Uploaded to the VFC Website

2019

This Document has been provided to you courtesy of Veterans-For-Change!

Feel free to pass to any veteran who might be able to use this information!

For thousands more files like this and hundreds of links to useful information, and hundreds of "Frequently Asked Questions, please go to:

Veterans-For-Change

If Veterans don't help Veterans, who will?

Note: VFC is not liable for source information in this document, it is merely provided as a courtesy to our members & subscribers.

THE CONVERGENCE OF INFECTIOUS DISEASES AND NONCOMMUNICABLE DISEASES

PROCEEDINGS OF A WORKSHOP

V. Ayano Ogawa, Cecilia Mundaca Shah, Yamrot Negussie, and Anna Nicholson, *Rapporteurs*

Forum on Microbial Threats

Board on Global Health

Health and Medicine Division

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

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

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

This activity was supported by contracts between the National Academy of Sciences and EcoHealth Alliance; Infectious Diseases Society of America; Johnson & Johnson (10003710); Merck & Co., Inc.; National Institute of Allergy and Infectious Diseases/National Institutes of Health (10003226); Sanofi Pasteur; The University of Hong Kong; Uniformed Services University of the Health Sciences (10003626); U.S. Agency for International Development; U.S. Army Medical Research and Materiel Command (10001249); U.S. Centers for Disease Control and Prevention (10002642); U.S. Department of Homeland Security (10003591); U.S. Department of Veterans Affairs (10003353); and U.S. Food and Drug Administration (10002125). 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: 978-0-309-49614-8
International Standard Book Number-10: 0-309-49614-4
Digital Object Identifier: https://doi.org/10.17226/25535

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. 2019. *The convergence of infectious diseases and noncommunicable diseases: Proceedings of a workshop*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25535.

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**.

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.

PLANNING COMMITTEE ON BREAKING DOWN SILOS: THE CONVERGENCE OF INFECTIOUS DISEASES AND NONCOMMUNICABLE DISEASES[1]

PETER DASZAK (*Chair*), President, EcoHealth Alliance
DAVID BRETT-MAJOR, Sanford Chair in Tropical Medicine, Uniformed Services University of the Health Sciences
KEIJI FUKUDA, School Director and Clinical Professor, School of Public Health, The University of Hong Kong
JESSE L. GOODMAN, Professor of Medicine and Infectious Diseases, Director, Center on Medical Access, Safety, and Stewardship, Georgetown University
KENT E. KESTER, Vice President and Head, Translational Science and Biomarkers, Sanofi Pasteur
RIMA F. KHABBAZ, Director, National Center for Emerging and Zoonotic Infectious Diseases, U.S. Centers for Disease Control and Prevention
PETER R. LAMPTEY, Distinguished Scientist and President Emeritus, FHI360
MOSA MOSHABELA, Dean and Head, School of Nursing and Public Health, University of KwaZulu-Natal
RACHEL NUGENT, Vice President, Global Noncommunicable Diseases, RTI International
JULIE PARSONNET, George DeForest Barnett Professor in Medicine, Professor of Medicine and of Health Research and Policy, Stanford University
PADMA SHETTY, Senior Infectious Disease Advisor, Emerging Threats Division, U.S. Agency for International Development

Health and Medicine Division and Board on Global Health Staff

CECILIA MUNDACA SHAH, Project Director, Forum on Microbial Threats
V. AYANO OGAWA, Senior Program Officer, Forum on Microbial Threats
YAMROT NEGUSSIE, Program Officer, Forum on Microbial Threats (*from August 2019*)
EDITH AMPONSAH, Research Associate, Forum on Microbial Threats (*from August 2019*)

[1] The National Academies of Sciences, Engineering, and Medicine's planning committees are solely responsible for organizing the workshop, identifying topics, and choosing speakers. The responsibility for the published Proceedings of a Workshop rests with the rapporteurs and the institution.

STEPHEN CHUKWURAH, Senior Program Assistant, Forum on Microbial Threats (*from August 2019*)
NATALIE LUBIN, Research Assistant, Forum on Microbial Threats (*until May 2019*)
JULIE PAVLIN, Director, Board on Global Health

National Academy of Medicine Staff

JARRETT NGUYEN, Program Specialist (*from May 2019*)
BHUMI SHAH, Intern (*from June to August 2019*)

FORUM ON MICROBIAL THREATS[1]

[1] The National Academies of Sciences, Engineering, and Medicine's forums and roundtables do not issue, review, or approve individual documents. The responsibility for the published Proceedings of a Workshop rests with the workshop rapporteurs and the institution.

SALLY A. MILLER, Professor of Plant Pathology and State Extension Specialist for Vegetable Pathology, Ohio Agricultural Research and Development Center, The Ohio State University
SUERIE MOON, Director of Research, Global Health Centre, Graduate Institute of International and Development Studies, Geneva
DAVID NABARRO, Advisor, Health and Sustainability, 4SD—Skills, Systems, and Synergies for Sustainable Development
RAFAEL OBREGON, Chief of Communications for Development, United Nations Children's Fund
KUMANAN RASANATHAN, Board Member, Health Systems Global
GARY A. ROSELLE, Chief of Medical Service, Veterans Affairs Medical Center; Director, National Infectious Disease Services, Veterans Health Administration
PETER A. SANDS, Executive Director, The Global Fund to Fight AIDS, Tuberculosis and Malaria
THOMAS W. SCOTT, Distinguished Professor, Department of Entomology and Nematology, University of California, Davis
JAY P. SIEGEL, Retired Chief Biotechnology Officer, Head of Scientific Strategy and Policy, Johnson & Johnson
PAIGE E. WATERMAN, Assistant Director for Biological Threat Defense, White House Office of Science and Technology Policy
MATTHEW ZAHN, Medical Director, Division of Epidemiology and Assessment, Orange County Health Care Agency

Health and Medicine Division and Board on Global Health Staff

CECILIA MUNDACA SHAH, Project Director, Forum on Microbial Threats
V. AYANO OGAWA, Senior Program Officer, Forum on Microbial Threats
YAMROT NEGUSSIE, Program Officer, Forum on Microbial Threats (*from August 2019*)
EDITH AMPONSAH, Research Associate, Forum on Microbial Threats (*from August 2019*)
STEPHEN CHUKWURAH, Senior Program Assistant, Forum on Microbial Threats (*from August 2019*)
NATALIE LUBIN, Research Assistant, Forum on Microbial Threats (*until May 2019*)
JULIE PAVLIN, Director, Board on Global Health

National Academy of Medicine Staff

JARRETT NGUYEN, Program Specialist (*from May 2019*)
BHUMI SHAH, Intern (*from June to August 2019*)

Reviewers

This Proceedings of a Workshop 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 proceedings as sound as possible and to ensure that it meets the institutional standards for quality, objectivity, evidence, and responsiveness to the charge. The review comments and draft manuscript remain confidential to protect the integrity of the process.

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

TOM FRIEDEN, Resolve to Save Lives, Initiative of Vital Strategies
RACHEL NUGENT, RTI International
JULIE PARSONNET, Stanford University

Although the reviewers listed above provided many constructive comments and suggestions, they were not asked to endorse the content of the proceedings nor did they see the final draft before its release. The review of this proceedings was overseen by **DAVID R. CHALLONER,** University of Florida. He was responsible for making certain that an independent examination of this proceedings was carried out in accordance with standards of the National Academies and that all review comments were carefully considered. Responsibility for the final content rests entirely with the rapporteurs and the National Academies.

Acknowledgments

The Forum on Microbial Threats staff and planning committee deeply appreciate the many valuable contributions from individuals who assisted us with this project. Thank you to Charlanne Burke, Bridgette Charles, and Naveen Rao for graciously hosting the workshop at The Rockefeller Foundation, and Tara Hoda and Anthony Ramos from the EcoHealth Alliance for their invaluable assistance organizing the logistics of the workshop. The workshop and this Proceedings of a Workshop would not be possible without the presenters and discussants at the workshop, who gave so generously of their time and expertise. A full list of the speakers and moderators and their biographical information may be found in Appendix C.

Contents

APPENDIXES

Boxes, Figures, and Tables

BOXES

FIGURES

TABLES

Acronyms and Abbreviations

BMI	body mass index
CDR	crude death rate
CMA	cow's milk allergy
COPD	chronic obstructive pulmonary disease
CVDRF	cardiovascular disease risk factor
DALY	disability-adjusted life year
EBV	Epstein-Barr virus
GLUT2	glucose transporter 2
GWAS	genomewide association study
HMP	Human Microbiome Project
HPV	human papillomavirus
NCD	noncommunicable disease
OTU	operational taxonomic unit
PEPFAR	The President's Emergency Plan for AIDS Relief
TB	tuberculosis

USAID	U.S. Agency for International Development
WHO	World Health Organization

1

Introduction

The understanding of how infectious diseases are related to noncommunicable diseases (NCDs) has evolved over time. With many challenges to showing the connection between microbial threats and NCDs over the past century, the idea was maintained that most infectious diseases are also acute illnesses and that chronic diseases have noninfectious sources (O'Connor et al., 2006). In the 1970s and 1980s, this thinking began to evolve when *Helicobacter pylori* was found to induce gastric inflammation (Marshall et al., 1985), and many other linkages began to be exposed, including human papillomavirus and cervical cancer (Hadley, 2006; Burnett-Hartman et al., 2008), hepatitis B and C viruses and chronic liver disease (Hadley, 2006), and *Borrelia burgdorferi* and chronic Lyme arthritis (Steere et al., 2004). These scientific discoveries spurred the development of more effective prevention and treatment programs that directly targeted the diseases and saved countless lives. With such growing evidence, scientists today believe that a significant portion of chronic diseases may be associated with microbes and infections.

While there has been growing recognition of the breadth of linkages between infectious diseases and NCDs, the two fields continue to be isolated from each other, with the two realms often supported by separate funding streams, studied using divergent research methodologies, and shaped by vertical health policies and programs. This is concerning as epidemics of infectious diseases and NCDs today are increasingly colliding on a global scale, with escalating consequences of mortality and morbidity that are poised to affect huge numbers of people in the coming decades (Marais et al., 2013). The balance of the global burden of disease is shifting toward

NCDs, with increasing numbers of low- and middle-income countries experiencing a double burden of infectious diseases and NCDs (Jamison et al., 2018). In fact, NCDs affect people in low- and middle-income countries disproportionately, where approximately 32 million people are dying from NCDs, with nearly half of those deaths occurring before the age of 70 (WHO, 2018b).

The convergence of infectious diseases and NCDs is becoming more apparent by a constellation of factors. Globalization enables both people and infectious diseases to travel swiftly around the world, while rapid urbanization and increasing interrelationships among humans, animals, plants, and the environment are driving the transmission of infectious diseases and contributing to NCD-related risks (Leon, 2008; Bygbjerg, 2012). Environmental and lifestyle factors such as dietary patterns are decreasing microbial diversity in the human microbiome and increasing NCDs and NCD risk factors (Xu and Knight, 2015; Sheflin et al., 2017; Billingsley et al., 2018). The convergence is also becoming more apparent owing to advances in molecular techniques and immunology, as well as culture methods, laboratory technology, and epidemiological techniques that are uncovering the linkages between microbes and NCDs. However, methodologies and analyses across these techniques must be scrutinized and standardized to ensure valid and reliable results (O'Connor et al., 2006).

The epidemiological transition and scientific advances are blurring the traditional lines between infectious diseases and NCDs. The convergent dynamics among microbes, infections, NCDs, normal health functioning, and shared risk factors are complex and intertwined. The evidence spans a wide spectrum. Some research shows infectious diseases as being a risk factor for developing NCDs (see Chapter 3), while the reverse connection is also seen with NCDs being associated with the development and severity of infectious diseases (see Chapter 4). Multimorbidities involving various permutations of infectious diseases and NCDs also add another layer of complexity. Moreover, the perturbation of the microbiome—such as from diet, other lifestyle factors, and use of antibiotics—has also been shown to affect human functioning and could be a risk factor for the development of NCDs (see Chapter 5). In fact, dozens of chronic diseases have already been associated with the human microbiome, some of which have been cured through microbiome manipulation in animal models (Zheng et al., 2018; Proctor et al., 2019). The field of syndemic research shows how the interplay between diseases is shaped by biological, behavioral, psychological, and social interactions that exacerbate the effect of disease–disease dynamics on human health (Singer et al., 2017) (see Chapter 2).

Research has only begun to reveal the enormous complexity of the microbial world and the extent to which microbes interact with humans and influence human health. Getting a better understanding of these linkages and

bridging cross-sectoral collaborations would help identify further research priorities, develop better targeted prevention and treatment interventions and policies, and leverage existing health systems to effectively respond to both infectious diseases and NCDs to ultimately reduce the public health impact and burden of the convergence from the local to national to global levels.

WORKSHOP OBJECTIVES

On June 11 and June 12, 2019, a planning committee under the auspices of the Forum on Microbial Threats at the National Academies of Sciences, Engineering, and Medicine held a 1.5-day public workshop at The Rockefeller Foundation in New York City, titled Breaking Down Silos: The Convergence of Infectious Diseases and Noncommunicable Diseases.[1] Building on the previous work of the forum (IOM, 2004, 2014), this workshop was convened to explore the growing understanding of how the interplay between humans and microbes affects host physiology and causes NCDs. Peter Daszak, president of EcoHealth Alliance who chaired this workshop, stated that the workshop intends to allow participants to gain a deeper understanding of the continuum between infectious diseases and NCDs, including how this continuum provides new opportunities for prevention and treatment. Naveen Rao, managing director for health and senior advisor to the president at The Rockefeller Foundation, reflected that he comes from a time in which the demarcation between communicable diseases and NCDs was clear, in contrast to the focus of this workshop. From his perspective, he noted that he is interested in how to bring the best data and advances in data science to community health in a way that bridges the emerging divide between people who have access to data as well as better health and people without access to data, who tend to have relatively poorer health. Rao described this workshop as an opportunity to extend the focus beyond health care to a broader concept of health, to a focus on the community, and to a focus on bridging the data divide.

Workshop speakers and discussants contributed perspectives from government, academia, and the private and nonprofit sectors. Specifically, participants discussed the following topics during the workshop[2]:

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

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

- Current knowledge on the known and suspected causal associations between micro-organisms and chronic diseases and conditions, as well as associated issues;
- The evolving understanding of how the microbiome affects the normal physiological functioning of humans and how these interactions vary depending on the population, geographic location, and other biological or environmental factors;
- Research needed to further understand the relationship between micro-organisms and chronic diseases and physiological functions;
- Opportunities for developing new approaches to prevent, detect, and mitigate chronic diseases and to reduce their public health impact and burden;
- Cutting-edge methods and tools as well as study designs being used to explore links between chronic diseases and infectious diseases; and
- Mechanisms to leverage cross-sectoral collaborations and break down silos among various stakeholders from research to practice.

ORGANIZATION OF THE PROCEEDINGS OF THE WORKSHOP

In accordance with the policies of the National Academies, the workshop did not attempt to establish any conclusions or recommendations about needs and future directions, focusing instead on information presented, questions raised, and improvements suggested by individual workshop participants. Chapter 2 includes highlights from the workshop's two keynote presentations that developed the rationale for convergent action for colliding epidemics and syndemics of infectious diseases and NCDs. Chapters 3 and 4 explore the current state of the science and emerging research on the convergence of infectious diseases and NCDs. Specifically, Chapter 3 features case studies on the possible associations of infectious diseases and microbes leading to the development of NCDs, including the role of oral bacterial infection in Alzheimer's disease, the contribution of the Epstein-Barr virus to the etiology of autoimmune and inflammatory diseases, and the effect of the microbiome on food allergies. Chapter 4 includes two case studies—one on metabolic syndrome and the risk of enteric infection and the other, converging epidemics of diabetes and tuberculosis—that examine the risks that chronic diseases pose to the development and severity of infectious diseases. Chapter 5 describes the plenary presentation that provides a broader perspective on the microbial dimension to human development and functioning, and the potential it offers for new approaches to human well-being.

The chapters thereafter cover issues on the practical implications of the convergence between infectious diseases and NCDs. Chapter 6 provides

highlights from the panel discussion on how to confront the "blind people and the elephant" metaphor to bridge the silos between infectious diseases and NCDs in the move toward convergent action. Chapter 7 explores strategies for integrating and revamping health care delivery models and interventions to address the convergence. Chapter 8 summarizes the small group discussions on potential strategies and actions to prioritize to advance the research agenda and effectively translate research into policy and practice in the immediate term, and finally Chapter 9 presents visionary statements from three global health experts on their views of top priorities for next steps.

2

An Overview of Colliding Epidemics and Syndemics

The workshop opened with two keynote addresses that provided an overview of the colliding epidemics and syndemics of infectious diseases and noncommunicable diseases (NCDs) and the potential approaches needed to address the convergence. In the first keynote address, Tolullah Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge, provided an overarching perspective on the trends of the dual global collision and burden of infectious diseases and NCDs, and she offered new ways to address the convergence. Emily Mendenhall, Provost's Distinguished Associate Professor at Georgetown University, delivered a keynote address that elucidated the concept of syndemics and how syndemics research could provide opportunities to consider tackling the convergence of infectious diseases and NCDs in new ways.

CONVERGENT ACTION FOR COLLIDING EPIDEMICS OF INFECTIOUS AND NONCOMMUNICABLE DISEASES

To establish the rationale for taking an integrated approach to address the colliding epidemics of infectious diseases and NCDs, Tolullah Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge, first described how mortality and morbidity trends have shifted in recent decades, with the contribution of NCDs to both of those burdens increasing relative to infectious diseases. She followed with a discussion of the role of false dichotomies in delaying convergent action, the range of interventions that exist for convergent action, and lessons to apply

from infectious diseases epidemic responses, as well as new approaches to convergent prevention and control.

Shifting Mortality and Morbidity Trends

Oni began by presenting data from the *Disease Control Priorities* (3rd edition), which shows that the global crude death rate (CDR) per 100,000 population generally improved during the period between 2000 and 2015 (Jamison et al., 2018). Looking more closely at the contribution of NCDs versus infectious diseases to the global CDR reveals shifting trends that warrant convergent action, explained Oni. In order of magnitude, the top 10 contributors to the global CDR in 2015 were ischemic heart disease, stroke, lower respiratory infections, chronic obstructive pulmonary disease, lung cancers, diabetes mellitus, dementias, diarrheal diseases, tuberculosis (TB), and road injuries (Jamison et al., 2018). Only 3 of the top 10 contributors were infectious diseases, all of which had substantial decreases in their CDRs between 2000 and 2015 (Jamison et al., 2018). In contrast, NCDs represented 7 of the top 10 contributors to the global CDR, and there were considerable increases in the CDRs for dementias, diabetes mellitus, lung cancers, and ischemic heart disease during the same period (Jamison et al., 2018).

An even more granular picture emerges when the CDR data are broken down by country income status (see Figure 2-1). In low-income countries, lower respiratory infections are associated with the largest CDR per 100,000 population, although that CDR dropped substantially between 2000 and 2015. The second and third leading contributors to CDR are stroke and ischemic heart disease, both of which had increases in CDR during that period. Similar patterns were seen both in lower-middle-income and in upper-middle-income countries during the same period. Ischemic heart disease was the largest contributor to CDR in lower-middle-income countries, with an increasing rate over the 15-year period, while lower respiratory infections, TB, and diarrheal diseases all had substantial decreases in CDR. Upper-middle-income countries had CDR increases for the top two contributors, ischemic heart disease and stroke. The CDR rates observed in high-income countries were most similar to the global averages (Jamison et al., 2018). The two leading contributors—ischemic heart disease and stroke—saw substantial decreases in CDRs, while the CDR rate for the third greatest contributor, dementias, increased by a large percentage (Jamison et al., 2018).

Similar transitional patterns are evident in morbidity trends. In South Africa, for example, HIV/AIDS, diabetes mellitus, and major depressive disorder were among the top 10 causes of disability-adjusted life years (DALYs) in 2010 that were not on the top 10 list of causes at all

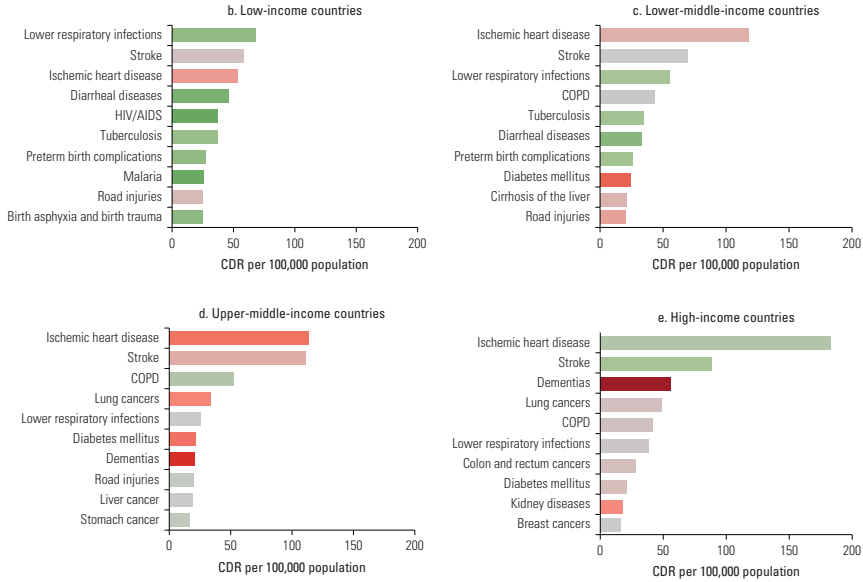

FIGURE 2-1 Crude death rate by country income status, 2015.
NOTES: The colors of the bars indicate causes for which overall death rates are increasing (red) or decreasing (green). CDR = crude death rate; COPD = chronic obstructive pulmonary disease; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome.
SOURCES: Oni presentation, June 11, 2019; Jamison et al., 2018.

in 1990 (Institute for Health Metrics and Evaluation, 2010). Between 1990 and 2010, the number of DALYs caused by diarrheal diseases and lower respiratory infections decreased (Institute for Health Metrics and Evaluation, 2010). During the same period, the following NCD causes of DALYs increased substantially (Institute for Health Metrics and Evaluation, 2010):

- Drug use disorders (around 200 percent)
- Chronic kidney diseases (around 130 percent)
- Hypertensive heart disease (around 100 percent)
- Diabetes (around 100 percent)
- Anxiety disorders (around 50 percent)
- Major depressive disorders (around 40 percent)
- chronic obstructive pulmonary disease (COPD) (around 20 percent)
- Stroke (around 10 percent)

Oni explained that infectious diseases and NCDs are conditions that co-occur but also interact, driving a rise in multimorbidity. In South Africa, the National Income Dynamics Study, which captures data about health as well as socioeconomic deprivation, found double, triple, and even quadruple multimorbidities (Weimann et al., 2016). Diabetes-hypertension was the most common double morbidity, but HIV-hypertension was also significant and underconsidered in many health systems. Significant triple multimorbidities included diabetes-hypertension-HIV and TB-diabetes-hypertension. Hypertension-diabetes-TB-HIV was a significant quadruple multimorbidity. She added that multiple regression analyses indicated spatial clustering of multimorbidities. Factors such as living in the most socioeconomically deprived areas, living in urban versus rural areas, and being obese were all significantly associated with multimorbidity.

Another emerging epidemiological trend is that multimorbidities are being seen in people of increasingly younger ages. This is counter to the norm, but Oni noted that this trend should help spur the global health community into action. A study of people receiving care for either HIV, TB, diabetes, or hypertension looked at patterns of multimorbidity across different age groups in peri-urban South Africa (Oni et al., 2015). Among people aged 18 to 35 years living with HIV, almost 20 percent had HIV and hypertension comorbidity, and around 12 percent had HIV and type 2 diabetes comorbidity, compared to rates of less than 5 percent for people of the same age without HIV (Oni et al., 2015). This is corroborated by global mortality trends, she added. One-third of deaths in lower-middle-income countries occur among people under the age of 60 years, while deaths in high-income countries primarily occur in people over 60 years (Rotheram-Borus et al., 2015).

Dispelling False Dichotomies to Move Toward Convergence

Moving toward convergence will require dispelling myths and false dichotomies about the chronicity, interactions, and risk factors related to infectious diseases and NCDs, said Oni. As an example, she noted that chronicity was generally considered to be an exclusive feature of NCDs until HIV changed that picture. At the center of the global epidemic stage was an infectious disease that is actually a chronic disease, which catalyzed a shift in thinking about how to care for its comorbidity patterns. Among people receiving treatment for HIV, around 20 percent had another health condition: hypertension (77 percent), TB (24 percent), and diabetes mellitus (17 percent) (Oni et al., 2015).

Oni explained that a false dichotomy also pertains to disease–disease interactions. This is the presumption that the causal relationship between NCDs and infectious diseases only works in one direction. However,

evidence suggests that the relationship is bidirectional. A 2015 study of population-attributable risk to TB worldwide found the emergence of smoking and alcohol abuse as factors, in addition to the previously known contributors of HIV and undernourishment (Bates et al., 2015). A more recent study of the patterns of the epidemiology of HIV, TB, and diabetes found a 14 percent population-attributable risk fraction of TB attributable to diabetes and in the context of HIV coinfection (Oni et al., 2017). She added that the reverse also holds true—NCDs can be a consequence of infectious diseases. Furthermore, interactions among co-occurring infections and NCDs can occur over the life course. For instance, malnutrition, stunting, and repeated enteric infections can affect cardiovascular risk later in life (Oni and Unwin, 2015).

Another false dichotomy noted in Oni's presentation is that NCDs and infectious diseases have distinct risk factors. In fact, shared risk factors are also a type of interaction between the two categories of conditions. Figure 2-2 illustrates a number of shared, often socioenvironmental and behavioral, risk factors in relation to both common infections and NCDs (Oni and Unwin, 2015). Considering these shared risk factors is a potential starting point for convergent action, she said. Rapid patterns of urbanization create an additional layer of complexity to shared risk factors, because many settings with emerging epidemics of NCDs coupled with high rates of mortality and morbidity are also experiencing rapid urbanization (Ezeh et al., 2017). Addressing this complexity will require identifying shared risk factors and developing convergent strategies for addressing them, she argued. For instance, urban built environments often have dense informal settlements that facilitate the transmission of infectious diseases (Patterson et al., 2017).

At the same time, unhealthy environments can impede healthy lifestyle choices and contribute to increases in NCDs and multimorbidities (Ezeh et al., 2017). Infectious and zoonotic diseases are reemerging as rapid urbanization pushes the boundaries of human settlements (Ko et al., 1999). This rapid urbanization is also creating waste and water demands that can overwhelm the inadequate urban infrastructure and contribute to the persistence of infectious diseases that should be controllable (Marsalek, 2014). Relatedly, large numbers of younger populations are drawn to urbanization, putting them at increasing levels of exposure and leading to onset of NCDs at earlier ages (Allender et al., 2011).

Spectrum of Interventions to Address the Convergence

The convergence of NCDs and infectious diseases warrants a spectrum of interventions, asserted Oni. Within this spectrum, primary prevention efforts can intervene on upstream factors and determinants that are often

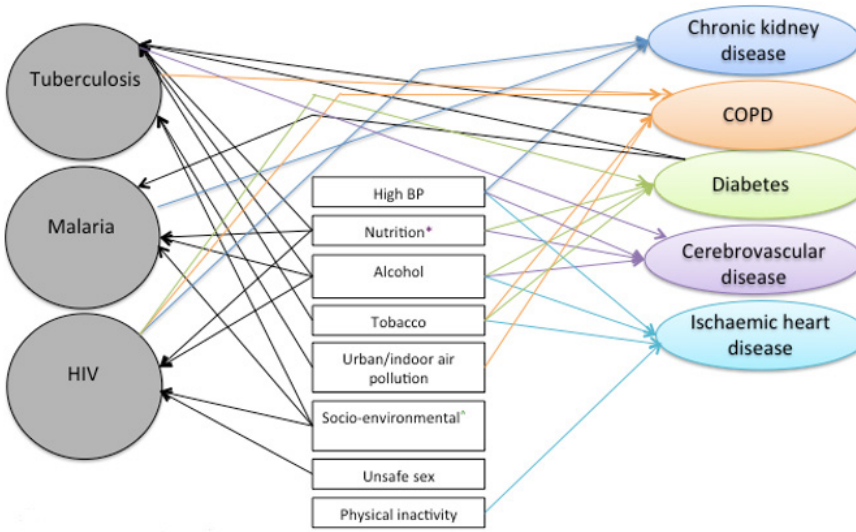

FIGURE 2-2 Risk factors shared between infectious and noncommunicable diseases.
NOTES: BP = blood pressure; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus. * = Encompasses underweight, overweight/obesity, low fruit/veg consumption, high glucose intake. ^ = Conditions associated with informality: overcrowding, unsafe water, and sanitation.
SOURCES: Oni presentation, June 11, 2019; Oni and Unwin, 2015.

shared between infectious diseases and NCDs. The spectrum extends to secondary prevention, such as screening and integrated services, through to tertiary prevention with integrated treatment and care. She emphasized the need to continue to consider health broadly as well as health care—the latter is an important but not exclusive component of health. Oni presented Table 2-1 to frame the spectrum in terms of exposures, health services needed to affect exposures, and the effect of those services on intermediate- and long-term health outcomes. She noted that traditional thinking about health services focuses on the dimensions of access with the aim of achieving long-term significantly positive effects on mortality and morbidity. However, she suggested thinking differently and broadening the concept of health services. For instance, habitation planning, transport, water and waste, and food could all be construed as health services, because the exposures that those services predetermine with respect to intermediate- and long-term effects could also affect both infectious diseases and NCDs (Weiss and McMichael, 2004; Ding et al., 2014).

TABLE 2-1 Spectrum of Exposures, Health Services, and Potential Outcomes

Health Services	Exposures	Intermediate Outcomes	Long-Term Outcomes
Food	Sugar Salt Greenhouse emissions	Eating behavior Obesity	Diabetes Hypertension/CVD/stroke Cognitive function Cancer Climate change
Water and Waste	Pest/vectors Poisoning Physical activity opportunities Air pollution Greenhouse emissions	Physical activity Obesity Health care episodes Health care admissions	Infectious disease Injury Cerebrovascular disease Acute respiratory disease Chronic respiratory disease Climate change
Transport	Noise pollution Social cohesion opportunities Physical activity opportunities Air pollution Greenhouse emissions	Physical activity Obesity Social cohesion	Diabetes Hypertension/CVD/stroke Mental ill-health Chronic respiratory disease Climate change
Habitation (and planning)	Damp Thermal comfort Ventilation Social cohesion opportunities Physical activity opportunities Air pollution	Physical activity Obesity Sleep and stress Social cohesion Health care episodes Health care admissions	Acute respiratory disease Chronic respiratory disease Hypertension/CVD/stroke Mental ill-health Infectious disease
Health Care (prophylaxis, treatment, palliation)	Availability Accommodation Affordable Accessible Acceptable	Health care episodes Health care admissions Disease control	Mortality Morbidity

NOTE: CVD = cardiovascular disease.
SOURCES: Oni presentation, June 11, 2019; Oni et al., 2019.

Oni explored how convergent action could be informed by responses to infectious disease epidemics by presenting a set of arguments made to activate political will, advocacy, research, and funding for HIV framed as a national security threat:

- The risk of exposure and threat of HIV are borderless, and HIV hits adults who are otherwise healthy, including educated populations that drive economic development.
- HIV affects people beyond marginalized populations and is overwhelming at the community scale, but even more detrimental at the macro scale.
- HIV's effect on society projects across a long-time arc, with cross-generational risk that accumulates over time.
- High-risk behavior related to HIV spreads with urban migration and population mobility.
- HIV has a high and growing prevalence in regions and states with significant population growth and urbanization rates, such as China, India, and countries in Africa.

Oni reflected that the same characteristics apply to NCDs such as hypertension, yet global action has not been spurred for NCDs as it has been for infectious disease epidemics. She cautioned, "If we cannot galvanize action for both, we will not be able to act effectively to converge our actions."

To explore reasons for the delay in convergent action against NCDs and infectious diseases, Oni presented some counterfactual points to consider. She drew a distinction between the understanding that a current situation is negative or abnormal as opposed to the shared perception that a situation is ordinary because it has been that way over time or it is not yet possible to predictably say or show the ways in which it is increasing. Similarly, it can be helpful when there is a direct link of cause and effect between an exposure and outcomes. If that link is more diffuse and distant, however, then there may be a lack of data to track the exposures that have a shared effect on shared outcomes. It can also be helpful when roles for interventions are clearly identified, she added, but complex adaptive systems do not necessarily allow for such clarity or delineation.

Potential New Approaches to Convergent Prevention and Control

Oni concluded with a discussion of new approaches to convergent prevention and action from a health care system perspective, which she stated are urgently needed. To that end, care for chronic conditions needs

to be integrated with care for the increasing burden of multimorbidities, rather than framing care around singular diseases per person. She argued that there is a need for this ethos to be integrated into the health care system at all levels and from all perspectives—from the effect of multiple chronic disease morbidities on patients, to health care providers' capacity to deal with the complexities of those patients' needs, to the biological interactions between chronic and infectious disease morbidities (Oni et al., 2014). At the policy level, she said these perspectives need to coalesce to inform integrated management and to engage patients with the health care system by incorporating disease interaction complexity with the perspectives of patients and providers (Oni et al., 2014). Oni added that public health science does not in and of itself create more equitable population health outcomes. This work can be achieved through systems for health that encompass the private sector, individuals and civil society, and policy at the global, regional, national, and subnational levels. Achieving equitable public health outcomes, she argued, will require consideration of each of those channels—for example, the influence of public health science on a population vis-à-vis the private-sector individuals and civil society.

Oni maintained that progress can be driven by fostering collaboration and building relationships to support and promote equitable population health outcomes by leveraging the beliefs, practices, and self-efficacy of individuals and civil society as well as harnessing the potential of economic and environmental drivers. In that context, she made the case for four approaches to convergent prevention and control.

First, adolescents and primary prevention warrant greater focus when considering the associations between co-occurring, preventable conditions and tools to better understand them (Oni and Unwin, 2015). She said that the scientific community has a responsibility to collaborate across sectors and work toward convergence in the intersectional science of prevention through a life-course approach at all socioecological levels, including families, communities, and broader structures.

Second, because treating comorbidities is a multidimensional science, she suggested adopting an integrated approach to capacity building by paying more heed to the workforce who will be implementing new systems and approaches. Integrated training for the new generation of researchers and health practitioners, she added, would provide them with the requisite inter- and transdisciplinary knowledge and experiences to break through silos.

Third, she suggested expanding surveillance beyond individual diseases. This could be done by building on evidence-based interventions around single outcomes to create more innovative approaches that address the need for sustained surveillance.

Fourth, she made the case for intersectoral collaboration focusing on

long-term outcomes by engaging with spatial determinants, particularly in urban settings. This could help shift the disproportionate amount of attention currently devoted to "quick wins" in public health, she said, which often neglect the delayed co-occurrence of morbidities, toward a focus on health outcomes rather than disease outcomes. Oni concluded her presentation by saying the following:

> We need to be bolder in the ways we build and strengthen our systems for health, by thinking beyond just treatment and secondary prevention to research that addresses long-term and delayed co-occurrence in order to improve our health outcomes.

SYNDEMICS OF INFECTIOUS AND NONCOMMUNICABLE DISEASES

In her keynote address, Emily Mendenhall, Provost's Distinguished Associate Professor at Georgetown University, explored how syndemics of infectious diseases and NCDs can inform new approaches to tackling the global burdens. She began by laying the conceptual groundwork for her discussion. Syndemic research builds on three core concepts of epidemiology: epidemics, pandemics, and endemics. An epidemic occurs when a disease has greater than expected frequency across a population. A pandemic is an epidemic that spreads across multiple populations, while an endemic is a well-established disease within a population that remains year after year. A syndemic is the dynamic relationships and synergies among a cluster of two or more epidemics and the various factors that precipitate their interaction within a population. She emphasized that the syndemic is the outcome of the interaction of the health conditions and the social and structural factors.

The concept of the syndemic originated in medical anthropology with Merrill Singer's ethnography work on the complexity of HIV in an inner-city setting. He found that HIV could not be understood without also considering violence and substance abuse, leading him to develop the original definition of a syndemic: "When adverse social conditions, such as poverty and oppressive social relationships, stress a population, weaken its natural defenses, and expose it to a cluster of interacting diseases" (Singer, 1994). Today, syndemic research focuses on locally driven factors that drive clustering of diseases as well as the social, political, and ecological factors that drive that clustering, said Mendenhall. It is helpful to look at those factors as differential and regionally significant, she added, because the historical and political factors that drive the clustering differ from place to place. She emphasized that syndemics are not pandemics, as they are always localized

and never "global" or uniform across contexts—thus the phrase "global syndemic" is by definition a misnomer (Swinburn et al., 2019).[1]

Because of the increasing attention they are receiving across disciplinary boundaries, syndemics need to be carefully defined, cautioned Mendenhall. She outlined three rules for identifying a syndemic:

1. It requires two or more diseases that cluster within a population.
2. Biological, psychological, or social interactions exist between these clustering diseases, with structural, social, and in some cases ecological factors precipitating the clustering.[2]
3. A syndemic is an interaction between the disease clustering and the drivers that comes together to create a more complicated health experience than any disease or social problem would create alone.

For example, in the context of disparity-promoting factors that lead to disease clustering, two diseases can interact in adverse ways that lead to enhanced disease transmission, progression, and negative health outcomes (Singer et al., 2017).

Syndemics of Diabetes, Depression, and Infectious Disease

Syndemic research provides opportunities to consider the convergence of infectious diseases and NCDs. Mendenhall's work on syndemics began when she explored rich epidemiological literature on the bidirectionality of depression and diabetes among women with diabetes who have lived experience of social trauma and sexual, physical, and emotional violence. In this case, the syndemic is the interaction between violence, trauma, diabetes, and depression, which is fundamental to understanding why those women have higher rates of mortality and morbidity than others with diabetes (Mendenhall et al., 2012). The socioeconomic reversal of diabetes parallels globalization, as diabetes escalates among low-income populations across the world (Hsu et al., 2012). Depression and poverty are also

[1] Mendenhall mentioned the various contributions of syndemic scholarship to date—from theorizing the complexities of what syndemics are, especially relative to the social and medical conditions concurrent to HIV (Singer, 1994, 1996, 2009) to theoretical consideration of how syndemics may have emerged through historical and ecological lenses (Singer, 2009). Syndemic thinking has been translated to global health and clinical medicine (Mendenhall, 2017; Mendenhall et al., 2017; Singer et al., 2017; Tsai et al., 2017; Willen et al., 2017). The efficacy of current quantitative approaches to syndemic analyses has also been reconsidered (Stall et al., 2003; Tsai and Burns, 2015; Tsai, 2018).

[2] An example of this is that climate change can drive the clustering of syndemics, such as when mosquitoes move to higher altitudes, thus increasing the risk of malaria and HIV infection.

strongly correlated (Heflin and Iceland, 2009). Although there may be dissimilar rates of acute depression among people with diabetes across income groups, people with untreated, unrecognized depression among low-income groups have much higher rates of diabetes-related morbidity and mortality (Mendenhall et al., 2012). These trends are driven by high lifetime levels of social stress, the interface with depression, the interface with chronic infections such as HIV and TB, and unreliable access to quality, affordable care (Reddy et al., 2007; Mendenhall et al., 2012). This type of syndemic is much more complicated than a straightforward comorbidity, she added. A study that examined the prevalence of type 2 diabetes, HIV/AIDS, TB, and depression in India, Kenya, South Africa, and the United States reveals that all four conditions are much more prevalent among low-income urban populations; those conditions also tended to cluster within the same populations (Mendenhall et al., 2017).

Mendenhall suggested that diabetes is actually a different condition across different contexts. This is because global narratives of diabetes are linked to different food systems and changes across the globe, but also because diabetes is syndemic when it is experienced and embodied by people in a community. She explained:

> The trauma of forced relocation and fragmented social worlds cannot be removed from this story, because real biological and pathological pathways of trauma and chronic stress lead to diabetes, from epigenetics to psychophysiology.

Understanding those syndemic interactions allows for setting-specific understanding of diabetes and its treatment. The population of the Somali region of Ethiopia, for example, has different interactions of food and nutrition (and even wasting) with diabetes, which underscores the need to understand the psychophysiology of trauma, crisis, hunger, and stress that are fueling various types of diabetes (Carruth and Mendenhall, 2019). In a community in South Africa, Mendenhall observed a phenomenon that pushed her to think about syndemic interactions in a different way. Faith healers in the community had been educating people that HIV was a condition just like cancer or diabetes, so people with diabetes would hide their diagnosis because of fears that other people would think they actually had HIV (Mendenhall and Norris, 2015). The social contagion of stigma linked to the experiences of diabetes and cancer in those communities is another interaction that prevents people from seeking care in these contexts, she added.

To illustrate the complexity of syndemics, Mendenhall presented the narrative of Esther, a woman living with diabetes and HIV in Nairobi, Kenya (see Box 2-1). Esther's story unpacks the external environment and

BOX 2-1
Esther's Narrative

Mendenhall described meeting Esther, a woman in her 50s living with HIV and diabetes, at a public diabetes clinic. Esther had to travel a long distance from her home to access the clinic, where she was exposed to people with tuberculosis being treated in other parts of the hospital. She was worried because she knew about the risk the infection would pose to her, given her immunosuppression. Esther had suffered from recent bouts of malaria and typhoid in the past year and was also struggling to manage her severe and sometimes disabling depression. Her upbringing had been difficult and impoverished; she had little education before moving to the city to escape the deep emotional pain related to her past. She had cared for and eventually lost six siblings to HIV before being diagnosed herself.

After the initial shock of diagnosis, Esther trained to become a community health worker to help others who had HIV/AIDS, for which she received a meager stipend that she used to buy food for those she served. During this time, Esther had gotten married and had four children, but her marriage dissolved abruptly after 15 years due to an infidelity. She took her children with her to Nairobi and settled in a slum that was plagued by insecurity and gun violence, fostering chronic stress. She felt these social experiences deeply in her body, linking them to wounds in her stomach. Esther sought counseling and eventually accepted this situation, redirecting her energy to serving those in need.

Six years after Esther was diagnosed with HIV, she was diagnosed with diabetes. She said that diabetes was a shock for her, not because of the diagnosis, but because of the cost. Only HIV services and treatment were free—she had to pay for her diabetes services. This was making her life difficult, because she could not afford the services and often skipped her diabetes medication. Esther wove a complicated story about her diabetes and HIV. Diabetes caused her CD4 count to drop, requiring her to take antiretroviral therapy earlier than she might have otherwise. She described her inability to buy new foods for diabetes care as an extraordinary stress. On the day of the interview with Mendenhall, Esther had been told that she needed to begin taking insulin injections. She explained that she would be not be able to take the insulin, because it is impossible to store insulin without having electricity or a fridge.

SOURCES: Mendenhall presentation, June 11, 2019a; Mendenhall, 2019b.

complexities driving these conditions, and depicts a larger epidemiological narrative that extends over generations. Diabetes and infections are also syndemic in settings with lower HIV presence, but higher rates of other infections (Mendenhall et al., 2017). As diabetes emerges within the context of crisis, displacement, and hunger, the condition will converge and interact with other common infections in those contexts, such as malaria and TB. In the Somali region of Ethiopia, for example, diabetes prevalence is not

well understood. An exploratory study found that most people diagnosed with diabetes did not know if they had type 1 or type 2 (Carruth and Mendenhall, 2019). Although most people were adherent to their medication, they were often underweight (Carruth and Mendenhall, 2019). This underscores the need to better understand the complex interactions between chronic infections, chronic malnutrition, and diabetes.

Why Syndemics Matter

Mendenhall explained that syndemics can change the way we think about disease. Syndemics inherently require consideration of the social, political, ecological, and embodied experiences of what it means to have an illness and what that means in a life. A tenet of anthropology is that a disease is an objective diagnosis, but an illness is experienced. Syndemics require the recognition that diseases rarely exist in isolation, and the identification of social, political, economic, and ecological factors are driving poor health. She noted that work is ongoing to find ways to test syndemics productively to inform upstream interventions and downstream integrated, universal health care. Syndemics also help to determine how co-occurring diseases, medications, social dynamics, and clinical barriers can actually make people sicker—powerful social dynamics underpin treatment adherence and compliance. The most effective interventions to mitigate syndemic interactions may be upstream, downstream, clinical, or community-based interventions. Syndemics also demand that social policies are recognized as key health interventions in people-centered care. For example, policies to promote desegregation, education, and school lunch programs can mitigate barriers to receiving care.

Mendenhall concluded that the concept of syndemics is framed within a transdisciplinary agenda. Syndemics shift thinking about disease and co-occurrence, putting context at the center of how disease emergence, experience, and intervention are understood. Cultivating a comprehensive view of how syndemics emerge, converge, interact, and change reveals how syndemics can affect populations differently, or affect the same population in different ways over time. Syndemics can shift how diseases are studied, moving from ethnography to epidemiology then back to ethnography, with complex biological, psychological, and social interactions assessed using quantitative analyses to better understand illnesses.

DISCUSSION

During the discussion, Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization, highlighted the importance of thinking about syndemics because it may help find

better ways to integrate and find synergies, but he also noted the importance of simplicity because many low- and middle-income countries do not always have all of the resources available. He stated that simple measures that require community engagement, such as measuring blood pressure or glucose levels at community centers, are critical as the first level of care. While there is value in drawing best practices and learning from efforts to integrate HIV and TB care, some of these approaches may not be taken up as the health workers may become fatigued with all of the different practices promoted to them. Espinal questioned, "How can we make sure health workers do their part and those simple measures are available in the community, because if we get too complex, then we might not be adopting those approaches."

Oni suggested differentiating between complexity and complicatedness to avoid the risk of being paralyzed by complexity. Achieving these long-term goals will require embracing complexity and framing simplicity within that complexity, she said. Simplicity is vital to achieving change, she stated, but it does not mean being overly reductive. Over the long term, the focus should be on providing enough care, especially in low-resource settings, to catch up to the demand. She warned that relying on economic growth to propel change will not be sufficient—immediate action is needed to strengthen primary prevention and protect young people at high risk. Oversimplifying without embracing complexity—for example, being entirely focused on screening—will not "turn off the tap" and reduce that risk.

