIDRAP. This analysis is available as an online supplement at https://www.nap.edu/catalog/26350.

After review of publicly available progress reports and consultation with agency staff, the CIDRAP analysis found that, according to the agencies' self-assessments, 93 percent of the 230 milestones laid out in 2015 action plan were completed successfully and on time, while 2.5 percent were partially completed, another 2.5 percent still in progress, and only 2 percent not achieved (Moore, 2021) (see Table 7-1). The committee cautions that interpretation of this seemingly exceptional success should be carefully qualified. The number of agencies involved and the number of actions assigned to them made it necessary for CIDRAP investigators to rely heavily on the agency staffs' own analysis of their progress. This is not, therefore, an impartial analysis. It is likely that a disinterested observer could reach different conclusions regarding how well agencies had implemented the 2015 action plan and, more importantly, if the work was effective at advancing the plans ultimate goals.

**TABLE 7-1** Summary of Federal Agency 2015 Action Plan Milestones and Progress Toward Achieving Them

| Agency | Total Milestones[a] | Completed | Partially Complete | In Progress | Not Achieved |
|---|---|---|---|---|---|
| HHS | 28 | 26 | — | 1 | 1 |
| BARDA | 13 | 13 | — | — | — |
| CDC | 92 | 89 | 2 | — | 3 |
| CMS | 14 | 11 | 1 | 1 | 1 |
| FDA | 56 | 54 | — | 3[b] | — |
| NIH | 34 | 34 | — | — | — |
| DOD | 32 | 30 | 1 | 1 | |
| EPA | 2 | 1 | — | — | —[c] |
| USAID | 10 | 10 | — | — | — |
| USDA | 57 | 53 | 2 | 3[b] | — |
| VA | 4 | 4 | — | — | — |

[a] Many of the milestones involved participation by more than one agency, so the total number of milestones presented in this table exceeds the 230 milestones in the 2015 action plan because of the overlap among agencies (Moore, 2021).

[b] For milestones that are in progress, the USDA and the FDA milestones overlap, so there are only three different milestones for these two agencies, giving a total of six milestones that were in progress at the time of this report (Moore, 2021).

[c] This applies to the following milestone under Goal 4, Objective 4.1: "On an annual basis: HHS, NIH, FDA, USDA, CDC, DOD, and EPA will conduct a review to ensure that U.S. government research resources are focused on high-priority antibiotic resistance issues (including basic research on the emergence and spread of resistance genes) and facilitate use of advanced technologies in research on antibiotic resistance (e.g., whole genome sequencing, proteomics, metagenomics, structural biology, bioinformatics)." The EPA had a minor role in the 2015–2020 action plan and did not have a research agenda or budget for antimicrobial resistance-related activities; therefore, no annual review was undertaken because no resources were focused on antimicrobial resistance. As a result, CIDRAP decided to classify this milestone as "not applicable" for the EPA. This milestone was completed for all of the other federal agencies listed, so this milestone was categorized as completed in the overall table SOURCE: Moore, 2021.

Table 7-2 lists selected highlights of each agency's accomplishments in this time. Readers seeking more detail should consult the CIDRAP final report in the online supplement available at https://www.nap.edu/catalog/26350.

**TABLE 7-2** Summary of Federal Agencies Progress and Challenges Implementing the *National Action Plan for Combating Antimicrobial-Resistant Bacteria 2015–2020*

| Agency | Selected Agency Accomplishments for 2015–2020 |
|---|---|
| HHS | • Assistant Secretary for Planning and Evaluation has coordinated the federal CARB Task Force<br>• Implemented Global Action Plan on Antimicrobial Resistance<br>• Released the *AHRQ Safety Program for Long-Term Care: Preventing Catheter-Associated Urinary Tract Infections and Other Hospital-Associated Infections* |
| BARDA | • Cosponsored Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X); success of CARB-X demonstrated by FDA approval of three antibiotics whose development was supported by BARDA |
| CDC | • Antibiotic Resistance Laboratory Network has expanded testing for pathogens, colonization testing, and use of whole genome sequencing<br>• CDC and FDA Antibiotic Resistance Isolate Bank<br>• New communication activities such as the "Be Antibiotics Aware" national awareness program for health care providers and public<br>• Increased support for laboratory and response capacities to health departments across the nation |
| CMS | • Published a final rule in 2016, "Medicare and Medicaid Programs: Reform of Requirements for Long-Term Care Facilities" (81 FR 68688)<br>• Finalized new regulations in 2019 that require hospitals to develop and implement antibiotic stewardship programs |
| FDA | • CDC and FDA Antibiotic Resistance Isolate Bank<br>• Developed and implemented a strategy with a voluntary approach with relation to the use of medically important pharmaceuticals in food-producing animals for growth promotion, resulting in the Veterinary Feed Directive Final Rule and follow-up activities<br>• Initiatives to streamline FDA's work such as a review of susceptibility devices to help in rapid detection of resistance, a website that helps streamline the review criteria, and guidance on coordinated development, which allows sponsors to approach the FDA early, so their devices are available when a drug is approved |
| NIH | • Launched (with BARDA) the National Database of Antibiotic-Resistant Organisms<br>• Cosponsored the Antimicrobial Resistance Diagnostic Challenge<br>• Cosponsored creation of CARB-X<br>• Expanded and strengthened the Antibiotic Resistance Leadership Group<br>• Completing several clinical trials to inform optimal use of existing antibiotics<br>• Supported the development of nontraditional therapeutics such as phage therapy, antivirulence inhibitors, monoclonal antibodies, and microbiome-based approaches |
| DOD | • Created a centralized laboratory network for early identification of emerging threats<br>• Implemented a mobile web application for clinicians on antimicrobial stewardship |

| | |
|---|---|
| | • Established Antimicrobial Stewardship Program Working Group to oversee the EpiData Center, Multidrug-Resistant Organism Repository & Surveillance Network, and the Pharmacovigilance Center |
| EPA | • Using the National Aquatic Resource Surveys program to look at antimicrobial resistance in surface water and generate national maps on antimicrobial resistance<br>• Entered formal agreement to work with National Antibiotic Resistance Monitoring System, including the formation of National Antibiotic Resistance Monitoring System environmental working group |
| USAID | • Provided support for countries to develop and implement national multisectoral antimicrobial resistance strategies or national action plans<br>• Strengthened infection prevention and control measures by development and strengthening of national infection prevention and control committees, national infection prevention and control action plans, and national infection prevention and control standards<br>• Supported Infection Prevention and Control Assessment Framework assessments at 111 facilities<br>• Supported the Clean Clinic Approach, a quality improvement strategy to strengthen water sanitation and hygiene in health facilities in partner countries<br>• Provided technical assistance, training, and commodities to strengthen laboratory capacity to detect antimicrobial resistance, including in large poultry markets<br>• Supported development of antimicrobial stewardship plans and activities that promote appropriate antibiotic use<br>• Provided support in 25 countries to strengthen the timely diagnosis and appropriate case management of severe bacterial infections<br>• Developed the Medicines Quality Database, a free, web-based internationally referenced database |
| USDA | • Conducted National Animal Health Monitoring System surveys in U.S. feedlots and swine operations in 2017<br>• Established the National Animal Health Laboratory Network<br>• Expanded antimicrobial resistance testing by including more commodities (e.g., chickens) and initiating the cecum sampling program<br>• Provided National Veterinary Accreditation Program modules for veterinarians<br>• USDA National Institute of Food and Agriculture funded research, extension, and education activities through the USDA Agriculture and Food Research Initiative Programs and Hatch Multistate projects<br>• Conducting whole genome sequencing for National Antibiotic Resistance Monitoring System and published data in National Database of Antibiotic-Resistant Organisms in near real time |
| VA | • Implemented functional stewardship programs at all VA centers<br>• All VA facilities are reporting antibiotic use data to CDC |

NOTE: AHRQ = Agency for Healthcare Research and Quality; BARDA = Biomedical Advanced Research and Development Authority; CDC = Centers for Disease Control and Prevention; CMS = Centers for Medicare & Medicaid Services; DOD = U.S. Department of Defense; EPA = U.S. Environmental Protection Agency; FDA = U.S. Food and Drug Administration; HHS = U.S. Department of Health and Human Service; NIH =

National Institutes of Health; USAID = U.S. Agency for International Development; USDA = U.S. Department of Agriculture; VA = U.S. Department of Veterans Affairs.

## Agencies' Self-Reported Key Challenges

The CIDRAP analysis, which relied heavily on agencies' self-reporting, found that few agencies had indicated substantial challenges in achieving the assigned milestones under the 2015 action plan and that the vast majority were accomplished on time (Moore, 2021). This finding was not accompanied by independent confirmation of agencies' progress, however.

The committee found the CIDRAP analysis to be helpful in summarizing the various agencies' milestones and their activities in response to the 2015 action plan and appreciates that obtaining data to measure actual progress toward the agencies' milestones would be difficult and labor intensive. Nevertheless, such data would highlight areas where more work is needed. It would also allow for better clarity as to which milestones are relatively straightforward and which ones are difficult. While the CIDRAP report provides an overview of agencies' activities in response to the 2015 action plan, its reliance on self-reporting and agency review could have introduced considerable bias into its findings. This analysis gives good insight into the scope of the work agencies took on in response to the 2015 action plan, but it is not an independent assessment of their work or achievements.

The CDC, for example, indicated that it has accomplished 89 of its 92 milestones and reported only 2 milestones as incomplete (conducting two randomized control trials to prevent the spread of multidrug-resistant tuberculosis) (Moore, 2021). The CDC was to establish up to 10 new sites to monitor drug-resistant pathogens as part of its Emerging Infections Program. The agency was not able to expand the program, however, citing limited resources, although it did increase the number of pathogens being reported by existing sites (Moore, 2021). This raises other questions, such as how and when expansion would proceed if funding were to become available, or what steps might be taken to ensure a representative cross-section of sites was chosen.

CMS participants noted that although the agency expanded requirements on antibiotic stewardship to hospitals as of 2019, it had not expanded the conditions of participation for dialysis centers, ambulatory surgery centers, and other sites. No explanation for the lack of expansion was given (Moore, 2021). Similarly, CMS efforts to monitor antimicrobial use through changes to the Inpatient Quality Reporting rules of the National Healthcare Safety Network were described as incomplete because "other issues [took] priority." but the respondents indicated that a formal rule may not be necessary if voluntary participation were good (Moore, 2021). It would be helpful to understand how the success of voluntary reporting was evaluated or what criteria might be used to determine if a reporting rule were necessary.

The DOD Chemical Biological Defense Program and the Defense Threat Reduction Agency were meant to fund a new antimicrobial to the investigational new drug stage but did not as its lead candidate failed toxicological studies (Moore, 2021).

USDA indicated that, as of spring 2021, two of its milestones were still in progress and two were partially complete. These involved implementation research on antimicrobial stewardship on farms and how the 2017 Veterinary Feed Directive changed practices. After initial surveys in 2016, a funding lapse prevented further work (Moore, 2021). The COVID-19 pandemic also prevented some monitoring of changes in antimicrobial stewardship in livestock (Moore, 2021).

USDA was also called on to provide veterinary accreditation training modules for use in low- or middle-income countries. This training would increase ability to monitor resistance and report outbreaks to the WHO and other stakeholders. USDA reported this task as partially

completed. Despite having translated training materials into Spanish, it has not had funding to translate training materials into other languages (Moore, 2021).

## *NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA, 2020–2025*

The *National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020–2025* (hereafter, the 2020 action plan) builds on the 2015–2020 action plan (FTF CARB, 2020). The 2015 action plan required federal and local departments and agencies and their partners to establish processes, especially processes for collaboration among agencies, with the private sector, and internationally, and set baseline measures. The 2020 action plan builds on the successes of the 2015 action plan and lays out a strategy for combating antibiotic resistance over the next 5 years. The goals of the 2020 action plan mirror the five goals of the 2015 action plan, but with updated targets and objectives to reflect the progress and challenges of the prior plan. Box 7-5 summarizes how the 2020 action plan will work.

**BOX 7-5**
**Building Off the Previous 5-Year Action Plan**

The *National Action Plan for Combating Antibiotic-Resistant Bacteria 2020–2025* cites ways it will build off the previous 5-year action plan, including:

- Expanding evidence-based activities that have already been shown to reduce antibiotic resistance, such as optimizing the use of antibiotics in human and animal health settings;
- Continuing to prioritize infection prevention to slow the spread of resistant infections and reduce the need for antibiotic use;
- Supporting innovative approaches to developing and deploying diagnostic tests and treatment strategies;
- Emphasizing a One Health approach that recognizes the relationships between the health of humans, animals, plants, and the environment; and
- Collecting and using data to better understand where resistance is occurring, supporting the development of new diagnostics and treatment options, and advancing international coordination.

SOURCE: PCAST, 2020, reprinted with permission.

The 2020 action plan has a greater One Health emphasis, though this does not translate, for example, into a greater role for the EPA (PCAST, 2020). The committee also notes that the relationship between climate change and antimicrobial resistance is not mentioned in the 2020 action plan, a serious concern given the potential for direct effects on water, soil, agriculture, and livestock. Climate change could also provoke migration of humans, their domestic animals, and wildlife, which will have implications for the spread of microbial pathogens (Podesta, 2019; Rojas-Downing et al., 2017; Seebacher and Post, 2015). A One Health orientation to the problem can be challenging to put into practice, but more explicit attention to the ways in which various agencies' work may be influenced by climate change could help make this One Health framework more concrete.

## Implementing the 2020 Action Plan

The 2020 action plan clearly lays out future challenges inherent to the global problem of antimicrobial resistance. Box 7-6 shows some of the challenges to reaching these goals, many informed by the experience of implementing the 2015 action plan.

