Institute on Science for Global Policy (ISGP)

Emerging and Persistent Infectious Diseases: *Focus on Antimicrobial Resistance*

Conference convened by the ISGP March 19–22, 2013
at the Baylor College of Medicine, Houston, Texas

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Conference convened by the ISGP in partnership with
the Baylor College of Medicine at the Baylor College of Medicine
Houston, Texas, United States
March 19–22, 2013

An ongoing series of dialogues and critical debates
examining the role of science and technology
in advancing effective domestic and international policy decisions

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Introduction

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Preface

The contents of this book were taken from material presented at an international conference convened by the Institute on Science for Global Policy (ISGP) on March 19–22, 2013, in cooperation with the Baylor College of Medicine in Houston, Texas. This ISGP conference was part of the ISGP program on Emerging and Persistent Infectious Diseases and focused on Antimicrobial Resistance (AMR).

The process underlying all ISGP conferences begins with the recognition that a scientific topic such as AMR has emerged on the international stage with advances that promise immense opportunities to improve the human condition while simultaneously challenging many cultural, ethical, and economic issues throughout societies worldwide. Decisions within societies concerning how to appropriately incorporate such transformational science into public and private sector policies rely on candid debates that highlight the credible options developed by scientific communities throughout the world. Since AMR can potentially have significant impact worldwide, it deserves attention from both domestic and international policy makers from a wide range of disciplines. ISGP conferences offer those rare environments where such critical debates can occur among credible scientists, influential policy makers, and societal stakeholders.

Based on extensive interviews conducted by the ISGP staff with an international group of subject-matter experts, the ISGP invited seven highly distinguished individuals with expertise in AMR to prepare the three-page policy position papers to be debated at the Houston conference. These seven policy position papers, together with the not-for-attribution summaries of the debates of each paper, are presented in this book. The areas of consensus and actionable next steps that were developed by all participants in the caucuses that followed the debates are also presented. The debate summaries and caucus results were written by the ISGP staff and are based on contributions from the conference participants.

Current realities

While the material presented here is comprehensive and stands by itself, its policy significance is best appreciated if viewed within the context of how domestic and international science policies have been, and often currently are being, formulated and implemented.

As the second decade of the 21st century opens, most societies are facing difficult decisions concerning how to appropriately use, or reject, the dramatic new opportunities offered by modern scientific advances and the technologies that emanate from them. Advanced scientific research programs, as well as commercially viable technologies, are now developed globally. As a consequence, many societal issues related to science and technology (S&T) necessarily involve both domestic and international policy decisions, both in the public and private sectors. The daunting challenges to simultaneously recognize immediate technological opportunities, while identifying those emerging and "at-the-horizon" S&T achievements that foreshadow transformational advantages and risks within specific societies, are now fundamental governmental responsibilities. These responsibilities are especially complex since policy makers must consider the demands of different segments of society, which often have conflicting goals. For example, decisions must balance critical commercial interests that promote economic prosperity with the cultural sensitivities that often determine if, and how, S&T can be successfully integrated into any society.

Many of our most significant geopolitical policy and security issues are directly connected with the remarkably rapid and profound S&T accomplishments of our time. Consequently, it is increasingly important that the S&T and policy communities (public and private) communicate effectively. With a seemingly unlimited number of urgent S&T challenges, both affluent and less-affluent societies need their most accomplished members to focus on effective, real-world solutions relevant to their specific circumstances. Some of the most prominent challenges involve (i) infectious diseases and pandemics, (ii) environmentally compatible energy sources, (iii) the consequences of climate change, (iv) food safety, security, and defense, (v) the cultural impact of stem cell applications, (vi) nanotechnology and human health, (vii) cyber security for advanced telecommunication, (viii) the security implications of quantum computing, and (ix) the cultural radicalization of societies.

Recent history suggests that most societies would benefit from improving the effectiveness of how scientifically credible information is used to formulate and implement governmental policies, both domestic and international. Specifically, there is a critical need to have the relevant S&T information concisely

presented to policy communities in an environment that promotes candid questions and debates led by those nonexperts directly engaged in decisions. Such discussions, sequestered from publicity, can help to clarify the advantages and potential risks of realistic S&T options directly relevant to the challenges being faced. Eventually, this same degree of understanding, confidence, and acknowledgment of risk must be communicated to the public to obtain the broad societal support needed to effectively implement any decision.

The ISGP mission

The ISGP has pioneered the development of a new type of international forum based on a series of invitation-only conferences. These ISGP conferences are designed to provide articulate, distinguished scientists and technologists opportunities to concisely present their views of the credible S&T options available for addressing major geopolitical and security issues. Over a two-year-plus period, these ISGP conferences are convened on different aspects (e.g., antimicrobial resistance) of a broad, overarching topic (e.g., Emerging and Persistent Infectious Diseases). The format used emphasizes written and oral, policy-oriented S&T presentations and extensive debates led by an international cross section of the policy and scientific community. ISGP conferences reflect global perspectives and seek to provide governmental and community leaders with the clear, accurate understanding of the real-world challenges and potential solutions critical to determining sound public policies.

ISGP programs rely on the validity of two overarching principles:

1. Scientifically credible understanding must be closely linked to the realistic policy decisions made by governmental, private sector, and societal leaders in addressing both the urgent and long-term challenges facing 21st century societies. Effective decisions rely on strong domestic and global public endorsements that motivate active support throughout societies.
2. Communication between scientific and policy communities requires significant improvement, especially concerning decisions on whether to use or reject the often transformational S&T opportunities continually emerging from the global research communities. Effective decisions are facilitated in venues where the advantages and risks of credible S&T options are candidly presented and critically debated among internationally distinguished subject-matter experts, policy makers, and private sector and community stakeholders.

Historical perspective

The dramatic and rapid expansion of academic and private sector scientific research transformed many societies of the 20th century and is a major factor in the emergence of the more affluent countries that currently dominate the global economic and security landscape. The positive influence of these S&T achievements has been extremely impressive and in many ways the hallmark of the 20th century. However, there have also been numerous negative consequences, some immediately apparent and others appearing only recently. From both perspectives, it would be difficult to argue that S&T has not been the prime factor defining the societies we know today. Indeed, the 20th century can be viewed through the prism of how societies decided to use the available scientific understanding and technological expertise to structure themselves. Such decisions helped shape the respective economic models, cultural priorities, and security commitments in these societies.

It remains to be seen how the prosperity and security of 21st century societies will be shaped by the decisions made by our current leaders, especially with respect to how these decisions reflect sound S&T understanding.

Given the critical importance of properly incorporating scientifically credible information into major societal decisions, it is surprising that the process by which this is achieved by the public and its political leadership has been uneven and, occasionally, haphazard. In the worst cases, decisions have been based on unrecognized misunderstanding, overhyped optimism, and/or limited respect for potentially negative consequences. Retrospectively, while some of these outcomes may be attributed to politically motivated priorities, the inability of S&T experts to accurately communicate the advantages and potential risks of a given option must also be acknowledged as equally important.

The new format pioneered by the ISGP in its programs seeks to facilitate candid communication between scientific and policy communities in ways that complement and support the efforts of others.

It is important to recognize that policy makers routinely seek a degree of certainty in evaluating S&T-based options that is inconsistent with reality, while S&T experts often overvalue the potentially positive aspects of their proposals. Finite uncertainty is always part of advanced scientific thinking and all possible positive outcomes in S&T proposals are rarely realized. Both points need to be reflected in policy decisions. Eventually, the public needs to be given a frank, accurate assessment of the potential advantages and foreseeable disadvantages associated with these decisions. Such disclosures are essential to obtain the broad public support required to effectively implement any major decision.

ISGP conference structure

At each ISGP conference, internationally recognized, subject-matter experts are invited to prepare concise (three pages) policy position papers. For the March 19–22, 2013 ISGP conference in Houston, these papers described the authors' views on current realities, scientifically credible opportunities and associated risks, and policy issues concerning AMR. The seven authors were chosen to represent a broad cross section of viewpoints and international perspectives. Several weeks before the conference convened, these policy position papers were distributed to representatives from governments, societal organizations, and international organizations engaged with the ISGP (the United States, Sweden, the United Kingdom, Canada, Australia, Netherlands, and France). Individuals from several private sector and philanthropic organizations also were invited to participate and, therefore, received the papers. All participants had responsibilities and/or made major contributions to the formulation and implementation of domestic and international policies related to AMR.

The conference agenda was comprised of seven 90-minute sessions, each of which was devoted to a debate of a given policy position paper. To encourage frank discussions and critical debates, all ISGP conferences are conducted under the Chatham House Rule (i.e., all the information can be used freely, but outside the conference there can be no attribution of any remark to any participant). In each session, the author was given 5 minutes to summarize his or her views while the remaining 85 minutes were opened to all participants, including other authors, for questions, comments, and debate. The focus was on obtaining clarity of understanding among the nonspecialists and identifying areas of consensus and actionable policy decisions supported by scientifically credible information. With active participation from North America, Australia, and Europe these candid debates are designed to reflect international perspectives on real-world problems.

The ISGP staff attended the debates of all seven policy position papers. The not-for-attribution summaries of each debate, prepared from their collective notes, are presented here immediately following each policy position paper. These summaries represent the ISGP's best effort to accurately capture the comments and questions made by the participants, including the other authors, as well as those responses made by the author of the paper. The views expressed in these summaries do not necessarily represent the views of a specific author, as evidenced by his or her respective policy position paper. Rather, the summaries are, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the debates.

Following the seven debates, caucuses were held by small groups each representing a cross section of the participants. A separate caucus for the scientific presenters also was held. These caucuses focused on identifying areas of consensus and actionable next steps for consideration within governments and civil societies in general. Subsequently, a plenary caucus was convened for all participants. While the debates focused on specific issues and recommendations raised in each policy position paper, the caucuses focused on overarching views and conclusions that could have policy relevance both domestically and internationally.

A summary of the overall areas of consensus and actionable next steps emerging from these caucuses is presented here immediately following this introduction under the title of **Conference conclusions.**

Concluding remarks

ISGP conferences are designed to provide new and unusual (perhaps unique) environments that facilitate and encourage candid debate of the credible S&T options vital to successfully address many of the most significant challenges facing 21st century societies. ISGP debates test the views of subject-matter experts through critical questions and comments from an international group of decision makers committed to finding effective, real-world solutions. Obviously, ISGP conferences build on the authoritative reports and expertise expressed by many domestic and international organizations already actively devoted to this task. As a not-for-profit organization, the ISGP has no opinions nor does it lobby for any issue except rational thinking. Members of the ISGP staff do not express any independent views on these topics. Rather, ISGP programs focus on fostering environments that can significantly improve the communication of ideas and recommendations, many of which are in reports developed by other organizations and institutes, to the policy communities responsible for serving their constituents.

ISGP conferences begin with concise descriptions of scientifically credible options provided by those experienced in the S&T subject, but rely heavily on the willingness of nonspecialists in government, academe, foundations, and the private sector to critically debate these S&T concepts and proposals. Overall, ISGP conferences seek to provide a new type of venue in which S&T expertise not only informs the nonspecialists, but also in which the debates and caucuses identify realistic policy options for serious consideration by governments and societal leaders. ISGP programs are designed to help ensure that S&T understanding is integrated into those real-world policy decisions needed to foster safer and more prosperous 21st century societies.

Conference conclusions

Area of Consensus 1

The appropriate use of antibiotics needs to be made a priority in treatment decisions if antibiotic effectiveness is to be preserved. Since the appropriate use of antibiotics differs significantly for specific human, animal, and plant sectors, the choice of specific drugs and the optimal dosing and duration of treatment requires serious consideration.

Actionable Next Steps

- Quantify current antibiotic use and provide results via comparative feedback for practitioners to reduce inappropriate antibiotic drug use.
- Educate providers concerning the risks of antibiotic resistance (e.g., via professional guidelines and health care training), regulators (e.g., via policies), and the public (e.g., via trusted sources, social and other new media) to discourage inappropriate antibiotic use. Such information must recognize the cultural, socioeconomic, and ethical diversity among stakeholders and societies.
- Develop and implement evidence-based strategies to reduce the unnecessary and inappropriate use of antibiotics in well-defined populations and treatment situations.

Area of Consensus 2

Hospital acquired and health care-associated infections must be significantly reduced through infection control programs in health care facilities if antimicrobial resistance is to be reduced and patient health care improved.

Actionable Next Steps

- Develop new and implement existing practices and technologies (e.g., novel surface coatings, hygiene surveillance and reporting systems) to enhance pathogen non-specific (horizontal) preventive strategies

(e.g., optimize hand hygiene, limit hospital stays, minimize patient movement, ensure effective cleaning of surfaces and fixtures).

- Empower patients and their families to monitor and insist on proper hygiene in health care facilities.
- Establish incentives (e.g., reimbursement schemes) that promote the reduction of antimicrobial resistance through the control of infection in health care facilities.
- Identify and utilize methods for the retention and promotion of healthy microbiota to minimize patient vulnerability to pathogenic microbes.

Area of Consensus 3

Large-scale integrated programs for collecting surveillance data, integrating analysis results, and sharing information at the local, regional, national, and international level are needed to improve the understanding and management of antimicrobial resistance.

Actionable Next Steps

- Adopt open access standards for existing and developing health care databases in systems that can operate in both more- and less-affluent countries.
- Incorporate into electronic health records the ability to automatically capture and analyze the information relevant to identifying antimicrobial resistance patterns that can inform drug research and development, clinical decisions, and policy decisions affecting infection control and antibiotic usage.
- Establish a system of consumer-focused reporting to the public of infection rates and antibiotic resistance data from health care facilities.

Area of Consensus 4

The ability to ensure the ongoing effectiveness of antimicrobial treatment will necessitate the discovery of new antimicrobials. Such innovative research and development needs to be correlated with improved regulatory standards for the approval of antibiotic drugs that reflect an understanding of the seriousness of antibiotic resistance.

Actionable Next Steps

- Re-examine existing patent laws and regulatory frameworks to ensure the availability of effective antimicrobials, especially considering wider social needs and the impact of infectious diseases (e.g., the Limited Population Antibiotic Development proposal, orphan drug approval process).
- Communicate to legislative bodies and the public the urgency of the threat to human health posed by increasing antimicrobial resistance.
- Consider the evolutionary adaptation of bacterial pathogens to new antibiotics as an important component in drug approval and regulatory procedures.