Mendenhall replied that inequality is driving extraordinary divides among health outcomes. For example, South Africa is a relatively wealthy country, but it has some health indicators of a low-income country that are driven (at least in part) by socioeconomic inequality (Omotoso and Koch, 2018). She added that caring for people and their general health conditions, rather than just specific diseases, could make a profound difference, but it requires larger conversations about training, resource allocation, and prioritization of strategies. She added that from an anthropological perspective, patients should feel that they are taken seriously and well cared for beyond just receiving medications; this can be addressed without requiring additional resources.

3

Emerging Research on Associations Between Infectious and Noncommunicable Diseases

The workshop's first session explored the current state of the science and emerging research on the convergence of infectious diseases and noncommunicable diseases (NCDs). Part A of the first session featured three case studies that focused on emerging and novel research on the associations between infections, microbial exposure, and NCDs. The presenters identified knowledge gaps and discussed overall implications for further research and practice. They also described cutting-edge study designs and tools being used to explore emerging associations between infectious diseases and NCDs, as well as the methods used to identify causal links and their temporal relationships.

The first part of the session was moderated by Julie Parsonnet, professor of medicine and of health research and policy, Stanford University. The first presenter, Casey Lynch, chief executive officer (CEO) and co-founder of Cortexyme, Inc., provided a case study on the role of infection in Alzheimer's disease. The case study presented by John Harley, founding director of the Center for Autoimmune Genomics and Etiology at Cincinnati Children's Hospital Medical Center, offered a new perspective on the Epstein-Barr virus (EBV) in autoimmune and inflammatory diseases. Finally, Cathryn Nagler, professor of pathology, medicine, and pediatrics at The University of Chicago, explored the role of the microbiome in food allergies in her case study.

ALZHEIMER'S DISEASE AND *P. GINGIVALIS*

Casey Lynch, CEO and co-founder of Cortexyme, Inc., explored the link between Alzheimer's disease and the bacterium *Porphyromonas gingivalis* (*P. gingivalis*). Her company has developed a novel treatment for Alzheimer's disease that is currently in late-stage clinical testing, and she discussed the data supporting the mechanism of action for this new therapy. Alzheimer's disease is a major public health issue affecting 5.7 million people in the United States and 37 million people worldwide. According to 2018 data from the Alzheimer's Association, the disease is associated with an estimated economic burden of $277 billion. Lynch said that *P. gingivalis*—the key pathogen in periodontal disease—is an instructive example of the difficulty establishing the role of infection in chronic disease because of the long latency period between infection and symptoms.

Neurobiology of Alzheimer's Disease

Lynch explained that over the past 30 years, drug development for Alzheimer's disease has focused primarily on the beta amyloid plaques in the brain of patients, a strategy that has not produced effective treatments (Soscia et al., 2010; Kolata, 2016; Kumar et al., 2016; Gosztyla et al., 2018). Research into the brains of patients with Alzheimer's disease has also revealed neurofibrillary tangles of dystrophic neurons as well as chronic neuroinflammation, microglia l activation of the immune cells, complement cascade activation in the immune system, and inflammasome activation, which is part of the defense against pathogens (Kolev et al., 2009; Cully, 2018; Newcombe et al., 2018; Dionisio-Santos et al., 2019). She explained that these inflammatory processes indicate that there could be an infection upstream of the pathology.

Evidence is converging on the hypothesis that an infection in the brain is driving the pathology related to Alzheimer's disease, said Lynch. The focus on eliminating beta amyloid plaques has shifted to investigating why that beta amyloid is being overproduced.[1] Beta amyloid was found to behave like other antimicrobial peptides that are produced in response to infection. These antimicrobial peptides share many properties with beta amyloid, including their size and their ability to form oligomers. She said that although infections can cause a wide variety of neurological diseases (such as

[1] *Amyloid* is a general term for protein fragments that the body produces normally. Beta amyloid is a protein fragment snipped from an amyloid precursor protein. In a healthy brain, these protein fragments are broken down and eliminated. Amyloid plaques are hard, insoluble accumulations of beta amyloid proteins that clump together between the nerve cells (neurons) in the brains of Alzheimer's disease patients (BrightFocus Foundation, 2017).

neurological Lyme disease, listeria, syphilis, and HIV), an infectious disease cause of Alzheimer's has been elusive.

Link Between Periodontal Disease and Alzheimer's Disease

Lynch explained that about a decade ago, epidemiological and twin studies began to emerge showing a link between periodontal and Alzheimer's disease. Tooth loss, periodontal disease, and the bacterium *P. gingivalis* were identified as risk factors for Alzheimer's disease, with prospective studies suggesting that having periodontal disease in one's 40s or 50s increased the risk for developing Alzheimer's disease later in life (Stein et al., 2007; Kaye et al., 2010; Sparks Stein et al., 2012; Kamer et al., 2015). These studies suggested that periodontal disease was happening first—that is, it was not just a case of people losing their memory and neglecting their oral health, she reported. The biology of periodontal disease has commonalities with Alzheimer's disease. They are both chronic, slowly progressing, age-related, degenerative diseases, featuring low-grade chronic inflammation (Abbayya et al., 2015). Lynch emphasized that epidemiology cannot prove causation, so this evidence catalyzed international research efforts into testing the hypothesis of whether *P. gingivalis*, a keystone in periodontal disease, could be entering the brain and contributing to the development of Alzheimer's disease.

P. gingivalis is a common infection in the mouth—half of elderly people have symptomatic periodontal disease and 80 to 90 percent are infected with this bacterium, Lynch reported. She then explained that this common gram-negative pathogen does not stay in the mouth if a person flosses and has bleeding gums—it can enter the circulatory system. A complex interaction of factors determines whether the bacterium then enters and infects the brain. Aging is a factor that can affect the immune system and the blood–brain barrier. Although genetic risk factors do exist, only a few hundred families have true familial disease, she stated. There are at least 25 genetic risk factors that predispose people to the disease, such as ApoE4 and immune system proteins, including TREM2, microglia l protein TLR4, and CR1 (Van Cauwenberghe et al., 2015). She said that this variability in the immune system might predispose certain people to brain infiltration and infection (Cao and Zheng, 2018). Traumatic brain injury, stroke, and microhemorrhage are also risk factors for Alzheimer's disease (Ramos-Cejudo et al., 2018).

Bacterial Brain Infiltration Triggers Alzheimer's Disease Pathology

The bacterial load of *P. gingivalis* in the brain is believed to directly cause neurodegeneration, said Lynch. *P. gingivalis* is an intracellular, asaccharolytic

bacterium that secretes enzymes to digest host, intracellular proteins. These enzymes gradually cause cell dysfunction and ultimately death. She added that the bacteria also cause downstream immune dysfunction, enhancing the organism's ability to infect and propagate in the brain.

Lynch presented findings to suggest that *P. gingivalis* brain infiltration precedes and is correlated with Alzheimer's disease symptoms and pathology. Gingipains are the putative virulence factor enzymes secreted by *P. gingivalis* (de Diego et al., 2013). In animal models, inhibition of gingipains has prevented neurodegeneration, inflammation, and other pathology related to Alzheimer's disease. The presence of *P. gingivalis* in Alzheimer's disease is supported by the identification of organism-specific DNA in cerebrospinal fluid and tissue gingipains through immunohistochemistry of Alzheimer's-affected tissue in 95 percent of patients (Dominy et al., 2019). These findings were specifically presented by a study using the University of Auckland Brain Bank's microarrays, which are tiny samples from many different brains. The study found that 95 percent of samples from Alzheimer's patients were positive for gingipains in the region of the brain affected by Alzheimer's disease (Dominy et al., 2019). Some of the control samples were also found positive with gingipains but asymptomatic, which is a helpful finding because it shows carriers of the bacteria prior to symptom manifestation, and establishes a timeline of infection. If only Alzheimer's patients were infected and all of the controls were negative, it would suggest that this is a late-stage event, she explained. However, Alzheimer's pathology is known to begin 10 to 20 years before symptoms emerge. In these asymptomatic people, the gingipain load continues to build up in their brains—along with their Tau pathology,[2] which she noted is a good correlate to cognitive decline—until they later become symptomatic.

Evidence of Causation from Animal Models

Animal models have demonstrated that *P. gingivalis* infection infiltrates the brain and causes Alzheimer's-like pathology, said Lynch. One study found that oral *P. gingivalis* infection in mice resulted in colonization and increased production of a component of amyloid plaques in their brains (Dominy et al., 2019). In another seminal study, wild-type mice were orally infected with *P. gingivalis*, inducing Alzheimer's pathology after 22 weeks (see Figure 3-1).[3] After entering the brain, the bacteria caused chronic, low-grade inflammation, which triggered beta amyloid plaques, caused activated microglia, and induced Tau tangle-like neurons. Approximately 50 percent of the neurons in the hippocampus, the memory center of the brain, died

[2] Tau is a protein needed for normal neuronal function.

[3] These are regular mice, not transgenic mice that overexpress proteins.

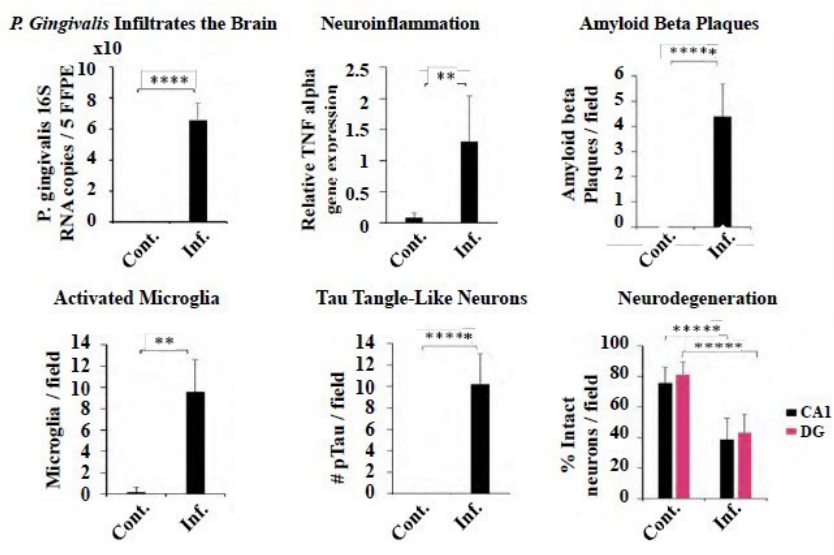

FIGURE 3-1 Oral *P. gingivalis* infection induces Alzheimer's disease pathology after 22 weeks.
NOTES: Cont. = control; Inf. = infected; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$; **** = $p < 0.0001$; ***** = $p < 0.00001$; 5FFPE = formalin fixed paraffin embedded; CA1 = carbonic anhydrase 1; DG = dentate gyrus; #pTau = Tau protein; TNF = tumor necrosis factor.
SOURCES: Lynch presentation, June 11, 2019; Ilievski et al., 2018.

(Ilievski et al., 2018). Lynch said that it is unprecedented for an animal model to mimic the characteristic pathology of Alzheimer's disease so closely. In addition to addressing causation, the mouse model may also provide a new model for drug development that will be more translatable to human studies.

Initial Clinical Studies on Gingipain Inhibition

Based on these breakthroughs, Lynch's company is developing a new drug, COR388, to treat patients with mild to moderate Alzheimer's disease. COR388 is the first gingipain virulence factor inhibitor. Available data support the key role of *P. gingivalis* in the disease's progression, she said. In a Cortexyme phase 1B clinical study for COR388, there were no serious adverse effects, with 20 percent of the placebo and 14 percent of the COR388 treated subjects experiencing drug-related adverse effects. She also noted that nine out of nine patients with mild to moderate Alzheimer's disease were found to have *P. gingivalis* DNA in their cerebral spinal fluid

(Dominy et al., 2019). She reported that a separate observational study found that all 50 patients with mild to moderate disease were also positive for *P. gingivalis* DNA fragments. Lynch said that these studies reinforce the prevalent immunohistochemistry data that *P. gingivalis* is highly prevalent in a well-diagnosed Alzheimer's population.

Lynch presented more data suggesting that gingipain inhibition shows beneficial effects upstream of neurodegeneration, inflammation, and other pathology. As part of the drug development process, researchers are developing biomarkers to track chronic *P. gingivalis* infection in the central nervous system and understand the effect of treatment. Cortexyme's clinical study found decreases in inflammatory biomarkers in the blood after a 28-day treatment with the COR388 molecule, as well as changes to fragmentation of important proteins in the cerebral spinal fluid (Dominy et al., 2019). The hope is that the clinical drug COR388 could reduce the fragmentation of proteins in the brains of Alzheimer's patients, thus preserving the integrity of the brain proteins.

She said preliminary exploratory cognitive testing of a small group of patients treated with COR388 for 28 days has suggested a trend to benefit or significant cognitive benefit. Although the ultimate goal of the intervention was to level off decline by blocking any further neurodegeneration caused by the bacteria, the investigators found potential improvement that is consistent with the mouse studies, in which COR388 reduced inflammation quickly. Neurons cannot be revived after they are dead, she noted, but the immune response is adaptable to any infection, including *P. gingivalis*. The mouse and clinical studies suggest that treating the infection can potentially make existing but dysfunctional neurons become functional again. She said that an ongoing international phase II/III study is currently enrolling, with top-line data expected by the end of 2021.

EPSTEIN-BARR VIRUS IN AUTOIMMUNE AND INFLAMMATORY DISEASES

John Harley, founding director of the Center for Autoimmune Genomics and Etiology at Cincinnati Children's Hospital Medical Center, provided a genomic perspective on EBV in autoimmune and inflammatory diseases. EBV infects more than 95 percent of the adult human population (Cohen, 2000).[4] EBV is a gamma-herpes virus that is transmitted through saliva and breast-feeding, infects the tonsils, and then disseminates to other parts of the body (Moss et al., 2007). He explained that in low- and middle-income countries, the virus tends to be acquired during the first 2 years of life. In middle- and

[4] This has been established most convincingly in children, who have a far lower rate of the virus than adults.

upper-income countries, approximately 70 percent of people acquire the virus during adolescence (Balfour et al., 2013). In the latent phase, the virus avoids and suppresses immune responses. Harley said that everyone who is infected with EBV is suppressing cancer—an EBV-transformed B cell that is in latency III of the virus (Saha and Robertson, 2019).[5]

Diseases Attributed to Epstein-Barr Virus

Many diseases have been attributed to EBV, said Harley. For instance, lupus, an idiopathic inflammatory disease affects an estimated 200,000 people in the United States and millions of people worldwide (Rees et al., 2017).[6] The molecular mimicry process that causes lupus may originate from humoral responses to EBV nuclear antigen 1 (Harley and James, 2006). Virtually all patients with lupus are infected with EBV, Harley said. However, most adults infected by EBV are asymptomatic or only have upper respiratory illness (Cohen, 2000). Approximately 3 percent of people develop mononucleosis from the virus—typically during adolescence. The virus lives in the memory B cells and then comes out of those memory B cells slowly during life (Tracy et al., 2012). EBV is associated with nearly all cases of multiple sclerosis, although the mechanism is yet unknown (Guan et al., 2019). It is also linked to almost all cases of nasopharyngeal cancer, which is highly prevalent in Southeast Asia (Cohen, 2000). Approximately one-third of cases of Hodgkin's lymphoma are attributable to EBV (Massini et al., 2009). EBV is also associated with carcinoma of the stomach, diffuse large B cell lymphoma activated cell type, immunoblastoid B cell lymphoma (particularly in people who are immunocompromised), leiomyosarcomas, T-cell and nasal natural killer lymphomas, and Burkitt's lymphoma (Okano and Gross, 2012).

Genomic Perspective on the Origin of Lupus

Harley explained that research is ongoing into the origins of lupus, from both environmental and genetic perspectives. Genetics provides an indication, or a tag, for mechanisms that operate to create disorders such as lupus, he stated. The most powerful tool for this work is a genomewide association study (GWAS), which compares large numbers of cases and controls to identify hundreds of thousands of markers across the human

[5] Depending on the viral gene expression pattern, primary EBV infection establishes three types of latent infection statuses. Type III latency occurs when most latent genes are expressed (Kang and Kieff, 2015).

[6] Women are 10 times more likely to have lupus than men; it is 3.5 times more frequent among people who are African American and of African ancestry.

genome (Welter et al., 2014). A concept in which genes related to disease susceptibility are localized or identified, called linkage disequilibrium blocks, are used to identify causal associations among many possible candidates (Robinson, 1998; Wangler et al., 2017). An estimated 40,000 of these blocks have been identified for almost 2,000 phenotypes in the human population, which are available in the online GWAS catalog, Harley stated. Researchers studying lupus have spent two decades working on these genes, he added. Meta-analyses of lupus genetic associations have determined that there are dozens of individual genetic mechanisms in the genome that alter risk for lupus (Langefeld et al., 2017).

Genetic and environmental factors converge in working toward a unified understanding of the etiology of lupus, said Harley. The aim is to find a parsimonious way to unify what is known about lupus into a conceptual construct that can be used to develop better diagnostics, therapeutics, prevention, and prognosis. A primary research aim is to identify the mechanism through which EBV causes lupus, based on the assumption that both genes and the environment contribute to the origins of disease. Population-level genetic factors, such as natural selection, have been suggested to change lupus allelic frequency, but there has not yet been insight into that mechanism (Ramos et al., 2014). GWAS studies are consistent in showing that an estimated 90 percent of the polymorphisms associated with lupus are regulatory, so research is looking for a regulatory type of explanation in the phenotypes that have been studied (Deng and Tsao, 2014). It has also been observed that EBV makes its own transcription factors, which are regulators of gene expression (Harley et al., 2018).

Harley and colleagues predicted that the transcription factors made by EBV are concentrated in the lupus genetic loci. He said that about 136 genes have now been identified using a procedure called chromatin immunoprecipitation[7] followed by next-generation sequencing (ChIP-Seq) (Szalkowski and Schmid, 2011). This procedure involves creating an antibody against the transcription factor and analyzing it after it immunoprecipitates (i.e., isolating the antigen using a specific antibody that binds to it) to determine the loci where the transcription factor shares a variant with the disease. Looking at 1,544 human datasets, they found that the co-factor for transcription EBV nuclear antigen 2 (EBNA-2) binds to half of the lupus loci (Harley et al., 2018). They also identified a regulatory cluster that is hypothesized to be EBV related, suggesting that the EBV-infected B cell is the only cell type in which this binding happens—this is not observed in B cells that are not EBV-infected or in any other cell type. Therefore, they concluded that the evidence suggests a substantial proportion of the EBV risk for lupus comes from the EBV-infected B cells that live in the patient.

[7] A technique used to identify physical interactions between proteins and DNA in cells.

Applying the Genomic Approach to Other Conditions

Harley explained that genome informatics approaches also apply to other conditions attributed to EBV, including multiple sclerosis, rheumatoid arthritis, and type 1 diabetes. Based on evidence linking these diseases to EBV, it is now possible to look at all diseases that qualify for the analysis against the transcription factors with ChIP-Seq datasets. Analysis suggests that chronic lymphocytic leukemia has an EBV story, with EBV nuclear antigen 3-C LP and EBNA-2 all clustering with chronic lymphocytic leukemia genes (Kim et al., 2017). He said that vitiligo has also been recently added to this group; in some instances, it shows allelic specificity consistent with the possibility that this is actually a genetic mechanism (Harley et al., 2018). Similar work can be done on diseases that are not EBV related, but have a similar regulatory story, such as breast cancer and coronary artery disease. He said that research is continuing to add a substantial number of disorders that are potentially related to EBV infection.

ROLE OF THE MICROBIOME IN FOOD ALLERGIES

Cathryn Nagler, professor of pathology, medicine, and pediatrics at The University of Chicago, focused her presentation on the role of the microbiome in food allergies. She opened by describing the scope of the food allergy epidemic and the dramatic increase in prevalence of food allergies (Gupta et al., 2018, 2019). An estimated 32 million people in the United States now have food allergies, including 1 in 10 adults and 1 in 13 children (Gupta et al., 2018, 2019; FARE, 2019). More than half of adults and more than 40 percent of children with food allergies have experienced a severe reaction (Gupta et al., 2018, 2019; FARE, 2019). Between 2007 and 2016, insurance claims with diagnoses of anaphylactic food reactions increased by 377 percent (FAIR Health, 2017; FARE, 2019). She said that to explain such a dramatic generational increase in food allergies, researchers turned to the microbiome. She defined the microbiome as the microbes that populate a person's skin and mucosal surfaces, which can have beneficial functions for health. Nagler explained that while the microbiome consists of all classifications of micro-organisms, bacteria tend to receive greater focus because they are understood most clearly at this point.

Effect of Modern Lifestyle Factors on the Microbiota

Nagler presented the hypothesis that modern industrialized lifestyle factors trigger shifts in the composition of our commensal[8] microbiota in ways

[8] *Commensalism* refers to the association between two organisms in which one benefits and the other is neither harmed nor benefits.

that are detrimental to human health (Iweala and Nagler, 2019). There is some evidence linking NCDs such as obesity, diabetes, autism, inflammatory bowel disease, and many other diseases to changes in the microbiome (West et al., 2015). Multiple lifestyle factors contribute to altered commensal microbial biodiversity, she said. Antibiotic use, including both prescribed antibiotics and antibiotics in our food and water supply, is one of the biggest lifestyle culprits (Langdon et al., 2016). The prevalent high-fat, low-fiber diet is also a significant factor in shaping the microbiome (West et al., 2015). Humans and our microbiota have coevolved over millennia, Nagler said, and human ancestors consumed a diet that was high in fiber, low in processed foods, and low in sugar. "Our bacteria eat what we eat, and we've changed their food source," she said. Another factor she suggested is the transition from rural and suburban living, in which people were in close contact with bacteria from the environment, to living in sealed houses in urban settings. Vaccine-induced immunity and reduced exposure to infection is a modern lifestyle factor that may help explain why NCDs have increased as the prevalence of infectious disease has decreased, according to Nagler. Yet another factor Nagler suggested is the eradication of previously common enteropathogens, like *Helicobacter pylori* and gastrointestinal helminths. She proposed that in a setting of genetic susceptibility, these lifestyle factors are driving up the prevalence of food allergies.

Colonizing Healthy Microbiota to Protect Against Allergic Response

To address the increasing prevalence of food allergies, Nagler and her colleagues have collaborated with a group at the University of Naples that provided fecal samples from 20 healthy infants and 20 infants with cow's milk allergy (CMA) (Berni Canani et al., 2016).[9] At 4 to 5 months of age, samples from the healthy infants showed the expected type of bacteria, which were dominated by yogurt-type bacteria—conventional probiotics, Lactobacillales, and *Bifidobacteria*. In the CMA infants, those types of bacteria were depleted; instead, they had an adult-type microbiota, suggesting that the normal ecological succession that populates microbiota from birth through the first few years of life had been accelerated (Berni Canani et al., 2016).

To study the interactions of the bacteria with the host, Nagler and colleagues created a germ-free mouse model to investigate whether mice colonized with a healthy microbiota would be protected against food allergy.[10] She explained that this is a powerful methodology because it allows investigators to identify specific populations of bacteria, then precisely control

[9] She noted that this study population was a much more homogeneous population than would be seen in a clinic in the United States in terms of racial, ethnic, and dietary diversity.

[10] In a germ-free mice facility, mice are housed in flexible film isolators to ensure sterility.

and introduce them into groups of mice. They collected fecal samples from four healthy donors and four CMA donors. All of the donors were 6 months of age and were controlled for all identified demographic variables. Each donor's sample was contained in its own isolator to keep the microbiomes of each donor intact. The first experiment involved transferring fecal samples from breastfed infants, but the translation of the fecal material from the humans into the mice was imperfect because of the presence of the breast milk–dominated bacteria, *Bifidobacteria*. To improve the transfer of human bacteria into mice, they used formula-fed human donors and fed the mice the same formula the infants were consuming. The results from 100 gnotobiotic mice demonstrate that the mice colonized with the healthy infant microbiota were protected from an allergic response to food. The mice that received microbiota from CMA donors were susceptible to anaphylaxis, as were the germ-free mice to a lesser extent. The anaphylaxis correlated with the induction of an antigen specific to bovine lactoglobulin-specific immunoglobulin E (IgE), bovine lactoglobulin-specific IgG1, and mucosal mast cell protease-1 response (Feehley et al., 2019).

The research team then identified the bacterial populations and discovered that differentially abundant operational taxonomic units (OTUs), or bacterial sequences, can distinguish mice colonized by the healthy versus CMA donors (Feehley et al., 2019). Nagler said that nine OTUs significantly correlated with genes upregulated in the ileum of healthy or CMA-colonized mice (Feehley et al., 2019). Three were from the family Lachnospiraceae, which had been previously identified as allergy protective. The closest match for the protective Lachnospiraceae OTUs was *Anaerostipes caccae* (*A. caccae*), which produces a butyrate found in the human infant gut.

Mice monocolonized with *A. caccae* were protected against an allergic response to food using the same parameters they had previously measured. Another study demonstrated that another species of bacterium from the Clostridia class (which contains the Lachnospiraceae) helps to protect against colonization with bacterial pathogens early in life (Velasquez-Manoff, 2015). The picture that emerges from these studies is that bacterial populations operate like the gut's "peacekeepers" (see Figure 3-2). Nagler explained that bacteria such as *Anaerostipes* and *Faecalibacterium prausnitzii* ferment dietary fiber to make short-chain fatty acids, including butyrate, which contribute to maintaining the healthy epithelial barrier function. Specifically, the epithelial barrier needs an intact mucous layer to keep opportunistic microbes and toxins in food from gaining access to the rest of the body and causing disease.

Potential Microbiome-Modulating Therapeutics

Microbiome-modulating therapeutics could help to prevent and treat allergic or inflammatory disease, said Nagler. She is part of an academic

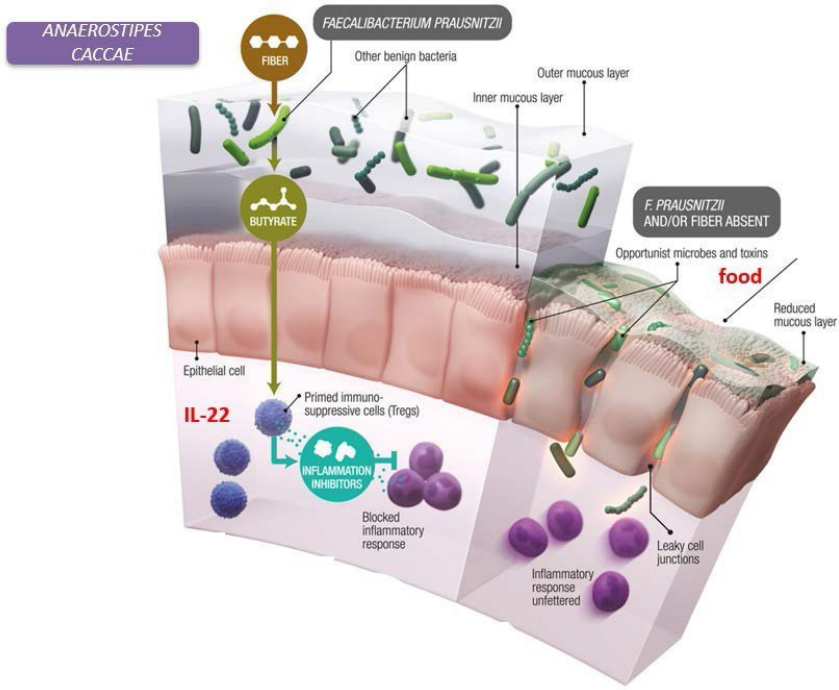

FIGURE 3-2 Some species of microbes keep humans healthy.
NOTE: IL-22 = Interleukin 22.
SOURCES: Nagler presentation, June 11, 2019; Bollrath and Powrie, 2013; modified from Velasquez-Manoff, 2015.

startup (ClostraBio) that is working to engineer synthetic drugs to mimic the protective function of healthy bacteria. The first approach is to make synthetic polymers to confer stability, solubility, and control of active ingredient release. To this end, ClostraBio is developing polymers that have conjugated microbial metabolites. The first candidate is butyrate; however, they are also considering live biotherapeutic approaches and prebiotic dietary fibers to present bacteria with their substrate and all of the components they need to be able to optimally produce the metabolites.

DISCUSSION

Julie Parsonnet, professor of medicine and of health research and policy, Stanford University, thanked the presenters and opened the floor for questions. The discussion further delved into issues specifically related to *P. gingivalis* and Alzheimer's disease, and food allergies and the microbiome.

P. gingivalis Infection and Alzheimer's Disease

Srinath Reddy, president of the Public Health Foundation of India, noted that the process of amyloid formation and Tau tangles are generally understood to be protective mechanisms that evolve against multiple microbial threats, not specific to *P. gingivalis*. For instance, studies have suggested that people treated for herpes virus are better protected against dementia than people who are exposed to herpes virus but not treated. He asked Lynch if antimicrobial peptide response could be an evolutionary protective mechanism. Lynch replied that this response certainly is a protective mechanism and not specific to one pathogen. She noted that the constellation of data around *P. gingivalis* is compelling with respect to causation, but more work is needed around other pathogens, and such hypotheses need to be tested in human clinical studies to progress beyond basic science and make a difference for patients.

Kent Kester, vice president and head of translational science and biomarkers at Sanofi Pasteur, asked whether antibiotics would be an effective treatment for Alzheimer's disease as related to intracellular infections by *P. gingivalis*. Lynch replied that it has been well studied in the dental field that *P. gingivalis* cannot be eradicated with broad-spectrum antibiotics because it is persistent, often resistant to antibiotics, exists inside biofilms inside cells, and is gram-negative. As result, it is a chronic recurring infection. Virulence factor inhibitors work against *P. gingivalis* by blocking the toxicity of gingipains. Even though the immune response to amyloid-beta characteristic of Alzheimer's disease is probably not specific to *P. gingivalis*, Lynch and her research team believe that the constellation of pathology it produces is tied to *P. gingivalis* and the activity of these gingipains. Therefore, they believe that the fragmentation of intracellular proteins in neurons is a gingipain-dependent effect. Blocking the gingipain toxicity renders the bacteria completely benign and staves off the *P. gingivalis* bacteria. This strategy represents a new type of approach to infection that has novel benefits in terms of both adverse events and antibiotic resistance.

Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention, asked if there are any epidemiologic associations between populations with different levels of dental hygiene and the occurrence of Alzheimer's disease or if it is so persistently difficult to eradicate that it may not even correlate to dental caries or other issues. Lynch responded that such an analysis is not very feasible, given the large number of variable factors related to having periodontal disease and Alzheimer's. She clarified that the contention is not that periodontal disease causes Alzheimer's—people can get Alzheimer's without having ever had symptomatic periodontal disease—but it is the same infection in two different organs.

Lynch emphasized that it is not yet known if treating periodontal disease will reduce the risk of Alzheimer's disease, because it is difficult to treat

the infection and inflammation well enough to test the hypothesis. Once an infection is established, the treatment itself could also cause translocation of the bacteria; the effect of reducing the bacterial load in the mouth versus moving it around the body is not yet understood. However, because the existing epidemiology suggests that a high bacterial load in the mouth is one of the risk factors for Alzheimer's disease (Harding et al., 2017), good oral health and preventive oral care beginning in childhood are likely to be beneficial.

Harley asked Lynch if their drug has been tested for periodontal disease. Lynch replied that it has been tested in a mouse model and a naturally occurring dog model that found efficacy in periodontal disease. They are carrying out a sub-study of the Alzheimer's study to assess efficacy in periodontal endpoints. There is potential for FDA approval for periodontal disease, because it is a chronic recurring disease with an unmet medical need.

Food Allergies and the Microbiome

On the topic of microbiome, Kester asked if repopulating the gut with butyrate-producing bacteria would be a feasible approach. Nagler replied that it is probably not possible, because repopulation is difficult. A patient with a food allergy has a dysbiotic—but complete—microbiome, so there is no niche in which to introduce new bacteria—hence her team's microbial metabolite approach. They have found that one of their drugs under development induces antimicrobial peptides in the small intestine, which may have a microbiome-modulating capability. Starting to modulate the microbiome with fiber and perhaps live therapeutics could begin to create a foothold that would allow it to repopulate to a certain extent, she said.

Varma asked if the so-called gut peacekeepers are exclusively acquired in the birth canal or if they can be acquired at some point during infancy. Nagler explained that Clostridia are obligate anaerobes that are acquired from the environment; they are highly oxygen sensitive and are predominantly spore formers. There is an association with mode of birth and susceptibility to disease, with higher rates of disease in children that are born by cesarean section (Neu and Rushing, 2011). However, the bacteria acquired at birth are *Lactobacilli* from the mother's vaginal tract, while babies born by cesarean section have skin-derived bacteria as their founder bacteria. How long that founder effect persists is still a matter of debate, she said.

Finally, Parsonnet asked if presenters anticipate that patterns of food allergies, lupus, or Alzheimer's disease will begin to affect low- or middle-income countries as they have higher-income countries. Nagler replied that the prevalence of food allergies in China and Japan has been increasing rapidly over the past decade or so, possibly caused by the lifestyle factors of diet and overuse of antimicrobials (Loh and Tang, 2018). She noted that in

the United States, the age of introduction of allergenic foods contributes to driving the increase, which may not be affecting other populations. Harley responded that in the case of multiple sclerosis, the age of infection is a contributor. People who get a serious EBV infection during their teenage years have an increased risk of between two- and seven-fold of multiple sclerosis (Endriz et al., 2017). Humans' primitive ancestors tended to acquire the virus in the first few years of life, which appears to be more of a T-cell response than the humoral response that tends to happen later in life.

4

Risks Posed by Chronic Diseases to the Development and Severity of Infectious Diseases

During the second half of the first session, two presenters explored the current knowledge on the known and suspected risk that chronic diseases pose to the development and severity of infectious diseases. Through the presentation of two case studies, they also discussed the knowledge gaps and implications of the cases on public health policy and practice. The first case was presented by Christoph Thaiss, assistant professor of microbiology at the University of Pennsylvania Perelman School of Medicine. He discussed the association between metabolic syndrome and the risk of enteric infection. The second case was presented by Julia Critchley, professor of epidemiology at the Population Health Research Institute, St. George's University of London, who examined the epidemiology and public health consequences of the converging epidemics of tuberculosis (TB) and diabetes. This part of the session was moderated by Kent Kester, vice president and head of translation science and biomarkers at Sanofi Pasteur.

METABOLIC SYNDROME AND THE RISK FOR ENTERIC INFECTION

Christoph Thaiss, assistant professor of microbiology at the University of Pennsylvania Perelman School of Medicine, explained that environmental factors influence susceptibility for many common diseases, including metabolic diseases like obesity and diabetes as well as general inflammatory diseases. A 2015 study of tens of thousands of people in Denmark concluded that a high body mass index (BMI) is associated with an increased risk for

infections overall (Kaspersen et al., 2015). The investigators subdivided the infections that were studied into different organ systems and infectious agents, determining that this association holds true across various diseases—respiratory infections, skin infections, mucosal infections, and gastrointestinal infections. From the perspective of scientists, the lack of scientific mechanistic data to explain the association between BMI and infections was an important one to address.

Association Between Obesity and Intestinal Barrier Dysfunction

To address this gap, Thaiss and his group worked with the db/db mouse model, which has a mutation in the leptin receptor that prevents the mouse from feeling satiety (Thaiss et al., 2018). Even when the mouse is fed a normal diet, it becomes morbidly obese. Compared with healthy wild-type control mice, they found that db/db mice experience a leaky gut phenomenon. They observed that, in these mice, the microbial molecules have triggered some of the receptors of the innate immune system (such as the toll-like receptors and the nod-like receptors) in their serum, spleen, and livers. The signal created by triggering these receptors was always much higher in the db/db mice, which indicates translocation of microbial molecules across the gut barrier to systemic sites (Thaiss et al., 2018). To look in more detail at the intestinal barrier, the researchers used RNA sequencing to quantify the expression of ZO-1, one of the main proteins involved in creating a tight barrier in the gastrointestinal tract. This confirmed that in addition to being morbidly obese, the db/db mice have poor barrier function in the gastrointestinal tract (Thaiss et al., 2018).

To explore the relationship between intestinal barrier dysfunction and enteric infection, they infected the mice with a bioluminescent version of a mouse pathogen called *Citrobacter rodentium*, which is the equivalent of pathogenic *Escherichia coli* in humans. The db/db mice were massively colonized and, over time, there was a huge outgrowth of these bacteria in the morbidly obese host (Thaiss et al., 2018). In addition to bacterial growth, the microbial molecules translocated to systemic tissues like the mesenteric lymph nodes, the spleen, and the liver. Thaiss explained that this type of massive colonization never occurs in wild-type mice because *Citrobacter rodentium* is a self-limiting infection that stays in the gastrointestinal tract unless there is a barrier problem.

Hyperglycemia Drives Susceptibility to Enteric Infection

Thaiss explained that to test the presumed association between obesity and enteric infection, the next step was a paired feeding experiment. They used this experiment to prevent obesity by limiting the amount of food that

the db/db mice could eat and pairing it to the amount of food the wild-type mice had eaten. Even though the db/db mice did not become obese, they were still susceptible to the infection, which meant that obesity was not a sufficient explanation (Thaiss et al., 2018). To determine that hyperglycemia—rather than obesity per se—was driving the susceptibility to enteric infection, they used a type 1 diabetes model to generate hyperglycemia in wild-type mice. They injected the mice with the toxin streptozotocin, which kills all of the insulin-producing pancreatic cells. In this model, despite not being obese, hyperglycemia rendered these mice highly susceptible to the same enteric infection (Thaiss et al., 2018).

The results suggested that hyperglycemia drives intestinal barrier dysfunction, said Thaiss. As observed in the db/db mice, the streptozotocin-treated mice had systemic colonization by the bacteria in their spleens and livers, indicating a massive intestinal barrier problem and abrogated levels of E-cadherin, a cell–cell adhesion molecule that is a component of intestinal barrier stability (Thaiss et al., 2018).

Epithelial Glucose Transporter 2 Deficiency Restores Barrier Function

These mice studies also provide insight into the mechanisms underlying glucose transport. Typically, glucose enters into the body co-transported with sodium (Navale and Paranjape, 2016). Then, it is transported along a passive concentration gradient—called glucose transporter 2 (GLUT2)—into the bloodstream by exiting the intestinal epithelial cells (Navale and Paranjape, 2016). The hypothesis was that in the case of metabolic disease, in which the host is hyperglycemic and has high concentrations of glucose in the blood, the concentration gradient is flipped (Thaiss et al., 2018). Instead of leaving the intestinal epithelial cells, glucose is now accumulating in the intestinal epithelial cells and causing damage to the barrier. To test this hypothesis, Thaiss and colleagues generated mice lacking GLUT2, which would prevent glucose flux into intestinal epithelial cells. GLUT2-lacking mice were then treated with streptozotocin to render them hyperglycemic; the researchers noted that, at least partially, this prevented the barrier dysfunction problems. The microbial molecule assay revealed that the accumulation of these molecules was no longer occurring. The mice were also protected from systemic spread of bacteria in the spleen and liver when compared to controls.

Epithelial Glucose Metabolism Influences Barrier Function

Thaiss ended his presentation by explaining how epithelial glucose metabolism may influence barrier function in a person with diabetes. As glucose follows a retrograde flow into intestinal epithelial cells, it leads to glucose metabolism in the cell and transcriptional and epigenetic

reprogramming. This ultimately alters barrier function, which allows microbial molecules to enter the systemic circulation (Thaiss et al., 2018).

To begin exploring the mechanisms in humans, Thaiss's group assessed a small cohort of healthy volunteers. They found that having high levels of hemoglobin A1c (HbA1c), an indicator of long-time glycemic control, was strongly correlated with having high abundance of microbial molecules, which is indicative of a leaky barrier in the gut. Interestingly, BMI was not correlated with an increased systemic presence of microbial molecules. In humans as in mice, it appears that it is specifically hyperglycemia—not obesity or metabolic disease per se—that is causing this phenotype (Thaiss et al., 2018). Expanding this human analysis will shed further light on the importance of glycemic control and the prevention of enteric infection, he said.

CONVERGING EPIDEMICS OF DIABETES AND TUBERCULOSIS

Julia Critchley, professor of epidemiology at the Population Health Research Institute, St. George's University of London, examined the epidemiology and public health consequences of the converging epidemics of TB and diabetes. Critchley began by describing the global burden of both conditions. TB is the leading cause of mortality from a single infectious agent worldwide, causing approximately 1.6 million deaths in 2017, 95 percent of which occur in low- and middle-income countries (WHO, 2018a). More than 10 million active TB disease cases are diagnosed annually, and it is likely that about one-quarter of the global population is infected with latent TB infection (WHO, 2018a). Around 425 million people worldwide are estimated to have diabetes, primarily type 2 (International Diabetes Federation, 2017). However, many of those people remain undiagnosed, particularly in low- and middle-income countries where the most rapid increases of diabetes burden are occurring (Zhou et al., 2016). The number of people living with diabetes is predicted to increase to 629 million over the next few decades, affecting about 1 in 10 adults (International Diabetes Federation, 2017).

Critchley explained that the prevalence of diabetes is increasing because of known risk factors that have been increasing in most parts of the world, including (1) changes in urbanization, (2) change in lifestyles, (3) reductions in physical activity, (4) less healthy diets, and (5) increases in obesity (Zimmet, 2017). She noted that population aging worldwide, especially in Asia where diabetes is common, is an important factor hypothesized to lead to the predicted rise in diabetes over the next few decades, but this is often not acknowledged. Therefore, simply reducing obesity would not have a substantial effect on the huge burden of diabetes that will emerge in the coming decades, she said. The regions of the world with the largest predicted increases in diabetes burden over the next few decades—such as sub-Saharan

Africa and Southeast Asia—are also the regions where TB is endemic (International Diabetes Federation, 2017).

Critchley noted that the population impact of the converging TB and diabetes epidemics could be large (Awad et al., 2019a), as people with diabetes can also transmit TB to other people in their families and communities who do not have diabetes. Working with mathematical modelers, Critchley developed two conceptual frameworks taking into account all of the pathways by which diabetes might be affecting TB. Based on these frameworks, she observed that in 1990 approximately 14 percent of TB-related mortality and 11 percent of TB incidence were statistically attributable to diabetes in India (Awad et al., 2019b). However, as diabetes prevalence rises and TB incidence starts to decline, the model suggests that the proportion of TB that is statistically attributable to diabetes is likely to increase dramatically over the next few decades (Awad et al., 2019a). This model predicts that more than 40 percent of TB deaths and about one-third of TB incidence could be attributable to diabetes in India by the year 2050 (Awad et al., 2019b).

Association Between Diabetes and Tuberculosis

Critchley emphasized that examining the associations between diabetes and TB is a matter of urgent concern. Historically, Richard Morton was the first to highlight this association in the seventeenth century (Morton, 1694; Olayinka et al., 2013). In the 1950s, joint treatment for TB and diabetes was delivered in special clinics in the United Kingdom (Luntz, 1954, 1957; Walker and Unwin, 2010). Attention dissipated when new drugs for both conditions were introduced and substantially reduced their death rates. Renewed interest in the association has been driven by the sharply increasing burden in low- and middle-income countries, leading to updated reviews synthesizing the evidence about the strength of the association between diabetes and risk of developing active TB disease (Stevenson et al., 2007; Jeon and Murray, 2008; Al-Rifai et al., 2017). Evidence from observational studies, prospective cohorts, and case control studies shows that people with diabetes have roughly double the risk of developing active TB (Restrepo et al., 2011). This association is not as powerful as the one between HIV and TB, Critchley noted, but so many people are living with diabetes that it is likely to be meaningful at the population level. Prospective cohort studies suggest a slightly stronger risk in low-income settings with high incidence as well as a higher risk in Asia compared with Europe or the United States (Suwanpimolkul et al., 2014). Studies with better case definitions through microbiological confirmation of TB and blood glucose or HbA1c testing for diabetes also suggest higher risks (Jimenez-Corona et al., 2012).

Glycemic Control, Tuberculosis Risk, and Tuberculosis Outcomes

Critchley said that evidence is limited about the associations between glycemic control, TB risk, and TB outcomes (Leung et al., 2008; Leegaard et al., 2011; Pealing et al., 2015; Lee et al., 2016). Observational data suggest a higher TB risk among people with poorly controlled diabetes, but no randomized controlled trials have looked into this (Lee et al., 2017). Although glycemic control may be helpful in reducing the risk of infections, direct evidence is not available (Lee et al., 2017). Primary care data collected in the United Kingdom from 2010 to 2015, including more than 85,000 patients with diabetes and more than 150,000 controls, show a nonlinear association between glycemic control (measured by HbA1c levels) and the risk of serious infections (Critchley et al., 2018). This is particularly observed once HbA1c levels reach about 9 millimeters per liter (Critchley et al., 2018). In the United Kingdom, which does not have a large burden of TB (except in London), she reported an estimated one-quarter of TB patients with diabetes could be statistically attributable to poor glycemic control. However, she noted that this does not prove that glycemic control would help reduce the risk.

Multiple systematic reviews have looked at TB treatment outcomes among people with diabetes. A 2011 review suggested that diabetes worsens treatment outcomes among TB patients, but the included studies were relatively poor in quality and relied on observational data (Baker et al., 2011). A more recent review of 102 studies included 44 studies that reported on mortality, including 56,122 individuals with TB-diabetes and 243,035 with TB (Huangfu et al., 2019). This meta-analysis suggests that the risk of poor treatment outcomes (i.e., death and relapse) are roughly doubled for someone with diabetes compared to a TB patient without diabetes. The better-designed and analyzed studies that adjusted for key epidemiological confounders showed a greater risk of poor outcomes.

Risk of Diabetes Among Tuberculosis Patients

Diabetes is known to be common in TB patients, Critchley explained. A recent meta-analysis of 200 studies reported that overall about 15 percent of patients with active TB also have diabetes—this varied from 0.1 percent in Latvia to 45.2 percent in the Marshall Islands (Noubiap et al., 2019). Certain hotspots with high prevalence of diabetes in TB patients were South India (54 percent), Kiribati in the Pacific Islands (37 percent), and the southern Texas–Mexican border (37 percent) (Restrepo et al., 2011; Viney et al., 2015; Kornfeld et al., 2016). She added that studies in sub-Saharan Africa have not yet identified a high prevalence of diabetes in TB patients, however.