**BOX 7-6**
**Challenges to Reaching the Goals in the *National Action Plan on Combating Antimicrobial-Resistant Bacteria 2020–2025***

Goal 1: Reduce the emergence of resistance

- Changing behaviors to ensure optimal infection-prevention practices and appropriate prescribing of antibiotics
- Identifying and scaling up best practices across spectrums of care, ensuring their continuity, and coordinating these practices across One Health
- Engaging all relevant stakeholders for buy-in and support of best practices

Goal 2: Strengthen testing, data collection and data sharing

- Maintaining ongoing support for laboratory staff, continuously maintaining their testing equipment, and advancing their testing methodologies
- Sharing electronic data on antibiotic use and resistance
- Developing and implementing minimum data-quality standards of measurement
- Ensuring enough resources to support isolate and data repositories
- Implementing new federal policies and processes for the secure and confidential storage and sharing of data

Goal 3: Support research, development, and adoption of rapid diagnostics

- Addressing the high cost of some components of the diagnostic tests
- Overcoming technical difficulties in preparing and obtaining clinical samples
- Identifying microbe–drug interactions
- Enhancing return on investment for new diagnostics

Goal 4: Research and development of new antibiotics, novel therapies, and vaccines

- Reducing the high rate of attrition within the antibiotic discovery pipeline
- Discovering new classes of antibiotics with activity against gram-negative bacteria
- Developing more nonantibiotic therapeutics
- Decreasing the lag time between completing and publishing the results of basic and applied research studies

Goal 5: Strengthen global collaboration

- Developing global consensus around updates to international guidance
- Supporting partner countries to better identify the emergence and spread of antibiotic resistance
- Addressing the need for substantial and well-aligned resources, including the ability to tap experts to help with the containment of resistance and to establish a well-functioning international network to detect and respond to antibiotic resistance

SOURCE: Adapted from FTF CARB, 2020.

Addressing these challenges shown in Box 7-6 requires an understanding of what outcomes will be most useful in determining success and how those outcomes will be measured. Many of the action plan's targets already have measurable outcomes for federal agencies, and each agency or department is to report progress on meeting its outcomes on an annual basis. At the same time, some targets are open ended and the agency that is responsible for meeting the target is not specified.[3] In such cases it is difficult to establish accountability for outcomes or to know which agency will and which will not support a given milestone. Other objectives may be difficult to achieve because they are vague or not amenable to evaluation, such as increasing surveillance networks capacity to control outbreaks. It is difficult to know how such progress might be measured, and if the measurements would be objective. The committee acknowledges that measurable outcomes are not necessarily useful ones. For example, a target of supporting 1,000 publications on antimicrobial resistance by 2021, though measurable and specific, is of questionable value. It is also arguably unrealistic given that 2020 national strategy was only published in 2021 (FTF CARB, 2020).

This is not to say that meaningful outcomes related to antimicrobial resistance are immeasurable. The CDC *Antibiotic Resistance Threats in the United States, 2019* report documented changes in the burden of resistant infections, including drawing attention to areas where targets had not been met (CDC, 2019). For example, although the 2015 action plan set a target of reducing methicillin-resistant *Staphylococcus aureus* 50 percent by 2020 (relative to 2011 levels), the 2019 report cited only a 21 percent reduction (CDC, 2019). The same pattern held for infections from multiresistant *Pseudomonas aeruginosa*, falling six percentage points short of the target (CDC, 2019). The report also indicated that despite progress on some pathogens, there was a 315 percent increase in the number of infections associated with erythromycin-resistant invasive group A *Streptococcus* and a 124 percent increase in drug-resistant *Neisseria gonorrhoeae* infections (CDC, 2019).

It would also be helpful to track expenditures in support of the action plan and report these annually. This process would give evidence for continued support for the program at the level of agency leadership and Congress. It could also highlight areas of effective and efficient achievement that might be replicated in other agencies.

The committee supports the systematic quantitative and qualitative tracking of activities and outcomes related to the milestones and goals presented in the 2020 action plan. Independent development and assessment of these goals would not only help the United States but also its international partners to understand the best and most effective strategies to combat antimicrobial resistance.

**Recommendation 7-1: Congress should direct the Government Accountability Office (GAO) to conduct biennial evaluations of federal agencies' progress toward meeting the goals of the 2020–2025 *National Action Plan for Combating Antibiotic-Resistant Bacteria* to ensure objective assessment of agencies' activities. Congress and the GAO should consider ways to use their evaluations to direct course corrections when necessary.**

[3] For example, for goal 3, objective 2.1, to stimulate research on the appropriate use of diagnostics and AHRQ, CDC, NIH, and DOD are to "invite research applications and support research on the appropriate use of CARB-related diagnostics in human clinical and veterinary care" (FTF CARB, 2020).

Both the 2015 and the 2020 action plans call on the U.S. government to report on progress. The federal Task Force for Combating Antibiotic-Resistant Bacteria prepared annual progress reports under the 2015 action plan. These are essentially self-reports, however. While helpful, such reports are not necessarily objective or comprehensive. As the task force explained, they are intended to provide "a narrative description of high-impact activities" (USTFCARB, 2018, p. 2). The CIDRAP analysis commissioned by this committee also provided a snapshot of agency accomplishments. But it also relied on progress reports, self-reports, and other sources reviewed by the agencies. Though informative, it is not an entirely objective status report.

As is evident from its previous work, GAO is well positioned to conduct objective independent evaluations of agencies successes and failures. These reviews might be made more manageable by focusing each biennial review on two or three goals and the activities undertaken across agencies to achieve that goal. GAO could also invite input from nongovernmental organizations, private industry, and professional societies to provide a more complete picture of progress across all organizations involved in the action plans.

Even an independent review can only look at progress against stated goals. A reliance on process outcomes (things like creating a databases, meeting with other agencies) makes it easier to claim successes. Meeting process milestones will not necessarily translate into meaningful improvements in antimicrobial use or the spread of resistant pathogens. There are many influences on the burden of resistant infections in health and inferring the casual relationship between health policy and health outcomes is difficult. Establishing causality might be an ambitious goal, but more attention to data describing the association between public policy and the burden of antimicrobial resistance would be helpful.

As part of the evaluation envisioned in this recommendation, implementing agencies could give some attention to defining outcome measures and concrete indicators of progress against the goals of the national strategy, not just the steps outlined in the action plan. This may also be a role for the President's Advisory Council on Combating Antibiotic-Resistant Bacteria. In its recommendations to the secretary of health the advisory council might be able to identify indicators that better reflect the relationships between the agencies' work and progress against antimicrobial resistance.

The committee also recognizes that agencies' priorities can change. Antimicrobial resistance is a dynamic problem, and it could be helpful to have a system in place to help agencies adjust to changes in the disease burden or to benefit from new technologies. One tool that Congress has used to facilitate course corrections on complex government programs is annual reporting on certain programs designated as high risk (GAO, 2021). Programs with a high-risk designation, such as federal oversight of food safety and medical products, have a higher visibility to Congress and to the heads of the agencies involved (GAO, 2000, 2021). This higher level of oversight can translate into greater support and resources directed to the agencies' needs. Risks to public health and safety are candidates for high-risk designation, as is the assessment of "agencies' management functions to determine how they contributed to program performance" (GAO, 2000). Both these criteria apply to the CARB program. Adding federal action against antimicrobial resistance to the GAO High Risk List might bring welcome attention to the topic. Such attention could be especially helpful in the face of uncertainty regarding how the COVID-19 pandemic will influence the emergence and prevalence of resistant pathogens (Knight et al., 2021; Rawson et al., 2020). Depending on how this relationship unfolds, it could be important to update national policies aimed at mitigating antimicrobial resistance (Rawson et al., 2020).

## REFERENCES

CDC (Centers for Disease Control and Prevention). 2019. *Antibiotic resistance threats in the United States, 2019.* Atlanta, GA: http://dx.doi.org/10.15620/cdc:82532.

FTF CARB (Federal Task Force on Combating Antibiotic-Resistant Bacteria). 2020. *National action plan for combating antibiotic-resistant bacteria 2020-2025.* Washington, DC: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation.

GAO (U.S. Government Accountability Office). 2000. *Determining performance and accountability challenges and high risks.* U.S. General Accounting Office.

GAO. 2017. More information needed to oversee use of medically important drugs in food animals. Washington, DC: U.S. Government Accountability Office.

GAO. 2020. Antibiotic resistance: Additional federal actions needed to better determine magnitude and reduce impact. Washington, DC: U.S. Government Accountability Office.

GAO. 2021. *Featured topic: High risk list* (accessed September 24, 2021).

Knight, G. M., R. E. Glover, C. F. McQuaid, I. D. Olaru, K. Gallandat, Q. J. Leclerc, N. M. Fuller, S. J. Willcocks, R. Hasan, E. van Kleef, and C. I. Chandler. 2021. Antimicrobial resistance and covid-19: Intersections and implications. *Elife* 10:e64139.

Moore, K. 2021 (unpublished). *Background analysis on progress toward meeting goals and objectives in the national action plan for combating antibiotic-resistant bacteria (2015-2020)*. Center for Infectious Disease Research and Policy, University of Minnesota.

PCAST (President's Council of Advisors on Science and Technology). 2020. *National action plan for combating antibiotic-resistant bacteria, 2020-2025.* Washington, DC: The White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

Podesta, J. 2019. *The climate crisis, migration, and refugees*. https://www.brookings.edu/research/the-climate-crisis-migration-and-refugees/ (accessed September 16, 2021).

Rawson, T. M., D. Ming, R. Ahmad, L. S. P. Moore, and A. H. Holmes. 2020. Antimicrobial use, drug-resistant infections and COVID-19. *Nature Reviews: Microbiology* 18(8):409-410.

Rojas-Downing, M. M., A. P. Nejadhashemi, T. Harrigan, and S. A. Woznicki. 2017. Climate change and livestock: Impacts, adaptation, and mitigation. *Climate Risk Management* 16:145-163.

Seebacher, F., and E. Post. 2015. Climate change impacts on animal migration. *Climate Change Responses* 2(1):5.

Shallcross, L. J., and S. C. Davies. 2014. The world health assembly resolution on antimicrobial resistance. *Journal of Antimicrobial Chemotherapy* 69(11):2883-2885.

The White House. 2014. *National strategy for combating antibiotic-resistant bacteria.* Washington DC: The White House.

The White House. 2015. *National action plan for combating antibiotic-resistant bacteria.*

USTFCARB (United States Task Force on Combating Antibiotic-Resistant Bacteria). 2017. National action plan for combating antibiotic-resistant bacteria: Progress report for years 1 and 2. Washington, DC: U.S. Department of Health and Human Services.

USTFCARB. 2018. National action plan for combating antibiotic-resistant bacteria progress report: Year 3. Washington, DC: U.S. Department of Health and Human Services.

USTFCARB. 2019. National action plan for combating antibiotic-resistant bacteria progress report: Year 4. Washington, DC: U.S. Department of Health and Human Services.

# 8

# A Role for the United States in Coordinated Global Action

The COVID-19 pandemic has reinforced how microbial pathogens can spread rapidly and without respect for national borders. The spread of resistant pathogens and resistance genes can be equally rapid but more insidious. The consequences of the spread of SARS-CoV-2 were relatively clear and direct, while resistant pathogens may move around the world undetected until they are established in a population.

The global dissemination pathways for antibiotic-resistant bacteria are well documented, and include international travelers carrying resistant bacteria on their skin, in their gut, or in their upper respiratory system (Arcilla et al., 2017; Nurjadi et al., 2015; Reuland et al., 2016; Walker et al., 2018; Worby et al., 2020). Returning travelers may also contract a resistant infection as a patient in a country where these infections are more prevalent and infection control measures inadequate (CDC, 2021; Khawaja et al., 2017). Importation of contaminated food, fish, and animals is another important dissemination pathway, as is the migration of wildlife (Arnold et al., 2016; Jung and Rubin, 2020). Once within the community and especially within a health system, resistant bacteria are difficult to control. As Chapter 3 discussed, the health and economic effects of antimicrobial resistance may extend far beyond the initial infection and its effects.

For all these reasons, a national strategy to combat antimicrobial resistance will depend on global investment and sustained international engagement integrated across human, animal, and environmental health. Part of the challenge of responding to antimicrobial resistance is that, while the U.S. strategy and action plan, like most countries' strategies and action plans, evoke a One Health grounding, putting it into practice is difficult (GCOA and IDSA, 2021). Ultimately, every implementing agency involved in the response to antimicrobial resistance has its own mandate and mission, and none of these is explicitly a One Health mission. As the previous chapter explained, the implementing agencies are to be commended on their progress in meeting the goals set in the *National Action Plan for Combating Antimicrobial Resistance, 2015–2020.* At the same time, meaningful and measurable progress against antimicrobial resistance will

hinge on cross-sectoral policies and the balancing of human, animal, and environmental health priorities. A recent assessment of 11 countries' progress against their national action plans found the environmental component of most national strategies needs more attention and that integrating private-sector involvement into the national strategy is also challenging (GCOA and IDSA, 2021). In short, the holistic management of a One Health agenda is challenging for most countries.

This challenge of coordinating a One Health response is compounded when working internationally, making global coordination essential. In surveillance, for example, an investment in improving our national system will return more if comparable effort is directed to integrating surveillance data internationally. A surveillance system that only detects and responds to resistant bacteria in the United States will be at a constant disadvantage, missing early signals of emerging resistance. An international link would provide U.S. authorities with prompt information about emerging threats, allowing them to communicate these risks to health officials throughout the United States. Early warning about such threats could help providers at hospitals, nursing homes, and other health care facilities to detect, prepare for, and control the widespread transmission of the resistant pathogens within their networks.

The integration of surveillance data from human, animal, and environmental sources will be a critical component of a global strategy against antimicrobial resistance. The largest increases in antimicrobial consumption over the past 2 decades, for both humans and livestock, have occurred in low- and middle-income countries (Klein et al., 2021; Tiseo et al., 2020). Between 2000 and 2015 these countries saw a 90 percent increase in use of antimicrobials on the World Health Organization (WHO) Watch List, including most of the highest-priority agents among the critically important antimicrobials for human medicine (Klein et al., 2021). As the Global Burden of Disease modeling shows, low- and middle-income countries bear the highest burden of resistant infections; deaths rates from resistant infections were highest in sub-Saharan Africa (AMR Collaborators).

Low- and middle-income countries frequently have a high burden of human infectious diseases and a growing demand for animal-source foods (IHME, 2021; Our World in Data, 2021; Tarawali, 2018). These needs can contribute to inappropriate antimicrobial use, especially when linked with poor health systems, inadequate infection prevention programs, weakly regulated access to antimicrobials, and minimal laboratory diagnostic capacity. For the rest of this century, human population growth will be concentrated in low-income countries, mostly in tropical or subtropical latitudes—sub-Saharan Africa's population is projected to double in the next 30 years and reach over 3 billion by 2100 (Vollset et al., 2020). This population trend will likely drive increased antimicrobial use in humans, animals, and crops.

The need for coordinated action against antimicrobial resistance is urgent and growing. An international investment in this problem is both morally compelling and in the best interest of the United States. As the COVID-19 pandemic has illustrated, infectious pathogens have no regard for national borders. COVID-19 has drawn attention to the ways in which the United States can use its technical depth in science and medicine for global public benefit. The National Institutes of Health (NIH) Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership discussed in Chapter 6, for example, brought together multiple government agencies, the European Medicines Agency, and various representatives from academia, industry, and philanthropy to hasten the development of novel medical products (NIH, 2021).