Area of Consensus 5

While the relationship between the use of antibiotics in animals and human infections remains under study, antibiotic use in animals needs to be more effectively managed to limit selection and persistence of resistance in non-target organisms that could be of significance to human health.

Actionable Next Steps

- Encourage regulatory authorities to control and, in some cases, eliminate the use to promote growth in animals of antibiotics found to be important for therapy in humans.
- Discourage uses of existing antimicrobials for prophylaxis and metaphylaxis that may lead to selection and persistence of resistance in non-target organisms that could be of significance to human health.
- Continue to examine the relationship between the use of antibiotics in animals and antimicrobial resistance in humans through review of existing data and ongoing research by researchers, drug sponsors, and regulatory authorities.

ISGP conference program

Tuesday, March 19

12:00 – 17:00 **Arrival and Registration: Hilton Houston Plaza/ Medical Center**

16:00 – 16:30 **Conference Meeting: Science**

16:30 – 17:30 **Conference overview: All presenters and participants**

17:30 – 18:45 *Reception*

18:45 – 19:00 ***Welcoming Remarks***
Dr. George Atkinson, Founder and Executive Director, Institute on Science for Global Policy (ISGP)
Dr. Paul Klotman, President, Baylor College of Medicine

19:00 – 19:45 *Dinner*

19:45 – 20:30 ***Evening Remarks***
Ambassador Thomas Pickering, Vice Chairman of Hills & Co, international consultants, and Strategic Adviser to NGP Energy Capital Management and former ambassador to the United Nations, the Russian Federation, India, Israel, El Salvador, Nigeria, and the Hashemite Kingdom of Jordan

Wednesday, March 20

06:30 – 08:15 *Breakfast*

Presentations and Debates: Session 1

09:00 – 10:30 **Dr. Brad Spellberg, University of California Los Angeles and Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, United States**
The Future of Antibiotics and Antibiotic Resistance

10:30 – 11:00 *Break*

11:00 – 12:30 **Dr. Eili Klein, Center for Advanced Modeling in the Social, Behavioral, and Health Sciences, Johns Hopkins University; Fellow, Center for Disease Dynamics, Economics, & Policy, United States**
How Misaligned Incentives Influence Antibiotic Prescribing and Resistance

12:45 – 14:15	*Lunch and presentations by Baylor College of Medicine scientists*

Presentations and Debates: Session 2

14:30 – 16:00	**Dr. H. Morgan Scott, Department of Diagnostic Medicine and Pathobiology, Kansas State University, United States** *Managing Antibiotic Resistance in Animal Agriculture Amidst Conflicting Moral Beliefs and Scientific Uncertainty*
16:00 – 16:30	*Break*
16:30 – 18:00	**Prof. Eriko Takano, Manchester Institute of Biotechnology, Faculty of Life Sciences, University of Manchester, United Kingdom** *Antimicrobial Resistance – A New Drug Discovery Perspective Using Synthetic Biology*
18:15 – 19:00	*Reception*
19:00 – 19:15	***Welcoming Remarks*** **Dr. George Atkinson**, Institute on Science for Global Policy (ISGP) Founder and Executive Director **Dr. Paul Klotman,** President, Baylor College of Medicine
19:15 – 19:35	***Evening Remarks*** **Dr. Robert Robbins,** President, Texas Medical Center
19:35 – 20:45	*Dinner*

Thursday, March 21

06:30 – 08:15	*Breakfast*

Presentations and Debates: Session 3

09:00 – 10:30	**Dr. Richard Wenzel, Department of Internal Medicine, Virginia Commonwealth University, United States** *Global Infection Prevention: A Strategy to Minimize Antibiotic Resistance*
10:30 – 11:00	*Break*

11:00 – 12:30	**Dr. Timothy Palzkill, Department of Pharmacology, Baylor College of Medicine, United States** *Mitigating Antibiotic Resistance with DNA Sequence Information*
12:45 – 13:45	*Lunch*

Presentations and Debates: Session 4

14:00 – 15:30	**Dr. Thomas O'Brien, World Health Organization Collaborating Centre for Surveillance of Antimicrobial Resistance and Department of Medicine, Brigham and Women's Hospital, United States** *Surveillance of Antibiotic Resistance Gene Epidemics*
16:00 – 17:00	*Break*

Caucuses

17:00 – 21:00	**Focused group sessions**

Friday, March 22

06:30 – 07:45	*Breakfast*
08:30 – 11:20	**Plenary Caucus Session** Dr. George Atkinson, *moderator*
11:20 – 11:30	***Closing remarks*** Dr. George Atkinson
11:30 – 12:30	*Lunch*
12:30	*Adjournment*

The Future of Antibiotics and Antibiotic Resistance**

Brad Spellberg, M.D.
Associate Professor of Medicine, Associate Medical Director for Inpatient Services, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Los Angeles, California, United States

Summary

Society is facing two converging public health crises: inexorably rising antibiotic resistance combined with a collapse of the antibiotic research and development pipeline. To successfully confront these crises and develop countermeasures that have lasting effects, we must come to grips with their fundamental causes. A fallacy of human egocentrism is the notion that we invented antibiotics and that we cause antibiotic resistance to occur. There are partial truths to this fallacy, but the consequence of our incomplete recognition of the origins of antibiotics and resistance is that we have been led astray in our efforts to combat resistance and develop new ways to treat infections.

Current realities

Clinical resistance has been with us since the very first use of antibiotics in the 1930s. However, as resistance caught up with treatments, the pharmaceutical industry has historically provided a solution by developing the next generation of new antibiotics. This is no longer the case. Antibiotic resistance continues to skyrocket even as the antibiotic research and development pipeline collapses. As a result, untreatable infections, resistant to all antibiotics, are now being encountered in the United States and throughout the world. We are also seeing common community infections that used to be readily treatable with oral antibiotics (e.g., urinary tract infections and abdominal infections) now resistant to all oral antibiotics. These infections require hospitalization for intravenous therapy and may lead to serious or even fatal consequences after failing oral antibiotic therapy.

Slowing the spread of or reversing antibiotic resistance is not a new concept. As far back as 1945, Alexander Fleming, discoverer of penicillin, was perhaps the first person to call for society to stop overusing antibiotics to slow resistance. Since that time, the medical community and society have repeatedly and widely acknowledged the need to control antibiotic use. Despite this acknowledgment,

we have not yet learned how to effectively protect antibiotics, as evidenced by the never-ending escalation of antibiotic use and resulting resistance. In 2009, in the U.S. alone, more than 3 million kilograms of antibiotics were administered to human patients. Furthermore, a staggering 13 million kilograms of antibiotics were administered to animals in the U.S. in 2010, the vast majority for promoting growth. We simply cannot confront resistance at a population level unless we stop exposing microbes in the environment to such a catastrophic selective pressure of antibiotics. Nor can we effectively deal with the threat of resistant infections without establishing better ways to prevent infections, slow resistance, and find new treatments for infections. It is time for disruptive, transformative tactics to be adopted, which requires us to understand the root cause of resistance.

Scientific opportunities and challenges

Humans did not invent antibiotics, and we do not create antibiotic resistance. Resistance is the result of bacterial adaptation to antibiotic exposure, likely dating back to the very invention of antibiotic synthesis by prokaryotes approximately 2 billion to 2.5 billion years ago. What are the fundamental implications of this reality? First, our use of antibiotics does not create resistance, but rather naturally selects out pre-existing resistant populations in nature. Second, it is safe to assume that in 2.5 billion years of evolution, prokaryotes have invented antibiotics that can attack every biochemical target that can be attacked, and thus have also developed resistance mechanisms to protect every one of those biochemical targets. Indeed, recent experimentation has confirmed the presence of resistance to essentially all antibiotic classes in bacteria isolated from the surface of the planet for 4 million years that have never been exposed to human manufactured drugs. Remarkably, resistance was found even to synthetic drugs that do not exist in nature, including daptomycin, which did not exist until the 1980s. These results underscore a critical reality that we must confront: antibiotic resistance exists, widely disseminated in nature, to drugs that are yet to be invented. Thus, resistance is truly inevitable to any agent that we invent that has a goal of killing microbes.

Third, the implication of the above two principles is that it is not just "inappropriate" antibiotic use that drives resistance to antibiotics. Rather all antibiotic use, appropriate or not, drives resistance via natural selection of pre-existing resistant bacteria. However, the speed at which resistance spreads should be proportionate to the level of environmental contamination by human-manufactured antibiotics, as documented by multiple population-based studies. Thus, humans do not create resistance, but directly impact its spread.

Fourth and finally, there are no "new" targets against which we can develop new antibiotics. All targets are old targets from the perspective of the microbes. Since 1931, when Domagk and colleagues discovered that chemical red dyes can kill bacteria (we now know by attacking folate synthesis), the arc of antibiotic research and discovery has been to discover new ways to kill the microbes. This strategy has saved countless lives and prolonged the average lifespan of people all over the world by years or decades. But it has also driven the resistance that plagues us and threatens the very miracle of antibiotics. Merely continuing to find new ways to kill microbes is unlikely to serve as the basis of a successful, long-term therapeutic strategy. Ultimately, over centuries or millennia, we will run out of targets and resistance mechanisms will become so prevalent as to preclude effective deployment of microbicidal antibiotics.

To truly transform treatment of infections, it will be necessary to encourage scientific approaches that do not seek to kill microbes but rather seek to modify the nature of the interaction between microbe and host so that host injury does not occur. Such therapies could include alterations in expression or activity of virulence factors, disarming the pathogen and thereby preventing it from causing disease without seeking to kill it. As well, sequestration of host nutrients, such as trace metals or other vital factors microbes need to replicate and survive, could prevent microbial growth without attacking the pathogen directly. Rather, the therapeutic target is the host, and as such, will not drive microbial resistance to the treatment. There is also potential to more effectively restore normal microbial flora, and/or use probiotics to combat infections by habitat competition within the host. The most immediate example of this is the potential to treat and prevent relapses of *Clostridium difficile* using fecal transplant or probiotics. However, normal flora have the potential to compete with many other pathogens that exist in skin and mucosal surfaces that are normally colonized with microbes.

Policy issues

- Transform infection prevention by dissemination of new technologies and practices (including establishing payor mechanisms) to more effectively and comprehensively disinfect environmental surfaces, people, and food. For example, self-cleaning hospital rooms, or portable technologies that enable rapid disinfection of all surfaces in a hospital room, would enable a far more effective disinfection process than relying upon manual application of disinfectants by the lowest paid, least-invested employees in the hospital (i.e., the janitorial staff). Such technologies

could include device-driven microaerosolization of Environmental Protection Agency (EPA)-approved disinfectants, application of hydrogen peroxide vapor, UV lights, or other technologies yet to be elaborated. Reimbursement for use of such technologies is critical to encourage their uptake and use in hospitals.

- Encourage development of new active or passive vaccines to prevent and treat infections. An ounce of prevention is worth a pound of cure: If we prevent infections from occurring in the first place, there will be no need to use antibiotics, which will decrease selective pressure driving resistance. Furthermore, passive immune therapies can work adjunctively with antibiotic therapy to more effectively treat infections, which could result in shorter course therapies or less therapeutic failures, thereby reducing salvage antibiotic therapy (i.e., treatment with a second antibiotic).
- Transform the economics of antibiotic development by use of public-private partnerships, via grants and contracts and establishment of nonprofit companies focusing in this space. Public-private partnerships can more effectively align which antibiotics are to be developed with areas of unmet medical need. For-profit development is primarily driven by market size, not unmet need, which explains the over-abundance of new antibiotics developed in the last decade to treat skin infections despite the absence of need for such new drugs.
- Establish a fundamental shift in regulatory approach to make easier, less expensive, and more timely development and approval of antibiotics using small studies of highly resistant pathogens, resulting in restrictive labeling and use post-marketing, combined with post-marketing safety surveillance (e.g., the Limited Population Antibiotic Drug [LPAD] proposal from the Infectious Diseases Society of America).
- Alter the regulatory approach so that labeling is granted for indications that reflect "appropriate use" of antibiotics, rather than granting indications that are perceived to result in more widespread use (and hence greater sales). Current U.S. Food and Drug Administration (FDA) approval processes encourage inappropriate use of antibiotics by enabling labeling of broad spectrum gram-negative-active antibiotics for common infections caused by much less resistant pathogens. Rather than preserving these critically needed new drugs for lethal highly resistant infections, they are routinely wasted on common infections for which many other antibiotic options exist.

- Slow the spread of resistance by encouraging widespread use of rapid molecular diagnostics to empower providers to withhold unnecessary antibiotics and stop empiric antibiotics (i.e., use of antibiotics in the absence of knowledge of what the pathogen is) as soon as possible.
- Eliminate antibiotics for growth-promoting purposes in animals.

***** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2013, at Baylor College of Medicine, Houston, Texas.***

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Brad Spellberg (see above). Dr. Spellberg initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Spellberg. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Spellberg, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate Conclusions

- The guidelines for the appropriate use of antibiotics formulated and approved to date by oversight bodies do not adequately reflect the need to limit their over-usage and therefore, these existing definitions of appropriate antibiotics usage need to be refined to address realistic conditions.
- While it is recognized that the use of antibiotics in animals encompasses a complex set of scientific, economic, and political perspectives, the use of antibiotics for disease prevention and control remains a priority, while antibiotic use for growth promotion is generally viewed negatively.
- Because the current paradigm for the discovery and development of new

antibiotics is recognized as not being adequate for meeting the current challenge of minimizing antimicrobial resistance, new regulatory and public/private partnering approaches are needed.

- New technologies, especially rapid, point-of-care diagnostics, are needed to enable physicians and patients to reduce unnecessary and/or suboptimal use of antibiotics.
- Education concerning the appropriate use of antibiotics is essential if medical practitioners are to have the confidence to make treatment decisions that will help reduce or eliminate antibiotic over-prescribing.

Current realities:

The geographic scope of the problem of antimicrobial resistance (AMR) was discussed extensively and specifically with respect to whether the issue is a limited country-level problem or whether it is exacerbated by the demand for antibiotics internationally. AMR was seen to be a concern with international ramifications for several reasons. Resistance can emerge anywhere in the world and spread to other countries including the United States in less than 24 hours via air travel. Additionally, in several less-affluent countries, antibiotics are used even more indiscriminately than in more-affluent countries.