Critchley said that the TANDEM consortium looked at diagnosing diabetes in TB patients and found substantial heterogeneity across the four study

populations in Indonesia, Peru, Romania, and South Africa (Grint et al., 2018). Although it is possible to develop screening strategies that can help detect diabetes in TB patients, it is more difficult in some populations than in others. In some populations, researchers seemed to be identifying many people with stress hypoglycemia, increases in glucose levels, or increases in HbA1c associated with TB infection. This is not necessarily diabetes, she stated, although it may develop into diabetes in the future, but longitudinal follow-up data are not available.

Screening for Tuberculosis Disease in Patients with Diabetes

Although the need to screen TB patients for diabetes has been broadly accepted, said Critchley, there is less evidence and more uncertainty about the benefits of screening people with diabetes for active TB disease. She noted that there is a need for simple and cost-effective screening algorithms, but for these patients screening may need to be repeated owing to infection-related stress hyperglycemia (Lin et al., 2019). A major concern is what happens to patients identified with diabetes at the end of TB treatment, she added. TB treatment is relatively more accessible, and it is possible to identify undiagnosed diabetes during TB treatment. However, diabetes services are much harder to access in many settings, owing to cost or poor quality of public services; longitudinal follow-up is rarely available in these settings. She said, "We are only really helping people if we can manage their diabetes better after the end of TB treatment."

Critchley summarized her presentation making the following main points:

- Diabetes increases the risk of TB disease (even when the mechanism is not fully understood), and it increases the risk of poor TB treatment outcomes, particularly mortality.
- Diabetes is common in TB patients and often goes undiagnosed.
- Higher glucose and HbA1c levels may increase the risk of developing TB and are related to negative TB treatment outcomes, but there is no evidence to support that this can be reversed.
- Screening for and managing diabetes during TB care would not be hypothesized to have a substantial effect on the overall burden—the estimated effect is less than 1 percent overall. However, strategies would have a larger effect if they were designed further upstream to reach people with diabetes before they develop active TB, or even better, to reduce the risk of developing diabetes and more severe hypoglycemia.

She said that confronting the converging epidemics will require addressing many heterogeneities with respect to diabetes, TB-diabetes, interactions with HIV, and other multimorbidities.

DISCUSSION

After both presentations, Kent Kester, vice president and head of translation science and biomarkers at Sanofi Pasteur, started the discussion by asking the presenters about the effect of sustained hyperglycemia on the immune system. Kester noted that hyperglycemia is known to have a negative effect on certain elements of the immune system, such as the inhibition of certain leukocytes (Graves and Kayal, 2008). Given that TB is related to impaired T-cell function and elevated HbA1c levels are typically a marker of sustained elevations in glucose over time, he asked about any insights into the association between diabetes and increased susceptibility to TB or worsening of TB disease.

Critchley replied that diabetes is a state of relative immune impairment that is associated with increased risks of infection, which warrants investigation into the immune system responses in both conditions. Immunologists in the TANDEM consortium have been looking at gene expression and have found different signatures for people with TB and diabetes compared to people with TB alone. An unexpected finding was that the signatures were also different for people with impaired HbA1c levels that were above normal, but below the diagnostic cutoffs for diabetes. Another group of researchers is looking at the benefits of host-directed therapies using statins or metformin in reducing TB risk or improving TB treatment outcomes; no randomized evidence is available as of yet, but there are animal and observational studies that suggest metformin may be associated with a reduced risk of TB (Lee et al., 2018; Tseng, 2018). However, Critchley cautioned about drawing conclusions from the observational evidence because of the potential for selection bias, as metformin is the first-line drug treatment for diabetes almost everywhere in the world. People who do not have access to metformin have different circumstances than people who do, whether the barrier is poverty, lack of insurance, socioeconomic status, severity of diabetes, or type 1 diabetes that is misdiagnosed as type 2. Randomized controlled trial evidence is needed, but getting this evidence is challenging owing to the ethics and pragmatics of running such a trial.

Kester also asked Thaiss if they were able to restore some of the barrier effect in their mice studies, while still controlling for the impaired leukocyte function when hyperglycemia is present. Thaiss replied that the restoration achieved by preventing epithelial dysfunction is not complete, so some of the residual problems may be accounted for by impaired immune function. When looking at neutrophils in a study, they observed differences that may result from a combination of both immune and nonimmune functions.

Correlation Between HbA1c and the Microbial Signal

Tolu Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge, asked Thaiss to elaborate on the strong

correlation between HbA1c (rather than glucose itself) and the microbial signal, along with potential implications for screening and management, as well as potential effects on the clinical outcomes. Thaiss replied that they did not expect to see both factors uncoupled, with a signal for HbA1c but not for glucose itself. This suggested that the association observed was with long-term glycemic control, not postprandial glucose responses, which is a meaningful distinction, considering the biology that underlies their differential regulation. His study included only healthy individuals without diabetes. Nonetheless, even within a small healthy cohort with healthy HbA1c ranges, they still saw a correlation with microbial molecules in the circulation system, which is indicative of barrier dysfunction (Thaiss et al., 2018). The implications for treatment are that the current approaches to long-term glycemic control, like metformin, might be more applicable than those for short-term glycemic control.

Critchley added that the TANDEM study included blood glucose and HbA1c testing, and the results were similar in terms of screening accuracy, although their data mainly identified people who had already been diagnosed with diabetes. She added that data from studies in Africa have found associations of different strength with HbA1c versus blood glucose markers of diabetes. She speculated that this difference may be caused by two different populations in these studies. One group includes people with TB who have undiagnosed diabetes that could be picked up with any test because their levels are high. The other group may include people for whom HbA1c is actually a marker of TB severity, rather than a marker of true diabetes. This could account for why HbA1c levels are correlated with poor outcomes. Her immunologist colleagues are looking at differences in gene expression that could provide a way to understand this biologically, although this may be less useful on the ground in clinics.

Converging Tuberculosis and Diabetes

The discussion turned to the socioeconomic dimension of the TB-diabetes convergence. Gene Bukhman, director of the Program in Global Noncommunicable Disease and Social Change at Harvard Medical School, asked whether any studies are collecting socioeconomic information about patients with both TB and diabetes, noting that in India, there are usually reverse gradients with diabetes and socioeconomic status. He wondered if the story with TB is more complicated or in line with expectations. Critchley replied that most of the studies she presented were based on clinical data from hospital or national TB database registries; they rarely collected any socioeconomic data. However, the TANDEM study that recruited 2,000 patients across Indonesia, Peru, Romania, and South Africa did collect detailed socioeconomic data (Grint et al., 2018). As expected, TB was

shown to be a disease of poverty. In Indonesia, for example, asking people if they had a bank account was almost as good a predictor as microbiological testing for TB. The situation with diabetes is relatively more complex as it becomes more common among all socioeconomic gradients—or even, as data from the population group studied by TANDEM suggest, that it is beginning to reverse and may even become more common in low- to middle-socioeconomic groups.

Patricia García, professor at the Cayetano Heredia University School of Public Health, moved the discussion to real-world practicalities of screening for TB-diabetes. She used as an example settings without the laboratory capacity to provide reliable HbA1c results, or where the only test available requires fasting on a person with TB receiving treatment. Most low-resource TB patients in Peru receive a food basket with high-carbohydrate foods to supplement their diets, she noted. It may be more complicated or expensive to provide appropriate food baskets for low-resource people with TB-diabetes. Critchley said that from a practical point of view, TB should generally be treated as the first priority, in order to reduce the risk of death from the infection or the transmission of drug resistance. Evidence is limited about the use of point-of-care tests for diabetes in TB clinics, but blood glucose testing could be a starting point because it is relatively inexpensive. Thinking about improving health rather than focusing only on disease outcomes requires ensuring accessibility and continuity of care for people being treated for TB who are identified or suspected as having diabetes. Once their TB has been cured, she said, having the knowledge and resources to effectively manage their diabetes contributes to long-term health outcomes. García asked about any associations between nonpulmonary TB and diabetes. Critchley replied that most of the studies have only looked at pulmonary TB and diabetes, which have the strongest evidence for an association, but the association between diabetes and less common extrapulmonary TB is unknown.

Building on García's comments, Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization, noted that there is a need for simple initiatives to strengthen health services that are accessible to the entire population. He asked Critchley about her experience with any efforts to synergize diabetes and TB treatment that could be potentially replicated on a broader scale to improve health system responses and patients' outcomes, as well as be more attractive to policy makers. Critchley noted efforts to integrate screening in places like India, but they are too recent to assess long-term outcomes. Blood glucose testing can be easily collected for TB patients, but longitudinal data are not available to assess patient experiences and outcomes. Initial steps around integration have been made in a limited number of places, but it is not yet clear how much they improve the experience for the individual.

Mosa Moshabela, dean and head of the School of Nursing and Public Health at the University of KwaZulu-Natal, South Africa, asked Critchley about the relative difficulty of studying the epidemiological patterns of patients with TB-diabetes and, given that TB is more immediately life-threatening than diabetes, about the opportunities to integrate care for those patients. Critchley said that from an epidemiological point of view, it is relatively straightforward to study TB-diabetes using evidence from registries and cross-sectional data. Data would improve if funders were prepared to invest in longitudinal studies. Reorganizing health systems to deliver integrated care could be supported by the recent sets of guidelines that provide simple frameworks for primary care clinics in rural settings to deal with suspected diabetes. A historical example comes from the joint TB and diabetes clinics in the United Kingdom that were apparently successful in reducing the mortality rate from those two joint conditions in the 1950s. Economic evidence is needed on the cost-effectiveness of integrating or reorganizing the health services to address the joint epidemics, she said. She estimated that only half of existing TB clinics would have access to blood glucose testing, so it would be helpful to look at the cost-effectiveness of putting point-of-care tests in place in primary care, for example.

Ultimately, however, cost-effectiveness comes down to providing long-term follow-up care for patients—identifying someone who had undiagnosed diabetes during TB care may or may not actually benefit the person's long-term health, depending on whether the person can later access high-quality diabetes services to support good glycemic control, she stated. Evaluation of cost-effectiveness should take into account the patients' journeys or health outcomes. For instance, some have speculated that the TANDEM study may have picked up people who were not actually undiagnosed—they knew they had diabetes, but they did not have access to care. The reasons why people drop out of care may be economically driven or related to lack of awareness of the importance of long-term care. She was optimistic that TB services could potentially provide a way for some patients to reintegrate with care, but only if the services are there to engage them at the end of TB treatment. She reflected:

> That is where the synergy most concerns me.... I can pick up and evaluate the epidemiological evidence, but the carrying on into the future and what happens to those patients is really a big gap.

5

Microbial Dimension to Human Development and Well-Being

The first day of the workshop concluded with a plenary presentation that delved into how microbes are not only associated with various noncommunicable diseases (NCDs) but also how they are integral to normal human physiological functions. Rob Knight, founding director of the Center for Microbiome Innovation, University of California, San Diego, explored how a holistic, complex view of the relationship between microbes and people can change the way health is approached. He began his presentation by explaining that microbes outnumber humans, even within our own bodies. The typical human body consists of 30 trillion human cells and 39 trillion microbial cells—by that measure, humans are only 43 percent "human" (Sender et al., 2016). The microbial dimension is even more astounding when looking at genetics instead of cells. The efforts of the Human Microbiome Project (HMP) have revealed that each human has around 20,000 human genes,[1] a measly comparison to the 2 to 20 million microbial genes in human bodies (Knight et al., 2017; NIH, 2019). By this measure, Knight stated that "we are actually 1 percent human at best" (Turnbaugh et al., 2007).

INFLUENCE OF THE MICROBIOME

Multiple systems in the body are affected by the human microbiome (Blacher et al., 2017). Microbes in the gut represent about 2 kilograms of

[1] The HMP was established by the National Institutes of Health to generate resources that allow the characterization of the human microbiome and analysis of its role in human health and disease. For more information on the HMP, see https://hmpdacc.org (accessed August 16, 2019).

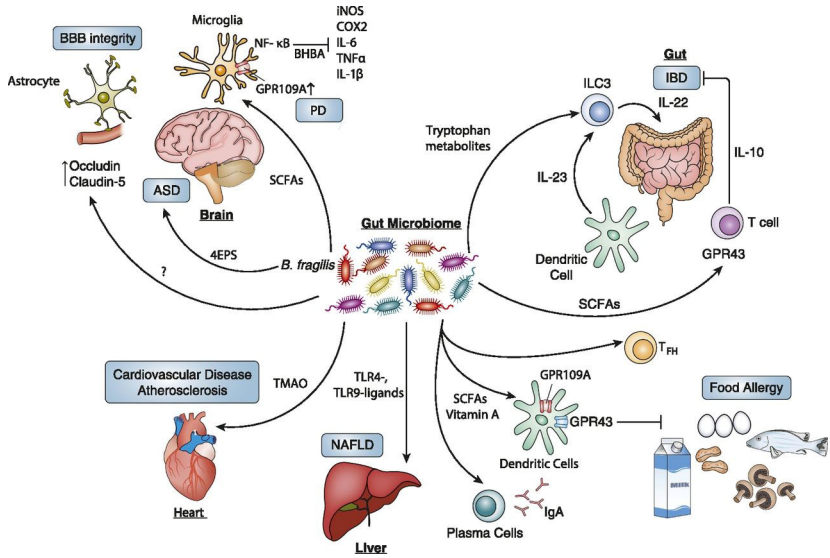

FIGURE 5-1 Linkages among the microbiome, metabolites, and diseases.
NOTE: ASD = autistic spectrum disorder; BBB = blood–brain barrier; IBD = inflammatory bowel disease; NAFLD = nonalcoholic fatty liver disease; PD = Parkinson's disease; SCFA = short chain fatty acid; TMAO = trimethylamine-N-oxide.
SOURCES: Knight presentation, June 11, 2019; Blacher et al., 2017.

the typical person's biomass (Qin et al., 2010; Forbes et al., 2016). These gut microbes can affect the body in obvious ways, such as inflammatory bowel disease, as well as more surprising ways, such as food allergies, liver disease, and cardiovascular disease (Blacher et al., 2017) (see Figure 5-1). Detailed mechanistic accounts also demonstrate how microbes can have a huge effect on the human brain in diseases like Parkinson's disease, multiple sclerosis, and autism (Turnbaugh et al., 2007; Kirby and Ochoa-Repáraz, 2018; Sharon et al., 2019). Knight noted that research based only on the human genome—such as genomewide association studies or systems biology—excludes 99 percent of the genes in the human body. Because these microbial genes encode the vast majority both of unique biochemical functions and of antigens, this type of work ignores the genes that can be changed and modified throughout humans' lifetimes to promote health and rather focuses instead on the 1 percent that are fixed when humans are conceived.

GLOBAL MICROBIAL BIODIVERSITY CRISIS

Despite the significant number of microbial genes in humans, however, humans are losing them (Smits et al., 2017). Studies of populations of people

with preindustrial lifestyles that are more characteristic of the past million years—rather than the past 100 years—have revealed major groups of bacteria (an entire phylum) that are not found in people living postindustrial lifestyles today (Clemente et al., 2015; Jha et al., 2018). To illustrate the potential consequences of dwindling global microbial diversity, Knight drew the analogy of turning a complex and diverse rain forest into a cityscape in which only the rats and pigeons survive. In the 1960s, conservationist and marine biologist Rachel Carson's work documented how DDT and other pesticides wiped out birds and other components of large-scale ecosystems (Carson, 1962). More recently, other scientists documented similar effects when humans eliminate microbes early in life and thus affect the inner human ecosystem, which may be growing into a biodiversity crisis (Blaser, 2014).

Knight explained that throughout the twentieth century, single-pathogen diseases such as measles and tuberculosis (TB) fell to advances in medicine and public health, while the rates of multiple sclerosis, Crohn's disease, type 1 diabetes, and asthma have skyrocketed. As presented in a review article in 2002, none of those chronic diseases were known to be linked to the microbiome (Bach, 2002). Today, all four of them—and dozens more—are known to be associated with the microbiome in humans (Pascal et al., 2017; Frati et al., 2018; Kirby and Ochoa-Repáraz, 2018; Zheng et al., 2018). Analogs of those diseases can be caused and cured in animal models through microbiome manipulation (Zheng et al., 2018). This raises questions about the unintended consequences of attempts to eradicate single pathogens such as TB and measles on the rest of the microbiome, he added.

COMPLEXITY OF THE HUMAN MICROBIOME

To better understand the complexity of the human microbiome, the HMP was launched by the National Institutes of Health, with a follow-up project that looked at specific diseases and recently published the results (Proctor et al., 2019). Samples were collected from about 250 healthy people, from up to 18 sites on the body at up to three time points, for a total of 4.5 trillion bases of DNA—about 1,500 human genome equivalents. Knight explained that this provided an unprecedented amount of DNA sequence data about the human microbiome (Caporaso et al., 2010; Human Microbiome Project et al., 2012). The abundance of DNA sequence data posed challenges for researchers, he noted. Similarly, the sheer volume of microbial data that can be gathered from the gut of a single individual can make it impractical for use diagnostically or therapeutically.

Knight's lab is trying to help make these complex multivariate profiles useful for comparison between people and within a single person over time to address the massive degree of complexity in the human microbiome.

When processed with Qiime, a platform developed by Knight's lab over the past 10 years, HMP data can be mapped using principal coordinates, which reduces the dimensionality of microbiome data to summarize the microbial community compositional differences in two or three dimensional scatterplots (Goodrich et al., 2014). Each point on the map represents a microbiome, and the distance between points represents how compositionally different the samples are from one another (see Figure 5-2). The maps reveal that different parts of the body are like different continents, with the mouth, skin, vaginal, and fecal communities quite distinct from one another. Knight added that although the microbiomes included on the map come from healthy people, many factors can affect the microbiome, including age, gender, the time of day the sample was collected, and what the person ate the day before.

To build this evidence base, the Earth Microbiome Project,[2] which aims to characterize global microbial taxonomic and functional diversity on Earth, crowdsourced tens of thousands of samples from scientists around the world (Gilbert et al., 2014). Knight noted that environmental microbiomes are just as different from each other as the mouth and gut microbiomes of one individual. The mouth can be thought of as a coral reef, complex mineralized structures covered with biofilms. The mouth is as far from the

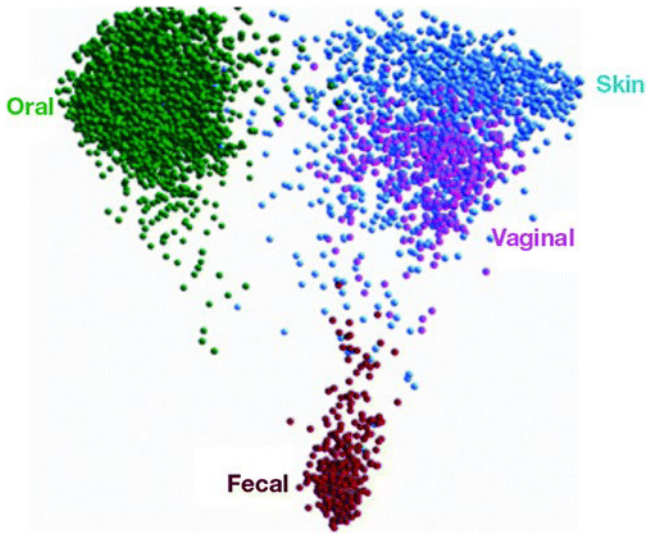

FIGURE 5-2 Map of the human microbiome.
SOURCES: Knight presentation, June 11, 2019; Knight, 2018.

[2] For more information on the Earth Microbiome Project, see http://www.earthmicrobiome.org (accessed August 13, 2019).

gut in terms of its microbiome ecology as the water in a coral reef is from the dirt in a prairie, he explained. Knight and his colleagues did not expect that a few feet along the length of a human body could make as much difference in terms of microbes as thousands of miles across the Earth's surface in completely different environments (Thompson et al., 2017).

To demonstrate the relevance of a person's position on this microbial map, Knight described work carried out on *Clostridium difficile* (*C. difficile*), a hospital-acquired infection that is rapidly increasing in incidence in the United States. Microbiome mapping illustrates that stool samples from patients with *C. difficile* have microbiomes that are profoundly altered compared to healthy stool microbiomes (Schubert et al., 2014). A study provided fecal transplants to patients with *C. difficile* from donors with samples in the healthy microbiome region (Kelly et al., 2016). The microbiomes of patients who received stool transplants quickly moved from an unhealthy to a healthy state within days. These patients had to fail antibiotic therapy for 2 years to qualify for the trial and within a short time after the transplant, they were producing firm stool for the first time in years. The changes in these *C. difficile* profiles are complex and multidimensional, but they can be simplified by using a microbiome map that plots the changes on a single axis from sick to healthy along one dimension.

Origins of Human Microbial Complexity

Microbiome maps can also be used to trace the origins of a human body's complex microbial communities. The way a person is born has a huge effect on those microbial origins. Babies delivered vaginally have microbial communities similar to their mother's vaginal microbe communities, but the starting point is completely different for babies delivered via cesarean section, who have communities throughout their bodies that are all similar to their mother's specific skin communities (Dominguez-Bello et al., 2010). Additionally, antibiotics, birth mode, and diet affect the microbiome in early life (Bokulich et al., 2016). He explained that it is possible to predict much about children at age 10—from their weight to their cognitive performance—from their microbiome a few days after birth. In particular, breast milk seems to reverse the adverse effects of the combination of antibiotics and cesarean sections on the microbiome and phenotype (Knight, 2018). The University of California, San Diego, has a new breast milk research center, the Mother–Milk–Infant Center of Research Excellence, which is studying components of breast milk that could be added to formula for families that cannot breastfeed.

Knight presented a series of images that demonstrated the development of an infant's fecal biome community over time. The fecal biome of a vaginally delivered infant starts out in the vaginal area of the microbiome map, and

over the next 2 years it moves to the fecal adult state at varying speeds (Koenig et al., 2011). From one week to the next, children are microbially more different from themselves 1 week prior than the difference between any two healthy adults in the HMP, Knight illustrated. If a child receives antibiotics for an ear infection, for example, it causes a massive regression of the microbiome, unwinding months of normal development (Yassour et al., 2016). He noted that the microbiome of some children will recover rapidly within a couple of weeks and continue to move toward the healthy adult fecal status. However, he said many adults and children are less resilient to antibiotics in terms of microbiome and phenotype. A major challenge is to determine why some people are less resilient and then develop a way to predict who is at risk.

These microbial development effects are so strong that they can be picked up cross-sectionally across populations at a specific point in time, Knight noted. A comparison of the adult state of the microbiome over the first 3 years of life in rural Malawians, Amerindians from the Amazonas of Venezuela, and U.S. populations from metropolitan areas found that the approach to the adult state is generally complete by age 3 (Yatsunenko et al., 2012). However, the final states of the microbiomes were completely different in the non-Western populations compared to the Western populations, with different infectious and noninfectious disease profiles. Knight noted that the HMP and other large-scale projects are focusing on Western adults; thus mapping the microbiome of children and non-Westerners depicts completely different configurations. This underscores the importance of building microbial growth curves for children in diverse populations, which can be used to measure the effects of breastfeeding, antibiotics, and delivery mode of maternal drugs. It could also be used to predict the effect of falling off the microbiome "growth curve," he added.

RESEARCH DIRECTIONS TO EXPLORE MICROBIOME COMPLEXITY

Knight described some of the research directions that could help provide a more realistic understanding of this complex relationship of microbes to infectious diseases, NCDs, and normal physiological functioning. The war against antimicrobial resistance is failing, and new approaches are urgently needed, he cautioned. Although much work has been devoted to combating individual species or entire taxonomic groups of microbes, much less work has gone into strengthening the host, which has great potential. It is well established that one way to strengthen the host is through diet, but the details of how to strengthen the host against infection and chronic disease through diet are yet unknown.

Knight remarked that there have been many attempts to supplement iron in childhood anemic populations but, in general, those attempts release

iron-limited pathogens that cause diarrheal diseases and other problems (Lonnerdal, 2017). Research using individual studies have discovered that *Salmonella enterica* serovar Typhimurium, an enteric bacterial infection transmitted through contaminated food or water, can be treated by a combination of copper, L-arginine, vitamin C, and linalool (Haque, 2012; Ghosh et al., 2019). However, he said more global approaches are needed to rapidly profile large numbers of pathogens, micronutrients, and dietary ingredients and assess their effects. This applies to viruses as well as pathogens, he added. A mouse model has demonstrated a reduction in mortality among mice exposed to influenza that were supplemented with the molecule desaminotyrosine, which is naturally produced by gut bacteria from flavonoids in the diet (Steed et al., 2017). Treating the exposed mice with antibiotics led to around 90 percent mortality, while giving them antibiotics plus desaminotyrosine brought mortality down to about 30 percent (Steed et al., 2017). Furthermore, the study found that certain microbes (*Clostridium orbidscindens*) had to be present to make the compound from the dietary ingredient. This is an example of why diet, microbiology, and immunity have to be integrated to comprehend the full picture, he said.

To contribute more robust research and an integrated picture of diet, microbiology, and immunity, Knight has cofounded the Global FoodOmics Project, which is running thousands of food samples through a mass spectrometer to find out what is in food products at the point of sale or at the point of consumption.[3] These data are cross-referenced with the American Gut Project, which has collected more than 20,000 stool samples contributed by citizen scientists, as well as performing meta-analyses with their other clinical projects.[4] He presented a picture of a molecular network from an early iteration of the project, which reveals the complete biotransformation of food in the human gut. In new mouse models, researchers have been 3D scanning conventionally raised, pathogen-free, and germ-free mice, then dicing them to sequence and running the mass spectrometer on each piece. They are then able to reconstruct full 3D models with any specific bacterium or molecule highlighted in the structure in the mouse. This technique has been used to demonstrate how soyasaponin accumulates in a germ-free mouse but not in a specific-pathogen-free mouse.[5] Conversely, soyasapogenol accumulates in the specific-pathogen-free mouse that has the necessary bacteria,[6] but it does not accumulate in the germ-free mouse. Both soyasapogenol and soyasaponin have been shown to modify immune

[3] For more information on Global FoodOmics, see https://sites.google.com/site/globalfoodomics/project-description (accessed August 12, 2019).

[4] For more information on the American Gut Project, see http://humanfoodproject.com/americangut (accessed August 12, 2019).

[5] Soyasaponin is a phytochemical found in vegetables, beans, and herbs.

[6] Soyasapogenol is created by cleaving the bond in soyasaponin.

response (Guang et al., 2014). The complete transformation of bioassay profiles and other metabolic details can also be observed in the mice through this work.

Knight called for a coordinated global effort to build a more comprehensive repository of information about the microbiomes of people with much more diverse demographic, geographical, and health-related characteristics. This effort should be catalyzed by the potential strides to be made against the sheer number of conditions that have now been linked to the gut microbiome, such as inflammatory bowel disease, irritable bowel syndrome, food allergies, asthma, cardiovascular disease, diabetes, multiple sclerosis, autism, and Parkinson's disease, he said. For instance, large amounts of money have been channeled into researching the genetics of human obesity, yet he noted that the accuracy in predicting obesity from human genes is significantly lower (57 percent) than predictions using microbial genes (90 percent). This holds for a large number of traits. Studies of microbial contribution versus host genetic contributions to phenotypes, and their microbial-genetic associations, show that microbial contribution dominates for traits such as lactose consumption and waist circumference, while traits such as height are determined by genetics (Rothschild et al., 2018). Because the microbial associations are so much stronger, Knight noted, traits can be associated with microbes with 10-fold fewer test subjects than are required for genetic associations. He also mentioned that dogs and their owners can be matched with a fair degree of precision by their shared microbes (Coelho et al., 2018). He added that people who are overweight tend to have overweight dogs and cats, suggesting that obesity may be transmissible microbially. While the environment and geography have a strong influence on human gut microbiota variations, he cautioned using generalized microbiota-based diagnostic models among various locations (He et al., 2018).

To assess causality rather than association, Knight and his collaborators are using a technology called gnotobiotic mice, which are mice raised in a bubble with no microbes of their own. To establish causality, these mice are then colonized with microbes that are thought to affect their phenotype. When gnotobiotic mice were colonized with microbes from an obese human, they became obese; when colonized with microbes from a lean human, the mice remained lean (Ridaura et al., 2013). Similar work has been done on inflammatory bowel disease, colon cancer, Parkinson's disease, multiple sclerosis, and most recently for autism (Sharon et al., 2019). It has also been done for many other traits including response to drugs and response to diet, particularly for components like emulsifiers and artificial sweeteners that are associated with highly individualized responses (Faith et al., 2011; Smits et al., 2016; Zimmermann et al., 2019). He explained that the approach can also be used to evaluate susceptibility to a wide range of bacterial, viral, and fungal pathogens that can be transmitted from humans

to mice on an individual level. This establishes that microbial genes can be causally implicated—at least to the extent to which the animal models are a good model of those diseases.

In his concluding remarks, Knight described his vision of future tools to track the microbiome (see Box 5-1) and outlined a set of research needs, including the following:

- More work integrating food, drugs, microbiology, immunology in studies with multiple data layers and large enough study populations to get adequate statistical power
- More comparative studies of microbiomes in populations where burdens of infectious and chronic disease differ

BOX 5-1
Future Tools for Personalized Microbiome Tracking

Knight described his vision of future molecular and data science tools for tracking the microbiome. Disorders linked to microbiomes—by association studies in humans and by causal evidence from animal models—need to be mapped to identify "good" and "bad" places on the microbiome map across different populations and medical specialties. He explained that this will allow for the development of a "microbiome GPS" that indicates where a person's microbiome is, where it needs to go, and how to change the microbiome to get there. The mechanism for the needed change could range from fecal transplant to phage therapy, or drugs like probiotics and prebiotics. The American Gut Project is showing that diet is one of the most powerful ways to reshape the microbiome, but it takes 6 to 12 months to do so. This microbiome GPS needs to be simple enough for anyone to use. Knight asked the workshop audience to imagine a toilet that analyzes stool when the toilet is flushed and delivers a microbiome analysis directly to a smartphone in real time.

Although these technologies rely on million-dollar sequencing equipment, Knight's vision is that a person could have access to instant data about their own microbiome activity, plot themselves visually on the microbiome map, and then track their risk and their progress along the axes of good and bad locations on the map. Augmented reality could connect the bathroom mirror with a smartphone, allowing people at the grocery store to see which products to choose based on the effect on their individual microbiome. This technology could potentially be used to record microbial data from everywhere a person goes, what they eat, and people they come into contact with to track their exposures and the effect on the gut microbiome. He envisioned that a smart mirror could even use these data to model an image of a person's face 5 or 10 years into the future based on their current microbiome profile.

SOURCE: Knight presentation, June 11, 2019.

- More prospective longitudinal studies that integrate microbiology and immunology, infection, and chronic disease
- More translational work relating animal studies to humans
- More longitudinal studies with defined perturbations using already-approved compounds, especially in early life
- Better molecular and data science tools

DISCUSSION

Following Knight's presentation, workshop participants had the opportunity to ask questions. The discussion covered topics on specific factors that shape the human microbiome, as well as the public health implications of microbiome research.

Factors Shaping the Human Microbiome

Srinath Reddy, president of the Public Health Foundation of India, asked about the nature of epigenetic changes in the microbial genes and long-term effects beyond changing the character of the colony, as well as whether environmental exposures are more likely to lead to epigenetic changes in the huge pool of genes in the microbiome. Knight replied that little is known about the epigenetics of the bacteria, but there is evidence of the epigenetic process of DNA methylation in the bacterial genomes themselves. Many bacterially produced metabolites, such as the histone inhibitor butyrate, have effects on the host epigenome. He said that recent publications have reported strong links between a person's microbes, host methylation, and histone modification markers. Knight explained that progress is being hampered, however, because the laboratories working on the microbiome are different than the ones that study epigenetics. Both types of laboratories require complex and expensive technology, making it challenging to fund projects at a level at which both of those techniques can be combined. He added that systems-level understanding is also being informed by research into metabolite profiles that lead to epigenetic changes and by profiling different tissues around the body—changes in the microbiomes in mice cause observable gene expression changes in their brains, for example.

Mary Wilson, clinical professor of epidemiology and biostatistics at the University of California, San Francisco, asked about research on the antibacterial activity of nonantibiotic pharmaceuticals, some of which are used to treat chronic conditions. Knight replied that a large number of pharmaceuticals (including metformin, antipsychotic drugs, and selective serotonin reuptake inhibitors) are not traditionally considered to be antibiotics, yet they have large effects on individual gut microbes (Maier et al., 2018; Spaniogiannopoulos and Turnbaugh, 2018). There is a dearth

of knowledge, however, because only a few dozen compounds have been tested, and they have only been tested against a limited range of microbiomes from Western adults, Knight added. It is not yet understood how those pharmaceuticals interact with the environment, or have downstream effects, in the microbiomes of fish, seawater, or soil. The effect of microplastics on the environment is a related issue, he added. Evidence is emerging that microbes attach easily to fibrils and that spatial structuring substantially modifies their activity in the gut (Tropini et al., 2017). It is likely that the same is true for microplastics and other nonnutritive substances that are commonly ingested, he said.

Kevin Olival, senior research scientist at EcoHealth Alliance, asked about the role of viruses, particularly bacterial phages, in shaping human microbial communities. Knight replied that the prospect of understanding phage bacterial dynamics is exciting. However, it will require large sample sizes and a dense time series, which are currently prohibited by the cost of shotgun metagenomics,[7] though the cost is likely to decrease and enable such studies in coming years. He noted that phage therapy has been remarkably clinically effective as a last-ditch measure for patients who had exhausted all other treatment options. Learning how to use phage to intentionally modify a microbiome has great potential, he said, given that total synthesis of a phage with a specific sequence is already possible. Phage engineering will need to be integrated with the microbiome research to carry out this type of work.

Relatedly, Dennis Carroll, director of the Emerging Threats Division at the U.S. Agency for International Development, asked Knight to comment on viruses and fungi in the microbiome. Knight explained that the microbiomes of Westerners tend to have relatively few genera of fungi, mostly *Candida*, *Saccharomyces*, and a few others, but people in Asian countries tend to have a much more diverse repertoire of fungi and microbial eukaryotes. The hope was that shotgun metagenomics would revolutionize knowledge about everything except bacteria, which are the only components that can be picked up efficiently and with decent taxonomic resolution by most other methodologies. However, a key limitation has been the lack of reference databases, particularly for viruses and fungi. Shotgun metagenomics provides many short fragments of DNA, which need to be matched up using reference databases. It would cost about $4 million to sequence every type strain of bacteria, he added. This is beyond the budget of most individual laboratories and falls between the mandates of different agencies that could

[7] Shotgun metagenomics is an environmental sequencing method that allows researchers to sample all genes in all organisms present in a given sample. The method aims to enable researchers to evaluate bacterial diversity and function and to detect the abundance of microbes in different types of environments.

potentially fund it. He emphasized that sequencing all of the type strains and as many fungi from human and animal stool isolates as possible would be an immensely valuable resource that would greatly increase the efficiency of all metagenomic studies.

Paul Miller, chief scientific officer at Artizan Biosciences, noted that much interest centers on the interplay between the gut microbiota, the gut epithelial, and the immune system, yet most of measurements and comparisons use stool samples. He asked about the use of biopsies and other sources of data that are closer to the epithelial side than the end product. Knight said that in general, biomarkers obtainable from stool are good but not always as good as biomarkers obtained from biopsy specimens. Stool is much more useful for biomarker studies than for mechanistic studies, which benefit from tissue sampling. He added that stool is more practical for daily sampling in longitudinal studies, because variation in the microbiome itself—even on a daily time scale—allows for predicting future-state immunologically linked phenotypes such as inflammatory bowel disease.

Public Health Implications of Microbiome Research

Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention, asked if microbiome research corroborates the current "super foods" trend and claims about how diet can boost a person's immunity. Knight replied that there is much emerging work on the intersection of microbiome research with public health advice about diet. The available evidence supports certain public health recommendations. For example, eating more fiber is beneficial for the production of butyrate in the gut by the microbes that ferment fiber (Baxter et al., 2019).[8] Evidence about artificial sweeteners and emulsifiers demonstrates how they are bad for the gut microbiome (Harpaz et al., 2018), which is consistent with policy recommendations. On the horizon are personalized dietary recommendations that have the potential for large effects, he said. Part of the reason why supermarket tabloid diets are broadly ineffective is that they tend to be based on a single person, rather than larger sample sizes. The aim with dietary recommendations is to discover a relatively small number of types of microbes in the gut that can inform public health recommendations by developing microbe-detection tests coupled with discrete evidence-based recommendations based on that test. He said that currently available data are not poised to change any public health recommendations at present, but the individual effect sizes of these findings are large. Some people are negatively affected by artificial

[8] Butyrate is a short-chain fatty acid that supports health through a number of mechanisms, such as immune system regulation (Baxter et al., 2019).

sweeteners or red meat, while others are not; this depends on the details of bacteria in the person's gut.

Finally, referring back to Knight's presentation that noted humans carry 1 percent of human genes, Rima Khabbaz, director of the National Center for Emerging and Zoonotic Infectious at Diseases at the U.S. Centers for Disease Control and Prevention, asked about studies that incorporate hosts to inform the development of risk assessments and personal recommendations. Knight said that an increasing number of studies are incorporating both hosts and microbial genomes, showing that microbiome associations with the phenotype were much greater than with the host. Personalized recommendations are still on the horizon, he said. Individual differences are known to be large, but there is no test available to evaluate a sample and integrate it into the data frame. To make this type of data useful and actionable at the individual level, he said, will require input from federal agencies and others to develop standards for integrating individual samples into consistent reference ranges, as well as work to standardize databases across specific geographical locations.

6

Confronting "The Blind People and the Elephant" Metaphor to Bridge the Silos

During the second day of the workshop, the focus shifted from a discussion on understanding the complex dynamics of microbes, noncommunicable diseases (NCDs), and human functioning to examining how to translate that knowledge into convergent actions. Session two featured a panel discussion that explored how to confront "the blind people and the elephant" metaphor to bridge the silos between infectious diseases and NCDs in the move toward convergent action.[1] The panelists spoke about the lens through which they are approaching the convergence and remarked on potential priorities, concerns, and opportunities for addressing the convergence. They discussed how to link and leverage disparate information produced by each field to address the convergence and offered suggestions about potential strategies to accelerate progress that the respective fields have already achieved. This session was moderated by Bridget Kelly, principal consultant of Burke Kelly Consulting. The panelists were Gene Bukhman, director of the Program in Global Noncommunicable Disease and Social Change at Harvard Medical School; Rachel Nugent, vice president of the Chronic Noncommunicable Diseases Global Initiative at RTI International; Nelson Sewankambo, president of the African Medical Schools Association; and Dennis Carroll, director of the Emerging Threats Division at the U.S. Agency for International Development (USAID).

[1] The metaphor of the blind people and the elephant depicts a group of people who are blind and encounter an elephant for the first time. Each person, touching the elephant from a different vantage point, has a unique interpretation of what the elephant resembles and what its purpose seems to be, thus leading to disagreement on the true nature of the elephant.

EXAMINING THE CHALLENGES AND OPPORTUNITIES OF THE CONVERGENCE

To open the panel discussion, moderator Bridget Kelly, principal consultant of Burke Kelly Consulting, asked each panelist to introduce themselves by sharing which lens they apply to the topic of convergence between infectious diseases and NCDs, in addition to key opportunities to address this intersection.

Extricating the Complexities of Infectious Diseases and Noncommunicable Diseases and Upholding the Equity Perspective

Gene Bukhman, director of the Program in Global Noncommunicable Disease and Social Change at Harvard University, began by describing his background working on tuberculosis (TB) in the former Soviet Union. He cited professional differentiation as one of the reasons that practitioners tend to view themselves as either in the infectious disease camp or in the NCD camp. As both a medical anthropologist as well as a cardiologist, Bukhman was drawn to working on drug-resistant TB because at the time, there had been less medical anthropological work on the issue and he was interested in exploring new stories from an ideological perspective. He has since transitioned to a broader focus of working on NCDs and injuries in populations living in extreme poverty.

The tendency to search for simplicity in public health problems has contributed to the separation between the infectious disease and NCD spaces, suggested Bukhman. He explained that historically, the discourse about health priorities among the world's poorest populations has found simplicity by identifying a number of largely infectious threats that are the major causes of death among children and young adults. This effort is underpinned by a strong equity imperative (i.e., serving the most vulnerable populations), which has the benefit of operational clarity, Bukhman noted. At the same time, there has been a sense that NCDs are too complicated to address at a global level, where large-scale organizations tend to focus on the top five or six causes of death. He suggested that this approach has shaped the evolution of the NCD space into the inverse of the infectious disease space of simplicity and operational clarity from the risk factor standpoint, particularly in high-income countries.

A separate conversation thus emerged about older populations and the nature of the epidemiology and risk factors associated with ischemic heart disease and stroke. This approach allows for two separate spaces that are defined by their own simplicities, he said, but it does not fully address the complexities within and between the two spaces. For instance, drug-resistant TB is an example of complexity within the major infectious diseases, he

added. The NCD side is complex as well. For example, cardiovascular diseases include much more than ischemic heart disease and stroke; they also include rheumatic heart disease, cardiomyopathies, and congenital heart disease. There is also enormous complexity within cancers. He added that complexity also pervades the other disease categories that constitute NCDs, from congenital conditions to musculoskeletal conditions to neurological conditions.

One potential type of convergence is the move toward developing new ways of dealing with complexity or simplifying the complexity of diseases, said Bukhman. Old models of achieving simplicity through a focus on single diseases or single risk factors are exhausting themselves as shared risk factors become evident, although he said it is still difficult to establish exactly how risk factors are shared between congenital hydrocephalus and ischemic heart disease, for example. This underscores the need for a new science of integration, particularly in global health delivery, that will help to navigate within the convergence, he said.

Bukhman concluded by highlighting an advantage of the general approach within the infectious disease world, which is the equity imperative—priority for the worst off—that is incidentally related to the diseases in some ways. It grants priority to those who are materially disadvantaged, for example, or to those who are most vulnerable in terms of lifetime health, such as children and adolescents. The equity imperative has imbued certain infectious disease movements with clarity and strength; however, this may also have limited efforts to address TB or other diseases that have less of an emphasis on child health, noted Bukhman. These lessons should not be lost on the NCD side, he cautioned. As with infectious diseases, there is enormous heterogeneity within NCDs. Some are childhood diseases, and some kill people later in life; some are highly lethal, while others are disabling. He remarked, "We shouldn't lose sight of those distinctions or lose sight of the focus on equity that came naturally to us in the infectious disease world."

Understanding the Economics of the Convergence

Rachel Nugent, vice president of the Chronic Noncommunicable Diseases Global Initiative at RTI International, shared her experiences from working in the NCD space from a global policy and health economics perspective. Health economics seeks to address the questions of value for money and how to improve that value related to health and health care, but what compelled her to work in NCDs was the lack of action and investment relative to the amount of evidence available. Her work centers on analyzing the economic aspects and evaluating the economic implications of NCDs (Davies, 2018). She focuses on how resources are being spent and whether they are being spent in ways that address the problems that people are facing.

It has become clear that increasing numbers of people in low- and middle-income countries are living with NCDs, although many are not even aware of it. Many of those who have had diagnoses have no access to care. In recent years, she added, this problem has only increased in magnitude.

Progress has been made in the NCD space, said Nugent, but catalyzing further action will require engaging with decision makers. Decision makers, of course, are interested in the cost of taking action and the potential value of different avenues of investment. The past decade has seen the emergence of much better evidence about productivity effects and impoverishment effects, for example (Nugent et al., 2018b). We can now establish with greater confidence the cost of a condition, how many people it impoverishes, and the effects of lack of access to medication on disease progression and the person's productivity (Essue et al., 2017). As efforts to draw attention and resources to NCD needs in low- and middle-income countries were largely unsuccessful, the need to think differently became apparent. A new vertical program or new global fund, she noted, is not seen as the answer. She suggested that ultimately, efforts need to focus on making care more integrated and more patient centered.

As an example, Nugent cited a review of the costs and cost-effectiveness of HIV and NCD integration in Africa (Nugent et al., 2018a), which found the evidence about the economic efficiency of integration to be deficient. It is often assumed that it will be cost saving—or at least cost-effective—to integrate screening and treatment. However, the authors were not able to find examples where it is cost saving or even cost-effective. The additional cost of integrating NCDs into the HIV platform identified in most of the studies ranged from 6 to 30 percent (Nugent et al., 2018a). The study design also included interviews with people working in global policy, donors, and people implementing in-country programs to integrate NCDs into HIV care. Almost all the interviewees thought that it would be cost-effective or cost saving to integrate NCDs in the populations with a need for NCD care (e.g., an identified burden of heart disease, stroke, or potentially cancer). They assumed that the economics would help make the case for integrating, but the evidence was not available. Nugent added that from an economic perspective, it would be helpful to demonstrate whether the assumption that integration is cost-effective is correct and, if so, under what conditions. She cautioned that continuing to operate based on unsupported assumptions is untenable and unaffordable, as has been seen in other areas of health. Many models of integration are emerging with varying results to make sense of, which she is interested in looking into. Finally, Nugent closed her remarks with the proposition that collecting a minimum economic dataset in settings that are working to integrate would be helpful in building the evidence base.

Engaging Decision Makers and Strengthening Health Systems

Nelson Sewankambo, president of the African Medical Schools Association, opened his remarks by sharing that his career began in cardiology but shifted focus to infectious disease when the HIV epidemic struck Uganda in the 1980s. As a medical school dean, a frequent concern was whether the students were being trained in the appropriate way to respond to the needs of the country. With the increasing attention on NCDs in the past 15 years—as well as members of his own family experiencing NCDs—his focus is now a mix of NCDs and infectious diseases.

He reflected on opportunities to spur progress in convergence. First, the implementation of programs at the country and local levels is shaped by how decision makers appreciate and interpret those programs. Therefore, Sewankambo asserted, policy makers and practitioners need to be brought to the table and engaged, because they have the ability to drive programs forward. They need to understand the effect of convergence, rather than feel overburdened by yet another issue to take on. He added that using evidence to inform policy and practice is taking root in many countries—producing evidence that speaks to convergence will help to gain attention and buy-in for moving in a direction that will help policy makers improve the health of their populations.