A national response to antimicrobial resistance proportionate to the size and scope of the threat would work across government agencies and in collaborative, bilateral and multilateral

relationships internationally. A program modelled on the President's Emergency Plan for AIDS Relief (PEPFAR) may be best suited to this problem.

Since its founding in 2003 PEPFAR has invested over $85 billion in the fight against the HIV epidemic, saving over 20 million lives in 50 countries and contributing to a 39 percent reduction in AIDS deaths since 2010 (UNAIDS, 2020; U.S. Department of State, 2021). Key to this success was the coordinated work of multiple government agencies, including those that are also essential to combat the threat of antimicrobial resistance.

An antimicrobial-resistance program modelled off PEPFAR would expand the global engagement of U.S. agencies. Key to this engagement would be the strengthening of international surveillance for resistant pathogens through increased support for both national and multilateral surveillance systems, such as the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) described in Chapter 4, and the coordinated efforts of the tripartite program on antimicrobial resistance of the WHO, the Food and Agriculture Organization of the United Nations (FAO), and World Organisation for Animal Health (known by the historical acronym OIE). Such support would allow for a better understanding of the true burden of resistant infections, allowing for better targeted response strategies, and provide critical, early warning information about emerging resistant threats. A PEPFAR-like program would also allow U.S. agencies to mitigate the need for antibiotics by improving infection prevention and antimicrobial stewardship in both human and animal health in low- and middle-income countries. Lastly, it would provide sustained leadership and accountability in the form of a Global Coordinator for Antimicrobial Resistance modeled on the Global AIDS Coordinator. The global coordinator would help ensure accountability. This person could also require rigorous program evaluations, setting up a cycle of increasingly more effective and better targeted interventions.

**Recommendation 8-1: Congress should expand the United States global engagement on antimicrobial resistance by (1) strengthening surveillance of resistant pathogens both by supporting existing, multilateral surveillance systems and by expanding U.S. agencies' international surveillance programs; (2) reducing need for antimicrobials by broadening agencies' work on infection prevention and antimicrobial stewardship in humans and animals; and (3) ensuring sustained leadership and critical evaluation by creating a Global Coordinator for Antimicrobial Resistance similar to the Global AIDS Coordinator.**

The urgent threat of antimicrobial resistance requires a sustained global response from the United States. The committee does not envision this program would replace U.S. support for various international efforts such as the Tripartite Program. Rather, the proposed program would work in collaboration with existing networks and build off existing bilateral relationships in order to better coordinate global and national efforts. For example, the Centers for Disease Control and Prevention (CDC) already works in over 60 countries in bilateral partnerships with ministries of health and other host country organizations (CDC, 2017). USAID works in over 100 countries; the agency's strategic plan emphasizes the prevention of outbreaks and infectious diseases (USAID, 2021c; USAID and Department of State, 2018).

The main novel contributions of the proposed program are the emphasis on supporting countries' surveillance capabilities and the global surveillance effort for antimicrobial resistance;

the efforts made to reduce the need for antimicrobials in low- and middle-income countries; and the creation of the global coordinator. By implementing these programs the United States could expand its leadership in combating antimicrobial resistance around the world.

## STRENGTHENING SURVEILLANCE

Since its start in 2015, the WHO GLASS program has enrolled 109 countries (WHO, 2020). GLASS provides a global system for collecting national data on antimicrobial use and resistance and a snapshot of each country's microbial surveillance systems. The Emerging Antimicrobial Resistance Reporting tool is an important component of GLASS, as it provides WHO with early notification about new resistance patterns (WHO, 2021c). The system provides a critical service in low- and middle-income countries, where the burden of infectious disease and antimicrobial use can create hot spots for the emergence and spread of resistant pathogens.

GLASS also coordinates with regional networks, including the Central Asian and European Surveillance of Antimicrobial Resistance, the European Antimicrobial Resistance Surveillance Network, the Latin American Network for Antimicrobial Resistance Surveillance, and the U.K. Fleming Fund, which helps low- and middle- income countries fight antimicrobial resistance by improving surveillance (WHO, 2017). These data sources are skewed, however, toward higher-income countries (WHO, 2020). In 2019, less than 15 percent of low- and middle-income countries reported any antimicrobial resistance information to these networks, and most of what was reported was from selected hospital and clinical laboratories (WHO, 2020). These samples are not representative of national burdens of resistant pathogens, as data may be based on bacterial isolates from only a few surveillance sites (Schnall et al., 2019; WHO, 2020). Since a surveillance system is only as good as the information that is entered into it, the lack of nationally representative, high-quality data on antimicrobial use and resistance limits the WHO's and member countries' ability to conduct risk assessments or to use these data to monitor resistant threats.

Since 2015 the WHO has expanded GLASS' scope to include information on antimicrobial use, health care-associated infections, and resistant pathogens in food (WHO, 2021c). It has also developed a capacity building component that includes technical support and laboratory strengthening (WHO, 2021c). The sustained effort from the WHO has also drawn attention to the need for antimicrobial surveillance and helped ministries in low- and middle-income countries build better integrated surveillance systems from the start (Charitonos et al., 2019; The Fleming Fund, 2016). GLASS also provides implementation guidance specifically tailored to meet the challenges encountered in low- and middle-income countries, such as lack of a national action plan on antimicrobial resistance, the need for an accredited, coordination laboratory at a sentinel surveillance site, and the need for training clinical, laboratory, information technology and public health personnel about antimicrobial resistance (Seale et al., 2017).

The GLASS program has also made efforts to measure antimicrobial consumption in certain countries (WHO, 2021d). Surveys can be useful to measure antimicrobial consumption, especially in structured settings such as hospitals (Versporten et al., 2018). Measuring consumption in animals, and even in outpatient human medicine, can be more complicated. Sales data, still widely used as a proxy for use in animals, are almost impossible to interpret (FDA, 2020). Proposed measures of use include veterinary antimicrobial sales, as well as total consumption expressed per 1,000 people per day, and consumption ratios of broad- to narrow-

spectrum antimicrobials (ECDC et al., 2017). All these measures have biases, and it is not clear which are best suited to facilitate comparisons between settings and over time.

### One Health Surveillance

In 2018 GLASS piloted a program for surveillance of extended-spectrum beta-lactamase *Escherichia coli* in human samples, poultry, water (specifically sewage), market runoff, and urban rivers in nine countries (WHO, 2021b). Such efforts are indicative of a long-term One Health vision for the program. But for the most part, GLASS's target population for routine surveillance is patients on whom clinical samples were drawn at health facilities (WHO, 2021a). This choice is understandable, and the narrow focus may help country surveillance experts and the WHO support staff keep the scope manageable and quality good. One useful role the United States could play would be in building off the GLASS framework to give more attention to animal and environmental sentinel surveillance.

This One Health attention would not necessarily need to be built from scratch. The FAO also supports countries in developing surveillance for resistant pathogens in food and agriculture. It provides guidelines on data management, susceptibility testing tools for aquaculture, and supports reference centers in eight countries to build tools and knowledge about antimicrobial surveillance in food and food-producing animals (FAO, 2016, 2019, 2021a,b,c; Smith, 2019). The WHO and FAO Codex Alimentarius Commission also supports the monitoring of resistant pathogens in food and agriculture (FAO, 2016). The U.S. effort would do well to work with these and other networks to integrate data from a range of sources. In veterinary surveillance in particular the efforts being made in low- and middle-income countries are often still in early stages. Deliberate attention from the United States could be a catalytic investment in moving animal and environmental surveillance forward.

To start, U.S. efforts could aim to integrate more and different types of surveillance information, as described in Chapter 4, to give a better picture of the burden of resistance across human, animal, and environmental health. Coordinating for data standardization and automated capture, for example, would reduce the reporting burden on hospitals, clinics, and public health laboratories, something that would be disproportionately valuable in parts of the world with shortages of health workers and infrastructure. Similarly, an effort to automate surveillance would mean faster turnaround on information, something valuable in low- and middle-income countries, where the opportunity costs of wasting time or resources are high and good data to guide antimicrobial stewardship activities are scarce.

Attention to surveillance would complement U.S. government agencies' existing programming. For example, the CDC is a national lead agency on the Global Health Security Agenda, an effort to strengthen the prevention, detection, and response to infectious threats (CDC, 2021). The CDC also leads the national Antibiotic Resistance Solutions Initiative, a program that improves capacity for surveillance, response, and containment of resistant pathogens in the United States (CDC, 2020f; PCAST, 2020). As part of the Global Health Security Agenda, USAID has worked with OIE and FAO on surveillance of zoonotic disease and on strengthening of veterinary laboratories, albeit on a relatively small scale (USAID, 2019a). The Department of Defense, through the Defense Threat Reduction Agency, has supported increased laboratory capacity for detecting specific zoonotic pathogens that pose a clear risk to human health (DARPA, 2019). The committee commends these efforts and encourages agencies to build off the knowledge gained from these programs to improve information flow between

these systems and human health surveillance networks and to work towards transferable strategies for use in low- and middle-income countries.

One useful strategy to build surveillance capacity is the network of networks approach (Novossiolova et al., 2020). In both agriculture and human medicine, there are so many diverse systems for collecting animal health information, many of them managed by industry, that working across networks is always desirable (Ashley et al., 2018; Lees and Prince, 2017). The network of networks approach has an advantage of redundancy; a signal missed in local or provincial-level surveillance may be picked up at the national level (Ashley et al., 2018; Lees and Prince, 2017). It can also integrate data from different types of surveillance systems. For example, The CDC works through its Antibiotic Resistance Laboratory Network and other networks such as PulseNet, which monitors foodborne outbreaks, to detect and respond to resistant pathogens (CDC, 2019; PCAST, 2020). This approach would be invaluable in low- and middle-income countries where there are often surveillance networks not a part of the WHO GLASS system (Africa CDC, 2018; Gandra et al., 2020).

In working against a complex health threat, most countries and organizations will understandably want to channel their efforts into direct health programs, likely programs for human health. This instinct is understandable; politicians and health experts already have ideas about what their communities need and how to use their resources. At the same time, any programming or policy intended to combat antimicrobial resistance depends on a foundation of information that surveillance networks supply. Without this information it will be almost impossible to know if programs are having their intended effect or if resources are being allocated wisely. Yet a recent analysis of 11 countries' ability to meet their commitments to combating antimicrobial resistance found that so far the problem has failed to inspire political action, especially evident in government allocations for surveillance, stewardship, and environmental management (GCOA and IDSA, 2021). The report described the environmental programming as "vastly underfunded, preventing the full integration of a One Health approach across sectors" (GCOA and IDSA, 2021). This may be the foundational problem complicating the global response to antimicrobial resistance. Leadership from the U.S. government on developing surveillance would have meaningful ramifications across the world.

## REDUCING NEED

The emergence and spread of antimicrobial-resistant bacteria are the inevitable consequence of antimicrobial use. Mitigating this problem requires attention to antimicrobial use especially in global hotspots. A higher burden of infectious disease and problems with infection control in health care contribute to the greater need for antibiotics in low- and middle-income countries. There is also a problem of inappropriate antimicrobial use, often a consequence of limited access to medicines and to quality health services (Das and Horton, 2016).

### Controlling Infection

One path to reduce the need for antimicrobials is to attack the root problems such as crowding, contaminated water and food, lack of sanitation, and inadequate infection prevention measures (Holmes et al., 2016). Improving wastewater management and sanitation in low- and middle-income countries may be the most important step to controlling antimicrobial resistance globally (GCOA and IDSA, 2021). This is an area where USAID has considerable experience

and relatively consistent involvement across administrations. The agency's water and sanitation programs operated in 51 countries, providing safe drinking water for over 53 million people between 2008 and 2019 (USAID, 2020, 2021b). One role the suggested program could take on might be expanding on USAID water and sanitation programs, as well as those implemented by foundations and nongovernmental organizations, to measure the effects of improving the water and sanitation infrastructure on the burden of infectious disease and antimicrobial use. Structured appropriately, analysis should be able to identify what components of the program drove the decrease, leading to better understanding of the relationship between hygiene, antimicrobial use, and the development of resistance.

The CDC also has a global water, sanitation, and hygiene portfolio, including a program that aims to improve sanitation in hospitals and clinics in eight partner countries (CDC, 2020b,d,e). As Chapters 2 and 5 discussed, hospital-acquired infections are dangerous; they can spread rapidly among a vulnerable, often immunocompromised, population. Figure 8-1 shows estimates of the sanitation conditions in health facilities (including hospitals, clinics, and dispensaries) across 78 low- and middle-income countries. The serious problems with piped water, infrastructure for handwashing and toilets, and unsafe waste disposal are all risk factors for the development and spread of antimicrobial-resistant infections. The CDC's programs emphasize observation and analysis of the conditions in the health center, evaluations, and in-depth interviews with administrators and staff (CDC, 2020a). Sometimes the programs introduce tools for hand hygiene or new latrines (CDC, 2020c). These efforts, much like the agency's global program in health care infection prevention have the potential to control the emergence and spread of resistant pathogens. Such work would be an excellent target for expansion and scaling up in partner countries.


**FIGURE 8-1** Environmental conditions in health facilities in 78 low- and middle-income countries. SOURCES: CDC, 2020e; Cronk and Bartram, 2018.

In low- and middle-income countries, the need for infection prevention is paramount but often difficult to put into practice. Problems with a reliable supply chain for disinfectants, personal protective equipment, and other consumables are common problems (Vilar-Compte et al., 2017). There is also evidence that lack of staff training on infection control and a shortage of infection control experts is at the root of the problem, as are general crowding and problems disposing of biomedical waste (Manchanda et al., 2018). Both the CDC and USAID have considerable experience in these areas. Expanding programming would serve the dual goals of protecting local communities and mitigating emergence and global spread of resistant pathogens.

The problem of unstable supply chains applies to medicines as well. Frequent stock outs and poor demand forecasting, combined with a background problem of substandard medicine

quality, all contribute to the emergence of resistance (Pisa and McCurdy, 2019). The supply of veterinary antimicrobials may be even less reliable, with some evidence indicating that informal, unregulated channels account for the vast majority of veterinary antimicrobials in some countries (Poupaud et al., 2021). This is an area where USAID has some experience that could be expanded upon in implementing this recommendation (USAID, 2019b).