Technological approaches to limiting the spread of AMR are likely to continue to be driven by those in more-affluent countries, particularly the U.S. However, there are also predictions that within five years the antibiotic market in China will surpass the U.S. market. This market reality may lead developers of new antibiotics to pursue a "China first" strategy to avoid U.S. regulations viewed as onerous. Such a strategy may result in the drugs needed to save lives being more available in Beijing than in Washington, D.C.

The use of antibiotics in human medicine, veterinary medicine, and plant health is largely unregulated and uncontrolled in several less-affluent countries. It was estimated that as many as 100 countries do not have the infrastructure, legislative framework, authority, or capability to properly and prudently regulate and distribute antibiotics. Although World Health Organization (WHO) recommendations may be a step in the right direction, they have proven inadequate to appropriately restrict the distribution of antibiotics and antibiotic prescriptions continue to be sold in great volumes with little oversight. While this concern was not directly addressed, rapid diagnostic technology was considered vital to proper prescribing. Preventive measures, particularly expanded use of vaccines, are considered important tools in less-affluent countries. However, it was emphasized

that the policy suggestions made in the policy position paper are not currently even under consideration by decision makers in many parts of the world.

While the World Organization for Animal Health (OIE) and other organizations have developed and published detailed guidelines on appropriate use of antibiotics, a consensus definition of "appropriate use" does not exist. Since there are many different definitions, it was contended that most are not fully adequate to define the overall issue of how antibiotics can be appropriately used. While several specific examples of inappropriate and/or suboptimal use of antibiotics were offered and discussed, it was agreed that existing guidelines do improve current use of antibiotics, although a broader consensus definition is essential.

The vast majority of inappropriate use of antibiotics was considered driven by on-label prescribing (i.e., using the product in compliance with FDA-required information). The current situation is primarily due to lack of consideration by regulators of a wider spectrum of activity for a new antibiotic when its label is being developed and approved. For example, more than 10 million prescriptions per year are written for upper respiratory tract infections in the U.S., all of which are on-label and half of which are inappropriate. However, there was a strongly held view that any new definitions must not hamper the off-label prescribing antibiotics (i.e. the ability to prescribe or use the drug for indications, conditions, patients, or dosages not yet evaluated and approved by the FDA). The example was offered of a new drug to treat pan-resistant *Klebsiella pneumoniae* in the lungs and blood. If a patient has pan-resistant *Klebsiella* in the brain, the treating physician must be able to use the new drug off-label when he or she determines it is the appropriate, and perhaps the only, treatment for that patient.

Scientific opportunities and challenges:

Rapid point-of-care diagnostics can both guide and drive prescribing behavior in industrialized countries, especially when physicians can determine in about 15 minutes whether the infection is Group A strep and therefore whether antibiotics will be effective. If a society desires appropriate stewardship to maintain the finite resource of antibiotic effectiveness, it is necessary to employ technology to empower physicians and patients to withhold antibiotics when this treatment is not indicated. Rapid diagnostics are a reasonable and promising method to achieve this goal. A real-world example of this technology and its impact is the "strep throat" test mentioned above which has dramatically reduced antibiotic prescriptions for viral pharyngitis. It was agreed that a wider array of effective point-of-care diagnostics is a fundamental weapon to battle AMR.

Another specific example of where avoidance of antibiotic overuse is critical arises in patients with in-dwelling urinary catheters. A consensus of guidelines exists across several relevant organizations, all agreeing that asymptomatic bacteria in a catheterized patient should not be treated. However, even with such strong consensus, antibiotics continue to be prescribed for such patients for a number of reasons. First is the lack of understanding or knowledge of what defines asymptomatic bacteria, coupled with the social norm to concur with an earlier treatment decision. Second is outcome expectancy in physicians who believe antibiotic prescriptions are required because they know of an incident of death by urosepsis. Third is the perceived need to act on information, specifically the identification of (asymptomatic) bacteria, through urine cultures. One solution to this problem has been to stop ordering urine cultures to screen for asymptomatic bacteria. In one hospital setting, this change has decreased antibiotic intervention by 50% compared with a control group.

Phage therapy was acknowledged as a reasonable alternative to treat infections in certain circumstances, relieving some pressure for the use of antibacterials. However, it was stated that alternatives are not a panacea and none are more effective than antibiotics. Because antibiotics are probably the single most potent life-saving medical intervention that humanity has ever had, the goal is not to replace, but to complement these therapies.

An opportunity exists for medical education to help new physicians make better decisions in the appropriate use of antibiotics. Experienced mentors were noted as powerful champions for the reduction of inappropriate use. However, the question remained as to how to provide practitioners with the moral courage that allows them to feel comfortable to stop or even not begin antibiotic therapy. Medical uncertainty among less-experienced health care providers tends to drive antibiotic overuse more than the fear of legal ramifications. Education also needs to be linked to patient safety. Patient safety is a current priority topic within the curriculum for medical students as well as medical residency programs, and physicians in training must be made aware of the negative side effects of antibiotics at the individual patient and societal levels.

Active vaccination to reduce the need for using antibiotics was seen as another important approach. The current focus in this area is on multidrug-resistant pathogens, with the highest priority being *Staphylococcus aureus,* because of its prevalence. Other priority pathogens include gram-negative bacteria; specifically *Acinetobacter*, carbapenem-resistant *Enterobacteriaceae*, and *Pseudomonas*. A key challenge for this approach is determining how to deploy an active vaccine and in what setting.

The continued use of growth-promoting antibiotics in livestock was discussed from scientific and political/economic perspectives. In Denmark, the elimination of antibiotics in hog food resulted in an overall doubling of the use of antibiotics nationwide (total kilogram use). However, the amount of antibiotic per hog decreased by two-thirds. The primary reason for this seeming dichotomy was that the number of hogs produced increased sixfold. This increase in production may have compensated for the economic cost of eliminating the use of growth-promoting antibiotics. Despite this example, there was consensus that the elimination of growth-promoting antibiotics in animal feed in the U.S. was still not politically feasible and was viewed as economically unwise.

Antibiotics are used in animals for two distinct reasons. The first is prevention and control of animal disease, which accounts for the vast majority of use. Use of antibiotics in animals for growth promotion was seen as relatively minor use — at only 13% of the total. It was argued that there is little or no evidence that the use of antibiotics in animals has contributed significantly to resistance problems in humans. Legislation in this area needs to preserve the use of antibiotics for prevention and control of diseases in animals.

A comparison between intensive livestock production and intensive health care delivery was made, suggesting a parallel between the two. Intensive agriculture could not exist in its current state without antibiotics to deter disease, and the health care-delivery infrastructure, particularly the existence of the intensive care unit (ICU), is also dependent on the antibiotic era. Although there was no consensus on the animal-use issue, it was agreed that antibiotics enable ICU care, and ICU care enables antibiotic resistance.

As a feasible, lower-cost opportunity, consideration could be given to development of Web applications and/or other information sources for the general public, with emphasis on the appropriate use of antibiotics. It was agreed that empowering patients to challenge the *status quo* is a good idea.

Policy issues

The limited population antibacterial drug (LPAD) proposal from the Infectious Disease Society of America (IDSA) was debated at some length. LPAD has both pre-launch ("push") and post-launch ("pull") economic incentives. The push incentives, to expedite clinical trials and other development activities, aim to reduce costs. The pull incentive is a very specific indication for a limited population, which creates the potential for a premium price. This restrictive label will also assist in the preservation of the effectiveness of a new medicine over time. A concern was raised about the LPAD concept of having high-priced antibiotics for hospital

use, for a specific indication, noting that this approach may further reduce development of antibiotics for routine outpatient use. While acknowledging this potential problem, two issues were noted that mitigate this concern. First is that receipt of an LPAD indication does not preclude subsequent expansion of indication. However, expansion of indication, and presumably expansion of market, will result in the loss of LPAD pricing. The second issue discussed is that only certain antibiotics with specific, narrow-indication characteristics will lend themselves to the pursuit of LPAD development and pricing. Ciprofloxacin was noted as an antibiotic that may have fit the LPAD profile, which would have limited its use to more serious and less common infections.

Judicious and appropriate use of antibiotics was widely agreed to be an appropriate and laudable goal. There was strong agreement that one of the fundamental needs of stewardship of antibiotic effectiveness is to attempt to define appropriate versus inappropriate use. However, the scientific community has not yet created such a definition. The question remains as to what entities and/or individuals would be given responsibility to define appropriate and judicious uses. A cross-functional, multi-stakeholder approach was argued to be more likely to result in acceptance and uptake of a policy framework in this area. Conversely, resistance to a policy among the affected populations is almost guaranteed if they are excluded from the discussion of defining appropriate and judicious antibiotic use. An opposing viewpoint was expressed that decisions regarding appropriate versus inappropriate use need to be made only by people who understand what antibiotics do, which may not necessarily include the public, most physicians, and regulators.

In terms of priority of effort in the near term, many of the proposed changes have different barriers. For example, the reduction or elimination of antibiotics in animal feed can be addressed through legislation, but there is not yet a political consensus to pass such legislation. Other changes, such as better disinfection technologies (e.g., hydrogen peroxide vapor), can be implemented, but require trials to demonstrate that such changes will reduce infection rates in hospital settings.

Because it currently costs billions of dollars to bring a new antibiotic to market, it was suggested that in 10 to 20 years the traditional entrepreneurial business model that companies have used to develop drugs generally, and antibacterials specifically, may no longer be viable. Instead, two paths for developing new antibiotics will exist. First, companies will shift into a mode of public-private partnerships, as is happening now on a limited basis. Second, companies that are not currently developing antibacterial drugs may be interested in orphan, or other narrow-market,

drugs. LPAD drugs, with a narrow profile and premium pricing, along with expedited development and approval, could also be a source for new antibiotics. The health economics aspect of significantly more expensive antibiotics was acknowledged as an issue requiring attention.

In the U.S. health care system, the fear of malpractice suits among physicians was viewed as a significant factor influencing the appropriate use of antibiotics. While education has been shown to provide short-term gains, improvements are difficult to sustain over time. A more powerful tool is accountability, particularly through national benchmarking, tied to reimbursement rates. As a large single-payer system, Medicare may provide a good demonstration project in this area. Questions such as "How much antibiotics do you prescribe?" and "How much antibiotics does your health care system prescribe?" were suggested as metrics to encourage appropriate use. Such data may already be gathered, but is not publicly available.

How Misaligned Incentives Influence Antibiotic Prescribing and Resistance**

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Summary

Antibiotic resistance is a significant threat to public and patient health. Its emergence has significantly reduced a physician's ability to treat infections and increases the probability of mortality for patients. It also threatens to reverse significant medical gains, particularly the ability to perform transplants and other surgical procedures that are dependent on antibiotic effectiveness. Drug-resistant infections cause significant morbidity and mortality: Approximately 2 million Americans are infected with hospital-acquired infections annually, the vast majority of which are resistant to antibiotics, resulting in about 99,000 deaths each year. Emergence and spread of antibiotic resistance is engendered by inappropriate use of antibiotics, which occurs largely because of the misalignment of incentives for using and producing antibiotics. Problems with resistant bacteria are compounded by the fact that there are also impediments to the development of new antibiotics that could be effective against these resistant organisms. All these problems are systemic and require interventions at both the consumer and producer level to ensure the long-term efficacy of antibiotics.

Current realities

Studies have continually shown that the rate at which resistance emerges and spreads is strongly related to the total amount of drug usage. Thus, in this respect, antibiotics are similar to natural resources such as oil, water, fish, and forests: Usage "uses up" their effectiveness, diminishing them for future use. The greater the usage, the faster the resource is "depleted" (though antibiotics can be "renewed" through the introduction of new drug classes). Thinking about antibiotics in this manner provides a framework for considering the incentives that result in the overuse of

antibiotics as well as under-investment in new drugs, and how to align incentives to improve the judicious use of antibiotics.

Most antibiotics in use today were invented decades ago. The rate at which new antibacterial agents have been introduced has fallen steadily for the last 40 years (see figure). One of the reasons for this is the high cost of bringing a new drug to market, a number that can exceed $100 million. However, this figure only includes the cost of clinical trials, and does not include the cost to discover new compounds, which can be highly variable and is often more the result of luck than a targeted investigation. In addition, regulatory hurdles cause additional expense, not least of which is that antibiotics can be approved only for specific infections, not for the organism they treat (e.g., treating skin infections rather than *Staphylococcus* infections generally). In addition to the cost and uncertainty of bringing a drug to market, revenues from antibiotics are generally less than "blockbuster" drugs. For example, in 2005 Pfizer reported revenue of more than $12 billion for Lipitor and revenue of only about $2 billion for Zithromax (generic name azithromycin), which at the time was one of the most highly prescribed antibiotics. This disparity is largely because antibiotics are generally only taken for 7-10 days while a drug such as Lipitor is taken for months to years. In recent years this has been further impacted by the emergence of resistance, as doctors reserve new antibiotics for when they are necessary. This reduces the gains that a pharmaceutical company can make before the patent on its drug expires, further reducing its incentive to invest.

There is also a lack of incentives for pharmaceutical companies to preserve the efficacy of their drugs. One reason for this is that the categorization of drugs into classes (and thus patents) is based on the chemical structure of the active molecule of the antibiotic rather than the mechanism that engenders resistance. Thus, newly patented antibiotics may be functionally similar in terms of resistance even if they are "different" as defined by intellectual property law. Because the resource embodied in the effectiveness of an antibiotic "class" is available to several pharmaceutical firms, no single firm has an incentive to take into full consideration the effect of its sales of antibiotics on future antibiotic effectiveness (an example of the economic theory of the tragedy of the commons). Patent expiration also plays a large role, as pharmaceutical companies have an incentive to sell as much of a drug as possible before their patent expires and generics enter the market.

Scientific opportunities and challenges

While pharmaceutical companies have incentives to push antibiotic sales, in theory doctors should only be prescribing antibiotics when they are clearly indicated.

Unfortunately, we know this is not true. Despite the significant morbidity and mortality associated with antibiotic-resistant infections, and the link between increased antibiotic use and resistance, a large percentage of antibiotic use in medicine continues to be inappropriate. Inappropriate treatment results from a number of factors: (i) patient expectations/demand for antibiotics; (ii) possibility of malpractice lawsuits for not prescribing an antibiotic; (iii) time pressure on visit length (e.g., it is easier and faster to write a prescription than to explain to a patient why they do not need antibiotics); and (iv) uncertainty of diagnosis (i.e., it can be difficult to diagnose the cause of an infection).