Furthermore, convergence can be facilitated by developing strong health systems that allow everyone to access quality care at affordable prices, as well as allowing for emergency detection and response capacities in the case of an emerging infectious disease event. He said the strength of Brazil's health system allowed the Zika virus epidemic to be picked up quickly, for example. Convergence can contribute to universal health coverage as well, particularly in countries with a high risk of infectious diseases, he added. The Ebola virus outbreaks demonstrate the enormity of the threat that an infectious disease can pose to a population's health. Sewankambo suggested finding ways to leverage this attention toward convergence across the spectrum from infections to NCDs. From the perspective of a medical educator, convergence provides an opportunity to mitigate the dichotomy between infectious diseases and NCDs by highlighting the need for medical education that is cross-cutting, rather than siloed, to more effectively address the health needs of the population.

The Implications of a Collision Between Emerging Infectious Diseases and Noncommunicable Diseases

Dennis Carroll, director of the Emerging Threats Division at USAID, provided comments that reflected the evolution of his own understanding about infectious diseases and the larger ecology in which they reside. He has

spent decades working in the infectious disease space but feels more comfortable framing his work at the nexus of infectious diseases and NCDs. In addition to addressing current threats, work on emerging infectious diseases also examines underlying drivers and attempts to project how those challenges will play out decades in the future, given the various demographic, economic, and ecological changes that are under way. In the process of trying to position this work in a more forward-leaning way, it becomes evident that the dynamics that will potentiate and exacerbate emerging infectious diseases will also contribute to another series of events, through which populations that are already challenged by emerging infectious diseases will become increasingly challenged by NCDs.

This epidemiological collision is significant in Carroll's work, because the populations that are most vulnerable to emerging infections tend to be the populations living with preexisting NCDs. For example, during the emergence of the H1N1 influenza pandemic in Mexico in 2009, the country had a much higher mortality rate than the rest of the world (Charu et al., 2011). This was largely associated with a population with severe obesity that exacerbated the infection (Dominguez-Cherit et al., 2009). He said it is likely that by 2050, because of the economic population settlement dynamics and consumer-driven emergent middle class in countries in sub-Saharan Africa, for example, there will be increases in the underlying conditions and lifestyle factors that make them hotspots for NCDs, such as diabetes and cardiovascular conditions. Carroll suggested considering what the epidemiological collision will mean for these urbanized populations with increasing prevalence of NCDs compounded by exposure to emerging infectious diseases. In the context of this trajectory, it will be impossible to solve the problem of emerging infectious diseases without thinking about NCDs, he maintained.

Preparing for an epidemic or pandemic is not simply about managing the emerging disease, said Carroll, but about understanding the context in which it is going to emerge. He added that preparedness plans need to account for the likely population risks for both NCDs and emerging diseases. Country-by-country preparedness exercises to manage—or more aptly, to co-manage—future events would be better informed by predictions about likely hotspots for both infectious diseases and NCDs within each country. However, there is a dearth of evidence about NCD hotpots and no existing protocols about how to manage coexisting conditions, such as coronavirus in someone with diabetes. He added that to maximize insight and manage the events that will play out in decades to come, infectious disease projections and forecasting need to be situated on an evidence base about the emergence of NCD hotspots and their convergence with emerging infectious disease hotspots. Then health systems will need to be reoriented to be more adaptable and integrated. For example, one of the first steps in the

diagnostic algorithm for dealing with an infectious disease is to identify any underlying condition. Developing a playbook with clear, clinical guidelines for co-management would help to reduce the effect of infectious disease events, he suggested.

LANGUAGE AND CONCEPTUAL BARRIERS

Following the panelists' remarks, Kelly observed that the panelists used language in particular ways—by drawing analogies and thinking about how to explain things to people with different perspectives and priorities. She asked the panelists to remark on any language barriers they have encountered and how language may influence people to understand the importance of this convergence.

Bukhman noted a difficulty with the term *noncommunicable disease*. In common parlance, NCDs are fairly narrowly defined as lifestyle diseases related to factors such as being overweight and lack of physical activity and their associated cardiometabolic problems. The infectious disease world has tended to focus on the world's poorest billion to frame infectious diseases as a priority. From an equity standpoint, this has created a disconnect in focusing on NCDs because when it is narrowly defined, the burden is underestimated. A broader definition of NCDs—like the definition used by the Global Burden of Disease, the definition used by the World Health Organization in global health estimates, and most of the *International Classifications of Diseases* (ICD) codes—captures a more diverse, heterogeneous set of diseases. Partners in Health, a nongovernmental organization largely focused on the poor in Africa and Haiti, has benefited from being more specific about setting NCD priorities at a disease-specific level and building on analogies with priorities in the infectious disease world, he said. This can create more commonalities among work focusing on conditions that do not fit neatly within conventional framing of NCDs—for example, congenital diseases, surgical conditions (such as appendicitis or unstrangulated hernias), rheumatic heart disease, or type 1 diabetes—but may be more consistent with the implicit ethical paradigm within which the global health infectious disease world has traditionally operated.

Defining NCDs too narrowly may lead to missed opportunities in national conversations that strive to forge links between infectious diseases and NCDs as conventionally construed, continued Bukhman. The co-occurrence of TB and overweight, or HIV and hypertension and diabetes, are issues that receive a large share of attention, but they are a relatively narrow subset of the larger set of issues at the interface of HIV and a broader definition of NCDs. He suggested that either the NCD category needs to embrace

the full diversity of its constituent conditions or there should be more specific acknowledgment when only a subset of NCDs is being discussed.[2]

Nugent commented that the concept of convergence has yet to be well defined or agreed upon. For instance, the 2013 report by the Lancet Commission on Investing in Health described the convergence of poorer countries toward the achievements of wealthier countries in terms of maternal and child health and infectious diseases, contending that it is possible for poorer countries to converge on the levels of mortality and burdens that have already been achieved in higher-income countries (Jamison et al., 2013). This is a different type of convergence than the workshop's focus; therefore, considering both explicit and implicit uses of language in these contexts is helpful, she added. The term *NCD* originated from a need to identify a term for a community to coalesce ideas, actions, and advocacy around. Nugent clarified that the term *NCDs* achieved that goal, albeit at some cost. Language can identify and categorize people, thus contributing to the sense of division between the NCD and infectious disease spaces. Though not often openly acknowledged, Nugent noted that the concept of NCDs has come to be associated with wealthy and privileged lifestyles among many in the global health community. These cognitive barriers can influence how these problems are understood, she said, which can hamper efforts to deal with them effectively.

Sewankambo said that the terms *infectious diseases* and *noncommunicable diseases* are so deeply engrained in the common vernacular of health professionals and in the medical education system that they are substantial barriers. However, he noted that recent events have provided opportunities to demonstrate that the two entities are related. The human papillomavirus (HPV) vaccine to reduce the risk of cervical cancer and the hepatitis B virus vaccine to reduce the risk of liver cancer both illustrate how an infectious agent can be linked to an NCD in the longer term (Chang, 2011; McClung et al., 2019; Song et al., 2019). Similarly, there is a link between malaria and Burkitt lymphoma, which was prevalent in the children in Uganda and a number of other countries (Legason et al., 2017). Demonstrating these types of potential linkages between infectious diseases and NCDs could lay the groundwork for approaching those two sets of conditions within a single system, he said.

Carroll maintained that the current global health agenda is defined by the epidemiological priorities of the 1980s and 1990s, which have not evolved to keep pace with changing epidemiology. This is reflected in the lack of flexibility to adapt to evolving epidemiology that restricts congres-

[2] Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention, also took issue with the language of NCDs, which he noted takes everything that is not caused by a single microbe and lumps everything left over together.

sional funding. A consequence of the paradigm's inflexibility, he added, is the lack of a documented evidence base about the current global burden of disease and the cost-effectiveness of combined packages for dealing with the interface between infectious diseases and NCDs. The 1993 *World Development Report*, for example, provided an evidence base that propelled an extraordinary increase in global health funding around the world (World Bank, 1993). A similar resource could facilitate shared understanding of the dual burden and cost–benefit discussion of strategies to address them. The transition will continue to be difficult without such a resource that maps the larger ecosystem of converging NCDs and infectious diseases, he said. Nugent replied that such an evidence base already exists in the second and third editions of the *Disease Control Priorities*, which provides an extensive body of evidence on cost-effectiveness, including high-priority packages of care for low-resource countries with cost estimates (Jamison et al., 2018). Carroll responded that the resource would benefit from broader dissemination and outreach to policy makers to bring it to the forefront of discussions.

DISCUSSION

Kelly opened up the floor for discussion. Workshop participants reacted to some of the remarks that the panelists had made and discussed approaches to strengthen health systems to address the convergence.

First, reflecting on the language issue of defining NCDs as lifestyle diseases, Cathryn Nagler, professor of pathology, medicine, and pediatrics at The University of Chicago, noted NCDs that are influenced by changes in the microbiome are not exclusive to high-income populations because they cut across all segments of the population. They may be referred to as lifestyle diseases, but they are not voluntary lifestyle choices; they are societal lifestyle choices. She also highlighted the fact that many of the factors that have led to changes in the composition of the microbiome over the past 30 to 50 years have been recommended by the medical and the societal advisory boards, such as the use of antibiotics and the transition toward processed foods.

Relatedly, on the topic of language and communication, Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention, emphasized the power of translating a message to policy makers to achieve action, drawing on his experience working in decision making in disease control programs. Lack of an evidence base is not the primary issue—although better understanding of the magnitude and precision of the association between the factor and the outcome is important. The issue is how to translate the scientific understanding that an intervention is likely to have an effect on the outcome in a way that is accepted by policy makers and resonates with their sense of causation. Concepts such as how the environment shapes

and affects health can become vague and abstract for policy makers, he added. The extent to which the scientific mechanism by which environmental and lifestyle factors are causing damage can be articulated clearly—that is, identifying the "enemy"—will determine acceptability of these interventions at a policy level. A powerful potential benefit of this convergence is the opportunity to create messages that are more clear, he suggested.

The discussion transitioned to the topic of strengthening health systems. Miriam Rabkin, associate professor of medicine and epidemiology at the Mailman School of Public Health, Columbia University, suggested that the real elephant in the room is the weakness of health systems. Neither infectious diseases nor NCDs are being treated with a trusted, well-staffed health system that provides high-quality and affordable services. The term *health system* may not be ideal, but well-trained people need to be in place to build trusted relationships with communities to engage them in care, she added.

Other participants followed up on the challenges and the different ways to strengthen health systems. John Harley, founding director of the Center for Autoimmune Genomics and Etiology at Cincinnati Children's Hospital Medical Center, suggested that the primary issue is the inadequacy of systems to deliver care—not the lack of knowledge about how to deal with infectious diseases. Similarly, Mahir Rahman, clinical associate from Eden Health, added that health systems would be able to serve patients more effectively if health literacy better empowered patients to be self-advocates and to articulate their needs. Syra Madad, senior director at NYC Health + Hospitals, commented on the blurring line between health care delivery and public health within health systems, although they are separate entities. Health care delivery focuses on individual patients, but policy and guidance are often provided by public health and not well translated at the health care delivery level; this is particularly evident in infectious disease outbreaks, she said.

Tolullah Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge, reflected on the need for a balanced system, based on experience in reorienting and reorganizing health systems. In South Africa and other countries in sub-Saharan Africa, many health care systems are designed around curative models to respond to diseases. Introducing primary prevention elements into those systems is challenging because of how those systems are currently functioning. Most health care providers are trained within a system of specialization and overspecialization, which requires vertical systems that allow those specialties to be exercised in delivering care. Although those health care systems have the capacity to treat diseases, she stated they have little capacity for health promotion or behavioral interventions within those systems. Discussions about the importance of behavior rarely extend to how to deal with problems that pertain to behavior—the tendency is to respond with a medical product, to the exclusion of interventions that relate to empowering people to manage

and improve their health. Oni suggested that a combination of responses within a balanced model allowing for both generalist and specialist care would be more effective. Discussions are ongoing in countries in sub-Saharan African to consider how to remodel primary health care such that health promotion and services can be delivered outside the health system as traditionally construed.

Oni raised the question whether the ultimate objective of convergence is (1) converging to treat co-occurring diseases, (2) converging in terms of screening and secondary prevention, or (3) converging in how primary prevention is done. She cautioned against conflating all people with patients, as is often the case in discussions about health system strengthening. It is helpful to think about convergence in terms of future proofing health and health care delivery as well as health proofing the future. "We have to somehow converge in terms of the science of primary prevention and work out how to slowly close the tap, instead of just working out how to plug the leaks in the bucket," she said.

Dorothy Indyk, associate clinical professor at the Icahn School of Medicine at Mount Sinai, suggested eliminating the dichotomy between prevention and treatment in discussions of convergence across different diseases. Prevention and treatment of HIV/AIDs were first integrated conceptually 15 years ago, she noted. In that continuum of prevention and treatment, the locus shifts into the community and the global realm at the prevention level, then it moves to the individual level and along the continuum toward treatment and care. In that sense, HIV/AIDS work has provided a wealth of insight and knowledge about the convergence of NCDs and HIV—how HIV is linked to comorbidities and NCDs, as well as learning about cancer through HPV. Prevention of biological disasters, for example, could help to bring together work on NCDs and HIV. Indyk suggested that the discussion should be focused on integration to achieve healthy lives in every environment by adapting and optimizing what we have learned across silos in a bottom-up way, rather than limiting the discussion to diseases and NCDs.

CONVERGING TOWARD THE MIDDLE

To wrap up the session, Kelly remarked that intentional work around convergence and integration provides an opportunity to move toward the center and reframe health systems. She asked panelists to describe their optimism about how things might be different moving forward.

Carroll replied that getting to that middle will require looking comprehensively at the entirety of the ecosystems involved to understand problems, not in isolation, but within the context of systems. Doing so, he said, will require funding streams to be aligned toward investing in integrated health systems.

Sewankambo commented that although he is an internist, many people think he is a public health physician because of the breadth of his work to engage communities, families, and patients. It would be helpful to make people beyond the workshop more comfortable with talking about convergence. Public engagement also contributes to helping people understand how they can prevent health challenges at an earlier stage.

Nugent suggested finding concrete ways to bring convergence to upstream factors that drive delivery—for example, engaging with governments and donors to address siloed budget lines and considering ways to address siloed training of practitioners. This focus needs to extend beyond the health system to address broader drivers across multiple sectors. For instance, the activities of different departments and ministries within governments—such as education, sports, agriculture, and transport—can affect prevention. A useful, concrete exercise is to measure the budgetary contributions that different ministries make to prevention of disease. The Organisation for Economic Co-operation and Development has developed a framework for the actions that can be taken by nonhealth ministries and departments to affect disease prevention and health promotion, she added.

Bukhman commented that this work should not lose sight of the opportunity to converge health outcomes for the poorest people in the world by applying what has been possible in some countries at reasonable cost (Jamison et al., 2013). There are disparities across multiple disease entities, including NCDs and injuries that extend beyond a few major conditions. However, he raised the concern that bringing NCDs into discussions about convergence for the poor entails different connotations about development and eradicating absolute poverty in general—in a sense, the "flip side" of convergence. The tendency to frame treatments in terms of epidemics, syndemics, and pandemics may occlude the importance of endemics, which are long-term problems that are difficult to apprehend and measure, said Bukhman.

He explained that the foundation of the ICD is William Farr's work in England in the mid-nineteenth century who categorized zymotic (*fermenting* in Greek) diseases as those that signal fermenting, evolving public health epidemics such as cholera that warrant attention, in contrast to NCDs. This distinction remains as the basis for the ICD classification system. He suggested that perhaps the current era is focused on "nonfermenting" diseases and their importance. Reflecting on his years spent working in Rwanda, Bukhman described the country's relative development in its health system and the improvement in its health statistics as community-level achievements that did not necessitate a functioning health system. However, he predicted that the current focus on addressing NCDs will likely require dealing directly with complexity within health systems.

7

Integrating Health Care Delivery Models and Interventions

The third session of the workshop focused on integrating and revamping health care delivery models and interventions to address the convergence of infectious diseases and noncommunicable diseases (NCDs). The session included four presentations that discussed how health systems are responding to the dual burden of infectious diseases and NCDs and how to leverage existing structures and build local capacity. The presenters offered examples of models that incorporate community-based and people-centered approaches to integrating care that have aimed to improve quality and expanded access to care. They also explored how primary care can help address the convergence in low- and middle-income countries and highlighted some approaches needed for prevention and control at the local and country levels. The session was moderated by Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization.

The first presenter was Miriam Rabkin, associate professor of medicine and epidemiology at the Mailman School of Public Health, Columbia University, and director for health systems strategies at ICAP Columbia, who discussed how the scale-up of HIV services can be leveraged to provide NCD services in health systems. Sylvester Kimaiyo, executive director of the Academic Model Providing Access to Healthcare (AMPATH), Kenya, described the successful outcomes of the AMPATH model in his country over the past two decades. Gene Bukhman, director of the Program in Global Noncommunicable Disease and Social Change at Harvard Medical School, provided an overview of the new discipline of integration science and how it can help to address the convergence of infectious disease and NCDs. Finally, Catherine

Oldenburg, assistant professor and Francis I. Proctor Foundation faculty member at the University of California, San Francisco, described how the use of mass administration of antibiotics can contribute to reducing child mortality.

HIV AND NONCOMMUNICABLE DISEASE INTEGRATION PLATFORMS

Miriam Rabkin, associate professor of medicine and epidemiology at the Mailman School of Public Health, Columbia University, and director for health systems strategies at ICAP Columbia, explored how the scale-up of HIV services can be leveraged to provide NCD services in health systems. Rabkin described ICAP's work on HIV, which has been a primary focus of the global health center and aims to deliver transformative solutions to strengthen health systems around the world through projects in more than 30 countries. In addition to policy-focused work, ICAP has extensive experience in implementation around HIV services and systems. Through ICAP-supported HIV services, more than 35 million people have been tested for HIV, more than 650,000 women have received antiretrovirals to prevent HIV transmission to their babies, approximately 2.5 million people have been enrolled in HIV care, and 1.5 million people have begun HIV treatment (ICAP, 2019; Rabkin, 2019).

Leveraging HIV Platforms to Deliver Care for Noncommunicable Diseases

Rabkin described the rationale for leveraging HIV platforms to deliver care for NCDs (Shigayeva et al., 2010; Rabkin et al., 2014). Many countries have both a high prevalence of HIV and a high prevalence of NCDs, although the colocated epidemics—or possibly syndemics—can play out quite differently in different contexts and geographies. Another reason to leverage HIV programs is that the expansion of HIV treatment and prevention services has been remarkably successful with the leadership of communities and ministries of health and support from the global community and donors. Population health impact surveys from several countries in sub-Saharan Africa demonstrate that today those countries have better HIV control than the United States (El-Sadr et al., 2019). HIV and certain NCDs also have shared systems challenges, such as the need for continuity of care—including primary prevention, secondary prevention and treatment—over the life cycle, rather than episodic, symptom-based care. The prevalence of NCDs and NCD risk factors among people living with HIV is at least as high as the rest of their communities, and even higher in some cases, she noted. Rabkin cited the relative resource wealth of HIV programs compared with NCD programs as another reason to leverage HIV platforms. Although diverting funds from

HIV platforms and redirecting them toward NCDs is not leveraging per se, it highlights the dearth of resources available for both prevention and treatment of NCDs in discussions about synergies or integration, she stated. In the landscape of available funding, there is no significant money for NCDs (Nugent, 2016). She said, "One plus zero is still one. You can't integrate something that does not exist."

Lessons from Scaling Up the Delivery of HIV Services

Rabkin outlined lessons gleaned from scaling up of the delivery of HIV services that are applicable to NCDs, particularly in austere health systems, which are characterized by a lack of health care providers and weak laboratory, infrastructure, drug procurement, monitoring, and governance systems (El-Sadr et al., 2017; Rabkin et al., 2018a). The first lesson is to use the public health approach to deliver services at scale through delivery mechanisms and platforms that do not require specialist physicians and academic health centers, she noted. Rather than focusing on how to treat symptomatic people who come to a hospital or clinic, the public health approach emphasizes the burden of a condition in the community and the associated cascade of the number of people:

- that have this condition,
- diagnosed,
- linked to treatment,
- who have engaged with treatment, and
- who have been successfully treated.[1]

Another lesson from HIV scale-up is the need to be realistic and innovative in dealing with health workforce constraints, said Rabkin. If platform services cannot be delivered by a nonphysician clinician, then they cannot be delivered at all in many parts of the world. HIV scale-up demonstrates the importance of engaging the private sector, faith-based organizations, and civil society organizations, as well as the need to prioritize meaningful involvement by people who are actually receiving the services. For instance, at meetings focused on HIV, there are generally attendees representing the recipients of HIV care, noted Rabkin. Further lessons from HIV scale-up are the importance of a rights-based approach, of working toward universal health coverage, and of investing in policy-relevant data systems.

[1] Treatment success can be operationalized differently for different conditions. For example, Rabkin said that treatment success for HIV may mean viral suppression, while for diabetes it may mean good glucose control.

Defining Key Terms and Concepts

Rabkin explored some of the different meanings associated with the concept of integration of services, systems, and programs. Although integration is an intuitively appealing strategy that is often presumed to be cost-effective, the evidence base from implementation science on the benefits of integration remains scant and is undermined by a lack of common understanding about what integration involves (Shigayeva et al., 2010). Precision is helpful when discussing integration, she said. Integration can refer to integrating clinical services at the point of care so people with more than one condition receive care for both that is holistic and not fragmented—such as integrating HIV and tuberculosis (TB) testing, prevention, and treatment services or integrating maternal and child health services with services to prevent mother-to-child transmission of HIV. Integration can also refer to integrating programs and systems on multiple fronts, including financing, budgeting, strategic planning, procurement and logistics, monitoring and evaluation systems, and health workforce and training plans.

Discussions about leveraging HIV platforms typically refer to leveraging HIV programs, said Rabkin. In many low- and middle-income countries, HIV programs were the first large-scale, public-sector continuity care initiative for chronic diseases (Rabkin and El-Sadr, 2011). These programs were designed to provide prevention and treatment throughout the life cycle in health systems with limited resources, and they were developed to be delivered by nonphysician clinicians, community health workers, and laypeople through a public health approach (Rabkin and El-Sadr, 2011). Initially, these programs were often vertical and siloed, although they are now more often diagonal (Farmer et al., 2013). The lessons learned around focusing on the public health approach and using nonphysician clinicians should not have to be relearned for NCDs, said Rabkin. This dialogue needs to center around people, with support from system components such as governance, information, financing, service delivery, human resources, and medicines and technologies, she said. Table 7-1 outlines the types of functions that HIV programs need to deliver, which are the same functions that many NCD programs also need to deliver, such as systems, strategies, a capacitated health workforce, and point-of-care delivery diagnostics to support people throughout the care cascade (Rabkin and El-Sadr, 2011).

Integrating Noncommunicable Disease Services into HIV Programs

To illustrate how NCD services might be integrated into HIV programs, Rabkin described the HEART study, an example of implementation science research carried out in Eswatini, also known as Swaziland. The prevalence and burden of both HIV and cardiovascular disease are high in the country

TABLE 7-1 HIV Program Functions Are Applicable to Many Noncommunicable Diseases

Key Elements of Chronic Care Delivery Systems	Examples Common to HIV and NCD Programs
Diagnosis and enrollment	Identification of risk factors, early diagnosis, opportunistic case-finding, point-of-service diagnostics, standardized diagnostic protocols.
Retention and adherence	Appointment systems, defaulter tracking, patient counseling, expert patients, secure medication supply chains, pharmacy support.
Multidisciplinary family-focused care	A multidisciplinary team of health care providers and community members delivers care in partnership with the patient.
Longitudinal monitoring	Health information systems have standardized and easily retrievable data.
Linkages and referrals	Links within the health facility (to lab, pharmacy, others), between facilities, and between facility and community.
Self-management	An informed, motivated patient is an effective manager of his/her own health.
Community linkages and partnerships	Need functional partnerships between health facility-based providers and community-based groups that facilitate access to services across the care continuum.

SOURCES: Rabkin presentation, June 12, 2019; ICAP, 2011.

(UNAIDS, 2017; WHO, 2018c). Swaziland has the highest prevalence of HIV in the world, but 11 percent of deaths are actually caused by cardiovascular disease (Palma et al., 2018). Cardiovascular disease risk factors (CVDRFs) screening and management are recommended for people living with HIV, but they are not routinely performed (Rabkin et al., 2015). The HEART study sought to explore the feasibility and acceptability of introducing CVDRF screening for people living with HIV into a busy HIV treatment clinic.[2] Additionally, the study compared integrated management of CVDRFs—with the HIV provider managing both HIV and CVDRFs during HIV clinic

[2] CVDRF screening for patients aged ≥ 40 years receiving antiretroviral treatment included blood pressure measurements to detect hypertension, point-of-care HbA1c tests for diabetes, point-of-care cholesterol test, and tobacco history. A subset of people who screened positive for CVDRF (with hypertension and/or ≥ 10 percent 10-year CVD risk) were randomized to integrated or referred management.

visits—versus referred management to an outpatient department, in which the HIV provider manages HIV clinical concerns at HIV clinic visits and a general internist manages CVDRFs at outpatient clinic visits. She noted that both randomized groups were treated in different departments of the same physical facility. The study randomized those who screened positive and collected data using screening results, exit interviews with screened patients, time-motion studies, key informant interviews with health care workers, and key informant interviews with patients randomized to integrated versus referred management.

Screening was high yield, with 39 percent of almost 1,800 people screened having at least one CVDRF (primarily hypertension) (Rabkin et al., 2018b). Screening added about 11 minutes per visit, Rabkin noted, largely because staff had to wait for the results of the point-of-care tests. It may seem trivial, she said, but this had substantive effects in a clinic where an average refill visit is about 5 minutes. Staffing challenges were a significant barrier to screening, although the screening and the wait time were acceptable to 100 percent of the patients who took part; 77 percent reported being willing to receive screening annually, even if it took more than 10 minutes (Rabkin et al., 2018b). Improvement in hypertension and diabetes control was seen in both integrated and referred arms, and retention rates were also similar in the two arms (Palma et al., 2018; Rabkin et al., 2018b).

Rabkin cited another study that compared the resources, systems, structures, job aid, and tools developed for HIV projects with those developed for diabetes services. The latter were being carried out in a relatively less resourced way, for example, using less organized, handwritten registries (Rabkin and Nishtar, 2011). In an Ethiopian setting, researchers leveraged HIV programs to support diabetes services. They tried to duplicate the systems used for the HIV clinic for the nearby diabetes clinic by implementing the same types of training, tools, job aids, and peer education program (Rabkin et al., 2012b). Compared to baseline, follow-up results showed increases in the following services documented at least once in a patient's three most recent visits:

- Blood pressure services (35 percent increase)
- Funduscopic examination (49 percent increase)
- Foot exams (78 percent increase)
- Neurological exams (53 percent increase)
- Oral or dental exams (76 percent increase)
- Visual acuity testing (37 percent increase)

In conclusion, Rabkin highlighted some barriers and opportunities to address gaps in HIV–NCD integration and to learn from HIV programs in implementing NCD programs for the general population. Regarding

challenges, she noted that funding barriers persist for NCD services and related implementation science research. Opportunities include the integration of NCD prevention, screening, and treatment services into HIV programs; sharing lessons, strategies, and tools from HIV scale-up to enhance selected NCD programs; and the integration of continuity care systems for chronic infectious and noninfectious diseases (Rabkin et al., 2012a).

THE AMPATH MODEL IN KENYA

Sylvester Kimaiyo, executive director of AMPATH, Kenya, described the outcomes of the AMPATH model in Kenya over the past two decades. AMPATH, an acronym for Academic Model Providing Access to Healthcare, was formed to seek funds from outside the realms of universities, hospitals, and ministries of health to support care, research, and training (Mamlin et al., 2004; Einterz et al., 2007). AMPATH differs from other university consortia in that care leads the way, but care is integrated with research and training. AMPATH has achieved its goals in terms of bringing funders and supporters to the table, Kimaiyo reported, including the U.S. Agency for International Development (USAID) and the U.S. Centers for Disease Control and Prevention.

Kimaiyo traced AMPATH's journey from its origin in 2001 with a nascent HIV care program in two clinics in and around Eldoret in western Kenya. In 2008, AMPATH expanded its focus to include chronic diseases and primary care, and in 2010, a memorandum of understanding was signed with the ministry of health in Kenya to work on NCDs (Bloomfield et al., 2011). In 2016, population health began in Busia and Uasin Gishu (Kimaiyo, 2019). As of 2019, AMPATH supports more than 800 clinics across Kenya, with a catchment population of about 15 million and about 150,000 patients currently receiving treatment (AMPATH, 2019). Along the way, they had to address challenges with respect to space, progressing from services delivered in tents to purpose-built structures, the latest addition being the Chandaria Cancer and Chronic Diseases Center. Staff-related challenges included morale, burnout, and transferral, according to Kimaiyo. Additional challenges have related to the availability of antiretroviral therapies, record keeping, addressing food security and poverty, transparency and accountability, and the development of exit and sustainability plans (Kimaiyo, 2019).

Foundational Elements of AMPATH's Success

Multiple factors have contributed to the success of AMPATH, said Kimaiyo. One advantage is that AMPATH has one "central nervous system." AMPATH is a parastatal of the government of Kenya, but it acts like a nongovernmental organization with autonomous financial management

when it receives funding. He noted that AMPATH has benefited from academic partnerships with Moi University College of Health Sciences and the Moi Teaching and Referral Hospital in Kenya, as well as a consortium of universities led by Indiana University. AMPATH also works closely with 10 county governments and the national ministry of health. Institutional and governmental support have been helpful in providing innovative, interactive medical education. The community-based education and service program has been a major contributor to AMPATH's success, providing a foundation for partnering with the community and the ministry of health, leveraging the potential of academic medical centers, creating the foundation for AMPATH's care system, providing opportunities for research, and influencing national policy and health indicators.

The AMPATH medical record system was developed as an electronic data repository of every visit in an open medical record system platform (Mamlin and Biondich, 2005). The numbers of patients treated are indicators of AMPATH's success, said Kimaiyo. AMPATH enrollments for HIV/AIDS increased from around 800 in 2002 to almost 200,000 in 2015 (Kimaiyo, 2019). Cumulative AMPATH research and training grants by year have followed a similar trajectory, from less than $1 million in 2002 to more than $125 million in 2018, as have the numbers of AMPATH publications per year—around 200 publications on their work in 2017 and 2018 alone, he stated.

Novel Models for Delivering Integrated Care

Kimaiyo described four projects related to integration that AMPATH has under way in Kenya. Three are existing novel models of care. In Busia and Trans Nzoia counties, AMPATH is providing integrated screening and care for chronic conditions (hypertension, diabetes mellitus, cervical cancer, and breast cancer) at the primary care level (Kimaiyo, 2019). Comprehensive community- and facility-based hypertension and diabetes screening and care are ongoing in Bungoma (Kimaiyo, 2019). In Uasin Gishu a population health model is providing comprehensive community- and facility-based screening and care to achieve universal health coverage (Kimaiyo, 2019). The fourth project was slated to begin in Bungoma in 2019 to evaluate the effect of strategies tailored to increase male participation in hypertension and HIV screening activities, as well as their linkage and retention in care. The model will implement comprehensive community- and facility-based hypertension and HIV screening. He reflected that integration may not be appropriate at all levels of the health system, but it is beneficial in at least a few levels.

ADDRESSING THE CONVERGENCE WITH INTEGRATION SCIENCE

Gene Bukhman, director of the Program in Global Noncommunicable Disease and Social Change at Harvard Medical School, discussed how to address the convergence of infectious disease and NCDs with integration science. He began by distinguishing between integration science and what is conventionally referred to as implementation science. Implementation science is an existing approach to studying how well delivery models perform, their uptake, and their barriers to uptake (Bauer et al., 2015). Integration science, which is still in its infancy, is the science of design of delivery and employs different kinds of techniques and approaches other than research trials (Bukhman, 2019).

The Long Tail of the Burden of Disease

To discuss integrated interventions for addressing NCDs, Bukhman drew on his clinical experience working in Rwanda with Partners In Health. The top panel of Figure 7-1 depicts the burden of disease in Rwanda in 2005, showing larger burdens of communicable, maternal, perinatal, and nutritional conditions on the left side and NCDs and injuries forming the long tail on the right side. The larger-burden conditions shown on the left side of the curve were addressed through vertical interventions—such as universal access to antiretroviral therapy and insecticide-treated bed nets—as well as interventions that were more integrated. For instance, the World Health Organization's (WHO's) Integrated Management of Childhood Illness guidance was used to manage diarrheal disease, malaria, and pneumonia in children.[3] Bukhman noted that vertical initiatives do not have a comparable population effect on NCDs and injuries that vertical strategies can have on other diseases, such as cancer-specific vertical initiatives. Because the conditions in the long tail are heterogeneous, interventions need to be packaged or clustered to address the aggregate burden of disease.

The bottom panel of Figure 7-1 provides a closer view of the lower-burden conditions in the long tail of the curve with examples of packaged interventions. Bukhman noted that from an ethical standpoint, many of the conditions in the long tail share properties with the larger-burden conditions on the left side of the curve, both in terms of cost-effectiveness and an affected population that skews toward children and the poor. Thirty years later, the curve of the ranked causes of all-age disease burden in Rwanda looks starkly different. Mortality attributable to diarrheal diseases and major

[3] More information about Integrated Management of Childhood Illness is available at https://www.who.int/maternal_child_adolescent/child/imci/background/en (accessed July 31, 2019).

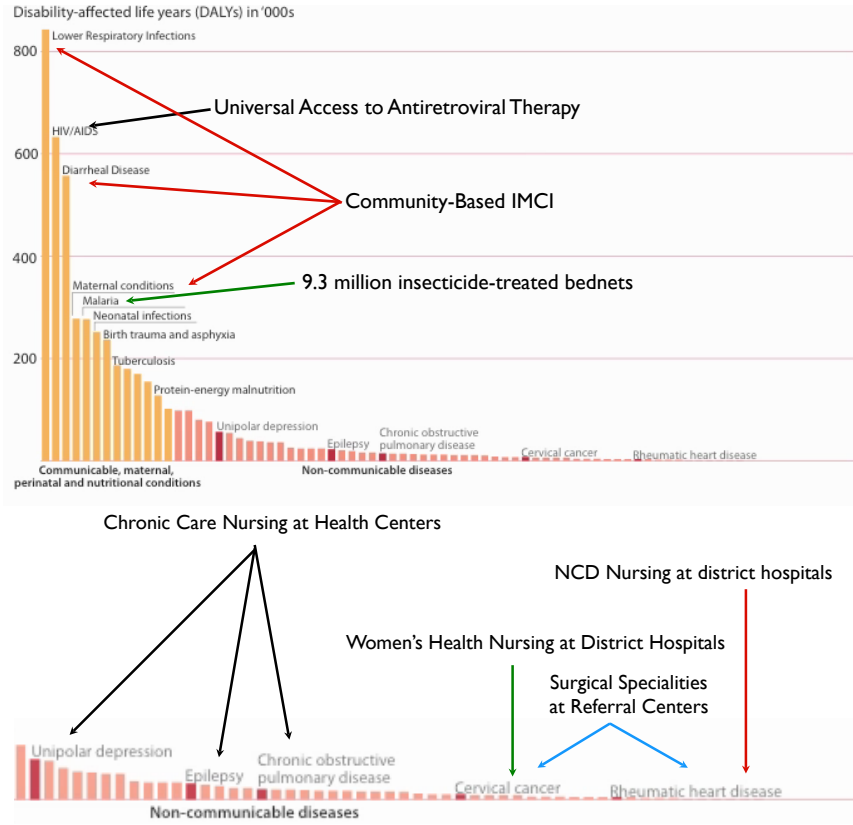

FIGURE 7-1 The long tail of global health equity in Rwanda. Top: Examples of interventions to address larger-burden conditions. Bottom: Examples of packages to address conditions in the long tail of the burden of disease.
NOTE: IMCI = Integrated Management of Childhood Illness; NCD = noncommunicable disease.
SOURCES: Bukhman presentation, June 12, 2019; WHO, 2008; PIH, 2011.

childhood illnesses have also declined dramatically. Bukhman described this new epidemiological phase as "all tail." He said that these outcomes were largely achieved through community-based interventions that were not contingent on a strong health system or functioning health centers. Achieving a population health effect requires thinking managerially and operationally about how to integrate services through clustering, he emphasized.

Developing a Science of Integration in Global Health Delivery

Declines in major causes of childhood deaths—such as diarrheal diseases and major childhood illnesses—have flattened the distribution of the global burden of disease, said Bukhman. Increasingly, the problems related to infectious disease and reproductive, maternal, neonatal, and child health are also "long-tail problems." The infectious disease space, for example, is now dealing with conditions like drug-resistant TB that are complex but not significantly affecting public health. Bukhman listed a set of more than 20 interventions for NCDs that he considers to be just as cost-effective and as compelling from an equity standpoint as interventions that are currently prioritized for infectious disease and maternal and child health.[4,5] These interventions cannot be operationalized or scaled up in isolation, so Bukhman offered three general principles of planning interventions for the long tail:

1. Leverage inefficiencies in existing space and staffing.
2. Decentralize progressively.
3. Optimize clustering of related services.

Bukhman maintained that moving toward a new science of integration would help to provide operational clarity and to link up evidence-based interventions, health-sector priority setting, and implementation. He offered a provisional definition for the science of integration in global health delivery: "the study of delivery model design, including optimal clustering of tasks among providers, and interfaces within and outside of the health system." A first step in developing an integration science is to define what is being optimized, such as equity, cost-effectiveness, and/or financial risk protection. The next step is to define the properties of interventions and related competencies to understand their underlying structures. Studying the historical team structure and task distribution within health systems can then be used to model the optimal redistribution of tasks. Existing

[4] The 23 interventions that Bukhman listed included the following: appendectomy, broken fractures, colostomy, combination therapy for moderate to severe rheumatoid arthritis, fracture reduction, gallbladder removal, hernia repair, integration debridement, management of bowel obstruction, management of epilepsy with generic antiepileptic medications, management of type 1 diabetes, medical management of acute decompensated heart failure, prophylaxis for bacterial infections in sickle cell anemia, relief of urinary obstruction by catheterization, repair of perforations, secondary prophylaxis of rheumatic fever, shunts for hydrocephalies, sickle cell screening, surgical treatment of early-stage breast cancer, trauma ileostomy, trauma-related amputations, treatment of acute pharyngitis, and urethrectomy.

[5] During the discussion, Bukhman noted that among the priority NCD interventions he listed during his presentation, most were acute care and surgical interventions, not chronic care interventions as conventionally understood.

computer-based techniques for supporting system design and analysis may be important to consider for smaller systems (Bellman and Landauer, 2000). However, constructing and integrating large systems will require an actual science of integration supported by principles and corresponding analytic methods, he added.

Chronic Care Decentralization and Integration in Rwanda

Bukhman described an example of an intuitive approach to chronic care decentralization and integration from Rwanda (Gupta and Bukhman, 2015). After the devastation of Rwanda's health system in the mid-1990s, health services were highly centralized and essentially limited to teaching hospitals, Bukhman recounted. Over time, there were progressive decentralization cascades based on shared competencies (Sekabaraga et al., 2011). Mental health and TB-HIV care were among the first to be decentralized to district hospitals (Binagwaho et al., 2014; Mohand et al., 2017). By 2005, a gap emerged in decentralized care for severe NCDs, such as type 1 diabetes and advanced rheumatic heart disease, Bukhman continued. To address this gap, they developed a delivery model for use at the referral center level. By 2015, the delivery model had been implemented in all central hospitals. In 2019, Rwanda is decentralizing simpler, more standardized chronic care for NCDs to health centers (PIH, 2011). They are also developing integrated chronic care at health centers and in the community (PIH, 2011).

Although the intuitive approach to decentralization used in Rwanda has benefits, Bukhman suggested that a more structured, model-based approach would be superior in determining the optimal clustering of interventions and in developing a typology of chronic care services. The experience in Rwanda demonstrates the benefits of decentralization cascades and the rationale for prioritizing the rollout of intervention packages in district-level hospitals at an early stage in the process, said Bukhman. The approach has the potential to reach the highest-risk individuals and provides an opportunity to build leadership for training, supervision, and mentorship of services at the health center level.

Ongoing Work in Integration Science

In many systems, an initial goal of complete coverage of complex chronic care service packages at the district-level hospitals is achievable in the short term, noted Bukhman. WHO has a Package of Essential Noncommunicable Disease Interventions (WHO PEN)[6] that is a set of cost-effective interven-

[6] WHO's Package of Essential Noncommunicable Disease Interventions is available at https://www.who.int/ncds/management/pen_tools/en (accessed July 31, 2019).

tions for primary care in low-resource settings, but it does not encompass services for more severe and chronic types of NCDs that cannot be managed well at the primary care level. To address this gap, the proposed PEN-Plus strategy would create specialized outpatient NCD clinics at first-level hospitals (Tapela et al., 2006; Kwan et al., 2013; Bukhman et al., 2015; Habineza et al., 2017; Eberly et al., 2018a,b, 2019; Rusingiza et al., 2018). The Global Health Delivery Partnership, comprising Partners In Health, teaching hospitals in Boston, and Harvard Medical School, is working with more than 15 low- and middle-income countries that have undertaken national NCDs and injury poverty commissions. They are exploring how emerging theories of health system integration can be applied to address NCDs and injuries among poor and vulnerable populations.

MASS ADMINISTRATION OF ANTIBIOTICS TO REDUCE CHILD MORTALITY

In her presentation, Catherine Oldenburg, assistant professor and Francis I. Proctor Foundation faculty member at the University of California, San Francisco, discussed the mass administration of antibiotics to reduce child mortality. She described how this integrated intervention emerged out of mass administration campaigns to prevent blinding trachoma. The Proctor Foundation, an organized research unit within the University of California, San Francisco, was originally founded for the elimination of blinding trachoma in the American Southwest. After that goal was achieved in the 1950s, they expanded the focus to eliminating trachoma worldwide through a combination of approaches, with mass distribution of azithromycin as a cornerstone.

Mass Drug Administration for Infectious Disease

Mass drug administration is a platform that can be used to administer preventive chemotherapy to an entire community or populations at risk when there is transmission of infectious disease. Oldenburg explained that mass administration is typically carried out using campaign-style delivery once or twice per year. More frequent administrations are not generally feasible because of associated logistic and supply chain complexities. These campaigns typically involve either door-to-door delivery or delivery at central points of distribution that are publicized and supported by mobilizers. Mass administration interventions require a safe, effective, and low-cost drug, said Oldenburg. For example, mass administration with doxycycline would not be appropriate for an infection that is predominantly affecting children because of the risk of adverse events. Common examples of mass drug administration include

- chemoprevention of seasonal malaria in areas with highly seasonal malaria epidemics,
- prevention of onchocerciasis using ivermectin,
- prevention of soil-transmitted helminths using albendazole,
- prevention of lymphatic filariasis using ivermectin, and
- prevention of trachoma using azithromycin.

Mass Azithromycin Administration for Trachoma Control and Mortality

Oldenburg described the natural history of trachoma, an infection caused by the *Chlamydia trachomatis* bacteria. In an infected child with an inflammatory response, the characteristic pattern is that after years of repeated infections—generally before the age of 10—the inflammation turns into scarring. Eventually the eyelash begins to turn and touch the cornea, so the eyelash rubs painfully on the cornea with each blink of the eye. This eventually results in a corneal infection that is no longer amenable to widely available treatments. Corneal transplant options are not available to most of the patients with end-stage trachoma. She said that progress is being made and rates are declining globally, but trachoma remains one of the most common infectious causes of blindness in the world (Bourne et al., 2013; Cox et al., 2017). A cluster randomized trial administered four annual mass treatments of azithromycin to an entire community in Ethiopia with hyperendemic trachoma.[7] The prevalence of ocular chlamydia decreased from about 40 percent at baseline to around 5 percent toward the end of the study (Gebre et al., 2012).

Azithromycin is a broad-spectrum antibiotic that also has activity against other bacteria. Oldenburg explained that during the early stages of some azithromycin trials for trachoma, there were questions about possible spillover effects of mass azithromycin administration, particularly on infectious burden in children. Studies that have looked at the effect of mass administration of azithromycin on diarrhea, malaria, and respiratory infections in children have generally shown positive results (Coles et al., 2011; Oldenburg et al., 2019). The children who received azithromycin for trachoma control also had reduced burdens of diarrhea, malaria, and respiratory infections—some of the most common causes of postneonatal mortality in areas where trachoma is endemic (Coles et al., 2011). A 2009 study established that mass administration of azithromycin for trachoma had significant benefits for the child recipients in Ethiopia (Porco et al., 2009). The study found a 50 percent reduction in mortality among children who lived in communities that received azithromycin for trachoma compared to children from communities in which

[7] Trachoma programs treat children who are 6 months of age and older, and those who are younger than 6 months get topical tetracycline.

treatment was delayed for 1 year. Oldenburg described this as a remarkable reduction in mortality for a single-dose administration.

Oldenburg presented the results of the MORDOR study in Malawi, Niger, and Tanzania, which was designed to reproduce the observed mortality benefits of azithromycin, but in rural communities with no trachoma (Keenan et al., 2018). Between 2015 and 2017, more than 1,500 communities were randomized to receive either biannual mass azithromycin or biannual placebo. Children between ages 1 month to 59 months were treated, because they are the subset of the population under 5 years of age that has the highest mortality. Communities were followed for 24 months with a biannual census to ascertain mortality. The deaths per thousand person years in the control arm varied widely, with the largest mortality rates, not unexpectedly, seen in Niger. Overall, there was 13.5 percent reduction in mortality in the azithromycin communities compared to placebo communities in each country (Keenan et al., 2018). When disaggregated by country, this effect was driven by the 18.1 percent mortality reduction in Niger, which had the largest national burden of child mortality in the study (Keenan et al., 2018). There was no evidence of a difference in Malawi and Tanzania specifically, but the study was not powered for country-level comparisons (Keenan et al., 2018).

Oldenburg noted that the absolute number of deaths averted per age group may give the impression that targeted administration to certain age groups would be preferential. However, the research suggests that mass treatment is the most effective way to reduce mortality, she said. The risk of mortality is higher in younger children, but the absolute number of deaths averted is lower because of the relative sizes of the population. Therefore, it is best to treat all children under 5 years in order to maximize the number of people that benefit, she said.