*Medical Tourism*

As with investment in surveillance, an investment in infection control would benefit the United States. Not only do health care–acquired infections contribute to the global burden of antimicrobial resistance, they have a more direct effect on the United States when its residents travel overseas for health care. It is difficult to know the volume of the market for medical tourism. Estimates of the number of patients travelling for health care range from 4 to 16 million, with roughly a million of them originating in the United States (Chen and Wilson, 2013; Dalen and Alpert, 2019). Of the top 10 destinations for medical tourism, six are middle-income countries (Costa Rica, India, Malaysia, Mexico, Thailand, and Turkey) (Dalen and Alpert, 2019). The care sought there can be weight loss, fertility, or cardiac treatments; surgeries are also common including transplantation, cosmetic surgery, and dentistry (Dalen and Alpert, 2019). Before COVID-19, this practice was predicted to be increasing, and it may return as the pandemic fades (Chen and Wilson, 2013; Dalen and Alpert, 2019).

Medical tourists are at high risk of acquiring a resistant infection (Chen and Wilson, 2013). Once home, these patients can be the source of drug-resistant outbreaks in their home countries (Bokhary et al., 2021). In 2018 the CDC identified an outbreak of carbapenem-resistant *Pseudomonas aeruginosa* among patients who had travelled to Mexico for bariatric surgery (Baum, 2019). The previous year, the CDC reported on an outbreak of nontuberculous mycobacteria surgical site infections among 52 patients in nine states, all of whom had undergone cosmetic surgery in the Dominican Republic (Gaines et al., 2018). These pathogens can then spread in U.S. hospitals and clinics, increasing the risk to other patients in the system. And while medical tourists are a special category of high-risk traveler, ordinary travelers frequently become colonized with drug-resistant pathogens, commonly resistant enteric bacteria, and may carry them a month or longer (Arcilla et al., 2017; Bokhary et al., 2021). Travelers may carry home bacteria that mirror the microbiological milieu of the place visited. A recent well-publicized case of a young volunteer in India who needed an emergency amputation and contracted multiple drug-resistant bacteria (including, but not limited to, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Morganella morganii*, and *Enterococcus*) are reminders of the vulnerability of the health system to imported resistant pathogens (IDSA, 2021; PBS, 2013).

## Stewardship and Research

Antimicrobial stewardship also faces unique challenges in low- and middle-income countries (Galindo-Fraga et al., 2018). In an effort to support countries in their health security programs, the WHO provides a voluntary external evaluation of countries' capabilities to comply with the International Health Regulations and respond to a variety of health threats, including antimicrobial resistance (WHO, 2021e). A recent analysis of these evaluations in sub-Saharan Africa found that countries' antimicrobial stewardship was the weakest link in overall response plans for antimicrobial resistance (Elton et al., 2020). It follows that attention to national stewardship guidelines, which most countries in the region still need to create and implement,

would produce major benefits in terms of controlling resistance (Elton et al., 2020). Antimicrobial stewardship is an area U.S. government agencies, especially the CDC and the NIH, have expertise: broadly across humans and animals and narrowly in hospitals.

Stewardship is also an area where government agencies could build on existing efforts. The WHO, for example, has a toolkit to guide the implementation of antimicrobial stewardship programs in low- and middle-income countries (WHO, 2019). Some research indicates that a lack of funding and staff can be serious barriers to implementing this toolkit, however (Maki et al., 2020). This is an area where U.S. government assistance modelled on the PEPFAR program could be helpful. Attention to the health workforce in partner countries was central to the PEPFAR strategy (USAID, 2021a). PEPFAR gives considerable attention to monitoring health workers, how they are deployed, and their capacity, central to routine monitoring and program management (USAID, 2021a). This kind of information would be useful in considering how to use staff most effectively in antimicrobial stewardship programs. More distal influences on antimicrobial stewardship, including management of the medicines supply chain, the capacity of microbiology laboratories, and the education of the health workforce, would also be key work areas for the proposed program.

Other barriers to implementing antimicrobial stewardship in low- and middle-income countries include a lack of microbiology laboratory capacity, patient expectations, and the need to provide "just in case" treatment for patients in rural or remote areas (Maki et al., 2020; Mathew et al., 2020). The best steps to address these barriers will vary by setting, though an emphasis on building laboratory capacity and tools to develop better, more reliable antibiograms may be common across many settings (Mathew et al., 2020; Nicholson et al., 2018). By working in partnership with host country governments, U.S. experts could be part of an iterative process to tailor stewardship programs to the local context (see Figure 8-2). Such international partnerships may also be good tools to drive more political will for designing stewardship programs suitable to the challenges and context in low- and middle-income countries (Mathew et al., 2020).

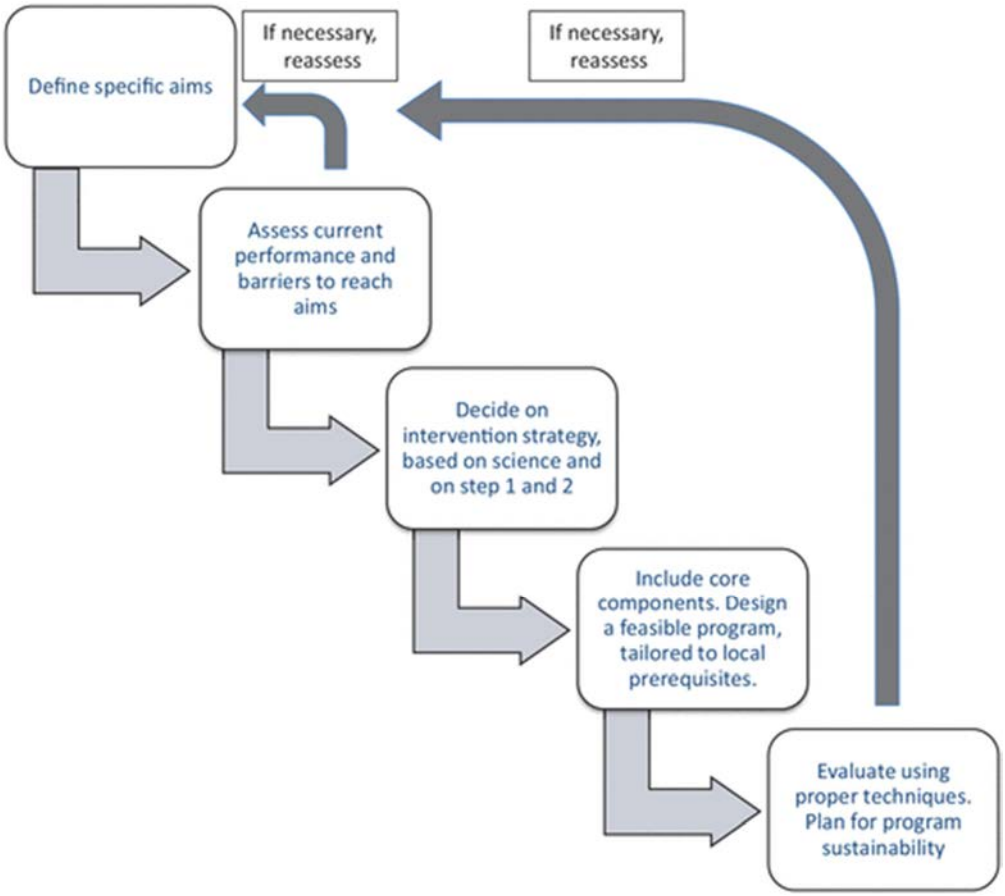



**FIGURE 8-2** The iterative steps of antimicrobial stewardship design.
SOURCE: Resman, 2020.

Respiratory and gastrointestinal infections lead to considerable antibacterial use even when the causative pathogen is viral. As Chapters 5 and 6 discussed, widespread vaccination could reduce the need for antimicrobials in both human and animal health, but the evidence for such an effect is limited and based largely on data from Europe and North America. The strategy described in Chapter 5 to improve our understanding of vaccination's effect on mitigating antimicrobial resistance in humans could be equally valuable in studying animal vaccination. Chapter 6 describes a strategy to help bring more animal health products to market, and attention to the ability of such products to reduce antimicrobial use as indicators of resistance would be important to measure in the rollout of these products. Respiratory and gastrointestinal disease drive both prophylactic and therapeutic antimicrobial use in terrestrial animals. Additional research on the downstream value and cost-effectiveness of vaccines and preventive products for use in animals could help drive a cycle of investment, development, and use of these products.

## ENSURING SUSTAINED LEADERSHIP

The ambitious, global program envisioned in this recommendation represents a significant investment from the U.S. taxpayer. Given the scope of this investment and the need for coordination with an increasingly large groups of stakeholders both in the United States and

abroad, there is a need for a designated national leader on the antimicrobial-resistance effort. This role would be modelled off the Global AIDS Coordinator, with the same responsibility for monitoring and oversight of international response (FBS, 2018).

PEPFAR's Global AIDS Coordinator oversees all the U.S. government's international work on combating HIV and AIDS, helping ensure efficiency and avoiding any duplication of effort. PEPFAR's success is in some ways attributable to this level of oversight, and the committee sees value in replicating this feature of PEPFAR to the efforts on antimicrobial resistance, creating a global antimicrobial-resistance coordinator. This person's responsibilities could include monitoring progress in reducing antimicrobial use and emerging resistance in the United States, as well as overseeing the government's activities in low- and middle-income countries. For example, the global coordinator envisioned in this recommendation would remain abreast of the work of the public–private partnership described in Recommendation 6-4. At the same time, the Department of Health and Human Services' (HHS's) Office of Global Affairs might provide continuous technical input to support the coordinator's efforts.

As is evident from this report, addressing the global threat of antimicrobial resistance and its direct effects on the U.S. health care system is complex, engaging multiple U.S. government agencies, various international organizations in human and animal health, national health systems, pharmaceutical and food production industries, and philanthropic partners (e.g., Wellcome Trust). Combating and controlling resistant pathogens requires ongoing action in a range of sectors, including hospital, laboratories, infrastructure (e.g., WASH), and animal, fisheries, and environmental management. These actions range from providing incentives for antibiotic discovery to changing health care practices or regulatory frameworks.

Coordinating the response to the threat of antimicrobial resistance is challenging, both within the U.S. government and with international partners such as WHO, OIE, and FAO, and in international economic forums such as the G20, the G7, and the Organisation for Economic Co-operation and Development. HHS's Office of Global Affairs has the main coordinating responsibility for these tasks. This role extends beyond technical coordination and includes multinational and intergovernmental commitments. *The National Action Plan for Combating Antibiotic-Resistant Bacteria, 2020–2025* also calls on other U.S. government departments, including the Department of State and the Department of Defense to engage with multinational organizations to provide financial and technical expertise on antimicrobial resistance (FTF CARB, 2020). However, the committee notes that although many departments are involved in global antimicrobial-resistance efforts, there is no mandate for coordination across all of the involved organizations (although there is some coordination and collaboration called for among a few agencies).

A recent review of 11 countries' response to antimicrobial resistance found that antimicrobial resistance is a low priority across most of the countries analyzed (GCOA and IDSA, 2021). By designating a Global Antimicrobial Resistance Coordinator similar to the Global AIDS Coordinator, the U.S. government could demonstrate national commitment to the problem and help build it in partner counties. The global coordinator could also work to mobilize interest of other key funding organizations, as the Global AIDS Coordinator has done in the past (Das, 2007). The interdisciplinary One Health nature of response to antimicrobial resistance makes accountability for results more important. Given the number and diversity of stakeholders in this field, there is considerable potential for duplication of effort or failure to build off of parallel and complementary work.

The committee recognizes that antimicrobial resistance is in some ways a more complicated problem than HIV as it is not the result of any one pathogen or type of exposure. But some of the lessons learned from preventing and treating HIV are applicable to other global health crises including antimicrobial resistance. Because of PEPFAR, there are processes in place for working with multiple government partners, intergovernmental agencies, the pharmaceutical industry, and various private philanthropic organizations. One common criticism of PEPFAR and other disease-specific programs is that they create distortions in health delivery and in the workforce where services of good quality are provided only to some, HIV-positive people for example, because of the vast donor infrastructure and spending to support the program for one disease (Biesma et al., 2009; Tangcharoensathien and Patcharanarumol, 2010). A global program for antimicrobial resistance might be able to build off the lessons learned from other global health initiatives and avoid this pitfall (Atun et al., 2008; Biesma et al., 2009).
Through its very nature, response to antimicrobial resistance involves action across different parts of the human, animal, and environmental health systems. Channeling resources wisely into such a varied response is, the committee recognizes, daunting. But by supporting a truly systemic, One Health response, this program may be able to drive meaningful progress on a range of health indicators. An investment in microbiology laboratory capacity, for example, could reverberate across the health system. Attention to animal health could improve livelihoods and food security. Across these sectors, the global coordinator would work as a champion, building support for antimicrobial resistance with international organizations and with counterpart programs abroad.

## REFERENCES

Africa CDC (Centres for Disease Control and Prevention). 2018. Africa CDC framework for antimicrobial resistance, 2018-2023: Africa Centres for Disease Control and Prevention.

AMR Collaborators (unpublished). *Global burden of bacterial antimicrobial resistance in 2019*. Lancet. In review.

Arcilla, M. S., J. M. van Hattem, M. R. Haverkate, M. C. J. Bootsma, P. J. J. van Genderen, A. Goorhuis, M. P. Grobusch, A. M. O. Lashof, N. Molhoek, C. Schultsz, E. E. Stobberingh, H. A. Verbrugh, M. D. de Jong, D. C. Melles, and J. Penders. 2017. Import and spread of extended-spectrum beta-lactamase-producing enterobacteriaceae by international travellers (combat study): A prospective, multicentre cohort study. *Lancet Infectious Diseases* 17(1):78-85.

Arnold, K. E., N. J. Williams, and M. Bennett. 2016. “Disperse abroad in the land”: The role of wildlife in the dissemination of antimicrobial resistance. *Biology Letters* 12(8).

Ashley, E. A., J. Recht, A. Chua, D. Dance, M. Dhorda, N. V. Thomas, N. Ranganathan, P. Turner, P. J. Guerin, N. J. White, and N. P. Day. 2018. An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000. *Journal of Antimicrobial Chemotherapy* 73(7):1737-1749.

Atun, R. A., S. Bennett, A. Duran. 2008. When do vertical (stand-alone) programmes have a place in health systems? *World Health Organization*.

Baum, S. G. 2019. Carbapenem-resistant p. Aeruginosa from medical tourism. *NEJM Journal Watch*.

Biesma, R. G., R. Brugha, A. Harmer, A. Walsh, N. Spicer, and G. Walt. 2009. The effects of global health initiatives on country health systems: A review of the evidence from HIV/AIDS control. *Health Policy and Planning* 24(4):239-252.