All these factors are generally the result of not accounting for the negative externality associated with antibiotic usage. An externality occurs when an individual's action results in costs or benefits to others that are not taken into consideration by the individual. For antibiotics, there are both positive and negative externalities. The positive externality is that an infected individual will not transmit the infection once cured. The negative externality is that every individual who takes antibiotics produces some resistant bacteria (at least transiently), though this does not necessarily mean pathogenic bacteria. These resistant bacteria are transmitted to other individuals, or are excreted from the body and enter the environment, spreading resistance genes to other bacteria, including pathogenic bacteria. Despite the importance of antibiotics to medicine, patients and physicians rarely consider these externalities of antibiotic use. Thus, policy options that increase the "costs" of antibiotics to take account of these externalities will be the ones most likely to have a significant impact on antibiotic resistance.

The scientific challenges facing the health care community regarding antibiotic resistance revolve around both finding new antibiotics and preserving the ones that we currently have. With respect to new drug discovery, it is likely that much of the low-hanging fruit has already been harvested. However, while drug discovery has become more expensive and more time-consuming, revolutions in computation allow for much faster discovery and testing of new antibiotics *in silico*. Challenges, though, are largely cost-based. It is expensive to develop new drugs, and regulatory hurdles can increase the challenges. On the other side of the equation is the need to increase the longevity of existing drugs. One primary means of doing this is through a reduction in the use of medically relevant antibiotics (particularly ones that are not needed for therapy). However, reducing drug use may impact the development of new drugs by reducing the incentives for production. Additional strategies, such as cycling and combination therapy, should also be explored as a means of increasing the lifespan of drugs.

Policy issues

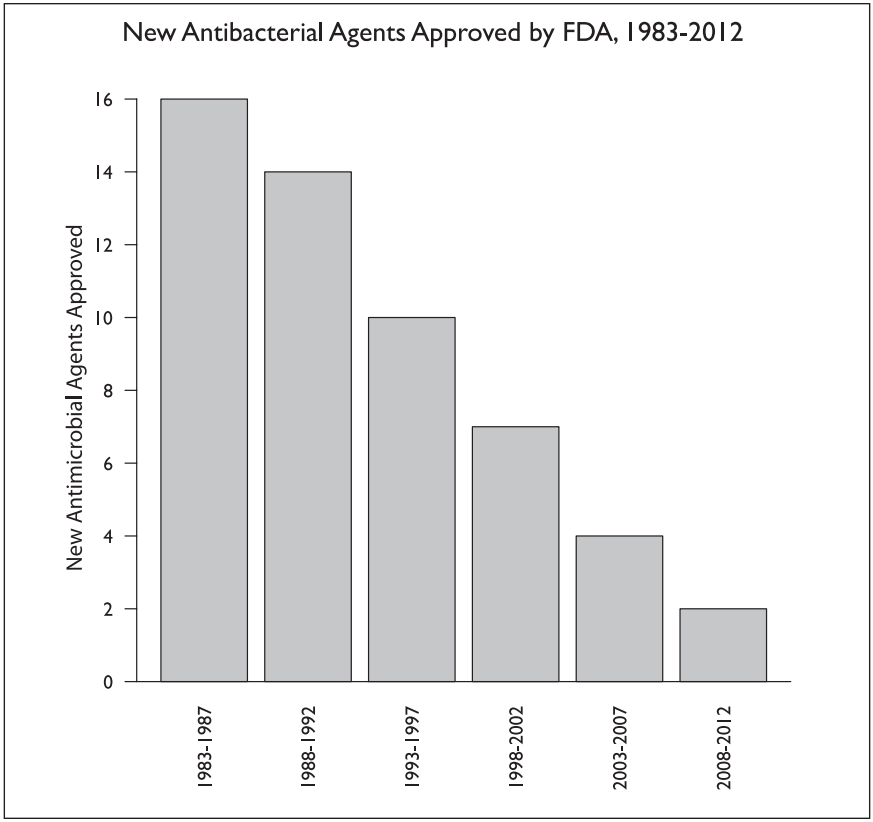
- The dramatic decline in new antibiotics requires new strategies for encouraging investment in the discovery of new antibiotics, but these strategies need to avoid creating new disincentives. Policies that just encourage investment in new antibiotics without worrying about resistance will not fully address the long-term challenge of antibiotic resistance. For instance, financial incentives that just result in development of "me-too" antibiotics or that encourage pharmaceutical companies to promote overuse of already approved antibiotics for fear of competition do not fully address the problem. Financial policies should thus be focused on the more difficult discovery component of research, through promotion of basic research. Additionally, public-private partnerships, which have been successful in the development of other antimicrobials in the past (e.g., antimalarials), may also be effective.
- In addition to new drugs, policies should also encourage pharmaceutical companies to care about the long-term efficacy of their drugs. Incentives such as tying patent expiration to disease incidence and resistance levels, patent consolidation (to avoid competition between drugs with the same mode of action), approval of drugs targeted at organisms rather than specific infections, or restrictions on the ability of other companies to create copy-cat drugs, present possible means of changing behavior. Conversely, fining companies or reducing their patent length because of rising rates of resistance could present alternative (and quite formidable) mechanisms to increase a company's incentive to preserve the efficacy of a drug.
- Increasing vaccination coverage, especially for the influenza vaccine, could reduce the number of individuals becoming sick in the winter, and thus reduce the rate of inappropriate prescribing of antibiotics. Increased investment in other vaccines, such as a *Staphylococcus* vaccine, could also significantly reduce antibiotic usage rates.
- Many drug-resistant infections are the result of in-hospital transmission; thus, improving infection control could reduce the spread of antibiotic-resistant infections. New technologies to track when clinicians/nurses wash their hands can help improve hand-washing compliance and may be cost-effective. Tying hospital reimbursement rates to resistance rates or not reimbursing for hospital-acquired infections (as the government has stopped doing for some infections in Medicare patients) could impact

the spread of resistance. Increasing coordination among hospitals on antibiotic resistance could also help. As people move back and forth among hospitals, hospitals have less incentive to spend on infection control if other hospitals are not also spending on infection control.

- Lastly, policies to discourage inappropriate antibiotic use need to be implemented through education, as well as by increasing the "cost" of antibiotics, which can be accomplished by higher co-pays or by making it more difficult for doctors to prescribe. Laws to insulate doctors from lawsuits for the nonprescription of an antibiotic should also be written.

***** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2013, at Baylor College of Medicine, Houston, Texas.***

Figure 1:
Fewer new antibiotics are being brought to market because of the cost and regulatory hurdles, as well as relatively lower revenue opportunities.



Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Eili Klein (see above). Dr. Klein initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Klein. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Klein, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Policy solutions to reduce inappropriate use of antibiotics have the potential for serious, unintended consequences (e.g., decreased reporting of infections in hospitals and the availability of antibiotics to consumers obtaining antibiotics through nontraditional, unregulated channels.
- Policy frameworks developed for more-affluent countries (e.g., the United States) are generally not useful in less-wealthy countries where the legislative, regulatory, and health care infrastructures needed to implement such policies are normally absent.
- While manipulation of patent life is a potential policy tool to preserve antibiotic effectiveness, there are significant concerns about the practicality and effectiveness in many economic (i.e., profit-driven) systems.
- To effectively address antimicrobial resistance, it is vital that the educational programs for health care practitioners and the communication linkages with the general public concerning how antibiotics are properly used (and not used) must both be tailored to the specific audience and cultures.
- Pharmaceutical companies may not be an appropriate control point for ensuring appropriate use of antibiotics.

Current realities

While acknowledging that the incentives outlined in this policy position paper were geared toward developed markets (primarily in the U.S.), the question was raised about the types of incentives that could be used in less-wealthy countries. In most more-affluent nations, the physician is the gatekeeper, or control point, for antibiotic recommendation and prescription, and the cost of filling the prescription is not a major issue. In less-affluent countries, the gatekeeper role of the physician is diminished and cost and access issues are the main barriers to appropriate antibiotic use. Due to cost issues alone, a less-than-full course of treatment will be purchased and/or taken in less-affluent settings. This scenario may require increased advocacy for larger antibiotic usage compared with the current norm. Country-specific concerns focused on increasing antibiotic usage. For example, in China resistance has increased to a level that commands governmental intervention. Incentives in China are misaligned, because physicians often are financially rewarded for prescribing antibiotics, which in turn increases the inappropriate use of some antibiotics.

While patent extensions were mentioned as possible incentives to preserve antibiotic effectiveness, such approaches were considered to be politically difficult if not impossible since longer patent periods are perceived as corporate welfare to the pharmaceutical companies. In addition, incentives through longer patent coverage required a fixed time horizon. Extensions offered for a compound in research and development project too far into the future to alter current behavior and decisions. However, extensions to products nearing the end of patent life may provide sufficient incentives to promote stewardship of the drug and reduce inappropriate use.

Given the recognition that the individual components of the pathway for the development of new antibiotics have distinct challenges, it was suggested that increased emphasis needs to be focused on the more difficult discovery components of antibiotic research. However, it was argued that discovering effective antibiotics is no more difficult than it has been historically, but that the current regulatory environment makes gaining approval significantly more difficult for all drugs and for antibiotics in particular.

A majority of countries worldwide have inadequate or no controls on the prescription and sales of antibiotics, (e.g., in 100 of 180 countries, the legislation and regulation controlling the importation and use, as well as assigning responsibility for properly prescribing, an antibiotic is considered to be inadequate). In such countries, antibiotics can be bought over the counter without a physician or veterinarian being involved. This lack of control results in large volumes of

antibiotics being used with little thought as to primary efficacy, much less the impact on antimicrobial resistance (AMR). Developing a better health care infrastructure in these countries will help reduce over-prescribing as well as incorrect prescribing. It was noted that in several of these countries an appropriate level of treatment of HIV/AIDS with antiretrovirals has been achieved, and that this example may provide lessons for antibiotic use.

While infectious disease specialists are important contributors to establishing the appropriate use of antibiotics, the vast majority of antibiotics are prescribed by family practice physicians. Consequently, it is critical to think holistically about antibiotic use throughout the entire health care system and not just in hospitals.

Scientific opportunities and challenges

There is potential for advanced modeling and other mathematical simulations to assist in distinguishing appropriate use of antibiotics from inappropriate use. Modeling can play an important role in examining and quantifying the trade-offs between positive and negative factors relating to a specific use of antibiotics. However, models and the data that feed them need to be validated, a task that is difficult to achieve in the current environment. As an example, little is known about transmission of bacterial pathogens. Thirty percent of people colonized with *Staphylococcus aureus* do not become infected. Since the relationship between colonization and infection is unclear, colonization is an imperfect predictor or risk factor for infection and transmission. Thus, a major limitation on the use of modeling to drive clinical practice in this area is the lack of definitive clinical data. Better data on bacterial resistance, antibiotic prescriptions, and how pathogens are transmitted are all needed, and programs to acquire these types of data are being vigorously pursued. It was also noted that in general all models are imperfect, but still useful.

A cautionary note was made concerning the statement that antibiotic resistance is inevitable. There are no scientifically credible data to confirm this statement, and that precision in language is critical to retain credibility by not overstating the problem. For example, the antifungal ciclopirox has been in use for 30 years with no cited clinical case of resistance. However, a large body of evidence shows that when one takes an antibiotic, resistant bacteria are excreted in the urine, even when no clinical resistance exists.

Metrics regarding measuring and reporting antibiotic use at the hospital or physician levels could be coupled with health outcomes to provide meaningful information. However, it must be recognized that required reporting of potentially negative information may lead to incomplete reporting. Even with such reporting,

combined with strict antibiotic-use guidelines within a single-payer system, there is still inappropriate prescribing and use of antibiotics. There could be potential unintended consequences from penalizing hospitals that deal with difficult-to-treat infection cases, especially for hospitals that may not have adequate resources to implement detailed infection treatment or control schemes. It was suggested that higher-level solutions, such as new technologies or more passive approaches, may yield better results.

The communication of credible information through generally available education programs on health care focused on the lay public can be a key element in reducing AMR. It was agreed that a simple message, even if some precision is omitted, is preferable to complex statements when addressing the general public. Alternatively, others suggested that sensationalizing the factual risks associated with inappropriate use of antibiotics may be necessary to gain the attention of the public. Different audiences depend on vastly different communication channels and media, and the medium needs to be tailored to the message and the intended audience.

Observational studies have shown more impact from messaging that displays benefits to an individual than messaging that discusses public good. Translating these findings to the issue of inappropriate use of antibiotics suggest that consumers could be educated on the individual risks and benefits of antibiotic use. As an example, while methicillin-resistant *Staphylococcus aureus (*MRSA) infection is currently a feared disease, the individual benefits of antibiotic use are a more powerful motivator. Lastly, it was agreed that societal benefit around appropriate antibiotic use is important, both as a goal and a potential motivator.

Policy issues

It was unclear whether the proposal to raise the cost of antibiotics would have the desired effect or result in unintended consequences. A recent study noted that it is quicker and easier for a physician to write a prescription for antibiotics than it is to explain to the patient why an antibiotic is not needed. The proposal seeking to address this imbalance by increasing the time and effort required for a physician to write such a prescription while not preventing the physician from doing so was discussed extensively. One such tactic requiring a three-day waiting period between the prescription being written and being filled has been successful in reducing unnecessary use of antibiotics. Because society is already paying increased costs related to the development of new antibiotics, (i.e., more expensive antibiotics and increased costs from resistant infections), the proposal was viewed positively as a practical approach to aligning costs with desired behaviors. While producers and consumers are the primary parties affected by the proposal, there is also a role for

regulators, especially in the definition and approval of appropriate labeling for new antibiotics.

Intellectual property policies, both patent extensions and reductions, could be used to encourage pharmaceutical companies to be better stewards of the long-term efficacy of their medicines. Focusing on patent extension or regulation of the antibiotic related solely to its efficacy against a target pathogen may, however, have unintended consequences. For example, an antibiotic approved to treat lung infections may be monitored using a surveillance model for resistance with incentives and/or disincentives to keep resistance low. However, antibiotics also have effects elsewhere in the body on "nontarget" bacteria. It was suggested that the obligations of the sponsor should be expanded to ensure that there are no unwanted effects related to resistance in nontarget organisms. Such unintended consequences are inherent in any policy solution, but should not thwart efforts to incentivize companies to pay attention to the efficacy of their drugs in the long term. There is currently no incentive for the patent-holding pharmaceutical company to be concerned about efficacy beyond the end of patent life. Incentives that consider a common mechanism of action among similar compounds may also prove to be a useful control point related to resistance. Reduction of patent life may have the unintended consequence of increasing inappropriate use of antibiotics through the introduction of lower-cost generics.