Mass Administration and Antimicrobial Resistance

Oldenburg described the results of a systematic review of adverse events following mass azithromycin for trachoma control, which looked at all of the evidence of antimicrobial resistance (O'Brien et al., 2019). In general, mass drug administration with azithromycin leads to increased selection for macrolide resistance in pneumococcus (O'Brien et al., 2019). The increase in resistance tends to follow immediately after the mass administration, she noted. Although there is some evidence that the resistance persists over time, it tends to reduce once the antibiotic selection pressure is removed. More research is needed to examine antibiotic resistance following mass administration targeted only at children, she noted. Short-term changes have also been observed in the composition of the microbiome—specifically, reduction in bacterial diversity—after mass azithromycin administration

(Oldenburg et al., 2018). Studies looking at longer-term changes to the microbiome following azithromycin treatment are ongoing, she added.

Targeting and Scaling Up Mass Administration

Mass drug administration works where there is a large burden of disease, said Oldenburg. Global child mortality rates are changing fairly rapidly over time, so consideration of where to implement mass administrations needs to be informed by the background mortality rate of the setting—for example, selecting geographic regions with more than 100 under-5 deaths per 1,000 live births (Golding et al., 2017). Discussions about the potential for global scale-up of mass administered azithromycin for child mortality are considering how to use existing mass drug administration platforms that are already in place for neglected tropical diseases. She noted that mass azithromycin administration for child mortality could potentially be integrated into existing trachoma programs or into other programs focused on overlapping epidemics. It could also be integrated into other existing platforms, such as vaccinations, through which children are already being treated. Regardless of the strategy, any scale-up will need to include monitoring for antimicrobial resistance, she added.

DISCUSSION

Following the presentations, the discussion portion of the session began with all four panelists. To open up the discussion, Marcos Espinal, director of communicable diseases and health analysis at the Pan American Health Organization, asked the presenters to identify some of the greatest bottlenecks to integration.

Bukhman replied that there are structural bottlenecks within WHO and ministries of health that are affecting the operational transformation toward strategies for chronic care integration. WHO has units focused on chronic care coordination and integration that are distributed across the range of categories—for example, rehabilitation services, mental health, and chronic care for infections and NCDs. He indicated that as part of its broader reforms focused on universal health coverage, WHO has an opportunity to break down the walls between units with a disease-specific focus and chronic care integration units. Ministries of health face similar problems, but developing chronic care integration units would allow for more operational clarity and better planning than units focused exclusively on NCDs, he added.

Kimaiyo cited financing as a barrier. Although HIV is well funded, programs that are candidates for integration with HIV programs typically do not have their own funding or staffing. The transition toward universal

health coverage could provide an opportunity for governments to assume more autonomy, he suggested, but the reality is that donors tend to prefer funding vertical projects.

Rabkin added that administrative silos tend to follow the funding. In her experience, ministries of health are not resistant to the idea of integrated chronic care, but NCD departments are severely underresourced compared with HIV departments. She predicted that this bottleneck will not be overcome without more funding for chronic diseases, even with the best of will and the best of science.

Bundling HIV Services with Noncommunicable Disease Services

Espinal opened the floor for questions. First, Emily Erbelding, director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, commented that The President's Emergency Plan for AIDS Relief (PEPFAR) was designed to be a siloed, vertical program. However, the consequent stigma associated with receiving PEPFAR-funded services, especially among men, has reduced the program's efficiency to an extent. Given that PEPFAR made gains when HIV testing was included as part of a chronic disease package, she suggested that HIV services might be enhanced if they were bundled with NCDs. Rabkin clarified that HIV testing uptake has been shown to improve when it is combined with testing and screening for other conditions, regardless of whether those other conditions are NCDs (Kabami et al., 2017; Young et al., 2018).

In Western Kenya, some of the approaches to finding men with HIV have taken an integrated screening approach, said Rabkin. However, follow through for NCD care tended to be poor owing to the expense of medications and transport and the lack of peer educators. Rabkin said that there are benefits to integration of NCDs into HIV programs, as well as benefits to the HIV programs into which the other programs are integrated. However, screening is not effective without funding for prevention, care, and treatment for the other conditions being detected, she noted. Kimaiyo emphasized that PEPFAR saves lives and has created invaluable infrastructure. PEPFAR's mistakes are not the issue, he said—the issue is the global community's neglect of other diseases.

Mass Administration: Barriers, Surveillance, and Long-Term Effects

Jay Siegel, retired chief biotechnology officer and head of scientific strategy and policy at Johnson & Johnson, remarked that most drugs used in mass administrations were initially developed for treatment of individuals, not entire populations. He asked if mass administration efforts ever encounter regulatory barriers in obtaining drugs or in importing drugs into

other countries. Oldenburg replied that azithromycin is approved for use and is indicated in the WHO guidelines for treating trachoma in children 6 months of age and older. The MORDOR study treated infants down to 1 month of age, giving rise to discussion about how the WHO guidelines may facilitate the entry of the drug for younger age groups. Patricia García, professor at the Cayetano Heredia University School of Public Health, Peru, said that in her experience as a health minister, most countries have fast tracks for the entry of medications associated with public health if it is properly coordinated with the ministry of health and aligned with existing guidance.

Rachel Nugent, vice president for the Chronic Noncommunicable Diseases Global Initiative at RTI International, remarked that the mechanism of mass drug administration becomes less effective as the disease burden declines and disease reservoirs shrink to progressively smaller areas. She asked about the potential benefit of bringing NCDs into existing surveillance mechanisms to better understand co-occurrences within specific populations. Oldenburg replied that mass drug administration and community surveillance programs developed for neglected tropical disease platforms have the power to bring care into communities, rather than requiring people to travel long distances from the community to a health care post. Going forward, leveraging platforms currently used for screening and epidemiological tracking can ensure that people actually receive care if they are referred, she added.

García asked about plans for follow-up research on the long-term effect of recurring mass administration of antibiotics, both on the microbiota and on antimicrobial resistance. She noted that these types of large-scale interventions can change the microbial ecosystem and cause unexpected consequences. Oldenburg replied that a long-term open-label extension of the MORDOR study is ongoing in Niger (Keenan et al., 2019). Communities are going into their fourth year of surveillance, with rectal and nasal swab samples collected from children to look for antibiotic resistance as well as microbiome changes. Other studies are evaluating different frequencies of administration and dosing strategies. Changes in the intestinal microbiome of children who received azithromycin compared to placebo are observed at 5 days after treatment—both changes in composition and a decrease in microbial diversity. Observed changes in the community microbiome tend to last slightly longer, but those changes are not as pronounced as the short-term changes seen in individual children. She added that ongoing studies are sampling children more frequently to analyze longitudinal changes and to evaluate the length of time it takes the microbiome to return to normal, if it does at all. The longer-term implications of mass azithromycin administration in the microbiome of children over the life course are not yet known, she stated. She added that children who receive mass azithromycin administra-

tion tend to receive, on average, far fewer courses of antibiotics than children in the United States, for example.

Domestic and External Funding Considerations

The discussion transitioned into a focus on funding. Bukhman stated that external funding needs to increase because the poorest countries simply do not have sufficient domestic resources. Chronic care integration presents an opportunity to galvanize global health solidarity around more severe diseases affecting children, then disaggregating the argument and explaining that chronic conditions are also within the remit of global health responsibility based on those same premises. Lumping all NCDs together from the outset could potentially do them a disservice, he cautioned. Nugent called for careful consideration about the specific objectives that could be achieved with different actions—such as better outcomes, cost savings, financial risk protection, or expanding services—and strategically selecting which ones to focus on.

Espinal highlighted a tension between national governments' responsibilities to fund care for their populations and the negative consequences of excluding donor funding. Funding concerns are not limited to low-income countries. Funds are also dissipating in middle-income regions like Asia and Latin America, where a common misconception is that NCDs are only a problem of high-income countries. Increasing and integrating care for NCDs will likely be beyond the financial capability of many middle-income countries. He noted the potential effect of having large-scale international donors push for integration based on lessons learned from investing in diseases and programs over the years.

Bukhman was concerned that maintaining the current disease-specific focus and architecture of development financing—in which, for example, countries graduate and move into middle-income status—will lead to a decline in development assistance. Instead, he offered the idea that financing structures for development assistance could be reframed to prioritize highly equitable and cost-effective interventions for the poorest people in the world, rather than specific diseases. Spending funds in that way will require broadening the mandate to account for transitioning burdens of infectious diseases and NCDs, however. This could lead to inequitable allocation of funds in middle-income countries, he cautioned, because some lower-middle and upper-middle countries may be better off than others in terms of domestic resources.

Espinal noted the need to broaden the focus beyond the African region. Latin America, for example, has the greatest inequity of all six WHO regions. Wealth is growing, but it is not well distributed, leaving many subpopulations vulnerable and lacking access to care. García added that coun-

tries' specific needs should be taken into account in funding decisions. For example, countries in Latin America may need only catalytic funding to pilot innovative, cost-effective interventions that governments can then take over, while countries in Africa may need more resources. Kimaiyo remarked that even in a country that has adequate domestic resources, the government's management of those resources can be challenged by corruption, political pressures, or poor prioritization of funding. A new USAID initiative called the Journey to Self-Reliance is trying to support and strengthen governments' management capacities.[8]

Person-Centered Approach to Integration

Finally, offering her perspective as the former minister of health in Peru, a middle-income country, García emphasized the need for changes in mindset on three fronts. First, communities need to be meaningfully empowered with knowledge as well as with practical tools to improve their health. Second, she suggested funding agencies should shift from a paternalistic focus on disease-centered responses to a focus on people-centered responses. Third, barriers to integration need to be addressed rather than ignored, she added. Years ago, Peru had no domestic funding for its HIV program. USAID offered funding that was contingent on creating a parallel program to the ministry of health. García and her colleagues were opposed to this idea, because it ran counter to the existing structure of the health system. In some countries in Africa, however, such parallel systems tend to be created because they are easier than working within existing systems, which she noted are often hampered by corruption.

One of García's major challenges as a health minister was dealing with corruption. She was adamant that corruption is a pervasive issue that needs to be dealt with head on with scientific rigor—perhaps through a new discipline of "anticorruption science"—rather than sweeping it under the rug. She added that the practice of creating new clinics in a parallel system is also a product of the myopic focus on HIV. She argued that everyone in the enterprise—from funders to researchers to politicians—have a responsibility to shift from a disease-funding mindset to a people-centered mindset as the fulcrum to achieving integration.

[8] More information about the Journey to Self-Reliance initiative is available at https://www.usaid.gov/selfreliance (accessed July 31, 2019).

8

Potential Approaches for Research, Policy, and Practice in the Immediate Term

The first part of the fourth session of the workshop focused on potential approaches in research, policy, and practice to address the convergence between infectious diseases and noncommunicable diseases (NCDs) in the near term. The workshop participants first individually reflected on where they believe to have the ability to take or influence action to address the convergence and then shared their ideas in small groups. In the small groups, participants specifically focused on areas where they converged as well as diverged, areas that had not yet come up during the workshop, and areas where they thought broader research or policy efforts could be enacted to support actions in the immediate term. After the small group discussions, a participant from each group reported on their conversations, and then the workshop participants engaged in a larger group discussion, which was moderated by Bridget Kelly, principal consultant of Burke Kelly Consulting. The topics ranged from strengthening health systems and health care, communication approaches and information access, and data collection and methodologies.

POTENTIAL PRIORITY STRATEGIES AND ACTIONS FROM TABLE GROUP DISCUSSIONS

The session began with a discussion on the way many health systems, and much of health care itself, are structured in the world today. Emily Erbelding, director of the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases, reported that her table discussed the challenge of overspecialization in the United States

as well as in low- and middle-income settings. For instance, she said that HIV has disease-specific community advocacy and disease-specific supply chain logistics, but other diseases and essential medicines do not. The number of specialists trained is often used as a country-level indicator of improved health care; this may have contributed to overspecialization and related problems in emerging health systems, she said. Some members of the group proposed identifying better quality metrics for evaluating health care systems, such as access to primary care, the number of health care providers, and availability of an essential medicines and primary care package at the community level. This package could potentially be designed by the ministry of health and include basic medicines, such as baby aspirin and hypertension treatments.

Mosa Moshabela, dean and head of the School of Nursing and Public Health at the University of KwaZulu-Natal, South Africa, reported that some participants at his table focused on the topic of understanding knowledge gaps and access to information. He said that it is often unclear which entities have which types of knowledge, or what knowledge is needed to influence the policy landscape and improve how work is carried out. Information access is a challenge, especially for entities that are not aware of what information they do not know; this problem is further compounded by siloing, he said. Some of the members of the group discussed developing strategies to access necessary information that already exists but is siloed, as well as developing research methodologies to generate new information when knowledge gaps are identified. In addition, a few participants suggested considering how to engage people with information at different stages in the life course. For example, information technology innovations could be leveraged to engage younger populations. Moshabela noted that efforts for innovation and invention should be directed toward evaluating what assets are already available and identifying how those assets can be maximally leveraged.

Furthermore, Moshabela said complexity can be embraced to achieve convergence. Some participants of the group discussed the use of dynamic approaches to plan services that are tailored to respond to a community's needs more effectively than a standard package of care. This could be informed by creating a socioecological profile of a community to identify the right mix of services to integrate infectious diseases and NCDs in that particular profile. He suggested shifting toward more inclusive language to elicit community-level knowledge—a people-centered approach that takes into account diverse voices may reveal opportunities or information that would otherwise be missed.

Emily Mendenhall, Provost's Distinguished Associate Professor at Georgetown University, noted that her table highlighted the importance of patient-centered, people-centered care, as well as issues on communication

and messaging approaches. She specified that some participants discussed how labels, such as *researcher* and *policy maker*, and categories, such as people who work on NCDs versus people who work on infectious diseases, can impede collaboration on complex problems. Some of the group members discussed the benefits of rethinking how messages are packaged and ensuring that health research is presented to people outside the health sector in productive ways. One strategy a few participants raised is to move upstream from individual-level interventions and frame health interventions as effective policy or social interventions.

Some of the members in Mendenhall's group also highlighted the importance of catalyzing political interest, working as activists to publicly promote this work, and developing coalitions across sectors, as well as tackling the issue of corruption, as potential strategies. A few participants considered how the food and agricultural systems influence health and wider societal consequences, such as the overproduction of corn for high-fructose corn syrup that is put into high caloric foods, which are prevalent in low-income communities. Beyond corporate responsibility and targeting commercial determinants, she said it would also be helpful to consider historical subsidy programs fueling the overproduction of corn products and other systemic inequalities associated with these effects. Some of the participants indicated that a planetary perspective on health may be the most inclusive framework for understanding convergence, its drivers, and its outcomes at a macro level.

In a similar vein, Emma Mendelsohn, modeling and analytics research scientist at EcoHealth Alliance, added that a few members of her group also noted that in the infectious disease space there are incentives to cure disease while at the same time there are profit incentives that can contribute to NCD risk factors, such as unhealthy foods. In addition, some participants of her group discussed issues about communication, highlighting that communication with the public about specific issues can be part of a strategy to address a larger problem. For example, describing the mechanisms of the microbiome can apply more generally to communicating why convergence is important in tangible, mechanistic ways that can be accessible by a general audience. Finally, she noted that a few members discussed the need to improve the quality of data and facilitate data sharing to better inform models and make more accurate predictions. This includes the need to disseminate data within communities, she said.

As mentioned by some other groups, Matthew Coates, associate in global health and social medicine at Harvard Medical School, reported that many members of his group also raised the importance of person-centered care and community engagement to improve health care, as well as helping to prevent corruption. In terms of data, he said large data sources could be used to identify clustered comorbidities that can then be used to identify

endemics or underlying social factors that contribute to the clusters. He noted some of the participants of his group also discussed the need to improve the regulatory pathways for microbiome therapeutics and ensure they are accessible broadly and equitably. Forging personal connections across sectors, he said, could help mitigate silos and help prevent new ones from forming.

Finally, Paige Waterman, assistant director for Biological Threat Defense at the White House Office of Science and Technology Policy, reported that her table members touched on several issues. On the topic of strengthening health systems, she reported that a few members suggested a cluster analysis of the factors that make health systems efficient, which includes disease-specific inputs, social determinants of health indicators, or any other shared inputs. Economists could perform cost analyses to understand the required services and the relationships between individual-level needs in order to develop a strategy for allocating limited resources and shaping policy, she added. Some participants also noted the potential of leveraging the ubiquity of cell phones to empower, educate, and involve communities in health-related topics. The issues of siloed funding and disease-focused donor interests as challenges to integration were also raised by the group. Waterman noted that a few members of the group wondered if the messaging and framing of the national security dimension contributes to why NCDs receive less attention as a public health concern relative to infectious disease outbreaks.

DISCUSSION

Bridget Kelly, principal consultant of Burke Kelly Consulting, opened the discussion by asking participants to offer any further highlights or insights from their tables' discussions. The discussion delved into issues related to trade-offs involved in the convergence, the role of industry and multisectoral collaboration, regulatory and funding considerations, and metrics.

First, Tolullah Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge, noted that convergence comes with trade-offs, because everything is interconnected. It is therefore helpful to understand how different components of the system interact, thus leveraging a systems approach. For example, there are interventions that could potentially improve an infectious disease but make an NCD worse (or vice versa), she stated. She also highlighted the benefits of broader multisectoral representation. Being more inclusive and seeking input from other sectors could help create a more holistic platform for leveraging a disaster as an opportunity to plan for and prevent infectious disease and NCD outcomes in future events. Kelly followed up, noting the need to think carefully about the assumptions being made regarding other sectors. Discussion often cen-

ters around what other sectors should do in terms of health interventions, but health may not be the priority of those sectors.

Cathryn Nagler, professor of pathology, medicine, and pediatrics at The University of Chicago, asserted that food allergies need to be recognized and advocated for as a global health problem. The food allergy community has received pushback because its prevalence has increased so rapidly in recent decades that relatively speaking, food allergies barely existed for an entire older generation, she explained. As a result, families in which a member has a food allergy often encounter problems accessing necessary accommodations, she noted. For example, peanuts on airplanes can be life threatening for a person with a peanut allergy, but there is still resistance from most airlines to allow families to preboard to wipe down seats and remove crumbs that could cause an anaphylactic response.

Moshabela suggested anticipating and preparing for pushback against the convergence agenda by proactively considering the potential unintended consequences of convergence as well as possible trade-offs that may arise. For instance, a focus on health promotion and upstream factors may be perceived as a threat by those who benefit from the current model. Kelly suggested working to mitigate the threat to people who may push back against the agenda. However, she noted that losses may be unavoidable for actors who benefit from profit incentives that are harmful to health.

Peter Daszak, president of EcoHealth Alliance, reflected on how various industries will be affected by convergence if the guidance being discussed at the workshop were to be actually implemented worldwide. For example, the livestock and vaccine industries would likely be less profitable, while the pharmaceutical industry might shift to developing microbiome-focused supplements and nutrients. Certain companies would likely exploit niches in this new market. Increasing obesity related to meat consumption in Asia could have significant implications in the future for companies supplying that meat, he added.

Following up on the role of industry, Oni noted that discussions about health and convergence of infectious diseases and NCDs often center on the private health industry. In countries in sub-Saharan Africa, for example, cities experiencing rapid urbanization are also subject to increasing environmental exposures related to infectious disease and NCDs. These exposures are being driven by private industries that are generally disengaged from public health policies and considerations, she said. To address this issue, Rachel Nugent, vice president of the Chronic Noncommunicable Diseases Global Initiative at RTI International, suggested that health impact assessments could be used to inform development decisions.

Regarding the U.S. Food and Drug Administration's (FDA's) regulation of the microbiome, the speed of the transition from knowledge to treatment is hugely influenced by the regulatory pathways, commented Jay Siegel,

retired chief biotechnology officer and head of scientific strategy and policy at Johnson & Johnson. For example, using fecal transplant to treat people with *Clostridium difficile* occurred before FDA decided that it was something to regulate. If such advances are relatively easy to do without regulation, it eliminates the incentive to invest in clinical trials. Regulation is at a critical juncture, said Siegel, because regulatory hurdles can have a major effect on the types of research that are carried out, the therapies that are developed, how much these therapies cost, and who has access to them. He highlighted that this has been illustrated in stem cell therapy, gene therapy, antibody therapy, and biosimilars.

The discussion transitioned to the implications of siloed funding, with Kelly remarking that siloed funding—such as earmarked government funding or disease-specific donor funding—is a cross-sectoral issue. She asked participants to comment on how efforts to reduce funding silos might affect the entities who hold the money. Siegel replied that while organizations may generally be interested in understanding the public health effect of their funding, they are often required to report back disease-specific metrics of effectiveness. It is more challenging to collect metrics to evaluate broader investments.

Along the topic of metrics, Patricia García, professor at the Cayetano Heredia University School of Public Health, Peru, noted the need for investments to strengthen the capacity to strategically collect information and analyze metrics on a systemwide level. She commented that sometimes funding agencies request too many metrics, which can often cause a burden for policy makers and other stakeholders when each funding agency is requesting different metrics. Being strategic about what metrics to collect and measure that would ultimately be reliable information is an important component of convergence, she asserted.

Mendenhall said that metric-driven interventions can be less effective and actually perpetuate inequalities and other problems, so making progress toward convergence will require moving beyond the current focus on individuated, disease-specific outcomes. She suggested that this message is not being heeded owing to the power of funders and their disease-specific motivations. It was noted that metrics that are not disease specific, such as health-related, quality-of-life indicators, are much more difficult to measure, and current information systems are not set up to capture those types of metrics. Oni added that even in projects that are explicitly designed to work intersectorally, the differentiation between infectious disease indicators and NCD indicators and outcome measures persists. Kelly pointed to the role of nonhealth sectors to inform new, integrated ways to measure health.

Finally, Siegel remarked that silos are also reinforced by the ways that health care providers are trained compared to the training received by public health professionals, particularly with respect to community health, epidemi-

ology, and a generally more holistic view of health. Kelly observed that it is easy to default to thinking about the convergence in terms of leveraging the successful practices of each side. In closing, as an alternative, she offered the framing that there is also space for both sides to recognize and collaborate to improve practices that are not working for either side to achieve mutually beneficial outcomes.

9

Visionary Statements on Potential Priorities to Address the Convergence

The final portion of the workshop in session four featured visionary statements on the potential priorities to break down silos and address the convergence of infectious diseases and noncommunicable diseases (NCDs). Speakers were asked to share insights on potential top priorities that would have a significant effect on the convergence, untapped opportunities that can be leveraged, and thoughts on how these efforts could synergize with existing global health initiatives, such as universal health coverage. This portion of the session was moderated by Mosa Moshabela, dean and head of the School of Nursing and Public Health at the University of KwaZulu-Natal, South Africa. Presentations on visionary statements were given by Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention; K. Srinath Reddy, president of the Public Health Foundation of India; and Patricia García, professor at the Cayetano Heredia University School of Public Health, Peru. The visionary statements were followed by a final synthesis discussion with the audience. The workshop concluded with closing remarks from Peter Daszak, president of EcoHealth Alliance.

ADAPTING PUBLIC HEALTH PRACTICE IN AFRICA TO A NEW UNDERSTANDING OF MICROBES AND HEALTH

Jay Varma, senior advisor at the Africa Centres for Disease Control and Prevention, presented a visionary statement that focused on integrated approaches and building the needed infrastructure to adapt a public health approach in Africa to address infectious diseases and NCDs. Varma

explained that the Africa Centres for Disease Control and Prevention—the new public health agency of the African Union, an intergovernmental agency that represents all 55 countries on the African continent—is dedicated to a vision of a fully integrated and prosperous Africa. The Africa Centres for Disease Control and Prevention was created in response to the health and disease transmission implications of the recently ratified continental free-trade agreement that ensures the free movement of goods, people, and services.

Varma stated that discussions of diseases or health challenges with policy makers should be linked to the concepts of universal health care and health security. The classical divide pins universal health care to NCDs and health security to infectious diseases, he noted, but it is possible to demonstrate how both types of diseases apply to both concepts. The concept of integration is a core component of the vision of the African Union, said Varma. It all extends from the colonial independence movement and the concept of Pan-Africanism to the need for a unified African voice, he added. This could mean a continental free-trade agreement, a single African passport (eventually), and a single air transport market. A component of this integration is the creation of institutions, including the Africa Centres for Disease Control and Prevention and the creation of a new African Medicines Agency that will be analogous to the U.S. Food and Drug Administration, Varma explained. The African Union is also committed to the creation of a National Public Health Institute in all 55 member states. Varma also highlighted the importance of infrastructure. Some areas in Africa have some of the fastest growing economies in the world, but infrastructure will need to be developed that permeates across countries in a way that promotes development across the continent, not just within individual countries, he noted.

Public Health Impact Pyramid

Varma presented an illustration of the public health impact pyramid (see Figure 9-1), as well as the ratio of population impact to individual effort at each level of the pyramid. He explained that the size of the population impact of interventions is greatest at the bottom of the pyramid and lowest at the top, while the individual effort needed to implement the intervention falls along an opposite gradient. For example, interventions that target socioeconomic factors through developmental, environmental, and structural changes may have the broadest population health impact while requiring the least amount of individual effort. At the next highest level are interventions to change the context to make individuals' default decisions healthier. Such interventions include taxation or banning certain products, like trans fats. Long-lasting protective interventions delivered to individuals—such as vaccines—require more individual effort, both on the health system side as

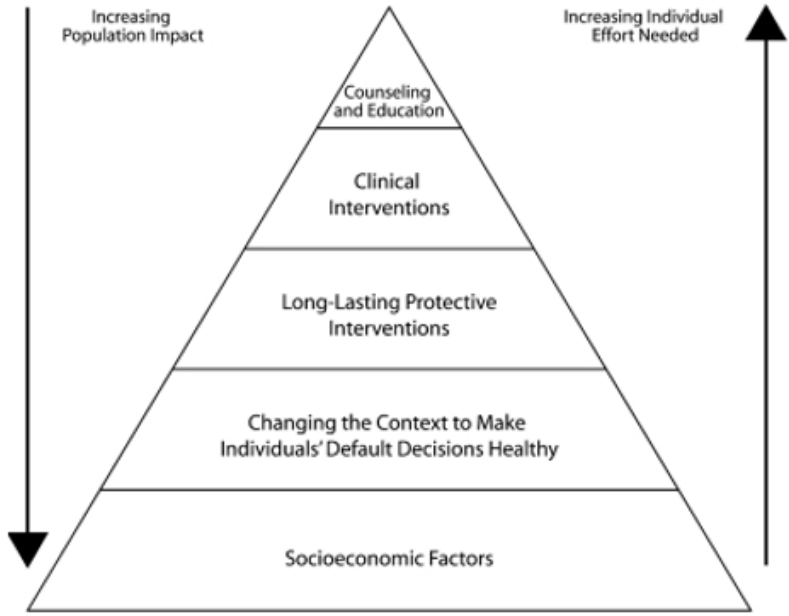

FIGURE 9-1 Public health impact pyramid.
SOURCES: Varma presentation, June 12, 2019; Frieden, 2010.

well as the human side. At the second highest level of the pyramid are clinical interventions through effective models of care. However, the dilemma is that clinical interventions impact less of the population and require much more individual effort, he noted. At the top of the pyramid are individual-level interventions such as counseling and education. Varma said that in the public health field, efforts are directed toward working from the bottom to the top of the pyramid, prioritizing interventions that can have an impact across the broadest population level while requiring the least amount of effort at the individual level.

Applying the Public Health Pyramid to Integrating Infectious and Noncommunicable Disease Interventions

Varma used the public health pyramid to suggest ways to integrate interventions against both infectious diseases and NCDs. At the level of clinical intervention, chronic disease screening and control could be introduced into vertical infectious disease programs, like those for HIV and tuberculosis (TB). He noted that HIV programs are more likely to be well funded and have

the existing infrastructure to provide comprehensive clinical services to an individual. The challenge is that this strategy will impact a smaller proportion of the population relative to the tremendous amount of individual effort required at both the patient and the provider levels, he added.

At the level of long-lasting protective interventions, Varma suggested deploying vaccines that prevent cancer. He noted that one of the greatest strides at the intersection of chronic diseases and infectious diseases was the discovery that infectious diseases cause cancer. Today, however, the hepatitis B virus vaccine and human papillomavirus (HPV) vaccine are both severely underused, he said. For the hepatitis B virus vaccine, immunization at birth is important to effectively prevent perinatal transmission (Mele et al., 2001; Hepatitis B Foundation, 2019). Barriers to administration of the HPV vaccine include the age requirement as well as enduring stigma around sexual health and the prevention of sexually transmitted infections (Holman et al., 2014).

Next steps, he stated, are to consider the role of seasonal influenza vaccination, the prevention of cardiovascular morbidity, and the prevention of diabetic ketoacidosis. A further step is to consider medical products that can be used to prevent cancer. Varma also noted that hepatitis C can now be treated more easily than TB, which is an instructive example of how some diseases (e.g., hepatitis C and HIV) are prioritized over others. Significantly reducing liver cancer deaths will require closing the gap that persists between HIV and hepatitis C in the infectious disease world, he added. Varma said this is a clear, easy win to reduce deaths from liver cancer. *Helicobacter pylori* administration could also be used to treat and prevent gastric cancer at this level of the pyramid.

At the level of changing the context to make individuals' default decisions healthy ones, Varma said that a primary aim is to ensure that universal health care is also high-quality care. This begins with patient safety as a subset of quality; a subset of patient safety is infection prevention (Varma, 2019). Efforts to create robust changes related to infection prevention are ongoing through advocacy for public health laws related to the standards and regulation of safety in health care facilities. Beyond the clear benefit for health security, this can also contribute to the longer-term benefit of infrastructure development. If it is possible to prevent infections and build an antimicrobial stewardship program, he said, then it should also be possible to build a patient safety program along the continuum of providing quality care. This is an organic way to create durable change in a health system that better manages both infectious and noninfectious diseases, he added.

Opportunities for Public Health Surveillance

Varma described strategies to improve public health through surveillance. Cancer registries are low-hanging fruit among surveillance opportunities in

many areas of Africa. Currently, cancer registries are underused across the continent, and the registries that do exist have low coverage, he explained. Furthermore, there is limited connection between the data being collected and national-level public health policies related to screening for malignancies, prevention of malignancies, and access to oncology treatments. Developing cancer registries can inform the assessment of the burden of disease, which can be used to build a case for the prevention of cancer through vaccines that target pathogens, he explained. This can also provide an entry point to the control and treatment of NCDs, he added.

Varma's next suggestion to improve surveillance involves genomic intelligence. The Africa Centres for Disease Control and Prevention is working to build a continent-wide infrastructure for pathogen genomic intelligence, said Varma. This has the potential to inform clinical decision making, outbreak control, and vaccine design. This could also contribute to the architecture needed to integrate human genomics into medicine and inform the development of precision medicine. He added that this effort will require new human resources, including bioinformatics-informed epidemiologists and microbiologists.

A MULTIFACETED UNDERSTANDING OF THE CONVERGENCE

K. Srinath Reddy, president of the Public Health Foundation of India, opened his visionary statement by explaining that he is a cardiologist and an epidemiologist by training, but a public health advocate by passion. The Public Health Foundation of India aims to address the diversity of public health challenges that India faces across the spectrum of infectious diseases and NCDs—thus, convergence is a lived reality for Reddy. He reflected on how the message about the need for convergence could be communicated to the world at large. A first step is to convey that there is already compelling evidence of convergence, both across countries and within countries—not just convergence of infectious diseases and NCDs occurring in the same populations. There is a reversal in the social gradient to the extent that the poorest people, both across and within countries, are disproportionately affected. Thus, there is also a convergence in the domain of equity, he added.

Convergence and the Health Transition

Convergence is under way within communities, families, and individuals and across the life course, said Reddy. This makes the case for the long-neglected concept of life-course epidemiology and exposes how epidemiology has been studied in a segmented and fragmented fashion. It is now recognized that communicable diseases and NCDs can coexist in an individual, either at different points in time or at the same point in time

across the life course. The advent of microbiome research implores us to rethink the artificial distinction between microbes and humans. "What evolution has brought together, let no siloed science tear asunder," he said. The health transition is shaping the manner and timing in which this convergence is manifesting, Reddy said, although the pace and progress may vary across continents. For instance, if Rwanda does not now have many of the traditional NCDs that pervade high-income and even middle-income countries, it is because Rwanda is at an earlier phase of health transition. He anticipated that the health transition will propel countries like Rwanda into the next phase, which calls for preemptive action against commercial, social, and other determinants to prevent some of those populations from acquiring and manifesting that risk. At the same time, it is necessary to deal with the reality of convergence as the health transition evolves.

In different populations across the world—and in rural and urban settings within the same countries—the health transition is happening at different paces, but the direction of transition is fairly clear, remarked Reddy. He quoted Rudolph Virchow's question about the epidemic of typhus in Upper Silesia, "Do we not always find the diseases of the populous traceable to defects in society?" If diseases are the expression of individual life under unfavorable circumstances, he explained, then epidemics must be indicative of the masses. In Virchow's time, typhus was related to poverty. Today, it is tobacco that is related to poverty, noted Reddy. Multimorbidities demonstrate that the convergence is manifesting in multiple ways—from clustered clinical presentations of people with diabetes and urinary tract infections, to clustered presentations of diabetes, HIV/AIDS, and TB. It is also clear that there are cross-linked pathogenic pathways, even when there is no direct assault of microbes that are causing NCDs, he added. These pathogenic pathways can trigger inflammation, which itself can become a systemic phenomenon that causes vascular damage, among other consequences. Reddy suggested that it is no longer tenable to use Koch's postulates as the necessary criteria for linking a microbial assault with vascular damage and other noncommunicable conditions, given the discovery, for example, of common pathways of inflammation in thrombogenesis that are triggered by microbial infections.

Embracing the Complexity of Convergence

Reddy explained that as the scientific understanding of convergence progresses, it will become evident that the spectrum of science is reductionist in content, but holistic in context. Biology is influenced by beliefs and behaviors, which, in turn, are influenced by a multitude of social, economic, and environmental determinants. He quoted the naturalist John Muir's observa-

tion that "When we try to pick out anything by itself, we find it hitched to everything else in the Universe." Complexity is the reality of the world and of nature, he added. It is now recognized that in people with multiple coexistent conditions, multiple risk factors operate in concert.

All of the environmental exposures that occur during the course of an individual's lifetime and the body's own responses to those exposures constitute the *exposome*. It is the genome in the exposome that ultimately interacts to produce the disease. All of these factors need to be investigated and, where possible, acted upon, said Reddy. Fortunately, powerful tools are now available to integrate data from social sciences, environmental sciences, life sciences, and clinical registries. This provides an opportunity to integrate and identify all of the connections and the key action points at which some effect can be achieved early on.

Reddy maintained that in the move toward person-centered health care, community-centered public health, and people-centered public policy, convergence is not a matter of choice—it is an imperative—and complexity should not be a deterrent. He highlighted a stepwise approach to solutions, despite the barriers to transdisciplinarity that range from siloed funding streams to lack of credit for multidisciplinary authorship. Developing enlightened policy requires scientific credibility, financial feasibility, operational stability, and political viability, said Reddy. He explained that each of those aims requires different streams of research. Scientific credibility is based on biomedical, epidemiological, and clinical research; financial feasibility requires health economics to assist in evaluating cost-effectiveness and affordability, he said. Health systems research is needed to achieve operational stability, scalability, and sustainability. Political viability is founded on social science research to bring together policy makers, health professionals, the community, and the industry to support new policy. This effort requires a changing of mindsets that will be challenging to achieve, said Reddy.

It is easy to talk about transdisciplinary research, he noted, but to operationalize, it will require change in health education for all health professionals to produce individuals shaped by a transdisciplinary understanding. Health professionals will need keen cultural understanding and the ability to collaborate, Reddy said, even when they are developing depth in one area of research in which their expertise will qualify them as leaders. He mentioned the potential effect of dedicated funding streams that could be established by national or international funding agencies to bring together postdoctoral students from different disciplines to jointly address multidisciplinary research challenges and find solutions. Inculcating the culture of transdisciplinary research from an early stage will build researchers who believe in the concept, said Reddy.

Multidisciplinary and Systemic Convergent Action

With respect to health systems, Reddy observed that the United Nations' Sustainable Development Goals and the push for universal health coverage provide a unifying platform to integrate health and prevention into primary health care and across the overall health system. But there is health beyond health care, he said, which will require multisectoral action in the areas of tobacco control and food systems in agriculture, for example. Empowering frontline health workers and engaging communities provide opportunities for improving health literacy at the primary care and community levels. Educating people about tobacco and appropriate nutrition, for example, can generate grassroots demand for a multisectoral policy response that politicians will have to heed, he noted.

Primary health care should not be considered merely to be a service channel, he said, but as a platform for actively engaging communities in the demand for policy change. Reddy added that addressing convergence will require bringing to the table multiple players who are already engaged in environmental and community work. This includes the message that these cross-sectoral partners are natural allies and that there are clear mutual benefits. A shift in mindset away from exclusively vertical programs has already occurred among funders, he noted. Large international funding agencies are now focusing on capacity building, health systems, and primary health care.

Potential Priorities for Convergent Action

In summary, Reddy outlined his five priorities for spurring continuous change and convergent actions:

1. Strengthening primary health care
2. Achieving universal health coverage
3. Fostering community engagement
4. Catalyzing demand for policy response
5. Supporting multisectoral and transdisciplinary research

All of those priorities require forging wide-ranging partnerships across multiple stakeholders to build collaborations, he said. The arena of research extends from molecules to markets. The arenas of advocacy and action extend from risk factors to human rights. To that end, he redefined the concept of public–private partnership as "partnership for public purpose." After defining the public purpose, the deliverables, and the accountability mechanisms, Reddy asserted that the public interest should ultimately set the agenda or it will create a laissez-faire system. Multiple partnerships could

be mobilized under this new definition of partnership for public purpose. Potential partnerships include partnerships between two individuals, partnerships between two private-sector entities, and partnerships between the government, private-sector entities, and nongovernmental organizations.

While local action should be emphasized, Reddy said, global efforts are also needed. In the past century, a sense of shared vulnerability to bioterrorism, pandemics, and other threats provided the impetus for global health. During this century, global health will need to gain momentum from shared values, equity, universal health coverage, and ensuring planetary health for our shared common future, he noted. To date, he stated:

> Research has only been sampling limited sections of the global human family, primarily in high-income [settings]. Sampling the entire human family and exploring the vast diversity of gene–environmental interactions is an example of the huge potential benefits of going global.

Going global also presents the opportunity to share lessons from other health systems, other cultures, and other social organization models in order to advance efforts to contain both infectious diseases and NCDs. Many of the determinants of those diseases are transnational, he said, such as pandemics of emerging infectious diseases, tobacco use, environmental change, and commercial determinants of health. He concluded by emphasizing that while equity matters, local capacity building is also crucial. In the words of Miguel Torga, the Portuguese writer, "Universal is local without the walls." Reddy concluded with a call for breaking down those walls through convergent action.

RETHINKING AND REFRAMING EFFORTS TO ADDRESS THE CONVERGENCE

Patricia García, professor at the Cayetano Heredia University School of Public Health, Peru, presented her visionary statement by highlighting five priorities to address the convergence:

1. Research support
2. Systems thinking
3. Advanced methods and tools
4. Public communication and health literacy
5. Policy changes

García opened her presentation by reflecting on two influential people in her life. One was her professor in medical school, who encouraged her to

specialize in infectious diseases based on the presumption that eventually it would become clear that most health conditions were related in some way to viral or bacterial infections. The second was her grandmother, who lived to the age of 100 years and was adamant about taking care of one's intestinal flora—a precursor to the current understanding of the microbiome.

Before presenting her five top priorities, García summarized her solution in a single sentence: "We need to undo all the things that we have been doing for years." The process should start with training, she said, because the current system of medical education has created professional silos and overspecialization. She suggested rethinking the education system for health professionals to create a system that is more comprehensive and person centered. Similarly, the mindset of funders will need to shift from a focus on diseases to a focus on people. Broader efforts should focus on strengthening health services, rather than creating parallel systems—separate models should not be created for lower- and middle-income countries and for middle- and high-income countries, she noted. García emphasized prevention and strengthening both day-to-day and specialized services at all levels of care, from the community to specialized hospitals.

Research Support for the Study of Convergence

García's first priority is to continue supporting research on the convergence of infectious disease and NCDs that takes into consideration life course, gender, ethnicity, and diverse environments. This includes a research focus on the influence of the maternal microbiota on infants (Dominguez-Bello, 2019). Gut bacteria cross-communicate with the neuroendocrine and immune systems to effect change in a wide range of social and affective behavior (Francis and Dominguez-Bello, 2019). The maternal microbiota is a determinant of the offspring's cognitive development, behavior, and health (Francis and Dominguez-Bello, 2019). Perturbations in the maternal microbiota can alter maternal–infant bonding (Francis and Dominguez-Bello, 2019). In the early-life microbiota of an infant, antibiotics can induce changes that have long-lasting metabolic consequences in body fat distribution and weight gain (Gibson et al., 2015; Francis and Dominguez-Bello, 2019). Research is also emerging about the relationship between microbial biota and cancer (Vivarelli et al., 2019).

She noted that microbiotas vary among people living in different environments, which warrants further study in areas of the world that have not yet been sampled. Microbiota are not composed of bacteria, she added. For example, parasites can be part of the microbiota. She highlighted the emergence of associations between parasitic infections and chronic diseases (Blitz et al., 2018) and the known link between people with human T cell leukemia virus type 1 and parasitic diseases (Gonçalves et al., 2010). There

are also diseases in which parasites likely cause some type of dysregulation of mucosal immunity, she said. A study of women living in the Peruvian Amazon found that they have high rates of parasites, and those infected with HPV more rapidly develop cancer and have a worse response to treatment (Gravitt et al., 2016). She cited this as an example of the type of research into diverse environments that needs to be supported.

Systems Thinking in Research, Study Design, and Analysis

García's second priority is to encourage more systems thinking in research and analysis to test the practical implementation of interventions. While basic science and academic research are necessary, the ultimate goal is to drive evidence-based policy actions. A shift in thinking will be needed to bring research into policies for prevention, surveillance and detection, control, and treatment. Funders tend to prefer randomized controlled trials, which are beneficial, but she said qualitative research and descriptive epidemiology within prespecified conceptual models warrant prioritization as well. She added that confining research will not help researchers understand all the complexities at hand.

Studying systems requires understanding the community context and all of the actors involved. She said because randomized trial research is carried out in sterile, controlled settings, the research output usually fails to become policy because reality is more much complex than the research environment. Systems-based research can be used to leverage cross-sectoral collaborations and break down silos among various stakeholders from research to practice, she continued. Actors in other sectors are not looking for randomized trial research. Policy makers, for example, are looking for cost-effectiveness analyses and community-based research about their constituents, she said.

Cutting-Edge Tools to Explore Links Between Infectious and Noncommunicable Diseases

García discussed the importance of developing cutting-edge methods and tools to explore links between infectious diseases and NCDs. She listed point-of-care diagnostics and user-initiated interventions to engage communities as part of the solution through self-testing, self-collection, and self-sampling. Better health information systems need to be developed, as well as better methods for analyzing big data, she added.

Improved Communication and Health Literacy

Better public and mass communication is García's fourth priority. She said information about the convergence needs to be communicated—

through positive messages—to health professionals and the general public to disseminate current knowledge about the known and suspected associations between micro-organisms and chronic diseases and conditions. She added that health literacy efforts need to go further in clearly explaining to the public that microbes can cause chronic diseases, that the microbiota can be shaped by diet, and that there are trade-offs associated with using antibiotics.

Potential Priority Policy Changes

García's final priority is to promote policy changes directed toward the integration of public health activities and health services for infectious diseases and NCDs as part of universal health coverage. The phrase *associated burden* is more apt than *dual burden*, she said, and the disease approach should be replaced with a person-centered approach supported by comprehensive health strategies. Convergent, comprehensive strategies for prevention, surveillance, and disease control should take into account overlapping high-risk populations that are in need of enhanced simultaneous surveillance for infectious diseases and NCDs, she said. This simultaneous surveillance will contribute to monitoring and measuring impact, she added.

These strategies could offer targeted, coordinated care delivered in innovative ways. She suggested investing in capacity building and promoting efficiencies in systems, while also managing expectations about potential cost savings. Providers need to be engaged in these policy changes to facilitate task sharing and task shifting when new activities arise, García stated; community engagement and empowerment are also needed. She suggested that the fight against corruption can begin at the community level, but progress should be measured to strengthen anticorruption efforts going forward.

FINAL SYNTHESIS DISCUSSION

Mosa Moshabela, dean and head of the School of Nursing and Public Health at the University of KwaZulu-Natal, South Africa, opened the floor for a final discussion. The topics of discussion focused on the role of establishing causality, communication and messaging strategies for relevant stakeholders, and furthering research on the microbiome and the exposome.

The Role of Establishing Causality

Moshabela asked García to comment about the need to establish evidence-based causality, given that real-world research is often criticized for not being robust in terms of establishing causality. García responded that she is challenging that notion and suggesting that research should be brought into the field, whether it is under the guise of implementation

research, integration science, or program science. Funders need to understand that a research ethos focused only on showing causality does not work in the real world, she said, because all of the other components of the systems have not yet been analyzed. To operationalize funding in the most cost-effective way and in a way that translates research into policy, she said, both quantitative and qualitative research are needed.

It is helpful to understand what people are thinking and why they behave the way they do, she added. Humans are so complex that successfully introducing any element into a human-based system is dependent on understanding and taking into account that complexity, she said.

Reddy remarked that causality is challenging because it cannot always be analyzed in a linear way. For NCDs, there are Bradford Hill criteria for causation, but construct validation can be used for more complex issues. If there is reasonable evidence of the ecological association of intake of external agents—such as secondhand tobacco smoke or sugar-sweetened beverages—with adverse health effects, then a precautionary principle can be applied and the evidence of the intervention can follow, he added.

Communication and Engagement with Policy Makers and Relevant Stakeholders

Peter Daszak, president of EcoHealth Alliance, asked the panelists how to simplify complex messages such that policy makers will understand and support this agenda. Varma replied that throughout his career, he has struggled to communicate not with the public, but with their representatives and decision makers at various levels. Even though there are ways to use science to communicate the direct linkages between the factor that is sought to be altered and the desired intervention or beneficial outcome, it is difficult to do so effectively without explicating the direct causal link and discussing correlation. In many settings, he said interventions to control sugar-sweetened beverages, for example, can come across as nanny state policy. In his experience, it is more effective to frame the intervention in terms of targeting a specific factor as an "enemy" that needs to be fought against. A challenge for the African Union, he added, is that it is an established deliberative body, but it does not yet have full institutional functioning capacity. It is relatively easy to pass declarations, but he noted the execution is not commensurate because supposedly binding commitments do not have tangible effects.