Bokhary, H., K. N. A. Pangesti, H. Rashid, M. Abd El Ghany, and G. A. Hill-Cawthorne. 2021. Travel-related antimicrobial resistance: A systematic review. *Tropical Medicine and Infectious Disease* 6(1):11.

CDC (Centers for Disease Control and Prevention). 2017. *CDC works worldwide 24/7 to protect the U.S. From disease threats*. https://www.cdc.gov/globalhealth/what/default.htm (accessed July 16, 2021).

CDC. 2019. *About pulsenet*. https://www.cdc.gov/pulsenet/about/index.html (accessed July 22, 2021).

CDC. 2020a. *Global water, sanitation, & hygeine (WASH): Data collection tools and communication*. https://www.cdc.gov/healthywater/global/healthcare-facilities/tools.html (accessed July 19, 2021).

CDC. 2020b. *Global water, sanitation, & hygiene (WASH)*. https://www.cdc.gov/healthywater/global/index.html (accessed July 19, 2021).

CDC. 2020c. *Global water, sanitation, & hygiene (WASH)*. https://www.cdc.gov/healthywater/global/healthcare-facilities/innovations.html (accessed July 19, 2021).

CDC. 2020d. *Global water, sanitation, & hygiene (WASH): Where we work*. https://www.cdc.gov/healthywater/global/healthcare-facilities/locations.html (accessed July 19, 2021).

CDC. 2020e. *WASH in healthcare facilities*. https://www.cdc.gov/healthywater/global/healthcare-facilities/overview.html (accessed July 16, 2021).

CDC. 2020f. *What CDC is doing: AR solutions initiative*. https://www.cdc.gov/drugresistance/solutions-initiative/ (accessed June 16, 2021).

CDC. 2021. *CDC and the global health security agenda*. https://www.cdc.gov/globalhealth/security/index.htm (accessed July 16, 2021).

Charitonos, K., A. Littlejohn, H. Kaatrakoski, A. Fox, V. Chaudhari, T. Seal, and N. Tegama. 2019. Technology-supported capacity building on AMR surveillance: Findings from the pilot phase: The Open University.

Chen, L. H., and M. E. Wilson. 2013. The globalization of healthcare: Implications of medical tourism for the infectious disease clinician. *Clinical Infectious Diseases* 57(12):1752-1759.

Cronk, R., and J. Bartram. 2018. Environmental conditions in health care facilities in low- and middle-income countries: Coverage and inequalities. *International Journal of Hygiene and Environmental Health* 221(3):409-422.

Dalen, J. E., and J. S. Alpert. 2019. Medical tourists: Incoming and outgoing. *American Journal of Medicine* 132(1):9-10.

DARPA (Defense Advanced Research Projects Agency). 2019. *A new layer of medical preparedness to combat emerging infectious disease*. https://www.darpa.mil/news-events/2019-02-19 (accessed July 16, 2021).

Das, P. 2007. Mark dybul: US global aids coordinator in charge of PEPFAR. *Lancet* 369(9568):1161.

Das, P., and R. Horton. 2016. Antibiotics: Achieving the balance between access and excess. *The Lancet* 387(10014):102-104.

ECDC (European Centre for Disease Prevention and Control), EFSA BIOHAZPanel (European Food Safety Authority Panel on Biological Hazards), and CVMP (EMA Committee for Medicinal Products for Veterinary Use). 2017. ECDC, EFSA and EMA Joint Scientific Opinion on a list of outcome indicators as regards surveillance of antimicrobial resistance and antimicrobial consumption inhumans and food-producing animals. EFSA Journal 15(10):5017.

Elton, L., M. J. Thomason, J. Tembo, T. P. Velavan, S. R. Pallerla, L. B. Arruda, F. Vairo, C. Montaldo, F. Ntoumi, M. M. Abdel Hamid, N. Haider, R. Kock, G. Ippolito, A. Zumla, T. D. McHugh, and the PANDORA-ID-NET Consortium. 2020. Antimicrobial resistance preparedness in sub-Saharan African countries. *Antimicrobial Resistance & Infection Control* 9(1):145.

FAO (Food and Agriculture Organization of the United Nations). 2016. *FAO and WHO activities to support monitoring and surveillance of antimicrobial resistance in the food and agriculture sectors*. http://www.fao.org/fao-who-codexalimentarius/news-and-events/news-details/en/c/1381093/. (accessed July 16, 2021).

FAO. 2019. Monitoring and surveillance of antimicrobial resistance in bacteria from healthy food animals intended for consumption. In *Regional Antimicrobial Resistance Monitoring and Surveillance Guidelines*. Bangkok, Thailand: FAO.

FAO. 2021a. *Antimicrobial resistance: FAO reference centres for antimicrobial resistance*. http://www.fao.org/antimicrobial-resistance/resources/reference-centres/en/ (accessed July 16, 2021).

FAO. 2021b. *Antimicrobial resistance: Surveillance and monitoring*. http://www.fao.org/antimicrobial-resistance/key-sectors/surveillance-and-monitoring/en/ (accessed July 16, 2021).

FAO. 2021c. *FAO reference centres for antimicrobial resistance*. https://www.fao.org/antimicrobial-resistance/resources/reference-centres/en/ (accessed October 11, 2021).

FBS (Functional Bureau Strategy). 2018. Office of the U.S. Global aids coordinator and health diplomacy (S/GAC).

FDA (U.S. Food and Drug Administration). 2020. *FDA releases annual summary report on antimicrobials sold or distributed in 2019 for use in food-producing animals*. https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2019-use-food-producing (accessed May 4, 2021).

FTF CARB (Federal Task Force for Combating Antibiotic-Resistant Bacteria). 2020. *National action plan for combating antibiotic-resistant bacteria 2020-2025.* Washington, DC: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation.

Gaines, J., J. Poy, K. A. Musser, I. Benowitz, V. Leung, B. Carothers, J. Kauerauf, N. Mollon, M. Duwell, K. Henschel, A. De Jesus, S. K. Head, K. Lee, N. Arboleda, and D. H. Esposito. 2018. Notes from the field: Nontuberculous mycobacteria infections in U.S. medical tourists associated with plastic surgery - Dominican Republic, 2017. *Morbidity and Mortality Weekly Report* 67(12):369-370.

Galindo-Fraga, A., M. Villanueva-Reza, and E. Ochoa-Hein. 2018. Current challenges in antibiotic stewardship in low- and middle-income countries. *Current Treatment Options in Infectious Diseases* 10(3):421-429.

Gandra, S., G. Alvarez-Uria, P. Turner, J. Joshi, D. Limmathurotsakul, and H. R. van Doorn. 2020. Antimicrobial resistance surveillance in low- and middle-income countries: Progress and challenges in eight south Asian and southeast Asian countries. *Clinical Microbiology Reviews* 33(3):e00048-00019.

GCOA and IDSA (Global Coalition on Aging and Infectious Diseases Society of America). 2021. 2021 AMR Preparedness Index.

Holmes, A. H., L. S. Moore, A. Sundsfjord, M. Steinbakk, S. Regmi, A. Karkey, P. J. Guerin, and L. J. Piddock. 2016. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 387(10014):176-187.

IDSA (Infectious Diseases Society of America). 2021. *Patient stories: David Ricci*. https://www.idsociety.org/public-health/patient-stories/david-ricci/ (accessed July 19, 2021).

IHME (Institute for Health Metrics and Evaluation). 2021. *Communicable, maternal, neonatal, and nutritional diseases—level 1 cause*. http://www.healthdata.org/results/gbd_summaries/2019/communicable-maternal-neonatal-and-nutritional-diseases-level-1-cause (accessed July 20, 2021).

Jung, D., and J. E. Rubin. 2020. Identification of antimicrobial resistant bacteria from plant-based food products imported into Canada. *International Journal of Food Microbiology* 319:108509.

Khawaja, T., J. Kirveskari, S. Johansson, J. Väisänen, A. Djupsjöbacka, A. Nevalainen, and A. Kantele. 2017. Patients hospitalized abroad as importers of multiresistant bacteria—a cross-sectional study. *Clinical Microbiology and Infection* 23(9):673. e671-673. e678.

Klein, E. Y., M. Milkowska-Shibata, K. K. Tseng, M. Sharland, S. Gandra, C. Pulcini, and R. Laxminarayan. 2021. Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000-15: An analysis of pharmaceutical sales data. *Lancet Infectious Diseases* 21(1):107-115.

Lees, V. W., and C. Prince. 2017. Lessons learned from the evolution of terrestrial animal health surveillance in Canada and options for creating a new collaborative national structure. *Canadian Veterinary Journal* 58(5):459-465.

Maki, G., I. Smith, S. Paulin, L. Kaljee, W. Kasambara, J. Mlotha, P. Chuki, P. Rupali, D. R. Singh, D. C. Bajracharya, L. Barrow, E. Johnson, T. Prentiss, and M. Zervos. 2020. Feasibility study of the world health organization health care facility-based antimicrobial stewardship toolkit for low- and middle-income countries. *Antibiotics (Basel)* 9(9).

Manchanda, V., U. Suman, and N. Singh. 2018. Implementing infection prevention and control programs when resources are limited. *Current Treatment Options in Infectious Diseases* 10(1):28-39.

Mathew, P., J. Ranjalkar, and S. J. Chandy. 2020. Challenges in implementing antimicrobial stewardship programmes at secondary level hospitals in india: An exploratory study. *Front Public Health* 8:493904.

Nicholson, A., I. Tennant, L. White, C. A. Thoms-Rodriguez, L. Cook, S. Johnson, T. Thompson, J. Barnett, and L. Richards. 2018. Correction to: The knowledge, attitudes and practices of doctors regarding antibiotic resistance at a tertiary care institution in the caribbean. *Antimicrobial Resistance & Infection Control* 7(1):77.

NIH (National Institutes of Health). 2021. *Medical research initiatives*. https://www.nih.gov/research-training/medical-research-initiatives (accessed September 30, 2021).

Novossiolova, T., L. Bakanidze, and D. Perkins. 2020. Effective and comprehensive governance of biological risks: A network of networks approach for sustainable capacity building. In *Synthetic biology 2020: Frontiers in risk analysis and governance*: Springer. Pp. 313-349.

Nurjadi, D., B. Friedrich-Janicke, J. Schafer, P. J. Van Genderen, A. Goorhuis, A. Perignon, A. Neumayr, A. Mueller, A. Kantele, M. Schunk, J. Gascon, A. Stich, C. Hatz, E. Caumes, M. P. Grobusch, R. Fleck, F. P. Mockenhaupt, and P. Zanger. 2015. Skin and soft tissue infections in intercontinental travellers and the import of multi-resistant staphylococcus aureus to europe. *Clinical Microbiology and Infection* 21(6):567 e561-510.

Our World in Data. 2021. *Infectious disease death rates, 2016*. https://ourworldindata.org/grapher/infectious-disease-death-rates (accessed July 20, 2021).

PBS. 2013. *Transcript: Hunting the nightmare bacteria*. https://www.pbs.org/wgbh/frontline/film/hunting-the-nightmare-bacteria/transcript/ (accessed.

PCAST (President's Council of Advisors on Science and Technology). 2020. *National action plan for combating antibiotic-resistant bacteria, 2020-2025.* Washington, DC: White House: Federal Task Force on Combating Antibiotic-Resistant Bacteria.

Pisa, M., and D. McCurdy. 2019. Improving global health supply chains through traceability. *Center for Global Development*.

Poupaud, M., V. Putthana, A. Patriarchi, D. Caro, A. Agunos, N. Tansakul, and F. L. Goutard. 2021. Understanding the veterinary antibiotics supply chain to address antimicrobial resistance in lao pdr: Roles and interactions of involved stakeholders. *Acta Tropica* 220:105943.

Resman, F. 2020. Antimicrobial stewardship programs; a two-part narrative review of step-wise design and issues of controversy part i: Step-wise design of an antimicrobial stewardship program. *Therapeutic Advances in Infectious Disease* 7:2049936120933187.

Reuland, E. A., G. J. Sonder, I. Stolte, N. Al Naiemi, A. Koek, G. B. Linde, T. J. van de Laar, C. M. Vandenbroucke-Grauls, and A. P. van Dam. 2016. Travel to Asia and traveller's diarrhoea with antibiotic treatment are independent risk factors for acquiring ciprofloxacin-resistant and extended spectrum beta-lactamase-producing enterobacteriaceae-a prospective cohort study. *Clinical Microbiology and Infection* 22(8):731 e731-737.

Schnall, J., A. Rajkhowa, K. Ikuta, P. Rao, and C. E. Moore. 2019. Surveillance and monitoring of antimicrobial resistance: Limitations and lessons from the gram project. *BMC Medicine* 17(1):176.

Seale, A. C., N. C. Gordon, J. Islam, S. J. Peacock, and J. A. G. Scott. 2017. AMR surveillance in low and middle-income settings - a roadmap for participation in the global antimicrobial surveillance system (GLASS). *Wellcome Open Research* 2:92.

Smith, P. 2019. The performance of antimicrobial susceptibility testing programmes relevant to aquaculture and aquaculture products. Rome: FAO Fisheries and Aquaculture Circular.

U.S. Department of State. 2021. *The United States President's Emergency Plan for AIDS Relief*. https://www.state.gov/pepfar/ (accessed September 22, 2021).

Tangcharoensathien, V., and W. Patcharanarumol. 2010. Commentary: Global health initiatives: Opportunities or challenges? *Health Policy and Planning* 25(2):101-103.

Tarawali, S. 2018. Food of animal origin: Demand and diversity. Paper read at Expert panel: Food of Animal Origin 2030: Solutions to Consumption Driven Challenges, Berlin, Germany.

The Fleming Fund. 2016. Antimicrobial resistance in low and middle income countries. The Fleming Fund.

Tiseo, K., L. Huber, M. Gilbert, T. P. Robinson, and T. P. Van Boeckel. 2020. Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics* 9(12):918.

UNAIDS. 2020. *Seizing the moment: Tackling entrenched inequalities to end epidemics.* Joint United Nations Programme on HIV/AIDS.

USAID (U.S. Agency for International Development). 2019a. *Global health security agenda*. https://www.usaid.gov/sites/default/files/documents/1860/Health_Project_Fact_Sheet_-_Global_Health_Security_Agenda.pdf (accessed July 16, 2021).

USAID. 2019b. *Supply chain*. https://www.usaid.gov/global-health/health-systems-innovation/health-systems/supply-chain (accessed July 19, 2021).

USAID. 2020. Global water and development. In *Report of Water and Sanitation Activities FY 2018/2019*.