Incentives to significantly reduce inappropriate usage will potentially curtail the incentives for pharmaceutical companies to continue to produce existing antibiotics and to research and develop new antibiotics. These competing incentives and their resulting outcomes must be balanced. The benefits of reductions in inappropriate use may be beneficial in reducing resistant infections, but this benefit may come at the expense of the development of novel antibiotics. One possible solution is for the government to guarantee purchases of a certain amount of a newly developed antibiotic, an approach similar to some vaccine-purchase programs.

As a viable alternative to putting the primary responsibility to preserve antibiotic efficacy on the pharmaceutical sponsor, an educational and advocacy partnership among health care providers, consumers, and pharmaceutical companies was proposed. Since companies are driven by economic and market forces, it will be difficult to craft appropriate incentive structures to preserve antibiotic efficacy without including other key stakeholder groups. In many countries, pharmaceutical companies have little or no control over the prescribing and ultimate distribution of their products, circumstances that would make it exceptionally difficult for such efficacy preservation incentives to be implemented

in those countries. It was agreed that a sole focus on pharmaceutical companies would be an incomplete solution, but that the market forces that drive inappropriate prescribing must be addressed, and that it was the direct responsibility of the regulators, not the companies, to do so. While consumers also play an important role, there was disagreement over whether direct education or financial measures would be more effective in driving consumers to reduce inappropriate use.

A suggestion was made to base patent life for antibiotics on total volume sold, rather than on a fixed number of years. Such a measure would relate better to the biology of antibiotics, and the total could be adjusted upward if the resistance level stayed low. While this novel idea was considered a valid concept, difficulties in its pragmatic implementation were identified. The two main concerns were the lack of upfront information to establish an appropriate "patent life volume" at time of launch of a new antibiotic, and the view that pharmaceutical companies should not have primary responsibility for stewardship of efficacy preservation. It was further argued that patent life in general may not be an effective policy tool for this issue.

Delaying a problematic burden of resistance is a complex goal with an inexact endpoint. The desired outcome of such delay is reduced morbidity and mortality due to resistant infections and thereby addressing the primary concern associated with a general inability to treat infections. However, as the case with any complex issue, policy solutions that impact one area may have deleterious effects in another. As an example, decreased use also reduces incentives for the development of new antibiotics which in turn can result in further overuse of drugs that may already have resistance.

A proposed policy to provide physicians with legal protection from lawsuits for not prescribing antibiotics could be linked to evidence-based guidelines for appropriate usage. If a physician follows the guidelines, he or she would be immune from malpractice lawsuits. The likelihood of such protections being enacted was unclear.

Managing Antibiotic Resistance in Animal Agriculture amidst Conflicting Moral Beliefs and Scientific Uncertainty**

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Summary

The moral imperative to use antibiotics for treating bacterial diseases in both humans and animals is obvious. Less obvious are the moral beliefs, social norms, and behavioral constraints (e.g., economic realities in a competitive industry) that face food animal producers and their consulting veterinarians. Anti-infective products such as antibiotics are unlike other technologies used in medicine and agriculture in that resistance — an inevitable consequence of their use — results in diminishing effectiveness over time. While such diminishing effectiveness operates on a nearly invisible scale in terms of day-to-day clinical practice and decision-making, its nonlinear decay yields an economic (or social) externality in much the same way that depletion of nonrenewable resources is seen by many to reduce natural capital.

Efforts to conserve the "resource" — in this case, the effectiveness of an antibiotic — may be thwarted by a multitude of paradoxical factors including: (i) patent laws that are inappropriate for antibiotics, since pharmaceutical company marketing efforts will necessarily aim to achieve a reasonable return on investment before cheaper generic products hit the market; (ii) the stifling of innovation if the World Health Organization (WHO) and others immediately and routinely classify newly discovered compounds as "critically important," thereby limiting their potential market; (iii) regulators removing classes of products (or certain indications) for routine use in food animals, thereby narrowing and intensifying the pressures applied on those that remain; and (iv) adopting risk assessment paradigms that misalign levels of antibiotic use with levels of antibiotic resistance, often ignoring the cumulative nature of the risk and well-documented phenomena such as co-selection by other antibiotics, and even heavy metals.

Current realities

The use of antimicrobials — especially antibiotics — in animal agriculture has been common practice for almost as long as in human medicine. Early on, the types of animal uses rapidly expanded beyond their more obvious therapeutic indications to include prevention and control of diseases, and even growth promotion. Resistance to antibiotics typically emerges soon after, and sometimes well before, the introduction of these products, and thereafter disseminates, expands, and persists as a function of readily explained, though sometimes paradoxical, selection pressures. Contrary to popular belief, most resistance factors do not develop *de novo*; rather, each tends to represent a modification or refinement of some pre-existing cell function.

The need to use antibiotics to treat acute bacterial diseases in humans is obvious. For food animals, almost all sides of the debate over the continued and future use of antibiotics in animal agriculture seem to agree that sick animals under producer and veterinary care likewise deserve to be treated. However, such agreement does not extend to the much more controversial use of subtherapeutic doses of antibiotics to enhance growth, or even to the use of timed mass treatment (or metaphylaxis) to control infectious disease in the face of an outbreak. When surveyed, both feedlot veterinarians and their feedlot producer clients placed as much emphasis on the moral duty to treat acutely ill cattle as the economics involved in such decision-making (see Figure 1). However, the attitudes and beliefs of feedlot producers and veterinarians regarding the other uses of antibiotics often differ greatly, specifically, for the treatment of chronically ill cattle, mass treatment for control of disease epidemics, and the use of subtherapeutic doses of antibiotics for growth promotion purposes (see Figure 1). Examined more closely, these differences seem to reflect internal conflict and core differences in attitudes regarding product efficacy (e.g., sense of duty to treat chronically ill cattle despite ineffectiveness) and the expectations of clients, bankers, and others to use approved feedgrade antibiotics to improve growth. Such differences suggest opportunities to enhance communications and to explore and enact policies that recognize differences among industry stakeholder attitudes, beliefs, and their likely behaviors under a variety of future scenarios.

Scientific opportunities and challenges

Two examples of pharmaceutical products approved a long time ago are tetracycline (an antibiotic) and furosemide (a diuretic). Both furosemide and tetracycline have been surpassed in relative efficacy by newer generations of similar products. However, while the absolute effectiveness of furosemide has not meaningfully

changed (i.e., patients have not evolved on a pharmaco-epidemiologic time scale), the relative effectiveness of tetracycline against many bacterial infections has diminished considerably since the product was introduced.

Because bacteria reproduce more rapidly than food animals and humans (i.e., on a scale of hours as opposed to months, years, and decades, respectively), their ability to adapt is reflected in the waning absolute clinical efficacy of the products used to treat bacterial diseases over periods of years to decades. Any decision by an individual to use an antimicrobial to treat an immediate problem thus has an immeasurably small but negative impact on its future effectiveness. Coast et al. (2001) describe the broad economics of such declining usefulness as a "negative externality because it has adverse consequences for society as a whole, whereby the cost borne by the individual is somewhat less than that borne by society." Recent controversy over a large Gates Foundation grant to fund research in children on what has been known about antibiotics and growth in animals (i.e., that antibiotics promote growth) arises almost entirely from the individual versus societal cost structure defined above.

It is important to note that the timescale of resistance development and expansion, and the timescale of policy development and implementation, do not coincide. In most cases (e.g., the third generation cephalosporin ceftiofur, an animal drug closely related to the human drug ceftriaxone), there is a post-introduction period of years to decades in which resistance appears to be nil, or very low, followed by expansion closely mimicking a logistic function (i.e., growing exponentially at first, then plateauing). On the other hand, when conducting *in vivo* research in animals we observe that while the prevalence of bacterial resistance (when present) rises during and immediately following treatment, it tends to fall back to baseline (or apparent zero) after a washout period. This latter phenomenon is the reason that classical quantitative risk assessment (QRA) approaches can be functionally useful for aiding in decisions about slaughter withholding times (whether using residue avoidance or microbial safety endpoints). However, these risk models are not adaptive on a microbiologically relevant evolutionary scale and thus can provide a false sense of security by relying on concurrent relations between antibiotic use and resistance in animals among enteric bacterial populations not receiving antibiotic treatment.

Policy issues

- Current patent laws are in many ways inappropriate for products whose absolute effectiveness decays with use. Novel patent laws to discourage

imprudent or excessive use, and to improve the likely success of voluntary or involuntary actions such as temporary withdrawal of products from markets, will have a greater chance of success if flexible policies such as "patent holidays" (extensions of patent protection commensurate with the withdrawal period) are made available to counter the pressing short-term need for pharmaceutical company return on investment.

- Encouragement of innovation is essential. Offering extended patent protection and market exclusivity to new classes of antimicrobials could help to spur research and development in this area. Attempts to overcome an absolute reduction of efficacy through "relative" improvements are more likely to be successful when new classes of antibiotics are discovered and introduced than when copycat or "me-too" products from the same class of antibiotic are reproduced and mass-produced.
- Routinely classifying all new antimicrobial classes as "critically important" or "human-only" is likely to discourage, rather than encourage, innovative investments. Identifying novel compounds suited to other uses and separating such categories not only on the basis of "bug-drug-indication" classifications, but also on human versus food animal use, and therapeutic versus prevention/control, would create market opportunities as well as assist in prudent planning for the inevitable resistance development.
- Removing longstanding classes of antibiotics, such as tetracyclines and penicillins, from certain uses in food animals necessarily increases the need for, and narrows the selection pressure onto, other antibiotics, including those identified as critically important for human medicine. A strategy that looks beyond simple drug-bug combinations and considers impacts of such bans will help to identify many unintended consequences.
- The current paradigm of risk assessment as applied to the approval process for new and existing antimicrobials is fundamentally flawed. Holistic risk assessment approaches that consider evolutionary adaptation by bacterial populations and include factors that can co-select for resistance are needed. The development of novel surveillance approaches to detect the emergence of resistance before it becomes prevalent, as well as establishing predetermined critical thresholds of resistance at which prescribed mitigations are deployed, should be part of the new drug approval process.

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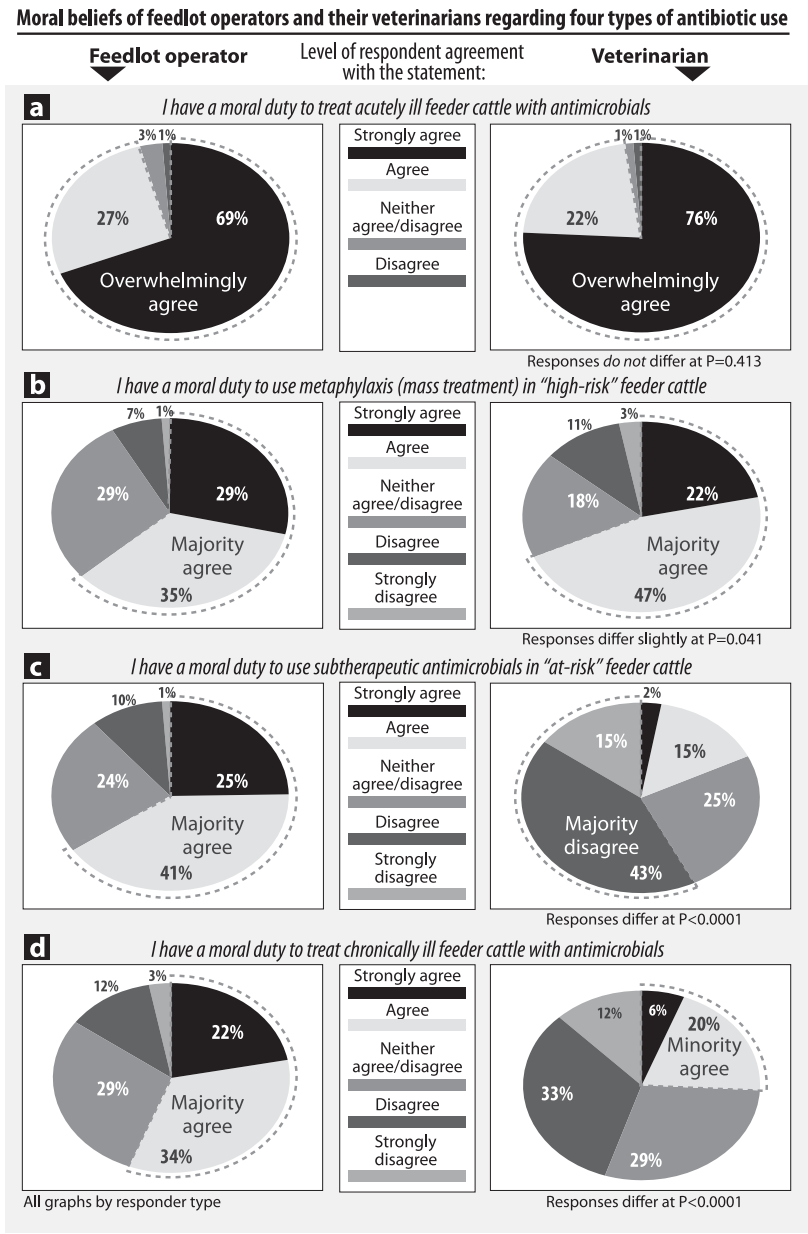
***** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2013, at Baylor College of Medicine, Houston, Texas***

Figure 1


Moral beliefs of feedlot operators and their veterinarians regarding four types of antibiotic use
Feedlot operator
Level of respondent agreement with the statement:
Veterinarian
a
I have a moral duty to treat acutely ill feeder cattle with antimicrobials
3%
1%
27%
69%
Overwhelmingly agree
Strongly agree
Agree
Neither agree/disagree
Disagree
1%
1%
22%
76%
Overwhelmingly agree
Responses do not differ at P=0.413
b
I have a moral duty to use metaphylaxis (mass treatment) in "high-risk" feeder cattle
7%
1%
29%
29%
Majority agree
35%
Strongly agree
Agree
Neither agree/disagree
Disagree
Strongly disagree
11%
3%
18%
22%
Majority agree
47%
Responses differ slightly at P=0.041
c
I have a moral duty to use subtherapeutic antimicrobials in "at-risk" feeder cattle
10%
1%
24%
25%
Majority agree
41%
Strongly agree
Agree
Neither agree/disagree
Disagree
Strongly disagree
2%
15%
15%
25%
Majority disagree
43%
Responses differ at P<0.0001
d
I have a moral duty to treat chronically ill feeder cattle with antimicrobials
12%
3%
22%
29%
Majority agree
34%
Strongly agree
Agree
Neither agree/disagree
Disagree
Strongly disagree
12%
6%
20%
Minority agree
33%
29%
Responses differ at P<0.0001
All graphs by responder type

Debate Summary

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Debate conclusions

- While there is significant disagreement concerning whether antibiotic resistance in animal agriculture contributes to the development of antibiotic-resistant infections in humans, there was consensus that antibiotics not be used for growth promotion in animals even though no scientific evidence demonstrates that such an elimination would improve human health.
- There is no scientific consensus that the use of fewer antibiotics at a higher intensity will reduce the rate of resistance development compared with the use of many antibiotics at lower levels.
- Policy approaches need to strive to prevent resistance before it develops, rather than limiting the spread of resistance once it emerges.
- A combination of risk assessment models and an international surveillance system with critical thresholds and antibiotic usage monitoring need to be used to guide policies to limit antibiotic resistance.