Reddy commented that the message communicated to policy makers could be that we do not have the luxury of dealing with infectious disease and NCD issues sequentially, particularly in a country like India. They need to be addressed simultaneously because both of them cause mortality, morbidity, and economic damage. Systems must be built to competently deal with both issues and their consequences, he noted. Reddy also commented

on the issue of choice versus policies perceived to be nanny state. Industry may push the importance of individual choice, but choices are often made on the basis of the information presented, he said—hence the importance of health literacy, so that choices are not shaped by aggressive marketing and peer pressure. Interventions to control the tobacco or alcohol industries could help to address this. He added that healthy choices, such as eating adequate fruits and vegetables, are also constrained by socioeconomic circumstances for many people. If the healthier choice is not made easier and affordable, he said, then the purported choice is actually a euphemism.

García remarked that messages need to be tailored for specific policy makers. Data can be helpful when they are presented in a simple way, especially in discussions about associations or correlations. Some policy makers will only be interested in potential cost savings, so working with an economist to create a cost-effectiveness analysis can bolster the communication strategy. She added that Peru is rolling out the process of labeling processed foods, which was achieved through using appropriate, consistent language about the cost savings created by consequent reductions in chronic disease. She said that human testimonies or stories can be powerful in gaining buy-in from policy makers, as well. Her final consideration was that the communication strategies be collaborative and engage with other partners. She illustrated that when she worked with mothers in communities on the benefits of HPV vaccination, it led to a grassroots campaign that filtered up and engaged female policy makers in government.

Varma commented on the power of generating public outrage in driving change. He suggested framing chronic diseases as a product of genetic fatalism or being "born that way," or "being stuck in lifestyle choices." If people believe that having a chronic condition is beyond their own control, as infectious diseases are, then he suggested they are more likely to demand that the government take action to protect them. García agreed and noted that people perceive infectious diseases as something that can be actively helped with medications. The association between infectious diseases and NCDs could be leveraged to promote preventive vaccines and technologies and garner public support, which will influence their policy makers to act. She reiterated that communication needs to be tailored for the audience, be it health providers, the general public, specific communities, or policy makers. There is also a role for international organizations and global health entities to support policy makers in shaping new policies or adjusting existing ones.

Reddy suggested identifying "prime movers" who need to be supported in terms of research, academia, and funding. Academia needs to articulate the need, he suggested, so that the funders who are entrenched in existing siloed funding streams will change their behaviors. Policy makers can bring about changes in the health system, but health system managers, planners, and patient groups also need to be actively engaged by health professionals.

Specifically, he said that health system managers will be the prime movers in the transition toward convergence at the service-delivery level. While the media can be a useful channel for communication, he said academics and civil society also have a role in correcting falsehoods (e.g., myths around vaccine safety) to ensure that they are not disseminated widely, while also holding the media accountable.

Microbiome and Exposome Research: Motivations and Implications

The need to expand the scope of surveillance beyond only diseases, for example, by using existing tools to carry out surveillance that capture information on socioeconomic contexts, was raised by Tolullah Oni, clinical senior research associate in the MRC Epidemiology Unit at the University of Cambridge. She asked why it seems easier to think about the microbiome than the exposome, and suggested thinking innovatively about surveillance approaches that incorporate both disease and the exposome. Additionally, she noted that rather than focusing on precision medicine, a push for precision public health may be more appropriate to support population health efforts.

García commented that some efforts are being made to measure exposomes in the form of social determinants of health. She suggested that measuring microbiomes may be more enticing because technology and interventions seem more marketable. Discussion of exposomes and social determinants of health involves complex societal issues that are beyond the capacity of many governments to address, especially in systems plagued by corruption and resource constraints, said García. Although microbiomes seem complicated, they are less complex to address than changing entrenched social determinants, such as poverty. The level of funding channeled toward infectious diseases, she added, could yield more benefits if it were used to fund interventions against poverty.

Daszak reflected that people are fundamentally drawn to a technological quick fix for problems, such as vaccines or antibiotics. Microbiome research is exciting because it is so complicated and so little understood, yet it holds such promise. He added that even the word *exposome* is more enticing than *social determinants of health*. Reddy noted the word *exposome* was coined in 2005 by Christopher Wild to include not only social determinants but also environmental determinants, toxic exposures, the body's response, and epigenetics. He said that this calls for reconsidering previous assumptions about genetic determinism, given the number of potentially modifiable factors in the exposome.

Moshabela recalled four points from Knight's plenary presentation: work on the microbiome requires a complex combination of food or diet, immunology, microbiology, and antibiotics. However, the overarching

focus is on how to manipulate the microbiome. Although a person can be empowered to manipulate the microbiome through dietary changes, it takes 6 to 12 months. It is feasible to empower people to manage their microbiomes autonomously, but it would be easier to manipulate the microbiome through some kind of technological intervention. Moshabela said that a tension lies in how to move from understanding the microbiome to developing medicalized interventions to manipulate it, while also developing interventions that can empower people to manipulate their own microbiomes. There is a need to carefully think about the quest for easy solutions compared to challenging solutions that may be more sustainable, he added.

Bridget Kelly, principal consultant of Burke Kelly Consulting, observed that the reasons for the excitement about the microbiome compared to the exposome may be caused by what "we think is safe and comfortable." She suggested that while there may be an element of personal discomfort at play in discussion about collecting samples for microbiomes, she noted the profound discomfort and perception of risk to embrace the unknowns and challenges that need to be faced head on.

Varma admitted that the public health sphere often tries to avoid messages that appear overtly political, to the extent possible, but he said, "It is not so much to avoid the discomfort but to find a way to thread the needle a little more." He explained that his own public health strategy when communicating with policy makers is to avoid talking about the benefits of health interventions and to focus on security from threats, opportunities to make or save money, and justice in alleviating inequities. Rather than avoiding discomfort, he clarified that he tries to frame the issues in ways that appeal to people across the spectrum, from genetic fatalists to those who attribute all outcomes to individual-level decisions.

Reddy said that communicating effectively with a policy maker also depends on the settings and the expectations. For example, policy makers may respond in one way to certain issues when they are acting in an individual capacity or in the context of limited potential for regional or national action. García pointed to conflicts of interest between providers who are delivering services and efforts to allow communities to gain power and autonomy. This is compounded by the history of paternalism toward communities. These tensions need to be resolved, she said, but that is unlikely to happen in a single generation. García said training the upcoming generation differently will help to create a different type of provider who is not uncomfortable in the ways Kelly described.

Building on the point about generational time frames, Oni introduced the concept of the Overton window from political science, describing it as a spectrum used to assess a desired goal on a scale of public acceptance that ranges from unthinkable, to radical, to acceptable, to plausible, to policy. He suggested that when people in public health think about an action, they

typically want to go directly from unthinkable to policy, and when people in public health think about impact, they are trained and conditioned by the funding structure to focus on policy relevance. Oni added that this paradigm could be applied to the microbiome and the exposome. Perhaps the microbiome is currently acceptable and moving toward policy, whereas the exposome is unthinkable or radical, and efforts should focus on moving it up to acceptable. Thinking about time frames can be useful when reflecting about interventions in terms of where they sit in current society in order to determine which interventions are more feasible.

Varma commented that his own experience is the converse of the Overton window—he finds himself advocating for change, but only being consulted when change is not feasible or affordable. He noted that over the past decade or so, the HIV movement has changed the paradigm in public health from the mindset of "only asking for a dollar because I might get a dollar" to demanding a sufficient amount of funding, even if that comes in a piecemeal fashion over time. He emphasized the importance of communication and engaging with communities and civil society to work toward rectifying the low expectations people have with respect to government-provided health services. Varma pointed to this issue as a root cause of infectious disease outbreaks, such as Ebola virus disease. He suggested establishing minimum common standards—for example, high-quality, safe, nutritious food—regardless of whether the motivation concerns the microbiome or standard thermogenesis that results in a healthy body. He concluded by calling for health care professionals and civil society groups to demand better quality of health services from their governments.

CLOSING REMARKS

Daszak provided the workshop's closing remarks. He highlighted three lessons that he gleaned from discussions over the 1.5 days. Calling back to the blind people and the elephant metaphor from the second session, he suggested that it may not even be an elephant that the blind people are trying to grasp, but something much more difficult to understand—convergence presents a complex, tangled web of information and ideas. He suggested trying to grasp nuggets of value that can be used to simplify the message and communicate more effectively with policy makers. The second lesson is that many people in the infectious disease space and in the NCD space may actually be self-selecting their respective silos, which are reinforced through different belief systems and behaviors, separate journals, distinct funding streams, and disparate research methods. This adds an additional layer of difficulty in trying to break down the silos, he said.

Finally, for Daszak the key lesson is that there is a massive inequity problem, yet convincing policy makers and politicians about investing

in NCDs is enormously challenging. Given that the sense of urgency and concern over pandemics generates huge amounts of attention and money, he suggested finding ways to make NCD-related issues more urgent and more directly applicable to decision makers and funders. This might involve borrowing language from the effective global health security agenda, he noted. For example, the concept of "NCD security" could be used to frame the threats related to political instability and security issues that arise in situations where an entire country or population has a large chronic disease burden that is compounded by poverty and hunger. He concluded by emphasizing the importance of improving public health systems to tackle both infectious diseases and NCDs from the local to national to global levels.

References

Abbayya, K., N. Y. Puthanakar, S. Naduwinmani, and Y. S. Chidambar. 2015. Association between periodontitis and Alzheimer's disease. *North American Journal of Medical Sciences* 7(6):241–246.

Al-Rifai, R. H., F. Pearson, J. A. Critchley, and L. J. Abu-Raddad. 2017. Association between diabetes mellitus and active tuberculosis: A systematic review and meta-analysis. *PLoS One* 12(11):e0187967.

Allender, S., K. Wickramasinghe, M. Goldacre, D. Matthews, and P. Katulanda. 2011. Quantifying urbanization as a risk factor for noncommunicable disease. *Journal of Urban Health* 88(5):906–918.

AMPATH (Academic Model Providing Access to Healthcare). 2019. *AMPATH*. Indianapolis, IN: AMPATH North America.

Awad, S. F., S. R. Dargham, R. Omori, F. Pearson, J. A. Critchley, and L. J. Abu-Raddad. 2019a. Analytical exploration of potential pathways by which diabetes mellitus impacts tuberculosis epidemiology. *Scientific Reports* 9(1):8494.

Awad, S. F., P. Huangfu, H. H. Ayoub, F. Pearson, S. R. Dargham, J. A. Critchley, and L. J. Abu-Raddad. 2019b. Forecasting the impact of diabetes mellitus on tuberculosis disease incidence and mortality in India. *Journal of Global Health* 9(2):020415.

Bach, J. F. 2002. The effect of infections on susceptibility to autoimmune and allergic diseases. *New England Journal of Medicine* 347(12):911–920.

Baker, M. A., A. D. Harries, C. Y. Jeon, J. E. Hart, A. Kapur, K. Lonnroth, S. E. Ottmani, S. D. Goonesekera, and M. B. Murray. 2011. The impact of diabetes on tuberculosis treatment outcomes: A systematic review. *BMC Medicine* 9:81.

Balfour, H. H., Jr., F. Sifakis, J. A. Sliman, J. A. Knight, D. O. Schmeling, and W. Thomas. 2013. Age-specific prevalence of Epstein–Barr virus infection among individuals aged 6–19 years in the United States and factors affecting its acquisition. *Journal of Infectious Diseases* 208(8):1286–1293.

Bates, M., B. J. Marais, and A. Zumla. 2015. Tuberculosis comorbidity with communicable and noncommunicable diseases. *Cold Spring Harbor Perspectives in Medicine* 5(11):a017889.

Bauer, M. S., L. Damschroder, H. Hagedorn, J. Smith, and A. M. Kilbourne. 2015. An introduction to implementation science for the non-specialist. *BMC Psychology* 3(1):32.

Baxter, N. T., A. W. Schmidt, A. Venkataraman, K. S. Kim, C. Waldron, T. M. Schmidt. 2019. Dynamics of human gut microbiota and short-chain fatty acids in response to dietary interventions with three fermentable fibers. *mBio* 10(1):e02566-18.

Bellman, K., and C. Landauer. 2000. Towards an integration science: The influence of Richard Bellman on our research. *Journal of Mathematical Analysis and Applications* 249(1):3–31.

Berni Canani, R., N. Sangwan, A. T. Stefka, R. Nocerino, L. Paparo, R. Aitoro, A. Calignano, A. A. Khan, J. A. Gilbert, and C. R. Nagler. 2016. Lactobacillus rhamnosus gg-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. *ISME Journal: Multidisciplinary Journal of Microbial Ecology* 10(3):742–750.

Billingsley, H. E., S. Carbone, and C. J. Lavie. 2018. Dietary fats and chronic noncommunicable diseases. *Nutrients* 10(10):1385.

Binagwaho, A., P. E. Farmer, S. Nsanzimana, C. Karema, M. Gasana, J. D. Ngirabega, F. Ngabo, C. M. Wagner, C. T. Nutt, T. Nyatanyi, M. Gatera, Y. Kayiteshonga, C. Mugeni, P. Mugwaneza, J. Shema, P. Uwaliraye, E. Gaju, M. A. Muhimpundu., T. Dushime, F. Senyana, J. B. Mazarati, C. M. Muzayire, L. Tuyisenge, V. Mutabazi, P. Kyamanywa, V. Rusanganwa, J. P. Nyemazi, A. Umutoni, I. Kankindi, C. Ntizimira, H. Ruton, N. Mugume, D. Nkunda, E. Ndenga, J. M. Mubiligi, J. P. Kakoma, E. Karita, C. Sekabaraga, E. Rusingiza, M. L. Rich, J. S. Mukherjee, J. Rhatigan, C. Concedda, D. Bertrand-Farmer, G. Bukhman, S. N. Stulac, N. M. Tapela, C. van der Hoof Holstein, L. N. Shulman, A. Habinshit, M. H. Bonds, M. S. Wilkes, C. Lu, M. C. Smith-Fawzi, J. D. Swain, M. P. Murphy, A. Ricks, V. B. Kerry, B. P. Bush, R. W. Seigler, C. S. Stern, A. Sliney, T. Nuthulaganti, I. Karangwa, E. Pegurri, O. Dahl, and P. C. Drobac. 2014. Rwanda 20 years on: investing in life. *Lancet* 384(9940):371–375.

Blacher, E., M. Levy, E. Tatirovsky, and E. Elinav. 2017. Microbiome-modulated metabolites at the interface of host immunity. *Journal of Immunology* 198(2):572–580.

Blaser, M. 2014. *Missing microbes*. London, UK: Oneworld Publications.

Blitz, J., M. S. Riddle, and C. K. Porter. 2018. The risk of chronic gastrointestinal disorders following acute infection with intestinal parasites. *Frontiers of Microbiology* 9:17.

Bloomfield, G. S., J. W. Hogan, A. Keter, E. Sang, E. J. Carter, E. J. Velazquez, and S. Kimaiyo. 2011. Hypertension and obesity as cardiovascular risk factors among HIV seropositive patients in western Kenya. *PLoS One* 6(7):e22288.

Bokulich, N. A., J. Chung, T. Battaglia, N. Henderson, M. Jay, H. Li, A. D. Leiber, F. Wu, G. I. Perez-Perez, Y. Chen, W. Schweizer, X. Zheng, M. Contreras, M. G. Dominguez-Bello, and M. J. Blaser. 2016. Antibiotics, birth mode, and diet shape microbiome maturation during early life. *Science Translational Medicine* 8(343):343–382.

Bollrath, J, and F. Powrie. 2013. Feed your tregs more fiber. *Science* 341(6145):463–464.

Bourne, R. R, G. A. Stevens, R. A. White, J. L. Smith, S. R. Flaxman, H. Price, J. B. Jonas, J. Keeffe, J. Leasher, K. Naidoo, K. Pesudovs, S. Resnikoff, and H. R Taylor. 2013. Causes of vision loss worldwide, 1990-2010: A systematic analysis. *Lancet Global Health* 1(6):339–349.

Bright Focus Foundation. 2017. *Amyloid plaques and neurofibrillary tangles*. https://www.brightfocus.org/alzheimers-disease/infographic/amyloid-plaques-and-neurofibrillary-tangles (accessed September 19, 2019).

Bukhman, G. 2019. *Addressing the convergence with "integration science."* PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Bukhman, G., C. Bavuma, C. Gishoma, N. Gupta, G. F. Kwan, R. Laing, and D. Beran. 2015. Endemic diabetes in the world's poorest people. *Lancet Diabetes and Endocrinology* 3(6):402–403.

Burnett-Hartman, A. N., P. A. Newcomb, and J. D. Potter. 2008. Infectious agents and colorectal cancer. A review of *Helicobacter pylori*, *Streptococcus bovis*, JC virus, and human papillomavirus. *Cancer Epidemiology, Biomarkers and Prevention* 17(11):2970–2979.

Bygbjerg, I. C. 2012. Double burden of noncommunicable and infectious diseases in developing countires. *Science* 337(6101):1499–1501.

Cao, W., and H. Zheng. 2018. Peripheral immune system in aging and Alzheimer's disease. *Molecular Neurodegeneration* 13(1):51.

Caporaso, J. G., J. Kuczynski, J. Stombaugh, K. Bittinger, F. D. Bushman, E. K. Costello, N. Fierer, A. G. Pena, J. K. Goodrich, J. I. Gordon, G. A. Huttley, S. T. Kelley, D. Knights, J. E. Koenig, R. E. Ley, C. A. Lozupone, D. McDonald, B. D. Muegge, M. Pirrung, J. Reeder, J. R. Sevinsky, P. J. Turnbaugh, W. A. Walters, J. Widmann, T. Yatsunenko, J. Zaneveld, and R. Knight. 2010. Qiime allows analysis of high-throughput community sequencing data. *Nature Methods* 7(5):335–336.

Carruth, L., and E. Mendenhall. 2019. "Wasting away": Diabetes, food insecurity, and medical insecurity in the Somali region of Ethiopia. *Social Science and Medicine* 228:155–163.

Carson, R. 1962. *Silent spring*. Boston, MA: Houghton Mifflin.

Chang, M. H. 2011. Hepatitis B virus and cancer prevention. In *Recent results in cancer research,* Vol. 188, edited by H. J. Senn and F. Otto. Berlin, Heidelberg, Germany: Springer. Pp. 75–84.

Charu, V., G. Chowell, L. S. Palacio Mejia, S. Echevarría-Zuno, V. H. Borja-Aburto, L. Simonsen, M. A. Miller, and C. Viboud. 2011. Mortality burden of the A/H1N1 pandemic in Mexico: A comparison of deaths and years of life lost to seasonal influenza. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 53(10):985–993.

Clemente, J. C., E. C. Pehrsson, M. J. Blaser, K. Sandhu, Z. Gao, B. Wang, M. Magris, G. Hidalgo, M. Contreras, Ó. Noya-Alarcón, O. Lander, J. McDonald, M. Cox, J. Walter, P. L. Oh, J. F. Ruiz, S. Rodriguez, N. Shen, S. J. Song, J. Metcalf, R. Knight, G. Dantas, and M. G. Dominguez-Bello. 2015. The microbiome of uncontacted Amerindians. *Science Advances* 1(3):e1500183.

Coelho, L. P., J. R. Kultima, P. I. Costea, C. Fournier, Y. Pan, G. Czarnecki-Maulden, M. R. Hayward, S. K. Forslund, T. S. B. Schmidt, P. Descombes, J. R. Jackson, Q. Li, and P. Bork. 2018. Similarity of the dog and human gut microbiomes in gene content and response to diet. *Microbiome* 6(1):72.

Cohen, J. I. 2000. Epstein-Barr virus infection. *New England Journal of Medicine* 343(7):481–492.

Coles, C. L., J. C. Seidman, J. Levens, H. Mkocha, B. Munoz, and S. West. 2011. Association of mass treatment with azithromycin in trachoma-endemic communities with short-term reduced risk of diarrhea in young children. *American Journal of Tropical Medicine* 85(4):691–696.

Cox, J. T., M. J. Kasubi, B. E. Muñoz, A. I. Zambrano, G. S. Greene, H. Mkocha, M. A. Wolle, and S. K. West. 2017. Trachomatous scarring and infection with nonchlamydia trachomatis bacteria in women in Kongwa, Tanzania. *Investigative Ophthalmology & Visual Science* 58(7):3249–3253.

Critchley, J. A., I. M. Carey, T. Harris, S. DeWilde, F. J. Hosking, and D. G. Cook. 2018. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. *Diabetes Care* 41(10):2127–2135.

Cully, M. 2018. Inflammasome protein seeds plaques in Alzheimer disease. *Nature Reviews Drug Discovery* 17:96.

Davies, R. 2018. Rachel Nugent: Global health economist making NCDs count. *Lancet* 391(10134):1987.

de Diego, I., F. T. Veillard, T. Guevara, B. Potempa, M. Sztukowska, J. Potempa, and F. X. Gomis-Ruth. 2013. Porphyromonas gingivalis virulence factor ginigpain RgpB shows a unique zymogenic mechanism for cysteine peptidases. *Journal of Biological Chemistry* 288(20):14287–14296.

Deng, Y., and B. P. Tsao. 2014. Advances in lupus genetics and epigenetics. *Current Opinion in Rheumatology* 26(5):482–492.

Ding, D., K. Gebel, P. Phongsavan, A. E. Bauman, and D. Merom. 2014. Driving: A road to unhealthy lifestyles and poor health outcomes. *PLoS One* 9(6):e94602.

Dionisio-Santos, D. A., J. A. Olschowka, and M. K. O'Banion. 2019. Exploiting microglial and peripheral immune cell crosstalk to treat Alzheimer's disease. *Journal of Neuroinflammation* 16(1):74.

Dominguez-Bello, M. G. 2019. Gestational shaping of the maternal vaginal microbiome. *Nature Medicine* 25:882–883.

Dominguez-Bello, M. G., E. K. Costello, M. Contreras, M. Magris, G. Hidalgo, N. Fierer, and R. Knight. 2010. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences* 107:11971–11975.

Dominguez-Cherit, G., S. E. Lapinsky, A. E. Macias, R. Pinto, L. Espinosa-Perez, A. de la Torre, M. Poblano-Morales, J. A. Baltazar-Torres, E. Bautista, A. Martinez, M. A. Martinez, E. Rivero, R. Valdez, G. Ruiz-Palacios, M. Hernandez, T. E. Stewart, and R. A. Fowler. 2009. Critically ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 302(17):1880–1887.

Dominy, S. S., C. Lynch, F. Ermini, M. Benedyk, A. Marczyk, A. Konradi, M. Nguyen, U. Haditsch, D. Raha, C. Griffin, L. J. Holsinger, S. Arastu-Kapur, S. Kaba, A. Lee, M. I. Ryder, B. Potempa, P. Mydel, A. Hellvard, K. Adamowicz, H. Hasturk, G. D. Walker, E. C. Reynolds, R. L. M. Faull, M. A. Curtis, M. Dragunow, and J. Potempa. 2019. *Porphyromonas gingivalis* in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors. *Science Advances* 5(1):eaau3333.

Eberly, L. A., E. Rusingiza, P. H. Park, G. Ngoga, S. Dusabeyezu, F. Mutabazi, E. Harerimana, J. Mucumbitsi, P. F. Nyembo, R. Borg, C. Gahamanyi, C. Mutumbira, E. Ntaganda, C. Rusangwa, G. F. Kwan, and G. Bukhman. 2018a. Nurse-driven echocardiography and management of heart failure at district hospitals in rural Rwanda. *Circulatory and Cardiovascular Quality Outcomes* 11(12):e004881.

Eberly, L. A., E. Rusingiza, P. H. Park, G. Ngoga, S. Dusabeyezu, F. Mutabazi, E. Harerimana, J. Mucumbitsi, P. F. Nyembo, R. Borg, C. Gahamanyi, C. Mutumbira, E. Ntaganda, C. Rusangwa, G. F. Kwan, and G. Bukhman. 2018b. Understanding the etiology of heart failure among the rural poor in sub-Saharan Africa: A 10-year experience from district hospitals in Rwanda. *Journal of Cardiac Failure* 24(12):849–853.

Eberly, L. A., E. Rusingiza, P. H. Park, G. Ngoga, S. Dusabeyezu, F. Mutabazi, C. Gahamanyi, E. Ntaganda, G. F. Kwan, and G. Bukhman. 2019. 10-year heart failure outcomes from nurse-driven clinics in rural sub-Saharan Africa. *Journal of the American College of Cardiology* 73(8):977–980.

Einterz, R. M., S. Kimaiyo, H. N. Mengech, B. O. Khwa-Otsyula, F. Esamai, F. Quigley, and J. J. Mamlin. 2007. Responding to the HIV pandemic: The power of an academic medical partnership. *Academic Medicine* 82(8):812–818.

El-Sadr, W. M., K. Harripersaud, and M. Rabkin. 2017. Reaching global HIV/AIDS goals: What got us here, won't get us there. *PLoS Medicine* 14(11):e1002421.

El-Sadr, W. M., K. H. Mayer, M. Rabkin, and S. L. Hodder. 2019. AIDS in America—Back in the headlines at long last. *New England Journal of Medicine* 380(21):1985–1987.

Endriz, J., P. P. Ho, and L. Steinman. 2017. Time correlation between mononucleosis and initial symptoms of MS. *Neurology: Neuroimmunology & Neuroinflammation* 4(3):e308.

Essue, B. M., M. Laba, F. Knaul, A. Chu, H. V. Minh, T. K. P. Nguyen, and S. Jan. 2017. Economic burden of chronic ill health and injuries for households in low- and middle-income countries. In *Disease control priorities: Improving health and reducing poverty*, edited by D. T. Jamison, H. Gelband, S. Horton, P. Jha, R. Laxminarayan, C. N. Mock, and R. Nugent. Washington, DC: The International Bank for Reconstruction and Development/The World Bank.

Ezeh, A., O. Oyebode, D. Satterthwaite, Y. F. Chen, R. Ndugwa, J. Sartori, B. Mberu, G. J. Melendez-Torres, T. Haregu, S. I. Watson, W. Caiaffa, A. Capon, and R. J. Lilford. 2017. The history, geography, and sociology of slums and the health problems of people who live in slums. *Lancet* 389(10068):547–558.

FAIR Health. 2017. *Food allergy in the United States: Recent trends and costs: An analysis of private claims data*. New York: FAIR Health, Inc.

Faith, J. J., N. P. McNulty, F. E. Rey, and J. I. Gordon. 2011. Predicting a human gut microbiota's response to diet in gnobiotic mice. *Science* 333(6038):101–104.

FARE (Food Allergy Research & Education). 2019. *New prevalence numbers demand an aggressive call to action*. https://www.foodallergy.org/about-fare/blog/new-prevalence-numbers-demand-an-aggressive-call-to-action (accessed September 20, 2019).

Farmer, P., J. Y. Kim, A. Kleinman, and M. Basilico. 2013. *Reimagining global health: An introduction*. Vol. 26. Oakland, CA: University of California Press.

Feehley, T., C. H. Plunkett, R. Bao, S. M. Choi Hong, E. Culleen, P. Belda-Ferre, E. Campbell, R. Aitoro, R. Nocerino, L. Paparo, J. Andrade, D. A. Antonopoulos, R. Berni Canani, and C. R. Nagler. 2019. Healthy infants harbor intestinal bacteria that protect against food allergy. *Nature Medicine* 25(3):448–453.

Forbes, J. D., G. Van Domselaar, and C. N. Bernstein. 2016. The gut microbiota in immune-mediated inflammatory diseases. *Frontiers in Microbiology* 7:1081.

Francis, A. P., and M. G. Dominguez-Bello. 2019. Early-life microbiota perturbations and behavioral effects. *Trends in Microbiology* 27(7):567–569.

Frati, F., C. Salvatori, C. Incorvaia, A. Bellucci, G. Di Cara, F. Marcucci, and S. Esposito. 2018. The role of the microbiome in asthma: The gut-lung axis. *International Journal of Molecular Sciences* 20(1):123.

Frieden, T. R. 2010. A framework for public health action: The health impact pyramid. *American Journal of Public Health* 100(4):590–595.

Gebre, T., B. Ayele, M. Zerihun, A. Genet, N. E. Stoller, Z. Zhou, J. I. House, S. N. Yu, K. J. Ray, P. M. Emerson, J. D. Keenan, T. C. Porco, T. M. Lietman, and B. D. Gaynor. 2012. Comparison of annual versus twice-yearly mass azithromycin treatment for hyperendemic trachoma in Ethiopia: A cluster-randomised trial. *Lancet* 379(9811):143–151.

Ghosh, T., S. K. Srivastava, A. Gaurav, A. Kumar, P. Kumar, A. S. Yadav, R. Pathania, and N. K. Navani. 2019. A combination of linalool, vitamin C, and copper synergistically triggers reactive oxygen species and DNA damage and inhibits *Salmonella enterica* subsp. *enterica serovar typhi* and *Vibrio fluvialis*. *Applied Environmental Microbiology* 85(4).

Gibson, M. K., T. S. Crofts, and G. Dantas. 2015. Antibiotics and the developing infant gut microbiota and resistome. *Current Opinion in Microbiology* 27:51–56.

Gilbert, J. A., J. K. Jansson, and R. Knight. 2014. The Earth Microbiome Project: Successes and aspirations. *BMC Biology* 12:69.

Golding, N., R. Burstein, J. Longbottom, A. J. Browne, N. Fullman, A. Osgood-Zimmerman, L. Earl, S. Bhatt, E. Cameron, D. C. Casey, L. Dwyer-Lindgren, T. H. Farag, A. D. Flaxman, M. S. Fraser, P. W. Gething, H. S. Gibson, N. Graetz, L. K. Krause, X. R. Kulikoff, S. S. Lim, B. Mappin, C. Morozoff, R. C. Reiner, Jr., A. Sligar, D. L. Smith, H. Wang, D. J. Weiss, C. J. L. Murray, C. L. Moyes, and S. I. Hay. 2017. Mapping under-5 and neonatal mortality in Africa, 2000-15: A baseline analysis for the Sustainable Development Goals. *Lancet* 390(10108):2171–2182.

Gonçalves, D. U., F. A. Proietti, J. G. R. Ribas, M. G. Araújo, S. R. Pinheiro, A. C. Guedes, and A. B. F. Carneiro-Proietti. 2010. Epidemiology, treatment, and prevention of human T-cell leukemia virus type 1-associated diseases. *Clinical Microbiology Reviews* 23(3):577–589.

Goodrich, J. K., S. C. Di Rienzi, A. C. Poole, O. Koren, W. A. Walters, J. G. Caporaso, R. Knight, and R. E. Ley. 2014. Conducting a microbiome study. *Cell* 158(2):250–262.

Gosztyla, M. L., H. M. Brothers, and S. R. Robinson. 2018. Alzheimer's amyloid-beta is an antimicrobial peptide: A review of the evidence. *Journal of Alzheimers Disease* 62(4):1495–1506.

Graves, D. T., and R. A. Kayal. 2008. Diabetic complications and dysregulated innate immunity. *Frontiers in Bioscience: A Journal and Virtual Library* 13:1227–1239.

Gravitt, P. E., M. Marks, M. Kosek, C. Huang, L. Cabrera, M. P. Olortegui, A. M. Medrano, D. R. Trigoso, S. Qureshi, G. S. Bardales, J. Manrique-Hinojosa, A. Z. Cardenas, M. A. Larraondo, J. Cok, F. Qeadan, M. Siracusa, and R. H. Gilman. 2016. Soil-transmitted helminth infections are associated with an increase in human papillomavirus prevalence and a T-helper type 2 cytokine signature in cervical fluids. *Journal of Infectious Diseases* 213(5):723–730.

Grint, D., B. Alisjhabana, C. Ugarte-Gil, A. L. Riza, G. Walzl, F. Pearson, R. Ruslami, D. A. J. Moore, M. Ioana, S. McAllister, K. Ronacher, R. C. Koeseomadinata, S. R. Kerry-Barnard, J. Coronel, S. T. Malherbe, H. M. Dockrell, P. C. Hill, R. Van Crevel, and J. A. Critchley. 2018. Accuracy of diabetes screening methods used for people with tuberculosis, Indonesia, Peru, Romania, South Africa. *Bulletin of the World Health Organization* 96(11):738–749.

Guan, Y., D. Jakimovski, M. Ramanathan, B. Weinstock-Guttman, and R. Zivadinov. 2019. The role of Epstein-Barr virus in multiple sclerosis: From molecular pathophysiology to in vivo imaging. *Neural Regeneration Research* 14(3):373–386.

Guang, C., J. Chen, S. Sang, and S. Cheng. 2014. Biological functionality of soyasaponins and soyasapogenols. *Journal of Agricultural and Food Chemistry* 62(33):8247–8255.

Gupta, N., and G. Bukhman. 2015. Leveraging the lessons learned from HIV/AIDS for coordinated chronic care delivery in resource-poor settings. *Healthcare (Amsterdam)* 3(4):215–220.

Gupta, R. S., C. M. Warren, B. M. Smith, J. A. Blumenstock, J. Jiang, M. M. Davis, and K. C. Nadeau. 2018. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics* 142(6).

Gupta, R. S., C. M. Warren, B. M. Smith, J. Jiang, J. A. Blumenstock, M. M. Davis, R. P. Schleimer, and K. C. Nadeau. 2019. Prevalence and severity of food allergies among US adults. *JAMA Network Open* 2(1):e185630.

Habineza, H., C. Mutumbira, B. L. Hedt-Gauthier, R. Borg, N. Gupta, N. Tapela, S. Dusabeyezu, G. Ngoga, E. Harerimana, E. Mpanumusingo, E. Ngabireyimana, E. Rusingiza, and G. Bukhman. 2017. Treating persistent asthma in rural Rwanda: Characteristics, management and 24-month outcomes. *International Journal of Tuberculosis and Lung Disease* 21(10):1176–1182.

Hadley, C. 2006. The infection connection. *Helicobacter pylori* is more than just the cause of gastric ulcers—it offers an unprecedented opportuity to study changes in human microecoogy and the nature of chronic disease. *EMBO Reports* 7(5):470–473.

Haque, S. S. 2012. Impact of nitric oxide precursor l-arginine on oxidative stress against typhoid. *Bratislava Medical Journal* 113(10):589–591.

Harding, A., U. Gonder, S. J. Robinson, S. Crean, and S. K. Singhrao. 2017. Exploring the association between Alzheimer's disease, oral health, microbial endocrinology and nutrition. *Frontiers in Aging Neuroscience* 9(398).

Harley, J. B., and J. A. James. 2006. Epstein-Barr virus infection induces lupus autoimmunity. *Bulletin of the NYU Hospital for Joint Diseases* 64(1–2):45–50.

Harley, J. B., X. Chen, M. Pujato, D. Miller, A. Maddox, C. Forney, A. F. Magnusen, A. Lynch, K. Chetal, M. Yukawa, A. Barski, N. Salomonis, K. M. Kaufman, L. C. Kottyan, and M. T. Weirauch. 2018. Transcription factors operate across disease loci, with EBNA2 implicated in autoimmunity. *Nature Genetics* 50(5):699–707.

Harpaz, D., L. P. Yeo, F. Cecchini, T. H. P. Koon, A. Kushmaro, A. I. Y. Tok, R. S. Marks, and E. Eltzov. 2018. Measuring artificial sweetners toxicity using a bioluminescent bacterial panel. *Molecules* 23(10):2454.

He, Y., W. Wu, H.-M. Zheng, P. Li, D. McDonald, H.-F. Sheng, M.-X. Chen, Z.-H. Chen, G.-Y. Ji, and P. Mujagond. 2018. Regional variation limits applications of healthy gut microbiome reference ranges and disease models. *Nature Medicine* 24(10):1532.

Heflin, C. M., and J. Iceland. 2009. Poverty, material hardship and depression. *Social Science Quarterly* 90(5):1051–1071.

Hepatitis B Foundation. 2019. *Guidelines*. https://www.hepb.org/prevention-and-diagnosis/vaccination/guidelines (accessed September 20, 2019).

Holman, D. M., V. Benard, K. B. Roland, M. Watson, N. Liddon, and S. Stokley. 2014. Barriers to human papillomavirus vaccination among U.S. adolescents: A systematic review of the literature. *JAMA Pediatrics* 168(1):76–82.

Hsu, C.-C., C.-H. Lee, M. L. Wahlqvist, H.-L. Huang, H.-Y. Chang, L. Chen, S.-F. Shih, S.-J. Shin, W.-C. Tsai, T. Chen, C.-T. Huang, and J.-S. Cheng. 2012. Poverty increases type 2 diabetes incidence and inequality of care despite universal health coverage. *Diabetes Care* 35(11):2286.

Huangfu, P., Y. V. Laurence, B. Alisjahbana, C. Ugarte-Gil, A. L. Riza, G. Walzl, R. Ruslami, D. A. J. Moore, M. Ioana, S. McAllister, K. Ronacher, R. C. Koesoemadinata, D. Grint, S. Kerry, J. Coronel, S. T. Malherbe, U. Griffiths, H. M. Dockrell, P. C. Hill, R. van Crevel, F. Pearson, and J. A. Critchley. 2019. Point of care HbA1c level for diabetes mellitus management and its accuracy among tuberculosis patients: A study in four countries. *International Journal of Tuberculosis and Lung Disease* 23(3):283–292.

Human Microbiome Project, C. Huttenhower, D. Gevers, R. Knight, S. Abubucker, J. H. Badger, A. T. Chinwalla, H. H. Creasy, A. M. Earl, M. G. FitzGerald, R. S. Fulton, M. G. Giglio, K. Hallsworth-Pepin, E. A. Lobos, R. Madupu, V. Magrini, J. C. Martin, M. Mitreva, D. M. Muzny, E. J. Sodergren, J. Versalovic, A. M. Wollam, K. C. Worley, J. R. Wortman, S. K. Young, Q. Zeng, K. M. Aagaard, O. O. Abolude, E. Allen-Vercoe, E. J. Alm, L. Alvarado, G. L. Andersen, S. Anderson, E. Appelbaum, H. M. Arachchi, G. Armitage, C. A. Arze, T. Ayvaz, C. C. Baker, L. Begg, T. Belachew, V. Bhonagiri, M. Bihan, M. J. Blaser, T. Bloom, V. Bonazzi, J. Paul Brooks, G. A. Buck, C. J. Buhay, D. A. Busam, J. L. Campbell, S. R. Canon, B. L. Cantarel, P. S. G. Chain, I. M. A. Chen, L. Chen, S. Chhibba, K. Chu, D. M. Ciulla, J. C. Clemente, S. W. Clifton, S. Conlan, J. Crabtree, M. A. Cutting, N. J. Davidovics, C. C. Davis, T. Z. DeSantis, C. Deal, K. D. Delehaunty, F. E. Dewhirst, E. Deych, Y. Ding, D. J. Dooling, S. P. Dugan, W. Michael Dunne, A. Scott Durkin, R. C. Edgar, R. L. Erlich, C. N. Farmer, R. M. Farrell, K. Faust, M. Feldgarden, V. M. Felix, S. Fisher, A. A. Fodor, L. J. Forney, L. Foster, V. Di Francesco, J. Friedman, D. C. Friedrich, C. C. Fronick, L. L. Fulton, H. Gao, N. Garcia, G. Giannoukos, C. Giblin, M. Y. Giovanni, J. M. Goldberg, J. Goll, A. Gonzalez, A. Griggs, S. Gujja, S. Kinder Haake, B. J. Haas, H. A. Hamilton, E. L. Harris, T. A. Hepburn, B. Herter, D. E. Hoffmann, M. E. Holder, C. Howarth, K. H. Huang, S. M. Huse, J. Izard, J. K. Jansson, H. Jiang, C. Jordan, V. Joshi, J. A. Katancik, W. A. Keitel, S. T. Kelley, C. Kells, N. B. King, D. Knights, H. H. Kong, O. Koren, S. Koren, K. C. Kota, C. L. Kovar, N. C. Kyrpides, P. S. La Rosa, S. L. Lee, K. P. Lemon, N. Lennon, C. M. Lewis, L. Lewis, R. E. Ley, K. Li, K. Liolios, B. Liu, Y. Liu, C.-C. Lo, C. A. Lozupone, R. D. Lunsford, T. Madden, A. A. Mahurkar, P. J. Mannon, E. R. Mardis, V. M. Markowitz, K. Mavromatis, J. M. McCorrison,

D. McDonald, J. McEwen, A. L. McGuire, P. McInnes, T. Mehta, K. A. Mihindukulasuriya, J. R. Miller, P. J. Minx, I. Newsham, C. Nusbaum, M. O'Laughlin, J. Orvis, I. Pagani, K. Palaniappan, S. M. Patel, M. Pearson, J. Peterson, M. Podar, C. Pohl, K. S. Pollard, M. Pop, M. E. Priest, L. M. Proctor, X. Qin, J. Raes, J. Ravel, J. G. Reid, M. Rho, R. Rhodes, K. P. Riehle, M. C. Rivera, B. Rodriguez-Mueller, Y.-H. Rogers, M. C. Ross, C. Russ, R. K. Sanka, P. Sankar, J. Fah Sathirapongsasuti, J. A. Schloss, P. D. Schloss, T. M. Schmidt, M. Scholz, L. Schriml, A. M. Schubert, N. Segata, J. A. Segre, W. D. Shannon, R. R. Sharp, T. J. Sharpton, N. Shenoy, N. U. Sheth, G. A. Simone, I. Singh, C. S. Smillie, J. D. Sobel, D. D. Sommer, P. Spicer, G. G. Sutton, S. M. Sykes, D. G. Tabbaa, M. Thiagarajan, C. M. Tomlinson, M. Torralba, T. J. Treangen, R. M. Truty, T. A. Vishnivetskaya, J. Walker, L. Wang, Z. Wang, D. V. Ward, W. Warren, M. A. Watson, C. Wellington, K. A. Wetterstrand, J. R. White, K. Wilczek-Boney, Y. Wu, K. M. Wylie, T. Wylie, C. Yandava, L. Ye, Y. Ye, S. Yooseph, B. P. Youmans, L. Zhang, Y. Zhou, Y. Zhu, L. Zoloth, J. D. Zucker, B. W. Birren, R. A. Gibbs, S. K. Highlander, B. A. Methé, K. E. Nelson, J. F. Petrosino, G. M. Weinstock, R. K. Wilson, and O. White. 2012. Structure, function and diversity of the healthy human microbiome. *Nature* 486:207.

ICAP. 2011. *Strengthening chronic disease services in Ethiopia: Lessons learned from HIV/AIDS program implementation conference report*. Addis Ababa, Ethiopia: ICAP at Columbia University.

ICAP. 2019. *Who we are*. https://icap.columbia.edu/who-we-are (accessed September 19, 2019).

Ilievski, V., P. K. Zuchowska, S. J. Green, P. T. Toth, M. E. Ragozzino, K. Le, H. W. Aljewari, N. M. O'Brien-Simpson, E. C. Reynolds, and K. Watanabe. 2018. Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice. *PLoS One* 13(10):e0204941.

Institute for Health Metrics and Evaluation. 2010. *Global burden of disease profile: South Africa*. Seattle, WA: Institute for Health Metrics and Evaluation.

International Diabetes Federation. 2017. *IDF diabetes atlas,* 8th ed. Brussels, Belgium: International Diabetes Federation.

IOM (Institute of Medicine). 2004. *The infectious etiology of chronic diseases: Defining the relationship, enhancing the research, and mitigating the effects: Workshop summary.* Washington, DC: The National Academies Press.

IOM. 2014. *Microbial ecology in states of health and disease: Workshop summary*. Washington, DC: The National Academies Press.

Iweala, O. I., and C. R. Nagler. 2019. The microbiome and food allergy. *Annual Review of Immunology* 37:377–403.

Jamison, D. T., L. H. Summers, G. Alleyne, K. J. Arrow, S. Berkley, A. Binagwaho, F. Bustreo, D. Evans, R. G. A. Feachem, J. Frenk, G. Ghosh, S. J. Goldie, Y. Guo, S. Gupta, R. Horton, M. E. Kruk, A. Mahmoud, L. K. Mohohlo, M. Ncube, A. Pablos-Mendez, K. S. Reddy, H. Saxenian, A. Soucat, K. H. Ulltveit-Moe, and G. Yamey. 2013. Global health 2035: A world converging within a generation. *Lancet* 382(9908):1898–1955.

Jamison, D., H. Gelband, S. Horton, P. Jha, R. Laxminarayan, C. Mock, and R. Nugent. 2018. *Disease control priorities: Improving health and reducing poverty,* 3rd ed. Washington, DC: World Bank Group.

Jeon, C. Y., and M. B. Murray. 2008. Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. *PLoS Medicine* 5(7):e152.

Jha, A. R., E. R. Davenport, Y. Gautam, D. Bhandari, S. Tandukar, K. M. Ng, G. K. Fragiadakis, S. Holmes, G. P. Gautam, J. Leach, J. B. Sherchand, C. D. Bustamante, and J. L. Sonnenburg. 2018. Gut microbiome transition across a lifestyle gradient in Himalaya. *PLoS Biology* 16(11):e2005396.

Jimenez-Corona, M. E., L. P. Cruz-Hervert, L. Garcia-Garcia, L. Ferreyra-Reyes, G. Delgado-Sanchez, M. Bobadilla-del-Valle, S. Canizales-Quintero, E. Ferreira-Guerrero, R. Baez-Saldana, N. Tellez-Vazquez, R. Montero-Campos, N. Mongua-Rodriguez, R. A. Martinez-Gamboa, J. Sifuentes-Osornia, and A. Ponce-de-Leon. 2012. Association of diabetes and tuberculosis: Impact on treatment and post-treatment outcomes. *Thorax* 68:214–220.

Kabami, J., G. Chamie, D. Kwarisiima, E. Biira, P. Ssebutinde, M. Petersen, E. D. Charlebois, M. R. Kamya, D. V. Havlir, T. D. Clark, and the SEARCH Collaboration. 2017. Evaluating the feasibility and uptake of a community-led HIV testing and multi-disease health campaign in rural Uganda. *Journal of the International AIDS Society* 20(1):21514.

Kamer, A. R., E. Pirraglia, W. Tsui, H. Rusinek, S. Vallabhajosula, L. Mosconi, L. Yi, P. McHugh, R. G. Craig, S. Svetcov, R. Linker, C. Shi, L. Glodzik, S. Williams, P. Corby, D. Saxena, and M. J. de Leon. 2015. Periodontal disease associates with higher brain amyloid load in normal elderly. *Neurobiology and Aging* 36(2):627–633.