USAID. 2021a. *Human resources for health: Optimizing the health workforce for hiv service delivery*. https://www.usaid.gov/global-health/health-areas/hiv-and-aids/technical-areas/human-resources-health (accessed July 19, 2021).

USAID. 2021b. *Water security and sanitation*. https://www.usaid.gov/sites/default/files/documents/2020_OnePager_final_revised_1.4.21.pdf (accessed July 16, 2021).

USAID. 2021c. *Who we are*. https://www.usaid.gov/who-we-are (accessed July 16, 2021).

USAID and U.S. Department of State. 2018. Joint strategic plan FY 2018 - 2022.

Versporten, A., P. Zarb, I. Caniaux, M. F. Gros, N. Drapier, M. Miller, V. Jarlier, D. Nathwani, H. Goossens, and Global-PPS Network. 2018. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: Results of an internet-based global point prevalence survey. *The Lancet Global Health* 6(6):e619-e629.

Vilar-Compte, D., A. Camacho-Ortiz, and S. Ponce-de-Leon. 2017. Infection control in limited resources countries: Challenges and priorities. *Current Infectious Disease Reports* 19(5):20.

Vollset, S. E., E. Goren, C. W. Yuan, J. Cao, A. E. Smith, T. Hsiao, C. Bisignano, G. S. Azhar, E. Castro, J. Chalek, A. J. Dolgert, T. Frank, K. Fukutaki, S. I. Hay, R. Lozano, A. H. Mokdad, V. Nandakumar, M. Pierce, M. Pletcher, T. Robalik, K. M. Steuben, H. Y. Wunrow, B. S. Zlavog, and C. J. L. Murray. 2020. Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: A forecasting analysis for the global burden of disease study. *Lancet* 396(10258):1285-1306.

Walker, T. M., M. Merker, A. M. Knoblauch, P. Helbling, O. D. Schoch, M. J. Van Der Werf, K. Kranzer, L. Fiebig, S. Kröger, and W. Haas. 2018. A cluster of multidrug-resistant mycobacterium tuberculosis among patients arriving in Europe from the horn of Africa: A molecular epidemiological study. *The Lancet Infectious Diseases* 18(4):431-440.

WHO (World Health Organization). 2017. *Global antimicrobial resistance surveillance system (GLASS) report- early implementation.* WHO.

WHO. 2019. Antimicrobial stewardship programmes in health-care facilities in low-and middle-income countries: A who practical toolkit.

WHO. 2020. Global antimicrobial resistance and use surveillance system (GLASS) report: Early implementation 2020 is the third GLASS report. Geneva, Switzerland: World Health Organization.

WHO. 2021a. *GLASS-AMR module*. https://www.who.int/initiatives/glass/glass-routine-data-surveillance (accessed July 16, 2021).

WHO. 2021b. *GLASS-One Health module*. https://www.who.int/initiatives/glass/glass-modules-7 (accessed July 16, 2021).

WHO. 2021c. *Global antimicrobial resistance and use surveillance system (GLASS)*. https://www.who.int/initiatives/glass (accessed June 14, 2021).

WHO. 2021d. Global antimicrobial resistance and use surveillance system (GLASS) report: 2021. *World Health Organization*.

WHO. 2021e. *Joint external evaluation (JEE)*. https://www.euro.who.int/en/health-topics/health-emergencies/international-health-regulations/monitoring-and-evaluation/joint-external-evaluation-jee (accessed July 13, 2021).

Worby, C. J., A. M. Earl, S. E. Turbett, M. Becker, S. R. Rao, E. Oliver, A. Taylor Walker, M. Walters, P. Kelly, and D. T. Leung. 2020. Acquisition and long-term carriage of multidrug-resistant organisms in us international travelers. Paper read at Open Forum Infectious Diseases.

# A

# Committee Member Biographies

**Guy H. Palmer, D.V.M., Ph.D.** (*Chair*), holds the Jan and Jack Creighton Endowed Chair at Washington State University (WSU) where he is the Regents Professor of Pathology and Infectious Diseases, Senior Director of Global Health, and Chief Scientist for the COVID-19 Taskforce. He also serves as Chair of WSU Global Health–Kenya. Dr. Palmer was elected to the National Academy of Medicine (NAM) in 2006, is a Medical Sciences Fellow of the American Association for the Advancement of Science, and is a founding member of the Washington State Academy of Sciences, where he served as President from 2012 to 2013. Dr. Palmer serves the National Academies as a member of the Board on Global Health and on the membership committee of the NAM. He serves on the Executive Roundtable of the Washington Global Health Alliance and chairs the Pacific Northwest Antibiotic Resistance Coalition. Dr. Palmer earned a B.S. (biology, summa cum laude) and a D.V.M., both from Kansas State University, and received his Ph.D. in infectious diseases from WSU. He completed his residency in pathology and laboratory medicine and is board certified in pathology. He holds honorary doctorates from the University of Bern (Switzerland) where he completed his fellowship in the Institute of Pathology, and from Kansas State University, where he serves on the External Advisory Board for the Biosecurity Institute. He has been recognized with the Poppensiek Professorship at Cornell, the IBM Professorship at Colby, the Schalm Lecturership at the University of California, the Distinguished Scientist Lectureship at the National Institutes of Health, the Science in Medicine Lectureship at the University of Washington, and the Merck Award for Creativity.

**Michael Baym, Ph.D.,** is an Assistant Professor of biomedical informatics at Harvard University. His research is centered around the problem of antibiotic resistance, at the intersection of experimental, theoretical, and computational techniques. His work ranges from understanding the basic mechanisms of evolution to the development of algorithms for computation on massive biological datasets. Dr. Baym received his Ph.D. in mathematics from the Massachusetts Institute of Technology and was a postdoctoral fellow at Harvard Medical School in systems biology. He has won several awards including a Packard Fellowship, a Pew Biomedical Scholarship, and a Sloan Research Fellowship. He is also a part-time inventor, holding over four dozen issued U.S. patents.

**César de la Fuente, Ph.D.,** is a Presidential Assistant Professor at the University of Pennsylvania, where he leads the Machine Biology Group, whose goal is to combine the power of machines and biology to understand, prevent, and treat infectious diseases. Current application areas in his lab include developing novel approaches for antibiotic discovery, building tools for microbiome engineering, and creating low-cost diagnostics. Specifically, he pioneered the development of the first antibiotic designed by a computer with efficacy in animal models, designed pattern recognition algorithms for antibiotic discovery, successfully reprogrammed venoms into novel antimicrobials, created novel resistance-proof antimicrobial materials, and invented rapid low-cost diagnostics for COVID-19 and other infectious diseases. Dr. De la Fuente is a National Institutes of Health Maximizing Investigators' Research Award investigator, a Brain & Behavior Research Foundation Young Investigator, and has received recognition and research funding from numerous other groups. Dr. de la Fuente was recognized by *MIT Technology Review* in 2019 as one of the world's top innovators for "digitizing evolution to make better antibiotics." He was selected as the inaugural recipient of the Langer Prize (2019), an American Chemical Society (ACS) Kavli Emerging Leader in Chemistry (2020), and received the Nemirovsky Prize (2020), American Institute of Chemical Engineers' 35 Under 35 Award (2020), and the ACS Infectious Diseases Young Investigator Award (2020). In addition, he was named a Boston Latino 30 Under 30, a 2018 Wunderkind by STAT News, a Top 10 Under 40 of 2019 by GEN, a Top 10 *MIT Technology Review* Innovator Under 35 (Spain), 30 Rising Leaders in the Life Sciences, and he received the 2019 Society of Hispanic Professional Engineers Young Investigator Award in addition to the Young Innovator in Cellular and Molecular Bioengineering and the Biomedical Engineering Society Cellular and Molecular Bioengineering Rising Star Award, both in 2021. Also in 2021, he received the Thermo Fisher Award, and the Engineering Medicine and Biology Society Academic Early Career Achievement Award "For the pioneering development of novel antibiotics designed using principles from computation, engineering, and biology." Most recently, Dr. de la Fuente was awarded the prestigious Princess of Girona Prize for Scientific Research. His scientific discoveries have yielded around 100 peer-reviewed publications, including papers in *Nature Communications*, *PNAS*, *ACS Nano*, *Cell*, *Nature Biomedical Engineering*, *Nature Chemical Biology*, *Nature Communications Biology*, *Advanced Materials*, and multiple patents.

**Jennifer Dien Bard, Ph.D., D(ABMM), F(CCM),** is an Associate Professor of pathology with Clinical Scholar designation in the Department of Pathology in the Keck School of Medicine at the University of Southern California. She is the Director of the Clinical Microbiology and Virology Laboratories at Children's Hospital Los Angeles (CHLA) and the Chief of Academic and Research Development in the Department of Pathology and Laboratory Medicine at CHLA. Dr. Dien Bard is also the program director of the Medical and Public Health Microbiology postdoctoral fellowship program at CHLA. She is a Diplomate of the American Board of Medical Microbiology. Dr. Dien Bard serves on several committees and working groups for organizations including the Association for Molecular Pathology, the American Society for Microbiology (ASM), the Clinical and Laboratory Standards Institute (CLSI), and the Antimicrobial Resistance Leadership Group (ARLG). She is currently a member of the CLSI Methods and Development Standardization working group and Co-Chair of the Coagulase-negative *Staphylococcus* species ad hoc working group. She also serves as a member of the ARLG Pediatric working group and ARLG diagnostics committee. She is a voting member for a number of CLSI documents including Principles and Procedures for Blood Culture and Methods

for active surveillance of multidrug-resistant organisms, and she has served on the ASM Laboratory Medicine Best Practice Guidelines Committee for the diagnosis of *Clostridioides difficile* infection and Bloodstream infections. Dr. Dien Bard also served on the editorial board of the *Journal of Clinical Microbiology*, the *Journal of Clinical Virology*, and she is an Editor for *Microbiology Spectrum Journal*. Prior to joining this committee, Dr. Dien Bard consulted with BioFire Diagnostics, Accelerate Diagnostics, and Karius, Inc. She is also a site Principal Investigator at CHLA for trials sponsored by Luminex Corporation, BioFire Diagnostics, and ChromaCode. Dr. Dien Bard has published over 90 scientific papers and is a frequent speaker in the areas of rapid molecular diagnostics for the identification of infectious diseases pathogens and detection of genotypic and phenotypic antimicrobial resistance. Her clinical research studies explore the application and effects of laboratory diagnostic, particularly molecular diagnostics, on patient diagnosis, antimicrobial utilization and overall clinical outcome. Dr. Dien Bard received her B.Sc. in medical laboratory sciences and Ph.D. in medical sciences from the University of Alberta, Canada. She completed a postdoctoral fellowship in medical and public health microbiology at the University of California, Los Angeles.

**Marta Gomez-Chiarri, Ph.D.,** is an aquatic pathologist and a Professor at The University of Rhode Island (URI), where she has been since 1997. Dr. Gomez-Chiarri earned her Ph.D. in biochemistry and molecular biology from the Universidad Complutense de Madrid (Spain) in 1992. Previous to joining URI, she was a postdoctoral fellow at Hopkins Marine Station, Stanford University, where she worked with biotechnological approaches to the culture of several aquatic species, including trout and abalone. Dr. Gomez-Chiarri held the position of Chair of the Department of Fisheries, Animal, and Veterinary Sciences (2014–2020) and is currently the Graduate Coordinator for programs in the areas of Aquaculture and Fisheries and Sustainable Agriculture and Food Systems. She is also coordinator of the interdisciplinary Sustainable Agriculture and Food Systems undergraduate program, a major that explores the food chain, from farm to plate to waste and back, emphasizing sustainability, impacts on human health, and resilience from economic, environmental, and societal viewpoints. Her research interests include the use of multidisciplinary approaches to the prevention and management of diseases in marine organisms, from probiotics and microbial-microbial interactions to genomics and comparative immunology. Her collaborative national and international research on marine diseases is driven by a desire to ensure equitable access to healthy food that is sustainably produced.

**Guillaume Lhermie, D.V.M., M.Sc., Ph.D.,** is an Associate Professor in animal health and veterinary public health economics at University of Toulouse, France, and an Adjunct Assistant Professor at Cornell University in Ithaca, New York. A veterinarian by training, he also has an M.Sc. in economics and a Ph.D. in pharmaco-epidemiology and innovation. Before working in academia, Dr. Lhermie worked in veterinary private practice for few years, as well as in the pharmaceutical industry, as research and development project manager, and medical director over 8 years. Dr. Lhermie research interests are in One Health and infectious diseases challenges, specifically the interface of animal agriculture and human health. He is studying the economics of antimicrobial use and resistance at the farm, supply chains, and global levels. Most recently, his research emphasis has been focusing on sustainability challenge, where he develops qualitative and quantitative models aiming to analyze the effect of antimicrobial use on social-

ecological systems, to inform policy makers. Dr. Lhermie also serves as expert in animal health economics for governmental organizations and nongovernmental organizations.

**Preeti Malani, M.D., M.S.J.,** is the University of Michigan's Chief Health Officer and a Professor of medicine in the Division of Infectious Diseases. She is also the Director of the University of Michigan's National Poll on Healthy Aging. Her clinical expertise includes both infectious diseases and geriatric medicine. Dr. Malani is a graduate of the University of Michigan. She received her M.D. from the Wayne State University School of Medicine. Prior to medical school, she completed a Master's in Journalism at Northwestern University's Medill School of Journalism. She completed her internal medicine residency and infectious diseases fellowship at the University of Michigan where she also received a master's degree in clinical research design and statistical analysis. Dr. Malani completed fellowship training in geriatric medicine at the Oregon Health & Science University. She has had a long-standing interest in both the clinical and policy aspects of antimicrobial resistance, infection prevention, and infections in older adults. Dr. Malani has published more than 150 peer-reviewed articles and editorials and has edited 5 books. She continues to dabble in journalism and her recent work has appeared in a variety of publications including *The New York Times*, *NPR*, the *Philadelphia Inquirer*, and *Michigan Rivals*. She serves as Vice Chair of the public health committee of the Infectious Diseases Society of America.