Current realities

Unlike most medicines, (e.g., aspirin) which can be used many times without any loss in efficacy to either an individual or within a population, repeated use of antibiotics will reduce the treatment efficacy over time for individuals and within populations. Such effects also can be observed for different antibiotics within the

same class. Development of resistance varies depending on the specific microorganism and antibiotic. Some bacterial organisms have been treated with antibiotics for many decades without developing resistance, while other bacterial organisms have developed resistance to treatment within a few years. The presence of linked antimicrobial-resistance genes also affects whether treatment with a particular antibiotic can lead to resistance.

Resistance genes passed among different bacterial organisms are usually linked, meaning that there are multiple resistance factors that are passed together from one organism to another. Because of these linkages, the use of one antibiotic can, at times, depress the efficacy of a whole host of other antibiotics in certain organisms. When multiple resistance factors are present, the use of one particular antibiotic can inadvertently select for multidrug-resistant organisms. There are relatively few antibiotics (e.g., tetracycline and streptomycin) for which resistance occurs for only one antibiotic at a time.

Resistance to newer antimicrobials tends to arise in plasmids, which already have many other resistance genes present. It is not uncommon to see plasmids with five to eight antimicrobial resistance genes. When newer antimicrobials are used, resistance to the new drug often arises coincidentally with resistance to several other drugs, leading to multidrug-resistant organisms. This is a very different situation than what is observed for most other drugs used in health care. The genes that code for resistance to antibiotics in bacteria are transmitted from humans to animals and vice versa as part of a multidirectional ecological phenomenon.

Although antimicrobial resistance is known to develop at different rates in different animal production systems, it is currently unknown whether antibiotic use for therapy, prevention, or growth promotion contributes more to resistance overall. Thus, it is not clear if a few antibiotics used intensively would contribute more or less to resistance than using many antibiotics at a lower level. The level of antibiotic resistance that passes from animals to humans also remains uncertain. There are no current data that define this probability, other than scientists stating that it is a theoretical possibility that may occur.

Scientific opportunities and challenges

The treatment of sick animals is a particular area that could be targeted to reduce the development of antimicrobial resistance. Newer models of treatment in agricultural operations may help reduce the risk of developing antibiotic resistance by treating sick animals on an outpatient basis rather than in veterinary hospitals. Using this method, animals may quickly reconstitute their normal gut flora by being exposed to other animals in a typical production environment. This could

reduce the number of animals that carry resistant infections when compared with the treatment model of the past, which has been shown to increase the animal's susceptibility to infection after treatment.

Regardless of whether it is deemed appropriate use in a regulatory sense, it was agreed that veterinarians and producers both feel a significant moral obligation to treat ill animals with antibiotics and have difficulty stopping treatment — similar to the obligation medical doctors feel to treat human patients. Producers also feel the need to continue treating an animal even if it is not responding well or is chronically ill. To reduce antibiotic use in these situations, it may help to remove the animal to a different location (e.g., a pasture or an off-site treatment facility) or to euthanize the animal if appropriate.

Stakeholders who view the reactionary use of antibiotics to treat sick animals as a failure in systems for disease prevention and control consider preventive uses in animals as acceptable. However, some argued that reducing overall antibiotic usage is largely meaningless and that reductions need to be targeted instead to address specific outcomes in certain animal populations. As an example, if an antibiotic is used extensively to improve animal health, but never for treating human infections, banning its use in animal agriculture would have no effect on improving human health. There was, however, strong disagreement on this point.

In addition to reducing the amount of antibiotics used in animal agriculture, new technologies can be used as alternatives to antibiotics. Some new vaccines target cellular mechanisms such as iron transport and may protect against organisms such as salmonella and E.coli. Currently, these vaccines are largely targeted at specific areas of concern to animal health (e.g., lung and skin pathogens) rather than at bacteria in the digestive system that are related to antibiotic resistance in humans. In addition, these new vaccines cost significantly more than comparable antibiotics.

The treatment of healthy animals with antibiotics (i.e., as growth promotion) was also discussed. Even if the overall health of farm animals was significantly improved through other means, there could still be a positive use of antibiotics for animal growth promotion. The mechanisms by which antibiotics act as effective growth promoters are only partially known, and more research in this area was considered urgently needed. Antibiotics may reduce subclinical infections, improve the absorption of food nutrients, and/or act as probiotics for certain organisms that increase animal growth. Given additional research, there may be ways to mimic the effect of antibiotics using other treatments that are as cost effective as current antibiotics. The understanding of the mechanisms of antibiotic actions is limited

because this knowledge was not required as part of the approval process for many drugs in the 1950s and 1960s.

Although some argued strongly that antibiotics never be used in healthy animals, others noted that producers see improvements in the efficiency of production when using antibiotics. The use of antibiotics as growth promoters does not benefit the healthiest and most robust animals, but rather improves the health of the smaller animals with poorer health. The overall result is a more uniform product and healthier animals. If the use of antibiotics for this purpose is phased out, producers would bear a financial cost. There was no agreement as to whether producers would be willing to be compensated in exchange for eliminating the use of antibiotics for growth promotion purposes.

Policy issues

An opportunity exists to develop a more integrated and effective regulatory system at the farm level. The application of risk assessment as a tool for managing the development of antibiotic resistance was seriously questioned because the model describing the spread of antibiotic resistance from the farm is based on food safety and importation guidelines. This risk assessment model identifies a farm as having an elevated use of antibiotics and assumes the genes related to the antibiotic being used could escape the farm and enter the food supply. If the long-term goal of regulation is to prevent the development of resistance, then the guidelines need to focus on preventing antibiotic resistance rather than seeking to limit or contain the spread of antibiotic resistance once it has arisen.

Current risk-assessment models for regulating antibiotics also assume that resistance in the animal is a danger to human health and that treatment with antibiotics for growth promotion purposes leads to antibiotic resistance in humans. However, little is known about the ratio of resistant infections stemming from treatment of ill animals versus animal treatments with antibiotics for growth promotion. The absence of this information results from the lack of data on antibiotic use by class and by indication. It is unknown whether using a few antibiotics intensively will lead to more or less resistance than using several antibiotics at a low level. In general, there was disagreement on the relationship between resistant bacteria in animals and clinical disease in humans.

Critical thresholds were considered as another potential piece of a more integrated regulatory system affecting animal agriculture and human health. Regulations based on risk assessment could be combined with an integrated surveillance system with defined critical thresholds of antibiotic resistance, which would identify when resistance against a given antibiotic had reached a critical

level. These critical thresholds could also be used to establish benchmarks against which the labeling of antimicrobial products could be evaluated over time, thereby restricting the use of the product once antibiotic resistance reached a certain level. Such traceability would be in contrast to the currently unchecked, continuous use of on-label products. Continuing use occurs despite the reality that resistance could be developing for those products.

Some argued that it may be difficult to establish the thresholds, as well as maintain a database of other active, systematic surveillance and management tools that can be used to measure antibiotic resistance levels. While one solution for addressing the difficulty of measuring thresholds would involve measuring antimicrobial resistance at slaughter, the ultimate measurement of success would be obtained by measuring the human infection rate. Thresholds would also need to be based on an active, targeted surveillance system. One potential regulatory action debated involved policies that combined keeping antibiotic resistance levels below these critical thresholds with increased patent protection (i.e., if resistance was kept below a critical threshold in the community, then the length of a patent would be extended).

It was also argued that to have an effective system, the surveillance of antibiotic usage is as important as the surveillance of antibiotic resistance. There was some agreement that data on the use of antibiotics in animals need to be published. The current policy of not publishing production levels when there are less than three suppliers of a class of antibiotics was considered outdated, especially given the consolidation in production companies that has occurred for both animal and human antibiotic producers. However, it was noted that the U.S. Food and Drug Administration (FDA) started publishing the sales data on animal health antibiotic production in 2010.

Another approach to reducing the development of antibiotic resistance in animal agriculture is to reduce the need for antibiotics by increasing disease prevention. While barriers such as cost exist to implementing prevention methods (e.g., increasing biosecurity, improving cleanliness of production facilities), there could also be ancillary benefits such as improving worker health and safety and/or reducing the number of farm-acquired infections. Certain vertically integrated animal-production systems (e.g., poultry production) in the United States are good candidates for improved hygiene and biosecurity approaches. Other animal production systems (e.g., the cattle industry) are organized in such a way that these types of measures would be less appropriate or successful.

There was significant debate about the need for new regulatory standards for antibiotics currently under development. There was support for considering all

new antibiotics licensed critical for human use until proven otherwise. Alternatively, the development of multiple categories of antibiotics, both to address resistant infections in animal agriculture and to encourage new antibiotics by identifying multiple areas for potential use, was also promoted.

Both domestic and international collaboration and communication will continue to be essential to effectively address antimicrobial resistance. It was noted that in the regulatory approach to antibiotics, there is a risk that national policies will not coordinate well with international policies. It will be important to consider that there are many different concerns to be addressed for both human and animal health, depending on which country and what type of production method is being used. For example, a critical aspect of agreements involves issues such as the washout period after treatment (i.e., antibiotic resistance returning to a baseline level). While this specific issue was discussed, there was no consensus on what this time frame is or whether the original baseline level is ever regained.

Antimicrobial Resistance — A New Drug Discovery Perspective Using Synthetic Biology**

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Summary

Antibiotic resistance is a significant international health issue that needs to be addressed and solved urgently. However, major pharmaceutical companies have reduced their efforts in novel antimicrobial discovery because of the low cost-to-profit ratio and the difficulty in actually finding new compounds with effective activity. Synthetic Biology (SB) will offer a new approach to the discovery of novel drugs, overcoming some of these problems. Using this state-of-art technology, antibiotics can be designed for novel activity and can be developed much more cost effectively. For SB to be fully exploited for discovering new antimicrobials, a number of policy changes are required (e.g., new funding mechanisms, more international collaboration, dedicated funding for high-risk fundamental research, stronger translation of new technologies to industry, new funding/research initiatives targeted at less-affluent country markets).

Current realities

The availability of antimicrobial drugs has dramatically changed the public health landscape since the 1940s. Serious diseases, which led to almost certain disability or death in a large number of patients, are now rapidly and safely cured with antibiotics. We now understand that microbial populations in the pre-antibiotic age already maintained a very low level of natural antibiotic resistance, and the treatment with antibiotics quickly selected the resistant strains, with rapid exchange of resistance genes leading to ever more intractable microbes. This mechanism is particularly effective and serious in hospital settings, and several generations of newly developed antimicrobials are already ineffective against a large fraction of hospital-acquired infections.

We are now threatened by the emergence of microbes that are resistant to all available antimicrobial drugs. This would potentially facilitate a return to the

pre-antibiotic situation, where a simple scratch or minor cold could develop into a life-threatening disease that could kill large parts of the population, especially among the very young and elderly. Chronic misuse of antibiotics, for example in animal husbandry or due to over-the-counter availability, accelerates the emergence of resistant pathogens.

The obvious challenge for drug discovery is to rapidly and continuously come up with new generations of antimicrobial drugs that overcome the resistance mechanisms and provide a new line of defense. However, at the same time that antimicrobial resistance is on the rise, we see a dramatic decline in the number of new antibiotics entering the market (Figure 1A), and currently the pipeline of new agents reaching the market is almost empty, especially for the treatment of gram-negative infections by bacteria such as *Escherichia coli (E. coli), Salmonella, Pseudomonas* and *Shigella,* all of which cause significant morbidity and mortality. Drugs with completely new modes of action are rarely becoming available, with new developments usually being based on derivatives of existing antibiotics. Only two new antibiotics entered the market in the last decade: telavancin, which was approved by the United States Food and Drug Administration (FDA) in September 2009, is a vancomycin derivative; and ceftaroline, approved in October 2010, which is a cephalosporin with a mode of action similar to penicillin; both are used to treat multidrug-resistant skin infections.

There are two main reasons for this. First, it is no longer economically attractive to develop new antibiotics: these are drugs that (if they work) are taken for a few weeks only, and then the patient is cured. Even if drugs for the treatment of multidrug-resistant hospital-acquired infections can be sold at a premium price, they pose difficulties earning back the immense costs associated with taking a new drug through the development pipeline (clinical tests, regulatory procedures, marketing). Second, traditional methods of searching for new antimicrobials have lost their effectiveness. Large-scale screening procedures tend to rediscover the same candidates repeatedly, further increasing the economic risk involved in the search for new antimicrobials.

Scientific opportunities and challenges

SB is defined as the use of new genome synthesis technologies to create new living systems with beneficial functionalities. This is a new approach to antibiotic discovery, which has the potential for discovering truly novel antimicrobials at the rate required by the rapid emergence of resistance after the introduction of each new drug. It exploits the fact that the vast majority of antibiotics are actually produced by microbes, using genetically encoded modular enzymatic "assembly

lines," which are particularly amenable to an engineering approach to biology. SB has the additional benefit of being a technology that can be used in academic research, moving the main drug discovery work from large pharmaceutical companies toward academia (and small biotech companies).