Kang, M. S., and E. Kieff. 2015. Epstein-Barr virus latent genes. *Experimental & Molecular Medicine* 47(1):e131. doi: 10.1038/emm.2014.84.

Kaspersen, K. A., O. B. Pedersen, M. S. Petersen, H. Hjalgrim, K. Rostgaard, B. K. Moller, C. Juul-Sorensen, S. Kotze, K. M. Dinh, L. T. Erikstrup, E. Sorensen, L. W. Thorner, K. S. Burgdorf, H. Ullum, and C. Erikstrup. 2015. Obesity and risk of infection: Results from the Danish blood donor study. *Epidemiology* 26(4):580–589.

Kaye, E. K., A. Valencia, N. Baba, A. Spiro, 3rd, T. Dietrich, and R. I. Garcia. 2010. Tooth loss and periodontal disease predict poor cognitive function in older men. *Journal of the American Geriatric Society* 58(4):713–718.

Keenan, J. D., R. L. Bailey, S. K. West, A. M. Arzika, J. Hart, J. Weaver, K. Kalua, Z. Mrango, K. J. Ray, and C. Cook. 2018. Azithromycin to reduce childhood mortality in sub-Saharan Africa. *New England Journal of Medicine* 378(17):1583–1592.

Keenan, J. D., A. M. Arzika, R. Maliki, N. Boubacar, S. Elh Adamou, M. Moussa Ali, C. Cook, E. Lebas, Y. Lin, K. J. Ray, K. S. O'Brien, T. Doan, C. E. Oldenburg, E. K. Callahan, P. M. Emerson, T. C. Porco, and T. M. Lietman. 2019. Longer-term assessment of azithromycin for reducing childhood mortality in Africa. *New England Journal of Medicine* 380(23):2207–2214.

Kelly, C. R., A. Khoruts, C. Staley, M. J. Sadowsky, M. Abd, M. Alani, B. Bakow, P. Curran, J. McKenney, and A. Tisch. 2016. Effect of fecal microbiota transplantation on recurrence in multiply recurrent *Clostridium difficile* infection: A randomized trial. *Annals of Internal Medicine* 165(9):609.

Kim, J. H., W. S. Kim, J. Y. Hong, K. J. Ryu, S. J. Kim, and C. Park. 2017. Epstein-Barr virus EBNA directs doxorubicin resistance of B cell lymphoma through CCL3 and CCL4-mediated activation of NF-κB and BTK. *Oncotarget* 8(3):5361–5370.

Kimaiyo, S. 2019. *Outcomes of the AMPATH model in Kenya.* PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Kirby, T. O., and J. Ochoa-Repáraz. 2018. The gut microbiome in multiple sclerosis: A potential therapeutic avenue. *Medical Sciences (Basel, Switzerland)* 6(3):69.

Knight, R. 2018. Integrated approaches to analyze big data in the perinatal/neonatal space. *Breastfeeding Medicine* 13(S1):S5–S6.

Knight, R. 2019. *A microbial dimension to human development and the potential for new approaches to human well-being.* PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Knight, R., C. Callewaert, C. Marotz, E. R. Hyde, J. W. Debelius, D. McDonald, and M. L. Sogin. 2017. The microbiome and human biology. *Annual Review of Genomics and Human Genetics* 18(1):65–86.

Ko, A. I., M. Galvao Reis, C. M. Ribeiro Dourado, W. D. Johnson, Jr., and L. W. Riley. 1999. Urban epidemic of severe leptospirosis in Brazil. Salvador leptospirosis study group. *Lancet* 354(9181):820–825.

Koenig, J. E., A. Spor, N. Scalfone, A. D. Fricker, J. Stombaugh, R. Knight, L. T. Angenent, and R. E. Ley. 2011. Succession of microbial consortia in the developing infant gut microbiome. *Proceedings of the National Academy of Sciences* 108(Suppl 1):4578–4585.

Kolata, G. 2016. Could Alzheimer's stem from infections? It makes sense, experts say. *The New York Times*. May 25.

Kolev, M. V., M. M. Ruseva, C. L. Harris, B. P. Morgan, and R. M. Donev. 2009. Implication of complement system and its regulators in Alzheimer's disease. *Current Neuropharmacology* 7(1):1–8.

Kornfeld, H., K. West, K. Kane, S. Kumpatla, R. R. Zacharias, C. Martinez-Balzano, W. Li, and V. Viswanathan. 2016. High prevalence and heterogeneity of diabetes in patients with TB in south India: A report from the effects of diabetes on tuberculosis severity (EDOTS) study. *Chest* 149(6):1501–1508.

Kumar, D. K., S. H. Choi, K. J. Washicosky, W. A. Eimer, S. Tucker, J. Ghofrani, A. Lefkowitz, G. McColl, L. E. Goldstein, R. E. Tanzi, and R. D. Moir. 2016. Amyloid-beta peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. *Science Translational Medicine* 8(340):340ra72.

Kwan, G. F., A. K. Bukhman, A. C. Miller, G. Ngoga, J. Mucumbitsi, C. Bavuma, S. Dusabeyezu, M. L. Rich, F. Mutabazi, C. Mutumbira, J. P. Ngiruwera, C. Amoroso, E. Ball, H. S. Fraser, L. R. Hirschhorn, P. Farmer, E. Rusingiza, and G. Bukhman. 2013. A simplified echocardiographic strategy for heart failure diagnosis and management within an integrated noncommunicable disease clinic at district hospital level for sub-Saharan Africa. *JACC Heart Failure* 1(3):230–236.

Langdon, A. N. Crook, and G. Dantas. 2016. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Medicine* 8(1):39.

Langefeld, C. D., H. C. Ainsworth, D. S. Cunninghame Graham, J. A. Kelly, M. E. Comeau, M. C. Marion, T. D. Howard, P. S. Ramos, J. A. Croker, D. L. Morris, J. K. Sandling, J. C. Almlof, E. M. Acevedo-Vasquez, G. S. Alarcon, A. M. Babini, V. Baca, A. A. Bengtsson, G. A. Berbotto, M. Bijl, E. E. Brown, H. I. Brunner, M. H. Cardiel, L. Catoggio, R. Cervera, J. M. Cucho-Venegas, S. R. Dahlqvist, S. D'Alfonso, B. M. Da Silva, I. de la Rua Figueroa, A. Doria, J. C. Edberg, E. Endreffy, J. A. Esquivel-Valerio, P. R. Fortin, B. I. Freedman, J. Frostegard, M. A. Garcia, I. G. de la Torre, G. S. Gilkeson, D. D. Gladman, I. Gunnarsson, J. M. Guthridge, J. L. Huggins, J. A. James, C. G. M. Kallenberg, D. L. Kamen, D. R. Karp, K. M. Kaufman, L. C. Kottyan, L. Kovacs, H. Laustrup, B. R. Lauwerys, Q. Z. Li, M. A. Maradiaga-Cecena, J. Martin, J. M. McCune, D. R. McWilliams, J. T. Merrill, P. Miranda, J. F. Moctezuma, S. K. Nath, T. B. Niewold, L. Orozco, N. Ortego-Centeno, M. Petri, C. A. Pineau, B. A. Pons-Estel, J. Pope, P. Raj, R. Ramsey-Goldman, J. D. Reveille, L. P. Russell, J. M. Sabio, C. A. Aguilar-Salinas, H. R. Scherbarth, R. Scorza, M. F. Seldin, C. Sjowall, E. Svenungsson, S. D. Thompson, S. M. A. Toloza, L. Truedsson, T. Tusie-Luna, C. Vasconcelos, L. M. Vila, D. J. Wallace, M. H. Weisman, J. E. Wither, T. Bhangale, J. R. Oksenberg, J. D. Rioux, P. K. Gregersen, A. C. Syvanen, L. Ronnblom, L. A. Criswell, C. O. Jacob, K. L. Sivils, B. P. Tsao, L. E. Schanberg, T. W. Behrens, E. D. Silverman, M. E. Alarcon-Riquelme, R. P. Kimberly, J. B. Harley, E. K. Wakeland, R. R. Graham, P. M. Gaffney, and T. J. Vyse. 2017. Transancestral mapping and genetic load in systemic lupus erythematosus. *Nature Communication* 8:16021.

Lee, M.-C., C.-Y. Chiang, C.-H. Lee, C.-M. Ho, C.-H. Chang, J.-Y. Wang, and S.-M. Chen. 2018. Metformin use is associated with a low risk of tuberculosis among newly diagnosed diabetes mellitus patients with normal renal function: A nationwide cohort study with validated diagnostic criteria. *PLoS One* 13(10):e0205807–e0205807.

Lee, M. R., Y. P. Huang, Y. T. Kuo, C. H. Luo, Y. J. Shih, C. C. Shu, J. Y. Wang, J. C. Ko, C. J. Yu, and H. H. Lin. 2017. Diabetes mellitus and latent tuberculosis infection: A systemic review and metaanalysis. *Clinical Infectious Disease* 64(6):719–727.

Lee, P. H., H. Fu, T. C. Lai, C. Y. Chiang, C. C. Chan, and H. H. Lin. 2016. Glycemic control and the risk of tuberculosis: A cohort study. *PLoS Medicine* 13(8):e1002072.

Leegaard, A., A. Riis, J. B. Kornum, J. B. Prahl, V. O. Thomsen, H. T. Sorensen, C. R. Horsburgh, and R. W. Thomsen. 2011. Diabetes, glycemic control, and risk of tuberculosis: A population-based case-control study. *Diabetes Care* 34(12):2530–2535.

Legason, I. D., R. M. Pfeiffer, K.-I. Udquim, A. W. Bergen, M. H. Gouveia, S. Kirimunda, I. Otim, E. Karlins, P. Kerchan, H. Nabalende, A. Bayanjargal, B. Emmanuel, P. Kagwa, A. O. Talisuna, K. Bhatia, M. Yeager, R. J. Biggar, L. W. Ayers, S. J. Reynolds, J. J. Goedert, M. D. Ogwang, J. F. Fraumeni, Jr., L. Prokunina-Olsson, and S. M. Mbulaiteye. 2017. Evaluating the causal link between malaria infection and endemic Burkitt lymphoma in northern Uganda: A Mendelian randomization study. *EBioMedicine* 25:58–65.

Leon, D. A. 2008. Cities, urbanization and health. *International Journal of Epidemiology* 37(1):4–8.

Leung, C. C., T. H. Lam, W. M. Chan, W. W. Yew, K. S. Ho, G. M. Leung, W. S. Law, C. M. Tam, C. K. Chan, and K. C. Chang. 2008. Diabetic control and risk of tuberculosis: A cohort study. *American Journal of Epidemiology* 167(12):1486–1494.

Lin, Y., A. D. Harries, A. M. V. Kumar, J. A. Critchley, R. van Crevel, P. Owiti, R. A. Dlodlo, and A. Dejgaard. 2019. *Management of diabetes mellitus-tuberculosis: A guide to the essential practice*. Paris, France: International Union Against Tuberculosis and Lung Disease.

Loh, W., and M. L. K. Tang. 2018. The epidemiology of food allergy in the global context. *International Journal of Environmental Research and Public Health* 15(9):2043.

Lonnerdal, B. 2017. Excess iron intake as a factor in growth, infections, and development of infants and young children. *American Journal of Clinical Nutrition* 106(Suppl 6):1681s–1687s.

Luntz, G. R. 1954. Tuberculous diabetics: the Birmingham regional service. *Lancet* 266:973–974.

Luntz, G. R. 1957. Management of the tuberculosis diabetic: follow-up of 84 cases for one year. *British Medical Journal* 1:1082–1086.

Lynch, C. 2019. *Alzheimer's disease and P. gingivalis*. PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Maier, L., M. Pruteanu, M. Kuhn, G. Zeller, A. Telzerow, E. E. Anderson, A. R. Brochado, K. C. Fernandez, H. Dose, H. Mori, K. R. Patil, P. Bork, and A. Typass. 2018. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature* 555(698):623–628.

Mamlin, B. W., and P. G. Biondich. 2005. AMPATH Medical Record System (AMRS): Collaborating toward an EMR for developing countries. *AMIA Symposium* 490–494.

Mamlin, J., S. Kimaiyo, W. Nyandiko, and W. Tierney. 2004. *Perspectives and practice in antiretroviral treatment: Academic institutions linking access to treatment and prevention: Case study.* Geneva, Switzerland: World Health Organization.

Marais, B. J., K. Lonnroth, S. D. Lawn, G. B. Migliori, P. Mwaba, P. Glaziou, M. Bates, R. Colagiuri, L. Zijenah, S. Swaminathan, Z. A. Memish, M. Pletschette, M. Hoelscher, I. Abubakar, R. Hasan, A. Zafar, G. Pantaleo, G. Craig, and A. Zumla. 2013. Tuberculosis comorbidity with communicable and non-communicable diseases: Integrating health services and control efforts. *Lancet Infectious Diseases* 13(4):285–287.

Marsalek, J. 2014. *Urban water cycle processes and interactions: Urban water series-UNESCO-IHP*: Boca Raton, FL: CRC Press.

Marshall, B. J., J. A. Amstrong, D. B. McGechie, and R. J. Glancy. 1985. Attempt to fulfil Koch's postulates for pyloric *Campylobacter*. *Medical Journal of Australia* 142:436–439.

Massini, G., D. Siemer, and S. Hohaus. 2009. EBV in Hodgkin lymphoma. *Mediterranean Journal of Hematology and Infectious Diseases* 1(2):e2009013.

McClung, N. M., J. W. Gargano, N. M. Bennett, L. M. Niccolai, N. Abdullah, M. R. Griffin, I. U. Park, A. A. Cleveland, T. D. Querec, E. R. Unger, and L. E. Markowitz. 2019. Trends in human papillomavirus vaccine types 16 and 18 in cervical precancers, 2008-2014. *Cancer Epidemiology, Biomarkers & Prevention* 28(3):602–609.

Mele, A., F. Tancredi, L. Romanò, A. Giuseppone, M. Colucci, A. Sangiuolo, R. Lecce, B. Adamo, M. E. Tosti, G. Taliani, and A. R. Zanetti. 2001. Effectiveness of Hepatitis B vaccination in babies born to Hepatitis B surface antigen-positive mothers in Italy. *Journal of Infectious Diseases* 184(7):905–908.

Mendenhall, E. 2017. Syndemics: A new path for global health research. *Lancet* 389(10072):889–891.

Mendenhall, E. 2019a. *Syndemics of infectious & noncommunicable disease*. Presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Mendenhall, E. 2019b. *Rethinking diabetes: Entanglements with trauma, poverty, and HIV*. Ithaca, NY: Cornell University Press.

Mendenhall, E., and S. A. Norris. 2015. When HIV is ordinary and diabetes new: Remaking suffering in a South African township. *Global Public Health* 10(4):449–462.

Mendenhall, E., R. Shivashankar, N. Tandon, M. K. Ali, K. M. V. Narayan, and D. Prabhakaran. 2012. Stress and diabetes in socioeconomic context: A qualitative study of urban Indians. *Social Science & Medicine* 75(12):2522–2529.

Mendenhall, E., B. A. Kohrt, S. A. Norris, D. Ndetei, and D. Prabhakaran. 2017. Non-communicable disease syndemics: Poverty, depression, and diabetes among low-income populations. *Lancet* 389(10072):951–963.

Mohand, A. A., Y. Kayiteshonga, C. N. Misago, J. D. Dusabeyezu, and J. D. Iyamuremye. 2017. Decentralization and integration of mental health care into primary health care: A case study of Rwwanda. In *Strengthening health systems: Evidence-informed approaches and lessons learned from Rwanda*, edited by A. van der Kwaak, and J. Mathijssen. Rwanda: Ministry of Health. Pp. 55–69.

Morton, R. 1694. *Phthisiologia: Or a treatise of consumptions*. London, UK: Smith and Watford.

Moss, D. J., S. R. Burrows, and R. Khanna. 2007. EBV: Immunobiology and host response. In *Human herpesviruses: Biology, therapy, and immunoprophylaxis*, edited by A. Arvin, G. Campadelli-Fiume, E. Mocarski, P. S. Moore, B. Roizman, R. Whitley, and K. Yamanishi. Cambridge, UK: Cambridge University Press.

Nagler, C. 2019. *The role of the microbiome in food allergies*. PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Navale, A. M., and A. N. Paranjape. 2016. Glucose transporters: physiological and pathological roles. *Biophysical Reviews* 8(1):5–9.

Neu, J., and J. Rushing. 2011. Cesarean versus vaginal delivery: Long-term infant outcomes and the hygiene hypothesis. *Clinics in Perinatology* 38(2):321–331.

Newcombe, E. A., J. Camats-Perna, M. L. Silva, N. Valmas, T. J. Huat, and R. Medeiros. 2018. Inflammation: The link between comorbidities, genetics, and Alzheimer's disease. *Journal of Neuroinflammation* 15(1):276.

NIH (National Institutes of Health). 2019. *NIH Human Microbiome Project*. Bethesda, MD: National Institutes of Health.

Noubiap, J. J., J. R. Nansseu, U. F. Nyaga, J. R. Nkeck, F. T. Endomba, A. D. Kaze, V. N. Agbor, and J. J. Bigna. 2019. Global prevalence of diabetes in active tuberculosis: A systematic review and meta-analysis of data from 2.3 million patients with tuberculosis. *Lancet Global Health* 7(4):e448–e460.

Nugent, R. 2016. A chronology of global assistance funding for NCD. *Global Heart* 11(4):371–374.

Nugent, R., R. V. Barnabas, I. Golovaty, B. Osetinsky, D. A. Roberts, C. Bisson, L. Courtney, P. Patel, G. Yonga, and D. Watkins. 2018a. Costs and cost-effectiveness of HIV/noncommunicable disease integration in Africa: From theory to practice. *AIDS* 32:S83–S92.

Nugent, R., M. Y. Bertram, S. Jan, L. W. Niessen, F. Sassi, D. T. Jamison, E. G. Pier, and R. Beaglehole. 2018b. Investing in non-communicable disease prevention and management to advance the sustainable development goals. *Lancet* 391(10134):2029–2035.

O'Brien, K. S., P. Emerson, P. J. Hooper, A. L. Reingold, E. G. Dennis, J. D. Keenan, T. M. Lietman, and C. E. Oldenburg. 2019. Antimicrobial resistance following mass azithromycin distribution for trachoma: A systematic review. *Lancet Infectious Diseases* 19(1):e14–e25.

O'Connor S. M., C. E. Taylor, and J. M. Hughes. 2006. Emerging infectious determinants of chronic diseases. *Emerging Infectious Diseases* 12(7):1051–1057.

Okano, M., and T. G. Gross. 2012. Acute or chronic life-threatening diseases associated with Epstein-Barr virus infection. *American Journal of Medical Science* 343(6):483–489.

Olayinka, A. O., O. Anthonia, and K. Yetunde. 2013. Prevalence of diabetes mellitus in persons with tuberculosis in a tertiary health centre in Lagos, Nigeria. *Indian Journal of Endocrinology and Metabolism* 17(3):486–489.

Oldenburg, C. E., A. Sié, B. Coulibaly, L. Ouermi, C. Dah, C. Tapsoba, T. Bärnighausen, K. J. Ray, L. Zhong, S. Cummings, E. Lebas, T. M. Lietman, J. D. Keenan, and T. Doan. 2018. Effect of commonly used pediatric antibiotics on gut microbial diversity in preschool children in Burkina Faso: A randomized clinical trial. *Open Forum Infectious Diseases* 5(11):ofy289.

Oldenburg, C. E., A. M. Arzika, A. Amza, T. Gebre, K. Kalua, Z. Mrango, S. Y. Cotter, S. K. West, R. L. Bailey, P. M. Emerson, K. S. O'Brien, T. C. Porco, J. D. Keenan, and T. M. Lietman. 2019. Mass azithromycin distribution to prevent childhood mortality: A pooled analysis of cluster-randomized trials. *American Journal of Tropical Medicine and Hygiene* 100(3):691–695.

Omotoso, K. O., and S. F. Koch. 2018. Assessing changes in social determinants of health inequalities in South Africa: A decomposition analysis. *International Journal for Equity in Health* 17(1):181.

Oni, T. 2019. *Infectious diseases and noncommunicable diseases—Convergent action for colliding epidemics*. PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Oni, T., and N. Unwin. 2015. Why the communicable/non-communicable disease dichotomy is problematic for public health control strategies: Implications of multimorbidity for health systems in an era of health transition. *International Health* 7(6):390–399.

Oni, T., N. McGrath, R. BeLue, P. Roderick, S. Colagiuri, C. R. May, and N. S. Levitt. 2014. Chronic diseases and multi-morbidity—a conceptual modification to the WHO ICCC model for countries in health transition. *BMC Public Health* 14:575.

Oni, T., E. Youngblood, A. Boulle, N. McGrath, R. J. Wilkinson, and N. S. Levitt. 2015. Patterns of HIV, TB, and non-communicable disease multi-morbidity in peri-urban South Africa—a cross sectional study. *BMC Infectious Diseases* 15:20.

Oni, T., N. Berkowitz, M. Kubjane, R. Goliath, N. S. Levitt, and R. J. Wilkinson. 2017. Trilateral overlap of tuberculosis, diabetes and HIV-1 in a high-burden African setting: Implications for TB control. *European Respiratory Journal* 50(1):1700004.

Oni, T., E. Mogo, A. Ahmed, and J. I. Davies. 2019. Braking down the silos of universal health coverage: towards systems for the primary prevention of non-communicable diseaes in Africa. *BMJ Global Health* 4(4):e001717.

Palma, A. M., M. Rabkin, S. Simelane, A. B. Gachuhi, M. L. McNairy, H. Nuwagaba-Biribonwoha, P. Bongomin, V. N. Okello, R. A. Bitchong, and W. M. El-Sadr. 2018. A time-motion study of cardiovascular disease risk factor screening integrated into HIV clinic visits in Swaziland. *Journal of the International AIDS Society* 21(3):e25099.

Pascal, V., M. Pozuelo, N. Borruel, F. Casellas, D. Campos, A. Santiago, X. Martinez, E. Varela, G. Sarrabayrouse, K. Machiels, S. Vermeire, H. Sokol, F. Guarner, and C. Manichanh. 2017. A microbial signature for Crohn's disease. *Gut* 66(5):813–822.

Patterson, B., C. D. Morrow, D. Kohls, C. Deignan, S. Ginsburg, and R. Wood. 2017. Mapping sites of high TB transmission risk: Integrating the shared air and social behaviour of TB cases and adolescents in a South African township. *Science of the Total Environment* 583:97–103.

Pealing, L., K. Wing, R. Mathur, D. Prieto-Merino, L. Smeeth, and D. A. Moore. 2015. Risk of tuberculosis in patients with diabetes: Population based cohort study using the UK clinical practice research datalink. *BMC Medicine* 13:135.

PIH (Partners In Health). 2011. Integration of chronic care services in Rwanda. In *The Partners In Health guide to chronic care integration for endemic non-communicable diseases: Rwanda edition*, edited by G. Bukhman and A. Kidder. Cambridge, MA. Pp. 3–4.

Porco, T. C., T. Gebre, B. Ayele, J. House, J. Keenan, Z. Zhou, K. C. Hong, N. Stoller, K. J. Ray, and P. Emerson. 2009. Effect of mass distribution of azithromycin for trachoma control on overall mortality in Ethiopian children: A randomized trial. *JAMA* 302(9):962–968.

Proctor, L. M., H. H. Creasy, J. M. Fettweis, J. Lloyd-Price, A. Mahurkar, W. Zhou, G. A. Buck, M. P. Snyder, J. F. Strauss, G. M. Weinstock, O. White, C. Huttenhower, and the Integrative Human Microbiome Project Research Network Consortium. 2019. The Integrative Human Microbiome Project. *Nature* 569(7758):641–648.

Qin, J., R. Li, J. Raes, M. Arumugam, K. S. Burgdorf, C. Manichanh, T. Nielsen, N. Pons, F. Levenez, T. Yamada, D. R. Mende, J. Li, J. Xu, S. Li, D. Li, J. Cao, B. Wang, H. Liang, H. Zheng, Y. Xie, J. Tap, P. Lepage, M. Bertalan, J. M. Batto, T. Hansen, D. Le Paslier, A. Linneberg, H. B. Nielsen, E. Pelletier, P. Renault, T. Sicheritz-Ponten, K. Turner, H. Zhu, C. Yu, S. Li, M. Jian, Y. Zhou, Y. Li, X. Zhang, S. Li, N. Qin, H. Yang, J. Wang, S. Brunak, J. Doré, F. Guarner, K. Kristiansen, O. Pedersen, J. Parkhill, J. Weissenbach, P. Bork, S. D. Ehrlich, and J. Wang. 2010. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature* 464(7285):59–65.

Rabkin, M. 2019. *HIV & NCD integration platforms: Leveraging HIV scale-up to provide NCD services in austere health systems*. PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Rabkin, M., and W. M. El-Sadr. 2011. Why reinvent the wheel? Leveraging the lessons of HIV scale-up to confront non-communicable diseases. *Global Public Health* 6(3):247–256.

Rabkin, M., and S. Nishtar. 2011. Scaling up chronic care systems: Leveraging HIV programs to support noncommunicable disease services. *Journal of Acquired Immune Deficiency Syndrome* 57(Suppl 2):S87–S90.

Rabkin, M., M. E. Kruk, and W. M. El-Sadr. 2012a. HIV, aging and continuity care: Strengthening health systems to support services for noncommunicable diseases in low-income countries. *AIDS* 26(Suppl 1):S77–S83.

Rabkin, M., Z. Melaku, K. Bruce, A. Reja, A. Koler, Y. Tadesse, H. N. Kamiru, L. T. Sibanyoni, and W. El-Sadr. 2012b. Strengthening health systems for chronic care: Leveraging HIV programs to support diabetes services in Ethiopia and Swaziland. *Journal of Tropical Medicine* 2012:137460.

Rabkin, M., E. Goosby, and W. El-Sadr. 2014. Echoing the lessons of HIV: How to serve the millions with cardiovascular disease. *Scientific American*. doi: https://doi.org/10.7916/D8F76C5J.

Rabkin, M., A. Mutiti, C. Chung, Y. Zhang, Y. Wei, and W. M. El-Sadr. 2015. Missed opportunities to address cardiovascular disease risk factors amongst adults attending an urban HIV clinic in South Africa. *PLoS One* 10(10):e0140298.

Rabkin, M., F. M. Fouad, and W. M. El-Sadr. 2018a. Addressing chronic diseases in protracted emergencies: Lessons from HIV for a new health imperative. *Global Public Health* 13(2):227–233.

Rabkin, M., A. Palma, M. L. McNairy, A. B. Gachuhi, S. Simelane, H. Nuwagaba-Biribonwoha, P. Bongomin, V. J. Okello, R. A. Bitchong, and W. M. El-Sadr. 2018b. Integrating cardiovascular disease risk factor screening into HIV services in Swaziland: Lessons from an implementation science study. *AIDS* 32(Suppl 1):S43–S46.

Ramos, P. S., S. R. Shaftman, R. C. Ward, and C. D. Langefeld. 2014. Genes associated with SLE are targets of recent positive selection. *Autoimmune Diseases* 2014:203435.

Ramos-Cejudo, J., T. Wisniewski, C. Marmar, H. Zetterberg, K. Blennow, M. J. de Leon, and S. Fossati. 2018. Traumatic brain injury and Alzheimer's disease: The cerebrovascular link. *EBioMedicine* 28:21–30.

Reddy, K. S., D. Prabhakaran, P. Jeemon, K. R. Thankappan, P. Joshi, V. Chaturvedi, L. Ramakrishnan, and F. Ahmed. 2007. Educational status and cardiovascular risk profile in Indians. *Proceedings of the National Academy of Sciences* 104(41):16263–16268.

Rees, F., M. Doherty, M. J. Grainge, P. Lanyon, and W. Zhang. 2017. The worldwide incidence and prevalence of systemic lupus erythematosus: A systematic review of epidemiological studies. *Rheumatology* 56(11):1945–1961.

Restrepo, B. I., A. J. Camerlin, M. H. Rahbar, W. Wang, M. A. Restrepo, I. Zarate, F. Mora-Guzman, J. G. Crespo-Solis, J. Briggs, J. B. McCormick, and S. P. Fisher-Hoch. 2011. Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases. *Bulletin of the World Health Organization* 89(5):352–359.

Ridaura, V. K., J. J. Faith, F. E. Rey, J. Cheng, A. E. Duncan, A. L. Kau, N. W. Griffin, V. Lombard, B. Henrissat, J. R. Bain, M. J. Muehlbauer, O. Ilkayeva, C. F. Semenkovich, K. Funai, D. K. Hayashi, B. J. Lyle, M. C. Martini, L. K. Ursell, J. C. Clemente, W. V. Treuren, W. A. Walters, R. Knight, C. B. Newgard, A. C. Heath, and J. I. Gordon. 2013. Cultured gut microbiota from twins discordant for obesity modulate adiposity and metabolic phenotypes in mice. *Science* 341(6150):1241214.

Robinson, M. A. 1998. Linkage disequilibrium. In *Encyclopedia of Immunology,* 2nd ed. Edited by P. J. Delves. Cambridge, MA: Academic Press. Pp. 1586–1588.

Rotheram-Borus, M. J., M. Tomlinson, and E. Davis. 2015. "Boring" family routines reduce non-communicable diseases: A commentary and call for action. *Archives of Public Health* 73(1):27.

Rothschild, D., O. Weissbrod, E. Barkan, A. Kurilshikov, T. Korem, D. Zeevi, P. I. Costea, A. Godneva, I. N. Kalka, and N. Bar. 2018. Environment dominates over host genetics in shaping human gut microbiota. *Nature* 555(7695):210.

Rusingiza, E. K., Z. El-Khatib, B. Hedt-Gauthier, G. Ngoga, S. Dusabeyezu, N. Tapela, C. Mutumbira, F. Mutabazi, E. Harelimana, J. Mucumbitsi, G. F. Kwan, and G. Bukhman. 2018. Outcomes for patients with rheumatic heart disease after cardiac surgery followed at rural district hospitals in Rwanda. *Heart* 104(20):1707–1713.

Saha, A., and E. S. Robertson. 2019. Mechanisms of b-cell oncogenesis induced by Epstein-Barr virus. *Journal of Virology* 93(13):e00238-19.

Schubert, A. M., M. A. Rogers, C. Ring, J. Mogle, J. P. Petrosiono, V. B. Young, D. M. Aronoff, and P. D. Schloss. 2014. Microbiome data distinguish patients with *Clostridium difficile* infection and non-*C. difficile*-associated diarrhea from healthy controls. *mBio* 5(3):e01021-14.

Sekabaraga, C., A. Soucat, F. Diop, and G. Martin. 2011. Innovative financing for health in Rwanda: A report of successful reforms. In *Yes Africa can: Success stories from a dynamic continent*, edited by P. Chuhan-Pole and M. Angwafo. Washington, DC: The World Bank. Pp. 403–416.

Sender, R., S. Fuchs, and R. Milo. 2016. Revised estimates for the number of human and bacteria cells in the body. *PLoS Biology* 14(8):e1002533.

Sharon, G., N. J. Cruz, D.-W. Kang, M. J. Gandal, B. Wang, Y.-M. Kim, E. M. Zink, C. P. Casey, B. C. Taylor, C. J. Lane, L. M. Bramer, N. G. Isern, D. W. Hoyt, C. Noecker, M. J. Sweredoski, A. Moradian, E. Borenstein, J. K. Jansson, R. Knight, T. O. Metz, C. Lois, D. H. Geschwind, R. Krajmalnik-Brown, and S. K. Mazmanian. 2019. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. *Cell* 177(6):1600–1618.

Sheflin, A. M., C. L. Melby, F. Carbonero, and T. L. Weir. 2017. Linking dietary patterns with gut microbial composition and function. *Gut Microbes* 8(2):113–129.

Shigayeva, A., R. Atun, M. McKee, and R. Coker. 2010. Health systems, communicable diseases and integration. *Health Policy and Planning* 25(Suppl 1):i4–i20.

Singer, M. 1994. AIDS and the health crisis of the US urban poor; the perspective of critical medical anthropology. *Social Science & Medicine* 39(7):931–948.

Singer, M. 1996. Farewell to adaptationism: Unnatural selection and the politics of biology. *Medical Anthropology Quarterly* 10(4):496–515.

Singer, M. 2009. Pathogens gone wild? Medical anthropology and the "swine flu" pandemic. *Medical Anthropology* 28(3):199–206.

Singer, M., N. Bulled, B. Ostrach, and E. Mendenhall. 2017. Syndemics and the biosocial conception of health. *Lancet* 389(10072):941–950.

Smits, S. A., A. Marcobal, S. Higginbottom, J. L. Sonnenburg, and P. C. Kashyap. 2016. Individualized responses of gut microbiota to dietary intervention modeled in humanized mice. *mSystems* 1(5):e00098-16.

Smits, S. A., J. Leach, E. D. Sonnenburg, C. G. Gonzalez, J. S. Lichtman, G. Reid, R. Knight, A. Manjurano, J. Changalucha, and J. E. Elias. 2017. Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania. *Science* 357(6353):802–806.

Song, C., J. Lv, Y. Liu, J. G. Chen, Z. Ge, J. Zhu, J. Dai, L.B. Du, C. Yu, Y. Guo, Z. Bian, L. Yang, Y. Chen, Z. Chen, J. Liu, J. Jiang, L. Zhu, X. Zhai, Y. Jiang, H. Ma, G. Jin, H. Shen, L. Li, and Z. Hu. 2019. Associations between Hepatitis B virus infection and risk of all cancer types. *JAMA Network Open* 2(6):e195718.

Soscia, S. J., J. E. Kirby, K. J. Washicosky, S. M. Tucker, M. Ingelsson, B. Hyman, M. A. Burton, L. E. Goldstein, S. Duong, R. E. Tanzi, and R. D. Moir. 2010. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. *PLoS One* 5(3):e9505.

Spanogiannopoulos, P., and P. J. Turnbaugh. 2018. Broad collateral damage of drugs against the gut microbiome. *Nature Reviews Gastroenterology and Hepatology* 15:457–458.

Sparks Stein, P., M. J. Steffen, C. Smith, G. Jicha, J. L. Ebersole, E. Abner, and D. Dawson, 3rd. 2012. Serum antibodies to periodontal pathogens are a risk factor for Alzheimer's disease. *Alzheimers and Dementia* 8(3):196–203.

Stall, R., T. C. Mills, J. Williamson, T. Hart, G. Greenwood, J. Paul, L. Pollack, D. Binson, D. Osmond, and J. A. Catania. 2003. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. *American Journal of Public Health* 93(6):939–942.

Steed, A. L., G. P. Christophi, G. E. Kaiko, L. Sun, V. M. Goodwin, U. Jain, E. Esaulova, M. N. Artyomov, D. J. Morales, M. J. Holtzman, A. C. M. Boon, D. J. Lenschow, and T. S. Stappenbeck. 2017. The microbial metabolite desaminotyrosine protects from influenza through type i interferon. *Science* 357(6350):498–502.

Steere, A. C., J. Coburn, and L. Glickstein. 2004. The emergence of Lyme disease. *Journal of Clinical Investigation* 113(8):1093–1101.

Stein, P. S., M. Desrosiers, S. J. Donegan, J. F. Yepes, and R. J. Kryscio. 2007. Tooth loss, dementia and neuropathology in the nun study. *Journal of the American Dental Association* 138(10):1314–1322; quiz 1381–1382.

Stevenson, C. R., J. A. Critchley, N. G. Forouhi, G. Roglic, B. G. Williams, C. Dye, and N. C. Unwin. 2007. Diabetes and the risk of tuberculosis: A neglected threat to public health? *Chronic Illness* 3(3):228–245.

Suwanpimolkul, G., J. A. Grinsdale, L. G. Jarlsberg, J. Higashi, D. H. Osmond, P. C. Hopewell, and M. Kato-Maeda. 2014. Association between diabetes mellitus and tuberculosis in United States-born and foreign-born populations in San Francisco. *PLoS One* 9(12):e114442.

Swinburn, B. A., V. I. Kraak, S. Allender, V. J. Atkins, P. I. Baker, J. R. Bogard, H. Brinsden, A. Calvillo, O. De Schutter, R. Devarajan, M. Ezzati, S. Friel, S. Goenka, R. A. Hammond, G. Hastings, C. Hawkes, M. Herrero, P. S. Hovmand, M. Howden, L. M. Jaacks, A. B. Kapetanaki, M. Kasman, H. V. Kuhnlein, S. K. Kumanyika, B. Larijani, T. Lobstein, M. W. Long, V. K. R. Matsudo, S. D. H. Mills, G. Morgan, A. Morshed, P. M. Nece, A. Pan, D. W. Patterson, G. Sacks, M. Shekar, G. L. Simmons, W. Smit, A. Tootee, S. Vandevijvere, W. E. Waterlander, L. Wolfenden, and W. H. Dietz. 2019. The global syndemic of obesity, undernutrition, and climate change: The Lancet Commission Report. *Lancet* 393(10173):791–846.

Szalkowski, A. M., and C. D. Schmid. 2011. Rapid innovation in ChIP-seq peak-calling algorithms is outdistancing benchmarking efforts. *Briefings in Bioinformatics* 12(6):626–633.

Tapela, N., H. Habineza, S. Anoke, E. Harerimana, F. Mutabazi, B. L. Hedt-Gauthier, S. Dusabeyezu, P. X. F. Uwiragiye, C. Mutumbira, G. Ngoga, D. Ndagijimana, E. Rusingiza, G. Bukhman, and C. Bavuma. 2006. Diabetes in rural Rwanda: High retention and positive outcomes after 24 months of follow-up in the setting of chronic care integration. *International Journal of Diabetes and Clinical Research* 3(2).

Thaiss, C. A., M. Levy, I. Grosheva, D. Zheng, E. Soffer, E. Blacher, S. Braverman, A. C. Tengeler, O. Barak, M. Elazar, R. Ben-Zeev, D. Lehavi-Regev, M. N. Katz, M. Pevsner-Fischer, A. Gertler, Z. Halpern, A. Harmelin, S. Aamar, P. Serradas, A. Grosfeld, H. Shapiro, B. Geiger, and E. Elinav. 2018. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* 359(6382):1376–1383.

Thompson, L. R., J. G. Sanders, D. McDonald, A. Amir, J. Ladau, K. J. Locey, R. J. Prill, A. Tripathi, S. M. Gibbons, G. Ackermann, J. A. Navas-Molina, S. Janssen, E. Kopylova, Y. Vazquez-Baeza, A. Gonzalez, J. T. Morton, S. Mirarab, Z. Zech Xu, L. Jiang, M. F. Haroon, J. Kanbar, Q. Zhu, S. Jin Song, T. Kosciolek, N. A. Bokulich, J. Lefler,

C. J. Brislawn, G. Humphrey, S. M. Owens, J. Hampton-Marcell, D. Berg-Lyons, V. McKenzie, N. Fierer, J. A. Fuhrman, A. Clauset, R. L. Stevens, A. Shade, K. S. Pollard, K. D. Goodwin, J. K. Jansson, J. A. Gilbert, and R. Knight. 2017. A communal catalogue reveals Earth's multiscale microbial diversity. *Nature* 551(7681):457–463.

Tracy, S. I., K. Kakalacheva, J. D. Lünemann, K. Luzuriaga, J. Middeldorp, and D. A. Thorley-Lawson. 2012. Persistence of Epstein-Barr virus in self-reactive memory B cells. *Journal of Virology* 86(22):12330–12340.

Tropini, C. K., A. Earle, K. C. Huang, and J. L. Sonnenburg. 2017. The gut microbiome: Connecting spatial organization to function. *Cell Host & Microbe* 21(4):433–442.

Tsai, A. C. 2018. Syndemics: A theory in search of data or data in search of a theory? *Social Science and Medicine* 206:117–122.

Tsai, A. C., and B. F. Burns. 2015. Syndemics of psychosocial problems and HIV risk: A systematic review of empirical tests of the disease interaction concept. *Social Science and Medicine* 139:26–35.

Tsai, A. C., E. Mendenhall, J. A. Trostle, and I. Kawachi. 2017. Co-occurring epidemics, syndemics, and population health. *Lancet* 389(10072):978–982.

Tseng, C.-H. 2018. Metformin decreases risk of tuberculosis infection in type 2 diabetes patients. *Journal of Clinical Medicine* 7(9):264.

Turnbaugh, P. J., R. E. Ley, M. Hamady, C. M. Fraser-Liggett, R. Knight, and J. I. Gordon. 2007. The human microbiome project. *Nature* 449(7164):804–810.

UNAIDS (Joint United Nations Programme on HIV/AIDS). 2017. *UNAIDS data 2017*. https://www.unaids.org/sites/default/files/media_asset/2017_data-book_en.pdf (accessed September 19, 2019).

Van Cauwenberghe, C., C. Van Broeckhoven, and K. Sleegers. 2015. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. *Genetics in Medicine* 18:421.

Varma, J. 2019. *Adapting public health practice to our new understanding of microbes and health in Africa*. PowerPoint presented at Breaking Down Silos: The Convergence of Infectious Diseases and Noncomunicable Diseases, Washington, DC.

Velasquez-Manoff, M. 2015. Gut microbiome: The peacekeepers. *Nature* 518(7540):S3–S11.

Viney, K., J. Cavanaugh, T. Kienene, D. Harley, P. M. Kelly, A. Sleigh, J. O'Connor, and S. Mase. 2015. Tuberculosis and diabetes mellitus in the republic of Kiribati: A case-control study. *Tropical Medicine and International Health* 20(5):650–657.

Vivarelli, S., R. Salemi, S. Candido, L. Falzone, M. Santagati, S. Stefani, F. Torino, G. L. Banna, G. Tonini, and M. Libra. 2019. Gut microbiota and cancer: From pathogenesis to therapy. *Cancers* 11(1):38.

Walker, C., and N. Unwin. 2010. Estimates of the impact of diabetes on the incidence of pulmonary tuberculosis in different ethnic groups in England. *Thorax* 65:578–581.

Wangler, M. F., Y. Hu, and J. M. Shulman. 2017. Drosophila and genome-wide association studies: A review and resource for the functional dissection of human complex traits. *Disease Models and Mechanisms* 10(2):77–88.

Weimann, A., D. Dai, and T. Oni. 2016. A cross-sectional and spatial analysis of the prevalence of multimorbidity and its association with socioeconomic disadvantage in South Africa: A comparison between 2008 and 2012. *Social Science and Medicine* 163:144–156.

Weiss, R. A. and A. J. McMichael. 2004. Social and environmental risk factors in the emergence of infectious diseases. *Nature Medicine* 10:S70–S76.

Welter, D., J. MacArthur, J. Morales, T. Burdett, P. Hall, h. Junkins, A. Klemm, P. Flicek, T. Manolio, L. Hindorff, and H. Parkinson. 2014. The NHGRI GWAS Catalog: A curated resource of SNP-trait associations. *Nucleic Acids Research* 42(D1):D1001–D1006.

West, C., H. Renz, M. C. Jenmalm, A. L. Kozyrskyj, K. J. Allen, P. Vuillermin, and S. L. Prescott. 2015. The gut microbiota and inflammatory noncommunicable disease: Associations and potentials for gut microbiota therapies. *Journal of Allergy and Clinical Immunology* 135(1):3–13.

WHO (World Health Organization). 2008. *The global burden of disease: 2004 update*. Geneva, Switzerland: World Health Organization.

WHO. 2011. *Collaborative framework for care and control of tuberculosis and diabetes*. Geneva, Switzerland: World Health Organization.

WHO. 2018a. *Global tuberculosis report 2018*. Geneva, Switzerland: World Health Organization.

WHO. 2018b. *Noncommunicable diseases*. Geneva, Switzerland: World Health Organization.

WHO. 2018c. *Noncommunicable disease country profile— Swaziland*. Geneva, Switzerland: World Health Organization.

Willen, S. S., M. Knipper, C. E. Abadia-Barrero, and N. Davidovitch. 2017. Syndemic vulnerability and the right to health. *Lancet* 389(10072):964–977.

World Bank. 1993. *Investing in health*. Washington, DC: World Bank.

Xu, Z. and R. Knight. 2015. Dietary effects on human gut microbiome diversity. *British Journal of Nutrition* 113:S1–S5.

Yassour, M., T. Vatanen, H. Siljander, A.-M. Hämäläinen, T. Härkönen, S. J. Ryhänen, E. A. Franzosa, H. Vlamakis, C. Huttenhower, D. Gevers, E. S. Lander, M. Knip, and R. J. Xavier. 2016. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Science Translational Medicine* 8(343):343–381.

Yatsunenko, T. F., E. Rey, M. J. Manary, I. Trehan, M. G. Dominguez-Bello, M. Contreras, M. Magris, G. Hidalgo, R. N. Baldassano, A. P. Anokhin, A. C. Heath, B. Warner, J. Reeder, J. Kuczynski, J. G. Caporaso, C. A. Lozupone, C. Lauber, J. C. Clemente, D. Knights, R. Knight, and J. I. Gordon. 2012. Human gut microbiome viewed across age and geography. *Nature* 486(7402):222–227.

Young, N., M. Taegtmeyer, G. Aol, G. M. Bigogo, P. A. Phillips-Howard, J. Hill, K. F. Laserson, F. Ter Kuile, and M. Desai. 2018. Integrated point-of-care testing (POCT) of HIV, syphilis, malaria and anaemia in antenatal clinics in western Kenya: A longitudinal implementation study. *PLoS One* 13(7):e0198784.

Zheng, P., Z. Li, and Z. Zhou. 2018. Gut microbiome in type 1 diabetes: A comprehensive review. *Diabetes and Metabolic Research Review* 34(7):e3043.