**Eleftherios Mylonakis, M.D., Ph.D.,** is the Charles C.J. Carpenter Professor of Infectious Disease at Brown University. He is also the Chief of Infectious Diseases at Rhode Island Hospital and the Miriam Hospital and Director of the COBRE Center for Antimicrobial Resistance and Therapeutic Discovery. He is Assistant Dean for Outpatient Investigations and Director of the Center for Outpatient and Longitudinal Medical Research at the Alpert Medical School of Brown University and a Professor of molecular microbiology and immunology. He was previously attending Physician of Infectious Disease at Massachusetts General Hospital and served as an Associate Professor at Harvard Medical School. Dr. Mylonakis studies host and microbial factors of infection and the discovery of antimicrobial agents. His research encompasses both clinical and laboratory studies and the use of mammalian and invertebrate model hosts systems to identify novel antimicrobial compounds and the elucidation of evolutionarily conserved aspects of microbial virulence and the host response. He has secured 8 patents, edited 5 books, and published over 400 articles in the peer-reviewed literature. He is currently named as a Principal Investigator on a study of novel antimicrobials for KODA Therapeutics.

**Iruka N. Okeke, Ph.D.,** is a Professor of pharmaceutical microbiology at the University of Ibadan, Nigeria, and a Fellow of the Nigerian and African Academies of Science. Her research group investigates the mechanisms bacteria use to colonize humans, cause disease, and gain drug resistance. She also studies laboratory practice in Africa. Dr. Okeke is a member of Nigeria's Technical Working Group on Antimicrobial Resistance and her laboratory currently provides the genomic surveillance service for Nigeria's antimicrobial resistance surveillance system as part of a collaborative UK National Institute for Health–supported Global Health Research Unit. Dr. Okeke received a B.Pharm., an M.Sc. and a Ph.D. from Obafemi Awolowo University (formerly University of Ife), Nigeria, and postdoctoral training at the University of Maryland, United States, and Uppsala Universitet, Sweden. She has held Fulbright, International Federation for

Science, Branco Weiss (Society-in-Science), and Institute for Advanced Studies (Berlin) fellowships as well as academic positions in Nigeria, the United Kingdom, and the United States. Dr. Okeke is author or co-author of several scientific articles and chapters as well as the books *Divining Without Seeds: The Case for Strengthening Laboratory Medicine in Africa* (Cornell University Press) and *Genetics: Genes, Genomes, and Evolution* (Oxford University Press). She is Editor-in-Chief of the *African Journal of Laboratory Medicine*. Dr. Okeke currently serves as a volunteer drug resistance consultant to the Nigeria Centre for Disease Control, the World Health Organization, and other organizations.

**Emmanuel Okello, M.Sc., Ph.D.,** is an Assistant Cooperative Extension Specialist in Antimicrobial Stewardship at the University of California (UC), Davis. The goal of his extension program is to develop antimicrobial stewardship guidelines and best management practices that reduce the spread of antimicrobial resistance while maintaining the health and welfare of the herds and flocks. His research work is focused on understanding the dynamics and risks for antimicrobial resistance in livestock, and the development of health management strategies for reduced antimicrobial resistance and improved health and welfare of herds and flocks. Other areas of interest include the use of alternatives to antibiotics to control infectious diseases in livestock, and the development and evaluation of vaccines and rapid diagnostics tests. Prior to joining UC Davis faculty in 2018, Dr. Okello was a postdoctoral scholar at the UC Davis Veterinary Medicine Teaching and Research Center in Tulare, California. His postdoctoral research included surveillance for antimicrobial resistance on California dairies and developing decision tools to guide antimicrobial drug use for dairy cows. Dr. Okello earned his Bachelor of Veterinary Medicine from Makerere University in Uganda, Master of Molecular Biology from Katholieke Universiteit Leuven, and a Ph.D. in bio-engineering sciences from Vrije Universiteit Brussel in Belgium.

**Aylin Sertkaya, Ph.D.,** is a Vice President and Senior Economist at Eastern Research Group, Inc. (ERG) with over 20 years of experience in health economics, econometrics, health policy analysis, and program evaluation. Throughout her career at ERG, she has formed and led teams of economists, scientists, and nationally recognized subject-matter experts to support dozens of high-profile regulatory initiatives, working closely with federal agency economists and policy makers. Her applied research has been published in peer-reviewed journals, such as *American Journal of Infection Control*, *Applied Health Economics and Health Policy*, *Clinical Trials*, and *Human and Ecological Risk Assessment*. Dr. Sertkaya has led dozens of economic/policy analysis studies related to antibacterial products, diabetes intervention, unit dose medication barcoding, adoption of MedDRA for postmarketing periodic safety report submissions to the U.S. Food and Drug Administration (FDA), drug compounding, among others under contract to the FDA and the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Planning and Evaluation. Her research on antibacterial products includes (1) the development of an analytical framework for evaluating the impact of different types of incentives on antibacterial product development, including drugs, vaccines, and rapid point-of-care diagnostics (see published reports *Analytical Framework for Examining the Value of Antibacterial Products and Economic Incentives for the Development of Rapid Point-of-Care (POC) Diagnostic Devices for* C. Difficile, *Carbapenem-resistant Enterobacteriaceae (CRE), and* Neisseria Gonorrhoeae), and (2) the evaluation of the market performance of antibacterial drugs against their clinical value; examination of potential market failures that underlie lack of

appropriate current or projected antibacterial therapies, and modeling the economic burden of antimicrobial resistance (ongoing project). Dr. Sertkaya holds a Ph.D. in economics and a dual bachelor's degree in physics and economics.

**Michelle Soupir, Ph.D.** is a Professor and Associate Chair for Research and Extension in the Department of Agricultural and Biosystems Engineering at Iowa State University. Her research program focuses on sustainable water systems with an emphasis on nonpoint source pollution control, watershed management, and water quality monitoring. Her research projects encompass multiple scales to answer basic and applied research questions regarding the occurrence, fate and transport of pathogens, pathogen indicators, and nutrients and contaminants of emerging environmental concern, such as antibiotics and antimicrobial resistance (AMR) to surface and groundwater systems. Her work is focused on the impacts of agricultural practices, primarily application of manure, on water quality. Through unique environmental monitoring, she works to design conservation practices to mitigate the impact of agricultural nonpoint source pollution on downstream waters, and reduce public exposure to these contaminants. Her recent work on AMR has included evaluation of prairie strips as a mitigation strategy to reduce export to downstream waters and watershed-scale monitoring of AMR indicators.

**Andy Stergachis, Ph.D., M.S., B.Pharm.,** is a Professor of pharmacy and global health and an Adjunct Professor of health metrics sciences, epidemiology and health systems and population health, Director of the Global Medicines Program, and Associate Dean for research, Graduate Studies and New Initiatives, School of Pharmacy, University of Washington (UW). He is also Interim Director of the UW Biomedical Regulatory Affairs Program. Previously, he served as Chairman of UW's Department of Pharmacy and the Department of Pathobiology, and Associate Dean of the School of Public Health and founding Director of the UW Pharmaceutical Outcomes Research and Policy Program, now the CHOICE Institute. He is an author of 175 peer-reviewed publications in areas such as pharmacovigilance, pharmacoepidemiology, and clinical epidemiology. A licensed pharmacist, he served as Editor-in-Chief of the *Journal of the American Pharmacists Association* for 6 years until 2019. He was a member of the Drug Safety and Risk Management Advisory Committee, U.S. Food and Drug Administration, and chaired the Expert Panel on the Review of Surveillance and Screening Technologies for the Quality Assurance of Medicines for United States Pharmacopeial Convention through 2020. His current research in the field of antimicrobial resistance includes serving as co-investigator for a study to estimate the magnitude and trends in the global burden of antimicrobial resistance (AMR). Called the Global Research on Antimicrobial Resistance (GRAM) Project, he collaborates with the UW Institute for Health Metrics and Evaluation and the University of Oxford. He recently worked with the U.S. Agency for International Development–funded Medicines, Technologies, and Pharmaceutical Services Program and Management Services for Health to conduct antimicrobial consumption and antimicrobial use projects in Tanzania. He recently joined Vivli's AMR Register Scientific Advisory Board. He is a pioneer in the validation and use of large linked databases to evaluate the safety of medicines used in the United States and, separately, in low- and middle-income countries. Dr. Stergachis is an elected member of the National Academy of Medicine and a Fellow of the American Pharmacists Association and the International Society for Pharmacoepidemiology. He has served on multiple National Academies of Sciences, Engineering, and Medicine committees, including the Committee on Evidence-Based Practices for Public Health Emergency Preparedness and Response; the Committee to

Review Long-Term Effects of Antimalarial Drugs; the Committee on Strengthening Regulatory Systems in Developing Countries; and the Committee to Assess the U.S. Drug Safety System.

**Mary E. Wilson, M.D.,** is a Clinical Professor of epidemiology and biostatistics at the University of California, San Francisco, and an Adjunct Professor of global health and population at the Harvard T.H. Chan School of Public Health, Boston. Her academic interests include antibiotic resistance, the ecology of infections and emergence of microbial threats, travel medicine, tuberculosis, and vaccines. She is a fellow in the Infectious Diseases Society of America, the American College of Physicians, the American Society of Tropical Medicine and Hygiene, and the International Society of Travel Medicine. She has served on the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC), 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, where she was Vice Chair of the Forum on Microbial Threats through 2019. 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 2008. She is the author of *A World Guide to Infections: Diseases, Distribution, Diagnosis* (Oxford University Press, 1991); senior editor, with Richard Levins and Andrew Spielman, of *Disease in Evolution: Global Changes and Emergence of Infectious Diseases* (NY Academy of Sciences, 1994); editor of *New and Emerging Infectious Diseases* (Medical Clinics of North America, 2008); author of *Antibiotics: What Everyone Needs to Know* (Oxford University Press, 2019); and one of the medical editors for the CDC's *Health Information for International Travel* (*The Yellow Book*). She has served as an advisor to the GeoSentinel Surveillance Network and is a contributing editor for *NEJM Journal Watch Infectious Diseases*. She served on the Board of Trustees for icddr,b in Bangladesh for 6 years, is a member of the Advisory Board for the Fogarty International Center at the National Institutes of Health, and is on the Board of Directors for the Center for Disease Dynamics, Economics & Policy.

**Qijng Zhang, M.S., Ph.D.,** is the Clarence Hartley Covault Distinguished Professor and Associate Dean for Research and Graduate Studies in the College of Veterinary Medicine at Iowa State University. Dr. Zhang received his Ph.D. in immunobiology from Iowa State University and postdoctoral training in molecular microbiology from the University of Missouri. Dr. Zhang worked as an Assistant Professor at The Ohio State University prior to returning to Iowa State University. For the past 20 years, Dr. Zhang's research has focused on antimicrobial resistance (AMR) at the interface of human and animal medicine. His research has discovered emerging AMR threats, novel antibiotic resistance mechanisms, and the co-evolution of bacterial virulence along with AMR in zoonotic and foodborne pathogens. His work has also provided key insights into the fitness, persistence, and transmission of AMR pathogens in the food chain, facilitating mitigation of AMR at the animal–human interface. In addition to AMR research, Dr. Zhang has broad perspectives on AMR surveillance, mitigation, and stewardship. Dr. Zhang is a fellow of American Academy of Microbiology and the American Association for the Advancement of Science. He is also an honorary diplomate of the American College of Veterinary Microbiologists.

# B

# Disclosure of Unavoidable Conflict of Interest

The conflict-of-interest policy of the National Academies of Sciences, Engineering, and Medicine (https://www.nationalacademies.org/about/institutional-policies-and-procedures/conflict-of-interest-policies-and-procedures) prohibits the appointment of an individual to a committee like the one that authored this Consensus Study Report if the individual has a conflict of interest that is relevant to the task to be performed. An exception to this prohibition is permitted only if the National Academies determine that the conflict is unavoidable and the conflict is promptly and publicly disclosed.

When the committee that authored this report was established a determination of whether there was a conflict of interest was made for each committee member given the individual's circumstances and the task being undertaken by the committee. A determination that an individual has a conflict of interest is not an assessment of that individual's actual behavior or character or ability to act objectively despite the conflicting interest.

Jennifer Dien Bard has a conflict of interest in relation to her service on the Committee on the Long-term Health and Economic Effects of Antimicrobial Resistance in the United States because of research support provided to Children's Hospital Los Angeles by diagnostic companies Luminex Corporation, BioFire Diagnostics, and Qiagen.

The National Academies determined that the experience and expertise of Dr. Dien Bard was needed for the committee to accomplish the task for which it was established. The National Academies could not find another available individual with the equivalent experience and expertise who did not have a conflict of interest. Therefore, the National Academies concluded that the conflict was unavoidable and publicly disclosed it on its website (www.nationalacademies.org).

# C

# Open Session Agendas

| SEPTEMBER 22, 2020<br>CLOSED SESSION<br>FULL SCHEDULE IN EASTERN TIME | |
|---|---|
| 11:00-11:15 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:15-12:45 | Bias and Conflict of Interest Discussion<br>**Lauren Shern,** *Director of Policy, Health and Medicine Division,* National Academies of Sciences, Engineering, and Medicine |
| 12:45-1:00 | Review Statement of Task and Study Timeline<br>**Guy Palmer,** *Committee Chair* |
| 1:00-1:30 | Framing the Report for Policy Makers<br>**Julie Eubank,** *Assistant Director, Congressional and Government Affairs,* National Academies of Sciences, Engineering, and Medicine |
| 1:30 | Adjourn |

| SEPTEMBER 23, 2020<br>OPEN SESSION<br>FULL SCHEDULE IN EASTERN TIME | |
|---|---|
| 11:00-11:10 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:10-11:50 | Sponsor Orientation to Statement of Task<br>**Jane Knisely,** *Program Officer,* Bacteriology and Mycology Branch, National Institute of Allergy and Infectious Diseases (NIAID) |

| | |
|---|---|
| 11:50-12:15 | ASPE Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Amanda Cash,** *Director,* Division of Evidence, Evaluation, and Data Policy, Office of the Assistant Secretary for Planning and Evaluation, U.S. Department of Health and Human Services |
| 12:15-12:40 | USDA Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Neena Anadaraman,** *Veterinary Science Policy Advisor,* Office of the Chief Scientist, U.S. Department of Agriculture (USDA) |
| 12:40-1:05 | NIH Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Jane Knisely,** *Program Officer,* Bacteriology and Mycology Branch, NIAID |
| 1:05-1:30 | BARDA Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Mark Albrecht,** *Branch Chief, Anti-Bacterial Program,* Division of CBRN Countermeasures, Biomedical Advanced Research and Development Authority (BARDA) |
| 1:30 | Adjourn |