Genome sequencing of thousands of bacteria and fungi has revealed that each species of microbe tends to contain the machinery to produce antibiotic compounds. Some soil bacteria are predicted to be able to produce several dozens of different antimicrobials. However, it has also become clear that the largest fraction of these potentially new compounds is invisible in classical screening: the biosynthetic machinery is "asleep" or silent (i.e., their potentially novel end-products are not detectable under the usual culture conditions in which microbes can be grown). The challenge for SB is to create new producer microbes that would "awaken" the silent biosynthesis of new antimicrobials and produce them in large and robust amounts. The general strategy has the following steps (Figure 1B):

1. Identify the biosynthetic machinery for new antimicrobials by large-scale genome sequencing of a large number of diverse organisms from distinct niches.
2. Isolate the responsible genes and put them under artificial, engineered control systems, so they can be activated as needed.
3. Transfer the engineered gene cluster into a host bacterium, which has been specifically designed to provide the necessary components for antibiotic biosynthesis in large amounts.
4. Isolate, identify, and characterize the new compound. Screening can also be extended beyond antimicrobials (e.g., to include antimalarial, anticholesterol or anticancer activity); all of these diseases are commonly treated with drugs derived from natural products and thus amenable to the same SB approach.)
5. Repeat this procedure many times, at high throughput, to increase the chances that clinically valuable compounds are detected.
6. Transfer the biosynthetic machinery for compounds of interest into pre-designed, industrially validated, and safe production hosts, minimizing the risk that active, valuable compounds drop out late in the pipeline, because of limitations in production efficiency.
7. As the genes for the entire biosynthetic machinery are produced synthetically, it is also possible to try out different variants: antibiotics are typically produced by large assembly lines of enzymes, and it is possible

to use SB to replace individual units or modules of these assembly lines systematically, so that instead of a single new compound, we obtain a library of slightly different variants, perhaps with better pharmacokinetics or broader activities.

Of course, like any emerging game-changing technology, SB raises a number of potential issues that could limit its industrial application. However, in its application to antibiotics discovery, these barriers are far less problematic than in many other fields. First, the host organisms for antibiotic production are well-characterized microbes that are generally regarded as safe, limiting ethical concerns associated with the creation of new life forms (e.g., compared to the manipulation of eukaryotic cells, higher animals, or security-relevant microorganisms). Second, drug discovery and production take place in fermentation tanks, limiting security concerns about the release and containment of genetically modified organisms (e.g., compared to agricultural applications). Third, antibiotic production, and the general biosynthetic production of high-value compounds (e.g., drugs, food and cosmetic additives, refined chemicals), is a highly efficient process, limiting economic concerns about resource competition (e.g., compared to biofuel production by SB).

Policy issues

SB approaches to drug discovery raise a number of important policy challenges:

- **Develop new funding mechanisms:** SB requires funding mechanisms that reflect its interdisciplinary approach, bringing together classical microbiology, natural products chemistry, and modern engineering and computational technologies. Examples include collaborative grants from the same or different institutions; interagency/cross-council funding initiatives; interdisciplinary SB training (discipline-hopping grants at various levels, support for initiatives like the International Genetically Engineered Machine competition [iGEM]); and interdisciplinary funding committees.
- **Stimulate more international collaboration:** This is essential, as the necessary expertise is sparse and often available only in single geographic areas (e.g., culture collections of exotic antimicrobial-producing bacteria and fungi). Cross-country funding initiatives are needed (e.g., the European Research Area grants on SB). Multilateral initiatives and funding from a single joint pot are strongly preferred over bilateral approaches and separate funding by country. As much as possible,

opportunities should be created for research partners to be chosen by scientific quality, not by geography.

- **Fund high-risk fundamental research:** SB is a new field, and ambitious innovative projects are crucial. There is a clear danger that funding is targeted at close-to-market, application-ready projects, while the true benefit for the long-term solution of the antimicrobial drug discovery issue would come from high-risk fundamental research that establishes novel tools and concepts. A counterintuitive, but scientifically and economically desirable move, would be to stop all funding for applied research in SB. Instead, increase the incentive for creative basic research that can become the basis for a new industrial revolution (e.g., by funding 10 SB proposals per year which are completely fundamental, out-of-the-box and risky). These proposals should be funded without the need for publications or proof-of-concept data, selected based on scientific creativity and vision, and funded long-term (10 years).
- **Translate new technologies to industry:** Close industry-academia ties are essential, but instead of being focused on doing applied research for immediate industrial deployment, the aim should be to enhance industry awareness of new technologies. Create technology centers associated with a critical mass of state-of-art academic research, with the explicit mission of identifying industrial opportunities and translating the novel technology toward commercialization (e.g., the National Graphene Institute at the University of Manchester).
- **Establish initiatives targeted at less-affluent markets:** Given the economic difficulties of developing new antimicrobials in a commercial setting, creative public and/or charitable initiatives are needed, along the lines established in the development of innovative drugs for less-affluent markets. Training in SB for less-affluent countries is needed, as are specific funding initiatives for the identification of SB targets to address specific needs in the developing world. This can go far beyond antibiotics and other drugs, but these are a good starting point, given that many infectious diseases are closely associated with poverty, and SB offers economically and environmentally attractive new routes to drug production.

A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2012, at Baylor College of Medicine, Houston, Texas.

Figure 1A (Courtesy of David Hopwood, UK)

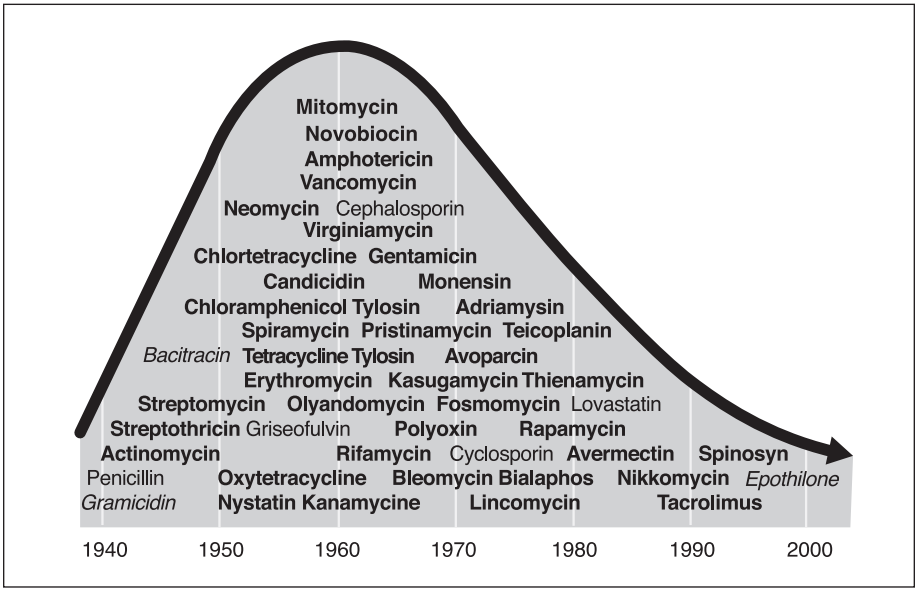
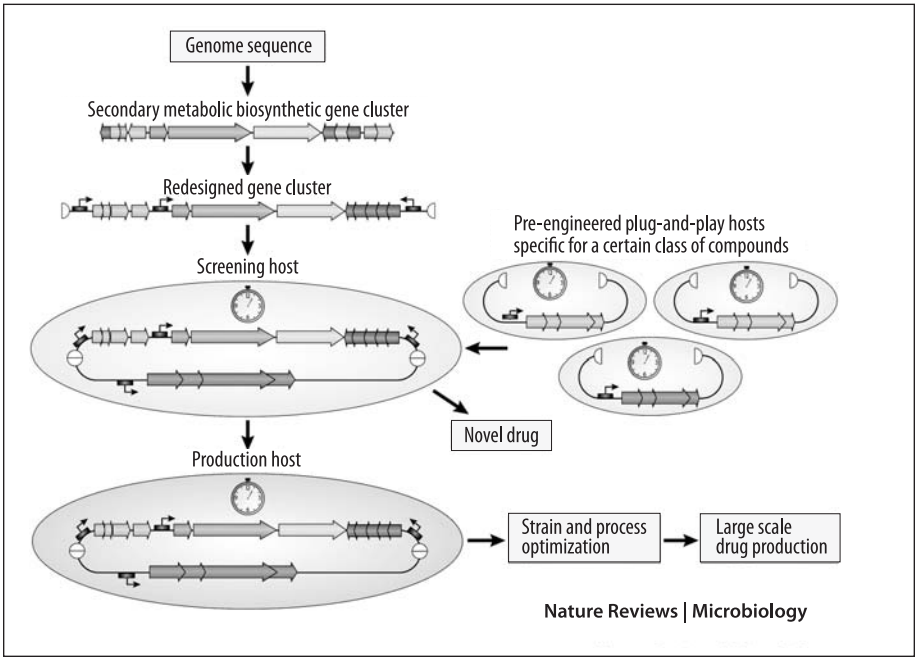


Figure 1B (from Medema, Breitling, Bovenberg, and Takano, Nature Reviews Microbiology, 2011, 9:131-137)



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Debate conclusions

- Since synthetic biology is a platform technology that requires public and private sector investment to generate useful products in a wide variety of areas, partnering across public and private sector cultures is needed to optimize the opportunity to create and test new antimicrobial compounds.
- Since new antibiotics are desperately needed and the current drug development pipeline is not producing new antibiotics in either sufficient quantities or over rapid time frames, synthetic biology is an increasingly important technology for meeting this need. Programs committed to produce significant quantities of new antimicrobial compounds via synthetic biology would provide a concrete example of the utility of this promising technology.
- While bringing multidisciplinary expertise together is critical to the successful practice of synthetic biology, the current structure of existing funding mechanisms and priorities for funding bodies to support basic research makes multidisciplinary funding less likely, especially when budgets are being decreased.

Current realities

Synthetic biology is an emerging field, and although most governments, academic institutions, and private industries see great promise in it, there has been early-

stage hesitation in funding because of the current absence of tangible benefits or viable products. In the context of antimicrobial resistance, it was argued that developing a new antimicrobial drug is an excellent objective by which to demonstrate the potential of the nascent field of synthetic biology. Developing a novel antibiotic provides a concrete direction for funding sources, and provides a bridge for synthetic biology to expand to other products and scientific arenas.

Synthetic biology is widely viewed as the next "industrial revolution" for biotechnology. It offers opportunities to create new drugs and target specific illnesses, and the potential for expanding personalized medicine by rapidly creating treatments for individual patients. While current technology allows the "reading" of DNA, synthetic biology offers the ability to synthesize or "write" DNA.

Although it was agreed that new antibiotics are vital in the response to the threat of antimicrobial resistance, the development of new antibiotics is not sufficient. Because new antibiotics likely will not provide a significant return on investment to private industry, there is little incentive for private industry to invest at the early stages of development of synthetic biology.

There was agreement that a *de novo* compound from synthetic biology research is at least five to 10 years away. While organic chemistry approaches have been able to produce new compounds in the past 20 years, the results have been limited. Practitioners acknowledge that synthetic biology is still at the early stage, and more fundamental research needs to be done before tangible products can be produced (i.e., proof of concept). However, for industry to commit substantial funding, the potential for significant return on investments will need to exist.

Because both the U.S. and Europe are facing austerity measures that cut across many disciplines and projects, proposals for new funding mechanisms are unlikely to be received favorably by policy makers. Without a specific product as an outcome, it was agreed that it is difficult, especially for the private sector, to justify more money for fundamental research in synthetic biology.

Since government sources of funding are subject to stringent cost-benefit analyses, outcomes need to be specific and justify significant funding. Panels evaluating proposals are looking for transformative research with guaranteed outcomes — goals that are often not congruent with high-risk research. Although the current state of synthetic biology is still at a fundamental level, a valid cost-benefit argument needs to be made. It was questioned whether proof-of-concept proposals are enough for government funding. Although the multidisciplinary nature of the field might make it possible to solicit support from already existing funding streams, new funding specifically earmarked for synthetic biology was thought to be unlikely. It was argued that it would be prudent to start gathering

groups of multidisciplinary experts before requesting funding, and that a multidisciplinary approach could improve the potential for successful funding requests. Constructing and consulting multidisciplinary panels could be done in stages, including different disciplines as the research progresses. It was agreed that research strategies would need to be re-evaluated periodically during this progression.

Scientific opportunities and challenges

Synthetic biology is a cutting-edge technology, and has the potential to alter existing and create new organic compounds. Creating new drugs, especially new antibiotics, is one of many possibilities that arise from the further development of synthetic biology. While the ability to read DNA has existed for several decades, the ability to use this knowledge to make real, applied products is only now being realized, and this is ultimately where the scientific opportunity lies. Many disciplines may use synthetic biology to alter the fundamental building blocks of biological elements, including engineering, medicine, combinational chemistry, and systems biology.

Although synthetic biology has been able to successfully synthesize sequences, a challenge exists in finding a host in which to effectively replicate new compounds. A successful host would need to be robust and able to replicate in high numbers, so the outcomes can be successfully analyzed and repeated.

Two suggested methods exist for manipulating DNA to create new antimicrobial compounds. One is high-throughput screening, in which computer algorithms are used to identify specific microbial targets from massive amounts of data. Efforts to design molecules to disrupt these targets would then be used. The other approach is to create chemically diverse molecular libraries, and using new chemical structures not seen in nature previously, to develop methods to combat current antimicrobial-resistant bacteria.

It was agreed that designing a specific molecule might not be the best approach, given the current state of the technology. Studies have recently been conducted, including some with pharmaceutical company partners, but these attempts have not been successful. Although not required, some companies voluntarily chose to publish their results, for which they were commended. While scientists have learned from these results, it was argued that the more fruitful approach would be one based on creating new chemical diversity. Initially, synthetic biologists would not try to design new drugs, but rather discover new drugs from chemically diverse panels. The end product would be a novel compound, but it

was agreed that starting with wide chemical diversity likely would be more productive than a targeted-design approach.

Equally as important is what would be learned in the process of developing new drugs via synthetic biology. The analysis of methodologies and specific modifications would lead to iterative improvements in the next generation of pharmaceuticals. Because there exists hidden information (e.g., silent gene clusters), utilizing this information through synthetic biology could help identify novel compounds, and while not completely predictive, offers an excellent starting point with great potential.

While synthetic biology can identify core sequences in DNA that may give rise to certain products, it is not yet possible to predict specific functions of products of individual genes or gene clusters merely by their sequence. A key benefit of synthetic biology is the opportunity to create more diverse, sustainable organic compounds than can be produced by current organic chemistry approaches. During the past two to three years, faster identification of metabolites has been possible using improved software. Because many microbes created with synthetic biology have been difficult to culture, another challenge is the ability to "write" the information and successfully place it in a host for replication.