Zhou, B., Y. Lu, K. Hajifathalian, J. Bentham, M. Di Cesare, G. Danaei, H. Bixby, M. J. Cowan, M. K. Ali, C. Taddei, W. C. Lo, B. Reis-Santos, G. A. Stevens, L. M. Riley, J. J. Miranda, P. Bjerregaard, J. A. Rivera, H. M. Fouad, G. Ma, J. C. Mbanya, S. T. McGarvey, V. Mohan, A. Onat, A. Pilav, A. Ramachandran, H. B. Romdhane, C. J. Paciorek, J. E. Bennett, M. Ezzati, Z. A. Abdeen, K. Abdul Kadir, N. M. Abu-Rmeileh, B. Acosta-Cazares, R. Adams, W. Aekplakorn, C. A. Aguilar-Salinas, C. Agyemang, A. Ahmadvand, A. R. Al-Othman, A. Alkerwi, P. Amouyel, A. Amuzu, L. B. Andersen, S. A. Anderssen, R. M. Anjana, H. Aounallah-Skhiri, T. Aris, N. Arlappa, D. Arveiler, F. K. Assah, M. Avdicová, F. Azizi, N. Balakrishna, P. Bandosz, C. M. Barbagallo, A. Barceló, A. M. Batieha, L. A. Baur, H. B. Romdhane, M. Benet, A. Bernabe-Ortiz, S. Bharadwaj, S. K. Bhargava, Y. Bi, P. Bjerregaard, E. Bjertness, M. B. Bjertness, C. Björkelund, A. Blokstra, S. Bo, B. O. Boehm, C. P. Boissonnet, P. Bovet, I. Brajkovich, J. Breckenkamp, H. Brenner, L. M. Brewster, G. R. Brian, G. Bruno, A. Bugge, A. Cabrera de León, G. Can, A. P. Cândido, V. Capuano, A. C. Carlsson, M. J. Carvalho, F. F. Casanueva, J. P. Casas, C. A. Caserta, K. Castetbon, S. Chamukuttan, N. Chaturvedi, C. J. Chen, F. Chen, S. Chen, C. Y. Cheng, A. Chetrit, S. T. Chiou, Y. Cho, J. Chudek, R. Cifkova, F. Claessens, H. Concin, C. Cooper, R. Cooper, S. Costanzo, D. Cottel, C. Cowell, A. B. Crujeiras, G. D'Arrigo, J. Dallongeville, R. Dankner, L. Dauchet, G. de Gaetano, S. De Henauw, M. Deepa, A. Dehghan, V. Deschamps, K. Dhana, A. F. Di Castelnuovo, S. Djalalinia, K. Doua, W. Drygas, Y. Du, V. Dzerve, E. E. Egbagbe, R. Eggertsen, J. El Ati, R. Elosua, R. T. Erasmus, C. Erem, G. Ergor, L. Eriksen,

J. Escobedo-de la Peña, C. H. Fall, F. Farzadfar, F. J. Felix-Redondo, T. S. Ferguson, D. Fernández-Bergés, M. Ferrari, C. Ferreccio, E. J. Feskens, J. D. Finn, B. Föger, L. H. Foo, A. S. Forslund, H. M. Fouad, D. K. Francis, C. Franco Mdo, O. H. Franco, G. Frontera, T. Furusawa, Z. Gaciong, S. P. Garnett, J. M. Gaspoz, M. Gasull, L. Gates, J. M. Geleijnse, A. Ghasemian, A. Ghimire, S. Giampaoli, F. Gianfagna, J. Giovannelli, A. Giwercman, M. G. Gross, J. P. González Rivas, M. B. Gorbea, F. Gottrand, D. Grafnetter, T. Grodzicki, A. Grøntved, G. Gruden, D. Gu, O. P. Guan, R. Guerrero, I. Guessous, A. L. Guimaraes, L. Gutierrez, I. R. Hambleton, R. Hardy, R. Hari Kumar, J. Hata, J. He, C. Heidemann, S. Herrala, I. T. Hihtaniemi, S. Y. Ho, S. C. Ho, A. Hofman, C. M. Hormiga, B. L. Horta, L. Houti, C. Howitt, T. T. Htay, A. S. Htet, M. M. Htike, Y. Hu, A. S. Hussieni, I. Huybrechts, N. Hwalla, L. Iacoviello, A. G. Iannone, M. M. Ibrahim, N. Ikeda, M. A. Ikram, V. E. Irazola, M. Islam, M. Iwasaki, J. M. Jacobs, T. Jafar, K. M. Jamil, G. Jasienska, C. Q. Jiang, J. B. Jonas, P. Joshi, A. Kafatos, O. Kalter-Leibovici, A. Kasaeian, J. Katz, P. Kaur, M. Kavousi, S. Keinänen-Kiukaanniemi, R. Kelishadi, A. P. Kengne, M. Kersting, Y. S. Khader, D. Khalili, Y. H. Khang, S. Kiechl, J. Kim, P. Kolsteren, P. Korrovits, W. Kratzer, D. Kromhout, U. M. Kujala, K. Kula, C. Kyobutungi, T. Laatikainen, C. Lachat, Y. Laid, T. H. Lam, O. Landrove, V. Lanska, G. Lappas, A. Laxmaiah, C. Leclercq, J. Lee, J. Lee, T. Lehtimäki, R. Lekhraj, L. M. León-Muñoz, Y. Li, W. Y. Lim, M. F. Lima-Costa, H. H. Lin, X. Lin, L. Lissner, R. Lorbeer, J. E. Lozano, D. Luksiene, A. Lundqvist, P. Lytsy, G. Ma, G. L. Machado-Coelho, S. Machi, S. Maggi, D. J. Magliano, M. Makdisse, K. Mallikharjuna Rao, Y. Manios, E. Manzato, P. Margozzini, P. Marques-Vidal, R. Martorell, S. R. Masoodi, E. B. Mathiesen, T. E. Matsha, J. C. Mbanya, S. R. McFarlane, S. T. McGarvey, S. McLachlan, B. A. McNulty, S. Mediene-Benchekor, A. Meirhaeghe, A. M. Menezes, S. Merat, Meshram, II, J. Mi, J. F. Miquel, J. J. Miranda, M. K. Mohamed, K. Mohammad, N. Mohammadifard, V. Mohan, M. F. Mohd Yusoff, N. C. Møller, D. Molnár, C. K. Mondo, A. Morejon, L. A. Moreno, K. Morgan, G. Moschonis, M. Mossakowska, A. Mostafa, J. Mota, J. Motta, T. T. Mu, M. L. Muiesan, M. Müller-Nurasyid, J. Mursu, G. Nagel, J. Námešná, E. E. Nang, V. B. NangThetia, E. M. Navarrete-Muñoz, N. C. Ndiaye, I. Nenko, F. Nervi, N. D. Nguyen, Q. N. Nguyen, R. E. Nieto-Martínez, G. Ning, T. Ninomiya, M. Noale, D. Noto, M. A. Nsour, A. M. Ochoa-Avilés, K. Oh, A. Onat, P. Ordunez, C. Osmond, J. A. Otero, E. Owusu-Dabo, E. Pahomova, L. Palmieri, S. Panda-Jonas, F. Panza, M. Parsaeian, S. V. Peixoto, C. Pelletier, M. Peltonen, A. Peters, N. Peykari, S. T. Pham, A. Pilav, F. Pitakaka, A. Piwonska, J. Piwonski, P. Plans-Rubió, M. Porta, M. L. Portegies, H. Poustchi, R. Pradeepa, J. F. Price, M. Punab, R. F. Qasrawi, M. Qorbani, R. Radisauskas, M. Rahman, O. Raitakari, S. R. Rao, A. Ramachandran, J. Ramke, R. Ramos, S. Rampal, W. Rathmann, J. Redon, P. F. Reganit, F. Rigo, S. M. Robinson, C. Robitaille, F. Rodríguez-Artalejo, C. Rodriguez-Perez Mdel, L. A. Rodríguez-Villamizar, R. Rojas-Martinez, K. Ronkainen, A. Rosengren, A. Rubinstein, O. Rui, B. S. Ruiz-Betancourt, R. V. Russo Horimoto, M. Rutkowski, C. Sabanayagam, H. S. Sachdev, O. Saidi, S. Sakarya, B. Salanave, J. T. Salonen, M. Salvetti, J. Sánchez-Abanto, D. Santos, R. N. dos Santos, R. Santos, J. L. Saramies, L. B. Sardinha, N. Sarrafzadegan, K. U. Saum, M. Scazufca, H. Schargrodsky, C. Scheidt-Nave, A. A. Sein, S. K. Sharma, J. E. Shaw, K. Shibuya, Y. Shin, R. Shiri, R. Siantar, A. M. Sibai, M. Simon, J. Simons, L. A. Simons, M. Sjostrom, J. Slowikowska-Hilczer, P. Slusarczyk, L. Smeeth, M. B. Snijder, H. K. So, E. Sobngwi, S. Söderberg, V. Solfrizzi, E. Sonestedt, A. Soumare, J. A. Staessen, M. G. Stathopoulou, J. Steene-Johannessen, P. Stehle, A. D. Stein, J. Stessman, D. Stöckl, J. Stokwiszewski, K. Stronks, M. W. Strufaldi, C. A. Sun, J. Sundström, Y. T. Sung, P. Suriyawongpaisal, R. G. Sy, E. S. Tai, A. Tamosiunas, L. Tang, M. Tarawneh, C. B. Tarqui-Mamani, A. Taylor,

H. Theobald, L. Thijs, B. H. Thuesen, H. K. Tolonen, J. S. Tolstrup, M. Topbas, M. Torrent, P. Traissac, O. T. Trinh, M. K. Tulloch-Reid, T. P. Tuomainen, M. L. Turley, C. Tzourio, P. Ueda, F. A. Ukoli, H. Ulmer, H. M. Uusitalo, G. Valdivia, D. Valvi, L. van Rossem, I. G. van Valkengoed, D. Vanderschueren, D. Vanuzzo, T. Vega, G. Velasquez-Melendez, G. Veronesi, W. M. Verschuren, R. Verstraeten, L. Viet, J. Vioque, J. K. Virtanen, S. Visvikis-Siest, B. Viswanathan, P. Vollenweider, S. Voutilainen, M. Vrijheid, A. N. Wade, A. Wagner, J. Walton, W. N. Wan Mohamud, F. Wang, M. D. Wang, Q. Wang, Y. X. Wang, S. G. Wannamethee, D. Weerasekera, P. H. Whincup, K. Widhalm, A. Wiecek, A. H. Wijga, R. J. Wilks, J. Willeit, T. Wilsgaard, B. Wojtyniak, T. Y. Wong, J. Woo, M. Woodward, F. C. Wu, S. L. Wu, H. Xu, W. Yan, X. Yang, X. Ye, A. Yoshihara, N. O. Younger-Coleman, S. Zambon, A. H. Zargar, T. Zdrojewski, W. Zhao, Y. Zheng, and J. Zuñiga Cisneros. 2016. Worldwide trends in diabetes since 1980: A pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet* 387(10027):1513–1530.

Zimmermann, M., M. Zimmermann-Kogadeeva, R. Wegmann, and A. L. Goodman. 2019. Separating host and microbiome contributions to drug pharmacokinetics and toxicity. *Science* 363(6427):eaat9931.

Zimmet, P. Z. 2017. Diabetes and its drivers: The largest epidemic in human history? *Clinical Diabetes and Endocrinology* 3(1):1.

Appendix A

Statement of Task

A 1.5-day public workshop will explore the growing understanding of how the interplay between humans and microbes affects host physiology and causes chronic diseases. The workshop will allow participants to gain a deeper understanding of the continuum between infectious and noncommunicable diseases, including how it provides new opportunities for prevention and treatment. Specifically, this workshop will feature invited presentations and discussions including the following:

- Current knowledge on the known and suspected causal associations between micro-organisms and chronic diseases and conditions, as well as associated issues;
- The evolving understanding of how the microbiome affects the normal physiological functioning in humans and how these interactions vary depending on the population, geographic location, and other biological or environmental factors;
- Research needed to further understand the relationship between micro-organisms and chronic diseases and physiological functions;
- Opportunities for developing new approaches to prevent, detect, and mitigate chronic diseases and to reduce their public health impact and burden;
- Cutting-edge methods and tools as well as study designs being used to explore links between chronic diseases and infectious diseases; and

- Mechanisms to leverage cross-sectoral collaborations and break down silos among various stakeholders from research to practice.

Workshop speakers and discussants will contribute perspectives from government, academia, the private sector, and the nonprofit sector.

Appendix B

Workshop Agenda

Breaking Down Silos:
The Convergence of Infectious Diseases and Noncommunicable Diseases:
A Workshop

Agenda
June 11–12, 2019

The Rockefeller Foundation
420 Fifth Avenue
New York, NY

DAY 1—TUESDAY, JUNE 11, 2019

1:00 pm ET Welcome Remarks
Naveen Rao, The Rockefeller Foundation

Workshop Overview and Goals
Peter Daszak, EcoHealth Alliance

Keynote Addresses
The Current State of the Dual Global Collision and Burden of Infectious Diseases and Noncommunicable Disease
Tolullah Oni, University of Cambridge

The Global Syndemic of Infectious Diseases and Noncommunicable Diseases: A New Approach to Tackling the Global Burden
Emily Mendenhall, Georgetown University

1:50 pm Q&A

Session I: Current State of the Science and Emerging Research

Part A: Case Studies
Julie Parsonnet, Stanford University, *Moderator*

2:05 pm Alzheimer's Disease and *P. gingivalis*
Casey Lynch, Cortexyme

Epstein-Barr Virus and Autoimmune Diseases
John B. Harley, Cincinnati Children's Hospital Medical Center

The Role of the Microbiome in Food Allergies
Cathryn R. Nagler, The University of Chicago

2:50 pm Q&A

3:20 pm Break

Part B: Case Studies
Kent Kester, Sanofi Pasteur, *Moderator*

3:35 pm Metabolic Syndrome and the Risk for Enteric Infection
Christoph A. Thaiss, University of Pennsylvania Perelman School of Medicine

Diabetes Mellitus and Tuberculosis
Julia Critchley, St. George's University of London

4:20 pm **Plenary Presentation**
A Microbial Dimension to Human Development and the Potential for New Approaches to Human Well-Being
Rob Knight, University of California, San Diego

4:55 pm Q&A

5:25 pm Observations from Day 1
Peter Daszak, EcoHealth Alliance

5:30 pm Adjourn

5:35 pm Reception

DAY 2—WEDNESDAY, JUNE 12, 2019

8:30 am Welcome and Recap Day 1
Peter Daszak, EcoHealth Alliance

Session II: Confronting "The Blind People and the Elephant" Metaphor to Bridge the Silos

Panel Discussion
Bridget B. Kelly, Burke Kelly Consulting, *Moderator*

8:40 am **Nelson Sewankambu,** African Medical Schools Associations
Rachel Nugent, RTI International
Dennis Carroll, U.S. Agency for International Development
Gene Bukhman, Harvard Medical School

9:20 am Q&A

10:00 am Break

Session III: Integrating and Revamping Health Care Delivery Models and Interventions

Presentation and Panel Discussions
Marcos Espinal, Pan American Health Organization, *Moderator*

10:15 am HIV/NCD Integration Platforms
Miriam Rabkin, Columbia University Mailman School of Public Health

The AMPATH Model
Sylvester Kimaiyo, AMPATH, Kenya

Addressing the Convergence with Integration Science
Gene Bukhman, Harvard Medical School

Mass Administration of Antibiotics as an Intervention to Reduce Child Mortality
Catherine Oldenburg, University of California, San Francisco

11:15 am Q&A

12:00 pm Lunch

Session IV: Moving Forward: Implications for Research and Public Health Practice

Part A: Table Group Discussion

1:00 pm Table Group Discussion
Bridget B. Kelly, Burke Kelly Consulting, *Moderator*

1:50 pm Report Back and Discussion
Mosa Moshabela, University of KwaZulu-Natal, South Africa, *Moderator*

Part B: Visionary Statements on Top Priorities for Next Steps

2:45 pm **Jay K. Varma,** Africa Centres for Disease Control and Prevention

K. Srinath Reddy, Public Health Foundation of India

Patricia J. García, Cayetano Heredia University School of Public Health, Peru

3:40 pm Final Synthesis and Discussion with Audience

4:20 pm Closing Remarks
Peter Daszak, EcoHealth Alliance

4:30 pm Adjourn

Appendix C

Speaker Biographies

Gene Bukhman, M.D., Ph.D., is a cardiologist and medical anthropologist who heads the Program in Global Noncommunicable Disease and Social Change at Harvard Medical School. He is an assistant professor of medicine and an assistant professor of global health and social medicine. He is also the senior health and policy advisor on noncommunicable diseases (NCDs) at Partners In Health (PIH) where he directs the NCD Synergies project. He is an attending cardiologist in the Cardiovascular Division and the Division of Global Health Equity at Brigham and Women's Hospital. He is director of the BWH Fellowship in Cardiovascular Disease and Global Health Equity. He is also the co-chair of the Lancet Commission on Reframing NCDs and Injuries for the Poorest Billion (NCDI Poverty Commission). Dr. Bukhman completed his medical training and doctorate in medical anthropology at the University of Arizona in 2001, during which time he studied the politics of tuberculosis control in the former Soviet Union. He completed his internal medicine residency at Brigham and Women's Hospital in 2003, and his cardiology fellowship at the Beth Israel Deaconess Medical Center in 2007. For the past 15 years, his career has focused on the NCD and injury (NCDI) burden among those living in extreme poverty, with a particular focus on low-income countries. His research explores both the political and historical context of NCDI interventions, as well as the development and implementation of integrated strategies to deliver these interventions. He was the senior technical advisor to the Ministry of Health of Rwanda between 2010 and 2015, and has worked with Health Ministry NCD divisions in many low- and lower-middle income countries. He is frequently invited to speak regarding NCDs, poverty, and development. He is lead author and editor of

the PIH *Guide to Chronic Care Integration for Endemic NCDs* (2011). In 2011, the University of Arizona Honors College named him Alumnus of the Year. In 2015, Dr. Bukhman was chosen to be a member of the Financing Working Group of the World Health Organization's Global Coordination Mechanism on NCDs.

Dennis Carroll, Ph.D., currently serves as director of the U.S. Agency for International Development's (USAID's) Global Health Security and Development Unit. In this position, Dr. Carroll is responsible for providing strategic and operational leadership for the agency's programs addressing new and emerging disease threats. Dr. Carroll also serves as USAID's Special Representative for Global Health Security. Dr. Carroll was initially detailed to USAID from the U.S. Centers for Disease Control and Prevention (CDC) as a senior public health advisor in 1991. In 1995, he was named the agency's senior infectious diseases advisor, responsible for overseeing the agency's programs in malaria, tuberculosis, antimicrobial resistance, and disease surveillance, as well as neglected and emerging infectious diseases. In this capacity Dr. Carroll was directly involved in the development and introduction of a range of new technologies for disease prevention and control, including community-based delivery of treatment of onchocerciasis, rapid diagnostics for malaria, new treatment therapies for drug-resistant malaria, intermittent therapy for pregnant women, and "long-lasting" insecticide-treated bed nets for prevention of malaria. He was responsible for the initial design and development of the President's Malaria Initiative. Dr. Carroll officially left CDC and joined USAID in 2005 when he assumed responsibility for leading the USAID response to the spread of avian influenza. Dr. Carroll has a doctorate in biomedical research with a special focus in tropical infectious diseases from the University of Massachusetts at Amherst. He was a research scientist at Cold Spring Harbor Laboratory where he studied the molecular mechanics of viral infection. Dr. Carroll has received awards from both CDC and USAID, including the 2006 USAID Science and Technology Award for his work on malaria and avian influenza, and the 2008 Administrator's Management Innovation Award for his management of the agency's Avian and Pandemic Influenza program.

Julia Critchley, M.P.H., Ph.D., is a professor of epidemiology at St. George's, University of London, with 20 years of experience working in cardiovascular disease and diabetes epidemiology and public health. She holds a Ph.D. in epidemiology (Oxford University) and an M.P.H. (University of London). For the past 10 years, her research program has focused on the association between common chronic and infectious diseases such as diabetes (DM) and tuberculosis (TB). As part of the recent European Commission (EC) FP7–funded TANDEM consortium, she helped develop and evaluate methods

to screen for DM in TB patients, including both standard DM markers and risk scores; this highlighted the heterogeneity between different populations and some challenges with screening and follow-up for DM during TB care. Dr. Critchley also co-led a project funded by the Qatari National Research Foundation using mathematical modeling to estimate the population impact of increasing DM prevalence on TB control and the potential effects of structural and clinical interventions on future joint disease burdens. The project found that more than 30 percent of TB incidence and 40 percent of TB mortality could be attributable to DM in countries like India in the future; however, improvements in DM control or preventive interventions targeted at people living with DM (such as TB vaccines, or treatment for latent TB) could ameliorate a substantial amount of this population burden. In the United Kingdom, she has investigated the effect of DM on infection risks and outcomes using large datasets from primary care, finding that one in six infection-related deaths or hospitalizations can be attributed to poor DM control, even in this high-income population; she continues to investigate the effects of instability in DM control on infection risks. Dr. Critchley recently co-authored joint International Union Against Tuberculosis and Lung Disease (IUATLD)/World Diabetes Foundation guidelines for TB-DM, aimed at frontline health care workers, and she continues to support IUATLD efforts to ameliorate this double burden.

Peter Daszak, Ph.D., is president of EcoHealth Alliance (EHA), a U.S.-based organization that conducts research and outreach programs on global health, conservation, and international development. Dr. Daszak's research has been instrumental in identifying and predicting the effect of emerging diseases across the globe. His achievements include identifying the bat origin of severe acute respiratory syndrome; identifying the underlying drivers of Nipah and Hendra virus emergence; producing the first ever global emerging disease "hotspots" map; developing a strategy to find out how many unknown viruses exist that could threaten to become pandemic; identifying the first case of a species extinction attributable to disease; and discovering the disease chytridiomycosis as the cause of global amphibian declines. Dr. Daszak is a member and chair-elect of the National Academies of Sciences, Engineering, and Medicine's Forum on Microbial Threats. He is a member of the National Research Council (NRC) Advisory Committee to the U.S. Global Change Research Program, the Supervisory Board of the One Health Platform, the One Health Commission Council of Advisors, the Center of Excellence for Emerging and Zoonotic Animal Diseases External Advisory Board, the Cosmos Club, and the Advisory Council of the Bridge Collaborative; has served on the Institute of Medicine Committee on Global Surveillance for Emerging Zoonoses, the NRC Committee on the Future of Veterinary Research, the International Standing Advisory Board of the

Australian Biosecurity Cooperative Research Centre; and has advised the director for Medical Preparedness Policy on the White House National Security Staff on global health issues. Dr. Daszak is a regular advisor to the World Health Organization (WHO), the World Organisation for Animal Health, and the Food and Agriculture Organization of the United Nations and is actively involved in the WHO Expert Group on Public Health Emergency Disease Prioritization. Dr. Daszak won the 2000 Commonwealth Scientific and Industrial Research Organisation medal for collaborative research on the discovery of amphibian chytridiomycosis. He is the EHA institutional lead for the U.S. Agency for International Development–Emerging Pandemic Threats–PREDICT; on the editorial board of *Conservation Biology*, *One Health*, and *Transactions of the Royal Society of Tropical Medicine & Hygiene*; and editor-in-chief of the journal *Ecohealth*. He has authored more than 300 scientific papers, and his work has been the focus of extensive media coverage, ranging from popular press articles to television appearances.

Marcos Espinal, M.D., Dr.P.H., M.P.H., is director of the Department of Communicable Diseases and Health Analysis at the Pan American Health Organization (PAHO), Regional Office of the World Health Organization (WHO) for the Americas. Dr. Espinal, a national of the Dominican Republic, holds a medical degree from the Universidad Autónoma de Santo Domingo, Dominican Republic (1985). He has an M.P.H. (1990) and a Dr.P.H. (1995) from the University of California, Berkeley, School of Public Health. His work experience includes positions in the Ministry of Health of the Dominican Republic and the National Center for Research on Maternal and Child Health; the New York City Public Health Department; and WHO, where he worked for 13 years. Before joining PAHO, Dr. Espinal served as executive secretary of the WHO Stop TB Partnership, a global movement aiming at the elimination of TB as a public health problem. Dr. Espinal has published more than 100 peer-reviewed publications in the field of communicable diseases. He is a recipient of the Scientific Prize of the International Union Against Tuberculosis and Lung Disease; the Walter and Elise A. Hass International Award by the University of California, Berkeley, for a distinguished record of service in international health; and the Princess Chichibu Memorial Tuberculosis Global Award by the Japan Anti-Tuberculosis Association.

Patricia J. García, M.D., M.P.H., Ph.D., is a professor at the School of Public Health at Cayetano Heredia University (UPCH) in Lima, Peru. She is the former minister of health of Peru, former dean of the School of Public Health at UPCH, and former chief of the Peruvian National Institute of Health. She is recognized as a leader in global health, has been a member of the Pan American Health Organization Foundation Technical Advisory

Group, and was a board member of the Consortium of Universities in Global Health and President of the Latin American Association Against STDs. She is affiliate professor of the Department of Global Health at the University of Washington and the School of Public Health at Tulane University. She is actively involved in research and training in global health, reproductive health, sexually transmitted infection/HIV, human papillomavirus, and medical informatics. She has been recently appointed as a member of the U.S. National Academy of Medicine, becoming the first Peruvian professional with such a distinction.

John B. Harley, M.D., Ph.D., has followed a career focusing on the genetic and environmental etiologies of autoimmune diseases, especially systemic lupus erythematosus (SLE). His training experiences include an M.D. and a Ph.D. in biochemistry from the University of Pennsylvania in Philadelphia; a postdoctoral fellowship at the Imperial Cancer Research Fund in tumor virology; a medical residency at Yale University; and clinical investigator fellowships at the National Institutes of Health in allergy and immunology and rheumatology, hosted by the Laboratory of Clinical Investigation at the National Institute of Allergy and Infectious Diseases. These were followed by faculty appointments at the University of Oklahoma and the Oklahoma Medical Research Foundation and then at Cincinnati Children's Hospital Medical Center and the University of Cincinnati. His early career work on the immunochemistry of SLE autoimmunity identified the earliest autoantigenic structures and nominated the heteroimmune response to Epstein-Barr virus nuclear antigen 1 as the origin for selected autoimmune responses in SLE. This was followed by more than two decades of work on the genetic origins of SLE that has contributed important contributions to the discovery of the more than 100 loci convincingly associated with SLE now known. He became the founding director of the Center for Autoimmune Genomics and Etiology at the Cincinnati Children's Hospital Medical Center in 2010, which has the overall goal of establishing the etiology of autoimmune disease.

Bridget B. Kelly, M.D., Ph.D., is the principal consultant of Burke Kelly Consulting, specializing in research and evaluation, policy analysis, strategy development, stakeholder engagement, and facilitation. She worked previously at the National Academies of Sciences, Engineering, and Medicine for 8 years leading a portfolio of projects that included early childhood, mental health, chronic diseases, HIV, and evaluation science. Among other projects, she was the study director for the 2010 report *Promoting Cardiovascular Health in the Developing World* and the study co-director for the 2013 *Evaluation of PEPFAR*. In her last position at the National Academies she served as the interim director of the Board on Children, Youth, and Fami-

lies. More recently, she co-founded the nonprofit Bridging Health & Community, with the mission of helping the health sector work more effectively with communities. Originally trained in medicine and developmental neurobiology, she received an M.D. and a Ph.D. from Duke University and a B.A. from Williams College. She is also an experienced dancer, choreographer, and arts administrator.

Kent E. Kester, M.D., is currently vice president and head of Translational Science and Biomarkers at Sanofi Pasteur. During a 24-year career in the U.S. Army, he worked extensively in clinical vaccine development and led multiple research platforms at the Walter Reed Army Institute of Research, the U.S. Department of Defense's largest and most diverse biomedical research laboratory—an institution he later led as its commander/director. His final military assignment was as the associate dean for clinical research in the School of Medicine at the Uniformed Services University of the Health Sciences (USUHS). Dr. Kester holds an undergraduate degree from Bucknell University and an M.D. from Jefferson Medical College. He completed his internship and residency in internal medicine at the University of Maryland and a fellowship in infectious diseases at the Walter Reed Army Medical Center. A malaria vaccine researcher with more than 70 scientific manuscripts and book chapters to his name, Dr. Kester has played a major role in the development of the malaria vaccine candidate known as RTS,S. Currently a member of the U.S. Government Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria, he previously chaired the Steering Committee of the National Institute of Allergy and Infectious Diseases (NIAID)-USUHS Infectious Disease Clinical Research Program, and has served as a member of the U.S. Food and Drug Administration's Vaccines and Related Biologics Products Advisory Committee, the NIAID Advisory Council, and the U.S. Centers for Disease Control's Office of Infectious Diseases Board of Scientific Counselors. Board certified in both internal medicine and infectious diseases, he holds faculty appointments at USUHS and the University of Maryland, and he is a fellow of the American College of Physicians, the Infectious Diseases Society of America, and the American Society of Tropical Medicine and Hygiene.

Sylvester Kimaiyo, M.D., has been involved in all aspects of the Academic Model Providing Access to Healthcare (AMPATH) since its inception in 2001. AMPATH represents a collaborative partnership among Moi Teaching and Referral Hospital, Moi University College of Health Sciences, and a North American consortium led by Indiana University. AMPATH initially was HIV focused but has expanded into chronic diseases. It is one of the largest and comprehensive HIV care and research institutions.

Rob Knight, Ph.D., is the founding director of the Center for Microbiome Innovation and professor of pediatrics, bioengineering, and computer science and engineering at the University of California, San Diego. He is the author of *Follow Your Gut: The Enormous Impact of Tiny Microbes* (Simon & Schuster, 2015), and co-author of *Dirt Is Good: The Advantage of Germs for Your Child's Developing Immune System* (St. Martin's Press, 2017). He cofounded the Earth Microbiome Project, and the American Gut Project, which is among the largest crowdfunded science projects of any kind to date. He has spoken at TED and Davos, written 3 books and more than 600 scientific articles, and in 2017 he won the Massry Prize, often considered a predictor of the Nobel. His work has linked microbes to a range of health conditions, including obesity and inflammatory bowel disease, has enhanced our understanding of microbes in environments ranging from the oceans to the tundra, and has made high-throughput sequencing techniques accessible to thousands of researchers around the world.

Casey Lynch, M.S., is chief executive officer (CEO) and co-founder of Cortexyme, Inc., a clinical-stage company developing novel potential therapeutics for Alzheimer's and other degenerative diseases. Previously, Ms. Lynch was the co-founder and managing partner of NeuroInsights, an investment advisory firm focused on neuropharmaceuticals and neurodevices. She was also the co-founder, president, and CEO of Aspira Biosystems, Inc., a proteomics company. Prior to 4 years building Aspira, Ms. Lynch oversaw toxicology screening and evaluated new product opportunities at Centaur Pharmaceuticals, where she managed animal screening protocols for a novel nitrone small molecule library. She has a scientific background in disease research, drug discovery, and cell biology. Ms. Lynch conducted preclinical testing for Alzheimer's disease treatment at the Wadsworth Medical Center and researched the neurological basis of schizophrenia and epilepsy at the University of California, Los Angeles (UCLA). Her graduate work on neurotrophic factor cell biology and neurodegenerative diseases was carried out in Mobley lab at the University of California, San Diego, and Stanford University. Ms. Lynch holds a B.S. in neuroscience from UCLA and an M.S. in neuroscience from the University of California, San Francisco. She has also completed the Management Development for Entrepreneurs.

Emily Mendenhall, Ph.D., M.P.H., is a medical anthropologist and a Provost's Distinguished Associate Professor in the Science, Technology, and International Affairs Program in the Edmund A. Walsh School of Foreign Service at Georgetown University. Dr. Mendenhall's scholarship focuses on how social trauma, poverty, and social exclusion become embodied in chronic mental and physical illness as well as the theory and concept of syndemics. Her most recent project is a book forthcoming with Cornell

University Press (2019), *Rethinking Diabetes: Entanglements of Trauma, Poverty, and HIV*. Dr. Mendenhall is also the author of *Syndemic Suffering: Social Distress, Depression, and Diabetes among Mexican Immigrant Women* (Routledge, 2012), and in 2017, led a series of articles on syndemics in the *Lancet* journal. For several years, Dr. Mendenhall has been engaged with the movement for global mental health. She co-edited a book with Dr. Brandon Kohrt titled *Global Mental Health: Anthropological Perspectives* (Routledge, 2015), along with a companion article published in *Lancet Psychiatry* (2016). In 2016, she co-organized an international conference titled Global Mental Health: Transdisciplinary Perspectives at Georgetown University and collaborated with and contributed to small projects associated with the Programme for Improving Mental Health Care (PRIME) and with the Africa Mental Health Foundation. She holds an Honorary Appointment in the Faculty of Health Sciences at the University of the Witwatersrand, where she mentors Ph.D. students and conducts research projects, primarily in the Developmental Pathways for Health Research Unit located at Chris Hani Baragwanath Hospital. In 2017, she was awarded the George Foster Award for Practicing Medical Anthropology by the Society for Medical Anthropology. The National Science Foundation, the National Institutes of Health Fogarty International Center, the South African Medical Research Council, and her research institutions have all supported Dr. Mendenhall's work. Most recently, she has benefited from many small grants from Georgetown University from the School of Foreign Service Dean's Office, Provost Office, Global Futures Initiative, Global Environmental Initiative, and the Global Health Initiative.

Mosa Moshabela, Ph.D., M.Sc., M.B.Ch.B., M.Fam.Med., Dip.HIV (SA), is currently the associate professor and dean in the School of Nursing and Public Health, University of KwaZulu-Natal, South Africa. A qualified physician in family medicine and primary health care, he works as a chief medical specialist in rural health medicine, and a public health scientist in health services, systems, and policy in KwaZulu-Natal, South Africa, with the aim of improving access, quality, and equity in health care. His current research portfolio on implementation science and people-centered approaches seeks to design, implement, and evaluate complex interventions in public health care services and programs in ways appropriate for resource-poor settings in sub-Saharan Africa. He is adjunct faculty and a Wellcome Trust Research Fellow at the Africa Health Research Institute, South Africa. He collaborates with the London School of Hygiene & Tropical Medicine, and conducts research in several countries in sub-Saharan Africa. His current research is funded by the National Research Foundation (South Africa), the Medical Research Council (United Kingdom), the Wellcome Trust (United Kingdom), and the National Institutes of Health (United States). He is a member (2018–2020)

of the Lancet Commission on Synergies between Health Promotion, Universal Health Coverage, and Global Health Security; a U.S. National Academies of Sciences, Engineering, and Medicine committee member (2018–2020) on Human Resources for Health in Rwanda; and the current national chairperson (2016–2019) of the Rural Doctors Association of South Africa. He was previously the regional health systems advisor for the Millennium Villages in West and Central Africa, based at the MDG Centre in Mali/Senegal, working with the Earth Institute at Columbia University. Prior to the Earth Institute, he was a senior lecturer in the School of Public Health at the University of Witwatersrand, Johannesburg, where he was also director of the Rural AIDS and Development Action Research Programme.

Cathryn R. Nagler, Ph.D., is the Bunning Food Allergy Professor and professor of pathology, medicine, and pediatrics at The University of Chicago. She graduated with honors from Barnard College, Columbia University. Dr. Nagler obtained her Ph.D. from the Sackler Institute of Biomedical Science at the New York University School of Medicine and did a postdoctoral fellowship at the Massachusetts Institute of Technology. She was associate professor of pediatrics (immunology) at Harvard Medical School prior to joining The University of Chicago in 2009. Dr. Nagler has participated in numerous review panels for the Crohn's and Colitis Foundation of America, the National Institute of Diabetes and Digestive and Kidney Diseases, and the National Institute of Allergy and Infectious Diseases, including the Food Allergy Expert Panel. She is in her second term on the research advisory board for Food Allergy Research and Education. She has served the American Association of Immunologists (AAI) as section editor for the *Journal of Immunology,* instructor for the Introduction to Immunology and Advanced Immunology courses, and as member of the Program, Clinical Immunology, Publications and Awards Committees. She was an inaugural senior editor for AAI's new journal *ImmunoHorizons*. She is currently deputy editor for the *Journal of Immunology*. She has also served as an elected Councilor of the Society for Mucosal Immunology and is an associate editor of the journal *Mucosal Immunology*. She recently began teaching in the Federation of Clinical Immunology Societies (FOCIS) Advanced Course in Basic and Clinical Immunology and joined the FOCIS Education Committee. Dr. Nagler has a long-standing interest in the mechanisms governing tolerance to dietary antigens and the potential immunomodulatory features of the oral route of antigen administration. Her most recent work examines how commensal bacteria regulate susceptibility to allergic responses to food. She has applied insights gained from studying preclinical gnotobiotic murine models of cow's milk allergy to launch a new company, ClostraBio, which is developing microbiome-modulating therapeutics for the prevention and treatment of food allergy.

Rachel Nugent, Ph.D., is vice president for Global Noncommunicable Diseases at RTI International. She leads a global initiative to prevent and reduce the health and economic burdens of chronic noncommunicable diseases in low- and middle-income countries. Prior to this position, Dr. Nugent was associate professor in the Department of Global Health at the University of Washington and director of the Disease Control Priorities Network. She received her M.Phil. and Ph.D. degrees in economics from The George Washington University in Washington, DC. She is a member of multiple advisory panels, including the World Health Organization Expert Panel on Management of Cardiovascular Disease, and currently serves on the Lancet Commission on NCDIs (Noncommunicable Diseases and Injuries) of the Poorest Billion. She recently was on the National Academies of Sciences, Engineering, and Medicine's Workshop Planning Committee on Global Obesity.

Catherine Oldenburg, M.P.H., Sc.D., is an infectious disease epidemiologist at the University of California, San Francisco. Her work focuses on antibiotic distribution strategies to prevent infectious morbidity and mortality and the epidemiology of antimicrobial resistance among children in sub-Saharan Africa.

Tolullah Oni, M.B.B.S., M.R.C.P., M.P.H., M.D., F.C.P.H.M., is a public health physician scientist and urban epidemiologist, and a clinical senior research fellow with the University of Cambridge's Medical Research Council Epidemiology Unit's Global Public Health Research program. She completed her medical training at University College London, postgraduate medical training in the United Kingdom and Australia, a Master's in Public Health (epidemiology) at the University of Cape Town, and her research doctorate in clinical epidemiology at Imperial College London. She spent 11 years conducting research in South Africa, where she also completed her public health medical specialty training. There, she established a Research Initiative for Cities Health and Equity, conducting transdisciplinary urban health research focused on generating evidence to support development and implementation of healthy public policies in rapidly growing cities with a focus on Africa. Research activities include Systems for Health projects: investigating how urban systems (e.g., housing, food) can be harnessed for health; and health systems projects: integrated health systems responses to changing patterns of disease and multimorbidity in the context of urbanization. She continues this focus within the Global Diet and Activity Research Group and Network, focusing on meso- and macrolevel determinants of diet and physical activity. She has published more than 40 manuscripts in high-impact journals, and has given presentations at international academic (urban health, HIV, tuberculosis) and nonacademic meetings, including the

United Nations High-Level Political Forum for Sustainable Development, New York; and the World Economic Forum Annual Meeting, Davos, 2018. She serves on several advisory boards, including Future Earth and the African Academy of Science Open Research Platform, and is an editorial board member of *Lancet Planetary Health*, *Cities and Health*, and the *Journal of Urban Health*. Profiled in the *Lancet* journal in 2016, she is a 2015 Next Einstein Forum fellow, and fellow of the Stellenbosch Institute for Advanced Study.

Julie Parsonnet, M.D., is the George Deforest Barnett Professor in Medicine and professor of health and research and policy (epidemiology) at Stanford University. She specializes in adult infectious diseases. She has a particular interest in gastrointestinal infections, including *H. pylori* infection and diarrheal diseases, tuberculosis, and illnesses with prolonged fever. Dr. Parsonnet also has an active research enterprise in which she studies the way infections contribute to the development of chronic diseases, including cancer, allergy, and obesity. She has had continuous funding from the National Institutes of Health for more than 25 years and has served as a member of numerous advisory boards, professional societies, and scientific review committees.

Miriam Rabkin, M.D., M.P.H., is an associate professor of medicine and epidemiology at Columbia University's Mailman School of Public Health. She has worked in global health for 20 years, focusing on strengthening health systems to improve the delivery of prevention, care, and treatment services for underserved populations. As the director for Health Systems Strategies at ICAP Columbia, she works to design, implement, and evaluate HIV and related health programs in low-resource settings, largely in sub-Saharan Africa. As a consultant to The Rockefeller Foundation, she worked with the Transforming Health Systems initiative on issues related to health systems strengthening and universal health coverage. From 2011 to 2014, she led The President's Fund for AIDS Relief's flagship course on health systems strengthening, in partnership with the U.S. Centers for Disease Control and Prevention and the U.S. Agency for International Development. Her current research focuses on implementation science and on ways in which to leverage the successes and lessons of HIV scale-up to strengthen broader health systems, and to enhance the quality of programs for HIV, maternal/child health, noncommunicable diseases, and infection prevention and control. She also leads several training and education projects and oversees ICAP's Quality Improvement portfolio. Dr. Rabkin has a B.A. from Harvard College, an M.D. from the Columbia University College of Physicians & Surgeons, and an M.P.H. in epidemiology from the Columbia University Mailman School of Public Health.

Naveen Rao, M.D., is the managing director for health and senior advisor to the president of The Rockefeller Foundation, and is leading a team focused on putting new digital tools in the hands of community health providers to reduce child and maternal deaths and better protect against the rapidly growing burden of noncommunicable diseases and pandemic threats. As senior advisor to the Foundation's president, Dr. Rao provides strategic counseling and executive engagement to help advance the Foundation's mission. For decades, Dr. Rao has been a leader in equipping health care providers with the skills, tools, and technologies they need to succeed. He has held numerous leadership positions at Merck & Co., Inc., and was previously head of Medical Affairs for Merck's Asia-Pacific region and managing director of Merck's subsidiary in India. Most recently, he led Merck for Mothers, where his work reached and empowered more than 6 million women, improving outcomes for safe pregnancies and healthy deliveries around the world. Board certified in internal medicine, Dr. Rao was associate director of the Department of Medicine at Lower Manhattan Hospital (formerly Beekman Downtown Hospital) in New York City and practiced medicine in New York for 10 years prior to joining Merck. He is a fellow of the American College of Physicians, a member of the Board of Overseers of Columbia University's Mailman School of Public Health, a member of the Board of Directors of GBC Health, and a member of the World Economic Forum Global Future Council on Health and Healthcare. He is also the private-sector representative on the Investors Group of the Global Financing Facility that supports country-led efforts to improve the health of women, children, and adolescents globally.

K. Srinath Reddy, M.D., D.M., M.Sc., is president of the Public Health Foundation of India and formerly headed the Department of Cardiology at All India Institute of Medical Sciences. Dr. Reddy is the first Indian to be elected as a foreign associate member of the National Academy of Medicine. He served as the first Bernard Lown Visiting Professor of Cardiovascular Health at the Harvard School of Public Health (2009–2013). He is presently an adjunct professor at Harvard and Emory, and Honorary Professor of Medicine at the University of Sydney. He has served on many World Health Organization (WHO) expert panels and has been the president of the World Heart Federation (2013–2014). He chaired the High-Level Expert Group on Universal Health Coverage for the Planning Commission of India. Dr. Reddy is a member of the Leadership Council of the Sustainable Development Solutions Network, established to assist the United Nations in developing the post-2015 goals, and chairs the Thematic Group on Health in the Sustainable Development Solutions Network. He is a member of the Global Panel on Agriculture and Food Systems for Nutrition. He has published more than 500 scientific papers. Dr. Reddy's several honors include

the WHO Director General's Award, the Luther Terry Medal of American Cancer Society for Outstanding contributions to global tobacco control, and the Queen Elizabeth Medal for health promotion. He was conferred Padma Bhushan by the President of India in 2005. Dr. Reddy has received honorary doctorates from the Universities of London, Glasgow, Aberdeen, Lausanne, N.T. Rama Rao Health Sciences, and the Institute of Liver and Biliary Sciences.

Nelson Sewankambo, M.B.Ch.B., M.Sc., M.Med., F.R.C.P., is the president of the African Medical Schools Association. He is also a professor of medicine, trained in general medicine and internal medicine at Makerere University, Uganda, and later in clinical epidemiology at McMaster University, Canada. From 1997, for 11 years, he served as the Medical School dean at Makerere University, and since then has been principal (head) of College of Health Sciences. He is a board member for the Foundation for Advancement of International Medical Education and Research, a fellow of the World Academy of Sciences, and an external affiliate member of the U.S. National Academy of Medicine. He serves on the National Academies of Sciences, Engineering, and Medicine's Global Forum on Innovations in Health Professional Education. He is the principal investigator on a multicountry research capacity-building consortium involving seven African institutions and two universities in the United Kingdom (Cambridge University and London School of Hygiene & Tropical Medicine). He is the chair of an Africa-wide initiative for Strengthening Research Capacity in Africa, the director of the Medical Education for Equitable Services for All Ugandans–Medical Education Partnership Initiative Consortium, and chair of the African Medical Schools Association.

Christoph A. Thaiss, M.Sc., Ph.D., is assistant professor at the Microbiology Department of the Perelman School of Medicine at the University of Pennsylvania. He performed his undergraduate studies in molecular biomedicine at the University of Bonn, Germany, and his M.Sc. studies in microbiology and immunology at Yale University and ETH Zurich, Switzerland. After a short-term scholarship at the Broad Institute of the Massachusetts Institute of Technology and Harvard University, he performed his graduate studies at the Weizmann Institute of Science in Israel, with a visiting fellowship at Stanford University. After completion of his graduate work, he established his research group at the University of Pennsylvania. His lab studies the role of host–environment interactions in metabolic and inflammatory diseases, with a particular focus on the role of the intestinal microbiota in the regulation of host physiology.

Jay K. Varma, M.D., is the senior advisor to Africa Centres for Disease Control and Prevention. He develops strategy and supports implementation of Africa Centres for Disease Control and Prevention's programs in surveillance, emergency preparedness and response, information systems, laboratory systems, and workforce development. After graduating magna cum laude with highest honors from Harvard, Dr. Varma completed medical school, internal medicine residency, and chief residency at the University of California, San Diego, School of Medicine. From 2001 to 2017, he worked on infectious diseases prevention and control for the U.S. Centers for Disease Control and Prevention with postings in Atlanta, Bangkok, Beijing, and New York City. Dr. Varma has authored 126 scientific manuscripts, 6 essays, and 1 book. He has been recognized as the U.S. Public Health Service Physician Researcher of the Year (2010) and Physician Leader of the Year (2017), and has received the two highest awards in the U.S. Public Health Service: the Distinguished Service Medal (2011) and the Meritorious Service Medal (2018).