**SEPTEMBER 24, 2020**
**OPEN SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:30 | USAID Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Jessica Petrillo,** *Senior Advisor for Antimicrobial Resistance and GHSA,* Emerging Threats Division, Office of Infectious Diseases, Bureau for Global Health, U.S. Agency for International Development |
| 11:30-11:55 | FDA Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**William Flynn,** *Deputy Director for Science Policy,* Center for Veterinary Medicine, U.S. Food and Drug Administration (FDA) |
| 11:55-12:20 | CDC Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Michael Craig,** *Senior Advisor for Antibiotic Resistance,* Antibiotic Resistance Coordination and Strategy Unit, Centers for Disease Control and Prevention |

| | |
|---|---|
| 12:20-12:45 | Department of Defense Involvement on the National Strategy for Combating Antimicrobial-Resistant Bacteria<br>**Paige Waterman,** *CARB Task Force Lead,* Walter Reed Army Institute of Research, U.S. Department of Defense |
| 12:45-1:30 | Q&A |
| 1:30 | Adjourn |

**SEPTEMBER 25, 2020**
**CLOSED SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-1:30 | Closed session for committee deliberations. |
| 1:30 | Adjourn |

---

**NOVEMBER 9, 2020**
**OPEN SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:35 | Additional Federal Actions Needed to Determine Magnitude and Reduce Impact of Antibiotic Resistance<br>**Timothy Persons,** *Chief Scientist and Managing Director,* Science, Technology Assessment, and Analytics, U.S. Government Accountability Office<br>**Mary Denigan-Macauley,** *Director,* Health Care, Public Health & Private Markets, U.S. Government Accountability Office |
| 11:35-12:05 | Convergence in Antimicrobial Use and Factor Influencing Resistance<br>**Ramanan Laxminarayan,** *Director and Senior Fellow,* Center for Disease Dynamics, Economics & Policy |
| 12:05-12:15 | Break |
| 12:15-12:45 | Measuring the Impacts of FDA's Actions to Promote Judicious Antimicrobial Use in Veterinary Medicine<br>**Susan Bright,** *Veterinary Medical Officer,* Office of Surveillance & Compliance, Center for Veterinary Medicine, FDA |
| 12:45-1:15 | National Scale Monitoring of Antimicrobial Resistance in Surface Water<br>**Jay Garland,** *Senior Research Scientist,* Office of Research and Development, U.S. Environmental Protection Agency |

| | |
|---|---|
| 1:15-1:45 | International Activities in AMR, Department of Health and Human Services<br>**Lynn Filpi,** *AMR Team Lead, Senior Global Health Officer,* Pandemic and Emerging Threat Office, Office of Global Affairs, HHS |
| 1:45-2:00 | Closing Questions |
| 2:00 | Adjourn |

**NOVEMBER 10, 2020**
**OPEN SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:35 | Monitoring Countries' Progress on Tripartite Global Action Plan<br>**Anand Balachandran,** *Unit Head,* AMR National Action Plans and Monitoring & Evaluation, AMR Division, World Health Organization (WHO)–Headquarters |
| 11:35-12:05 | The Norwegian National Strategy Against Antibiotic Resistance<br>**Gunnar Skov Simonsen,** *Professor of Clinical Microbiology,* University of Tromsø; *Director of the Department of Microbiology and Infection Control,* University Hospital of North Norway |
| 12:05-12:15 | Break |
| 12:15-12:45 | Antibiotic Resistance in the Food Chain<br>**Frank Møller Aarestrup,** *Professor, Head of Division,* Division for Global Surveillance, Research Group for Genomic Epidemiology, National Food Institute, Technical University of Denmark |
| 12:45-1:15 | Antimicrobial Use in Companion Animals<br>**Mark Papich,** *Professor of Clinical Pharmacology, Burroughs Wellcome Fund Professorship in Veterinary Pharmacology,* College of Veterinary Medicine, North Carolina State University |
| 1:15-1:45 | Antimicrobial Use in Chilean Aquaculture<br>**Felipe C. Cabello,** *Professor Emeritus,* Department of Microbiology and Immunology, New York Medical College |
| 1:45-2:00 | Closing Questions |
| 2:00 | Adjourn |

**NOVEMBER 11, 2020**
**OPEN SESSION**

**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:35 | The Global Antibiotic-Resistance Surveillance System<br>**Carmem L Pessoa-Silva,** *Unit Head - Surveillance, Evidence and Laboratory Strengthening,* AMR Division, WHO |
| 11:35-12:05 | Shaping Strategies for Prevention and Response to Antibiotic Resistance<br>**Tim Jinks,** *Head Drug-Resistant Infections Priority Program,* Wellcome Trust |
| 12:05-12:15 | Break |
| 12:15-12:45 | The Fleming Fund Support for AMR Surveillance<br>**Tom Pilcher,** *Head of Country Coordination,* The Fleming Fund, Department of Health and Social Care<br>**Claire Gordon,** *Lead Clinical Microbiologist,* Mott MacDonald/The Fleming Fund |
| 12:45-1:15 | The Bill & Melinda Gates Foundation's Strategy in AMR<br>**Padmini Srikantiah,** *Senior Program Officer*, *Global Health Antimicrobial Resistance Strategy Lead,* Bill & Melinda Gates Foundation |
| 1:45-2:00 | Questions and Discussion |
| 2:00 | Adjourn |

**NOVEMBER 13, 2020**
**CLOSED SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-12:30 | Debrief on Presentations<br>**Guy Palmer,** *Committee Chair* |
| 12:30-1:30 | Next Steps<br>**Guy Palmer,** *Committee Chair* |
| 1:30 | Adjourn |

**JANUARY 5, 2021**
**OPEN SESSION**
**THE ANTIMICROBIAL PRODUCT PIPELINE AND INCENTIVES FOR MARKET VIABILITY**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:30 | The Post-Approval Challenges of Antimicrobial Development<br>**Kevin Krause,** *Vice President, Clinical Science and Development Operations,* AN2 Therapeutics Inc. |
| 11:30-11:55 | Pricing of Antibiotics and Proposals to Strengthen the Pipeline<br>**John Rex,** *Chief Medical Officer and Director,* F2G, Ltd; *Editor-in-Chief,* AMR Solutions; *Operating Partner,* Advent Life Sciences |
| 12:00-12:15 | Break |
| 12:15-1:45 | Panel Discussion on Push and Pull Incentives<br>**Lefteris Mylonakis,** *Moderator*<br>**Wes Kim,** *Senior Officer, Antibiotic Resistance Project,* The Pew Charitable Trusts<br>**Kevin Outterson,** *Executive Director,* Combating Antibiotic-Bacteria Biopharmaceutical Accelerator<br>**Ryan Cirz,** *CSO and Acting CEO,* Revagenix, Inc.<br>**Mark Albrecht,** *Branch Chief,* Anti-Bacterial Program, Division of CBRN Countermeasures, BARDA |
| 1:45-2:10 | Championing Patient and Public Health Needs: IDSA Efforts to Strengthen the Antibiotic Pipeline<br>**Helen Boucher,** *Chief, Division of Geographic Medicine and Infectious Diseases,* Tufts Medical Center<br>*Director*, Levy Center for Integrated Management of Antimicrobial Resistance<br>*Treasurer,* Infectious Diseases Society of America |
| 2:10-2:35 | A New, Sustainable Model for Antibiotic R&D<br>**Brad Spellberg,** *Chief Medical Officer,* Los Angeles County-University of Southern California Medical Center |
| 2:45 | Adjourn |

**JANUARY 6, 2021**
**OPEN SESSION**
**DIAGNOSTICS AND SUSCEPTIBILITY TESTING**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:30 | The Relationship Between Antimicrobial Susceptibility Testing Devices and Antibiotic Markets<br>**Kevin Krause,** *Vice President, Clinical Science and Development Operations,* AN2 Therapeutics Inc. |
| 11:30-11:55 | Regulatory Challenges in Antimicrobial Diagnostics<br>**Barbara Zimmer,** *Principal Scientist, Microbiology Scientific Affairs,* Beckman Coulter, Inc. |
| 11:55-1:15 | Diagnostics Panel Discussion<br>**Jenn Dien Bard,** *Moderator*<br>**Mark Miller,** *Chief Medical Officer,* bioMerieux<br>**Fred C. Tenover,** *Vice President, Scientific Affairs,* Cepheid<br>**Angela Caliendo**, *Warren Alpert Foundation Professor of Medicine, Executive Vice Chair of Medicine,* Alpert Medical School, Brown University<br>**Barbara Zimmer,** *Principal Scientist, Microbiology Scientific Affairs,* Beckman Coulter, Inc. |
| 1:15-1:30 | Break |
| 1:30-1:50 | VetCAST Susceptibility Test Breakpoints<br>**Peter Panduro Damborg,** *Associate Professor,* Veterinary Clinical Microbiology, University of Copenhagen |
| 1:50-2:10 | Addressing Challenges in Veterinary Diagnostics<br>**Brian Lubbers,** *Associate Professor,* College of Veterinary Medicine, Kansas State University |
| 2:10-2:45 | Discussion on Veterinary Diagnostics and Susceptibility Test Breakpoints<br>**Emmanuel Okello,** *Moderator*<br>**Peter Panduro Damborg,** *Associate Professor,* Veterinary Clinical Microbiology, University of Copenhagen<br>**Brian Lubbers,** *Associate Professor,* College of Veterinary Medicine, Kansas State University |
| 2:45 | Adjourn |

**JANUARY 7, 2020**
**OPEN SESSION**
**ANTIMICROBIAL STEWARDSHIP**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:30 | Telehealth and Antimicrobial Stewardship<br>**John Lynch,** *Associate Medical Director,* Harborview Medical Center Antimicrobial Stewardship Program; *Associate Professor,* Division of Allergy and Infectious Diseases, University of Washington School of Medicine |
| 11:30-11:55 | Antimicrobial Stewardship in Remote Areas<br>**Marc Mendelson,** *Professor of Infectious Disease,* Division of Infectious Diseases & HIV Medicine, University of Cape Town |
| 11:55-12:20 | Antimicrobial Stewardship in Nursing Homes: Barriers and Opportunities<br>**Chris Crnich,** *Chief of Medicine,* Madison VA Hospital; *Associate Professor of Medicine,* Division of Infectious Diseases, University of Wisconsin School of Medicine and Public Health |
| 12:20-12:35 | Break |
| 12:35-1:00 | The Road to Research and Development of Alternatives to Antibiotics in the United States<br>**Cyril Gay,** *Senior National Program Leader,* Animal Production and Protection, Agricultural Research Service, USDA |
| 1:00-2:30 | Panel Discussion on Incentives for Stewardship in Agribusiness<br>**Marta Gomez-Chiarri,** *Moderator*<br>**Bruce Stewart-Brown,** *Senior Vice-President of Food Safety, Quality, and Live Operations,* Perdue Foods<br>**Bill Keleher,** *President and CEO,* Kennebec River Biosciences<br>**Craig Wilson,** *Vice President, GMM,* Costco Wholesale<br>**Heather Fowler,** *Director of Producer and Public Health,* National Pork Board |
| 2:30 | Adjourn |

**JANUARY 8, 2020**
**OPEN**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** *Committee Chair* |
| 11:05-11:35 | Anthropology of Antimicrobial Resistance<br>**Clare Chandler,** *Professor in Medical Anthropology and Director,* London School of Hygiene & Tropical Medicine |
| 11:35-12:05 | The Global Burden of Antimicrobial Resistance<br>**Chris Murray,** *Director,* Institute for Health Metrics and Evaluation; *Chair and Professor,* Health Metrics Sciences, University of Washington |
| 12:05 | Open Session Adjourn |

**CLOSED SESSION**
**FULL SCHEDULE IN EASTERN TIME**

| | |
|---|---|
| 12:05-12:20 | Break |
| 12:20-1:20 | Debrief<br>**Guy Palmer,** *Committee Chair* |
| 1:20-2:00 | Next Steps<br>**Guy Palmer,** *Committee Chair* |
| 2:00 | Adjourn |

---

**MARCH 16, 2021**
**OPEN SESSION**

| | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer**, *Committee Chair* |
| 11:05-11:35 | GARDP and Antimicrobial Development<br>**Manica Balasegaram**, *Executive Director,* Global Antibiotic R&D Partnership<br>**Jennifer Schneider,** *Senior Advisor External Affairs,* Global Antibiotic R&D Partnership |
| 11:35-12:05 | Inpatient Reimbursement and the Antimicrobial Market<br>**Anand Shah,** *former Deputy Commissioner for Medical and Scientific Affairs,* FDA |
| 12:05 | Adjourn Open Session |

| **MARCH 16, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 12:15-12:30 | Overview Draft Recommendations, Guidance on Writing Recommendations |
| 12:30-3:00 | Discussion of Draft Recommendations and Conclusions in Stewardship and Prevention |
| 3:00 | Adjourn |

| **MARCH 17, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 11:00-12:00 | Discussion of Draft Recommendations and Conclusions on Push and Pull Incentives |
| 12:00-12:15 | Break |
| 12:15-2:45 | Discussion of Draft Recommendations and Conclusions on Diagnostics and Related Questions |
| 2:45 | Adjourn |

| **MARCH 18, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 11:00-12:00 | Discussion of Draft Recommendations and Conclusions on International Action |
| 12:00-12:15 | Break |
| 12:15-2:00 | Discussion Draft Recommendations and Conclusions on Health and Economic Burden |
| 2:00 | Adjourn |

| **MARCH 19, 2021**<br>**OPEN SESSION** | |
|---|---|
| 11:00-11:05 | Welcome<br>**Guy Palmer,** Committee Chair |
| 11:05-11:45 | Direct, Predictive Application of Sequencing and Informatics<br>**Gautam Dantas,** *Professor,* Washington University School of Medicine |
| 11:45 | Adjourn Open Session |

| **MARCH 19, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 12:00-1:00 | Discussion of Draft Recommendations and Conclusions on Surveillance |
| 1:00 | Adjourn |

| **MAY 11, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 11:00-2:00 | Deliberation on Report Recommendations |
| 2:00 | Adjourn |

| **MAY 12, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 11:00-12:15 | Deliberation on Report Recommendations |
| 12:15-12:30 | Break |

| **MAY 12, 2021**<br>**OPEN SESSION** | |
|---|---|
| 12:30-1:30 | Agencies' Progress on National Action Plan, Mixed Methods Analysis<br>**Kris Moore,** *Medical Director,* Center for Infectious Disease Research and Policy, University of Minnesota |
| 1:30 | End Open Session |

| **MAY 12, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 1:30 | Debrief on Presentation |
| 2:00 | Adjourn |

| **MAY 13, 2021**<br>**CLOSED SESSION** | |
|---|---|
| 11:00-2:00 | Deliberation on Report Recommendations |
| 2:00 | Adjourn |

**MAY 14, 2021**
**CLOSED SESSION**

| | |
|---|---|
| 11:00-2:00 | Deliberation on Report Recommendations |
| 2:00 | Adjourn |