Although these new compounds would eventually be susceptible to resistance, it was argued that synthetic biology can identify new compounds much faster than existing approaches, such that every time a compound was compromised, a new compound would already be in development or held in reserve. While the same "arms race" currently exists in fighting antibiotic resistance, synthetic biology gives medicine a faster way to respond. It was also highlighted that the inevitability of microbial resistance to synthetically created compounds must not discourage further research. It was considered vitally important to develop new drugs, even if the effective life of such drugs may be limited to a few decades.

It is estimated that it will take five to 10 years before new compounds could be produced via synthetic biology and there is no guarantee that the first attempt will produce an ultimate "wonder drug." However, with the costs of DNA synthesis rapidly decreasing and the mass production of synthesis equipment becoming commonplace, antibiotic development via this route should become increasingly more cost effective.

Another opportunity offered by synthetic biology is related to the development of personalized medicine, an area that encompasses many ethical concerns. A potential future scenario could involve a patient diagnosed with an illness for which his/her genome sequence suggests an effective treatment using existing drugs. However, if the drugs will not work, synthetic biology could then

be used to rapidly access expensive DNA systems to create the exact, personalized compounds needed to treat the disease.

Policy issues

There was extensive discussion of ways to make a new field such as synthetic biology an attractive investment for governments and industry alike. While antibiotics may be commercially unattractive for industry and there is not a market for a billion-dollar antibiotic, using synthetic biology to create replacements for petroleum products is more likely to receive attention because of its market value. Therefore, the petroleum industry may be more likely to develop policies favorable to synthetic biology. Synthetic biology could be featured as a "platform" technology with many possible uses to maximize its attractiveness to funders.

Government-managed funding sources include the U.S. National Institutes of Health (NIH), the Innovative Medicines Initiative (IMI), and the Biomedical Advanced Research and Development Authority (BARDA). The IMI is a joint undertaking between the European Union and the European pharmaceutical industry to support collaborative research and build networks of industrial and academic experts to increase pharmaceutical innovation. In the U.S., BARDA funds trials of antibiotics but only if potential bioterrorism application exists. Both groups currently fund industry projects developing and testing new antimicrobial compounds.

At NIH, the National Institute of Allergy and Infectious Diseases (NIAID) has launched the Centers for Excellence in Translational Research (CETR) program. The goal of CETR is to identify platform concepts that will lead to multiple variants of interventions (i.e., multiple vaccines from a single platform). Synthetic biology fits in that category. Unlike IMI, the CETR is not only for U.S.-based researchers, but is intended to fund the best research regardless of country. As opposed to private industry, NIH invests in more fundamental research aimed at improving public health for U.S. citizens and the rest of the world. In the past several decades, NIH has invested in other types of combinatorial chemistry, but the results from these studies have been underwhelming. As a result, NIH is seen as hesitant to fund large-scale synthetic biology programs.

While the current state of synthetic biology is at the stage of discovery and evidence of efficacy, it was argued that the eventual goal should be to turn products from the technology over to industry to conduct clinical studies. According to industry experts, the eventual cost of such trials will be hundreds of millions, if not a billion, dollars. Industry will therefore be a key partner to provide the capital required to conduct these trials.

Because funding sources prefer to support targeted, applied outcomes, assembling multidisciplinary elements may be critical to the success of synthetic biology. Recognizing the broad future appeal of synthetic biology, there was discussion of new programs that may provide innovative sources of funding. One example is the "sandpit scheme" in the United Kingdom that sets aside funding for short symposiums involving interdisciplinary ideas. These sandpit workshops typically last several days and involve 20 to 30 participants. An essential element of a sandpit is the multidisciplinary mix of participants, some being active researchers and some being potential users of research outcomes. This helps to drive lateral thinking and radical approaches to addressing particular research challenges.

The E.U. also provides some funding for multidisciplinary efforts, but places country representation requirements on the mechanisms, meaning there must be diverse participation from a preapproved selection of countries. It was argued that although egalitarian in concept, not all countries have a synthetic biology contingent, and that the best experts are often concentrated at one university or country. There was also a question about international streamlining; as a multidisciplinary and international effort, how to keep the real goal in sight and effectively share information? It was suggested that having a communal "pot" of funding could be an effective way to encourage communication among different countries and researchers.

It was widely acknowledged that multidisciplinary partnerships must extend beyond academia. These partnerships must include manufacturers, industry, and physicians — stakeholders with tangible experience. There have already been academic collaborations with pharmaceutical companies, but the results of these partnerships have not been publicly released, making it difficult to assess success or failure. It is also essential to take ethical, societal, and governance considerations into account as development progresses. Recognizing the multidisciplinary needs of synthetic biology, Rice University in Houston, Texas, for example, has introduced a doctoral program that encompasses several research fields in life sciences. The new interdisciplinary degree program in systems, synthetic, and physical biology (SSPB) will enroll its first students in Fall 2013.

Partnerships between government and industry have created difficulties regarding both funding and profits. While government partnering with industry is not new, payoff for the public has become a political issue. Cited was a March 2013 *New York Times* article, Seeking Profit for Taxpayers in Potential of New Drug, in which an arthritis drug developed by NIH and Pfizer led U.S. lawmakers to call for review of federal policies that they assert allow businesses to profit on government research, with limited return for taxpayers or consumers. Public-private partnerships will need to make eventual payoffs equitable for all stakeholders.

Global Infection Prevention: A Strategy to Minimize Antibiotic Resistance**

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Summary

Infection control throughout the world operates in an increasingly crowded planet challenged by poverty, hunger, malnutrition, and limited expertise globally to improve health in many communities, clinics, and hospitals. Rising rates of human, animal, and cargo traffic across international boundaries have increased opportunities for international transmission of pathogens. Often such pathogens are not responsive (i.e., are resistant) to available antibiotics. Patients with these emerging infections initially seek help in clinics and hospitals. Therefore, early recognition and containment are strategies to prevent transmission to health care workers and other patients and thus society at large. Furthermore, with increasing rates of antibiotic-resistant microbes, clinicians have a shrinking repertoire of useful drugs for prevention and treatment. Currently, however, the era of alarming antibiotic resistance is challenged by fewer pharmaceutical companies investing in anti-infective discovery.

Current realities

Among the 7 billion global inhabitants, 1 billion cannot buy food, medicines, or vaccines, and they lack access to medical expertise. Of patients entering hospitals, 5% to 10% in developed countries and 25% to 50% in developing countries acquire an infection that was not present or incubating on admission. These are health care-associated infections, which are responsible for significant (incremental) morbidity, mortality, and costs above those expected from the underlying diseases alone. Often, these infections are caused by agents for which medicine has never treated (e.g., viruses) or those not susceptible to currently available antibiotics. The recent pandemic spread of SARS, H1N1 influenza, and ongoing global transmission of multidrug-resistant tuberculosis, community-acquired Methicillin-resistant *Staphylococcus aureus* (MRSA), and multidrug-resistant gram-negative

rods (MDR GNR) have emphasized the fact that, in the words of author and columnist Thomas Friedman on the globalization of societies and nations, "the world is flat!" Antibiotic resistance, infection prevention and control, and antibiotic stewardship are global issues, not regional ones. A key point is that the most health-threatening microbes with antibiotic resistance enter our hospitals and clinics early on and can spread in the health care setting, often before they are recognized.

Scientific opportunities and challenges

There are five strategies that could be employed globally to minimize the transmission of antibiotic-resistant pathogens. Implementation would put an emphasis on early detection and control, ongoing practices to limit spread of all pathogens, and prevention. The five strategies are as follows:

1) Emphasize horizontal programs to limit spread of new (unknown) and old (known) health care pathogens. The effort expended will affect all organisms, thus influencing the total burden of infections rather than focusing only on a subset of the infections (e.g., only MRSA).
2) Develop real-time international surveillance, rapid reporting, and a rapid response team to assist in the detection and control of an emerging pathogen. The sooner new organisms are identified, the earlier they can be controlled, specific patterns of transmission can be recognized, and a dedicated team of experts called into action.
3) Invest in technology focused on rapid diagnostics and whole gene sequencing for organism fingerprinting. Rapid diagnostics can identify pathogens within hours, and whole gene sequencing is currently the most discriminating method for the fingerprinting of organisms needed to separate the offending pathogens from others in the same species.
4) Invest in vaccine prevention of key hospital and community pathogens. Prevention is always less expensive and more efficient in the long term than treatment.
5) Substantially commit to reducing poverty and hunger. The reduction of poverty will improve hygiene and natural immunity, thus reducing susceptibility to infections.

Policy issues

- An initial emphasis in all hospitals should be on horizontal prevention systems (i.e., programs reducing all pathogens) rather than vertical systems

(i.e., focusing on specific agents such as only MRSA or only MDR GNR). Expecting greater than 95% compliance with hand hygiene will limit the spread of known, emerging, and unrecognized pathogens; it is inexpensive yet effective, especially for resource-poor countries. There is value in maintaining emphasis on clean water and soap (e.g., the "Clean the World" program to collect soap from hotels in the developed world and reprocess it for use in developing countries). An example of a horizontal program in surgery is one in which a multisite study of surgical skin preparations showed that 40% of all surgical site infections could be prevented with the use of chlorhexidine-alcohol versus the standard povidone alcohol preparations. Similarly, the use of daily scrubs of hospitalized patients with chlorhexidine-alcohol has been shown to reduce vancomycin-resistant enterococcal bloodstream infections by 73% and Acinetobacter bloodstream infections by 85%.

- A global center for real time surveillance and tracking of newly emerging, antibiotic-resistant infections currently is needed. This center should have the capacity for accurate fingerprinting of organisms to track them over time and space, and genetic analyses of virulence factors and specific genes coding for antibiotic resistance. As a result, there could be rapid reporting using updated maps of global movement of resistant organisms, which would allow a rapid response team of expert clinicians, epidemiologists, and microbiologists to be deployed to help control the transmission.
- A bold investment in vaccines for MDR organisms would eventually lead to less transmission and to reduced usage of antibiotics for therapy. For example, for decades the organism most frequently causing meningitis in children was H. influenzae, and rising rates of antibiotic resistance were a continual worry; yet with the deployment of the conjugate vaccine in the early 1990s, it has almost been eliminated. Similarly reduced rates of both infections and nasopharyngeal carriage have been observed after the use of pneumococcal and meningococcal conjugate vaccines in children, in part the result of herd immunity. Current vaccine priorities should include the following leading health care associated antibiotic-resistant pathogens: S. aureus, Ps. Aeruginosa, C. difficile, K. pneumonine and Acinetobacter. Priorities for community-acquired organisms should include a universal vaccine for all strains of influenza, and a vaccine for tuberculosis. These pathogens are responsible for a large proportion of deaths in the hospital and community.

- Finally, global policies should aim to reduce poverty and thus reduce malnutrition, preserve the immune system, and improve hygiene. In his book, The End of Poverty, Jeffrey Sachs estimates that extreme poverty could be eliminated by 2025 at the cost of 0.7% of the Gross Domestic Product (GDP) of the more-affluent nations. In 1976, Thomas McKeown, in his book "The Role of Medicine — Dream, Mirage or Nemesis," described how death rates of both whooping cough and tuberculosis plummeted with improved hygiene and food supplies decades before the availability of vaccines and antibiotics. Global sponsors of such efforts today working in concert could include the World Health Organization (WHO), the World Bank, Centers for Disease Control and Prevention (CDC), the United Nations (UN), large multinational companies (e.g., Google), and world leaders from leading and emerging economies. Priorities must include the provision of safe water and food, and reduced exposure to zoonoses (i.e., pathogens transmitted from animals).

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***** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Antimicrobial Resistance, convened by the Institute on Science for Global Policy (ISGP) March 19–22, 2013, at Baylor College of Medicine, Houston, Texas.***

Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Richard Wenzel (see above). Dr. Wenzel initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made

by Dr. Wenzel. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Wenzel, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Because the concept of limiting infection transmission with horizontal infection-control programs, such as hand washing, has proven to be effective and inexpensive, more widespread adoption has the potential to reduce the development of antibiotic resistance.
- Truly effective international surveillance for infectious diseases will require more transparency and information sharing from governments and individual medical institutions.
- There is great potential for the public (as patients and families) to be more involved in the delivery of health care, including by contributing important information to treatment decisions and requiring accountability from providers.

Current realities

The efficacy of currently available antibiotics is decreasing because of the spread of resistant strains of bacteria. There are two major environments where resistance is of concern. One is in relatively controlled, high-density populations such as found in nursing homes and hospitals. Key pathogens in these settings (e.g., *Clostridium difficile* [c-diff], MRSA, and Vancomycin-resistant *Enterococcus* [VRE]), tend to infect already ill or susceptible people. Private care facilities, especially nursing homes, have seen largely unsupervised dispensing of antibiotics and poor follow up. The other area of resistance is in the general population where relatively healthy and fit people encounter infections such as gonorrhea and enteric fevers, both of which have proven to be worldwide problems that are highly resistant to antibiotics. Some of these diseases are primarily problems in Asia, but have spread through global travel.

Although practitioners seek to fight resistance by developing new drugs, an important alternative is limiting the prevalence of resistant microbes, primarily through the implementation of horizontal programs that can be applied in hospital settings (i.e., programs such as hand washing that do not target specific pathogens but rather aim to reduce all infections). There is often a linear relationship between

antibiotic use and prevalence of drug resistance. Horizontal programs reduce the spread of disease and, subsequently, the need to use antibiotics to reduce the prevalence of resistant disease.

Prevalence has two determinants: the rate of new infections and duration of each infection. Much of the debate focused on preventing new infections, but the issue of reducing an infection's duration was another important point of focus. Medically speaking, there are few drugs that have effectively reduced duration of infection after diagnosis. Vaccines have been proven to reduce transmission, but are given prior to infection. The development of new drugs that can reduce the time patients are ill can prevent further transmission. One problem is that duration varies in different populations. For example, the typical duration for H1N1 in adults is five to seven days, but in children can be up to three weeks. The horizontal approach requires these individuals to be isolated from their respective populations (e.g., work or school) for the appropriate time.

Other ways to reduce prevalence were offered, including increasing international surveillance, and developing new rapid diagnostics and vaccines. Regarding international surveillance, it is known that some countries have withheld information regarding outbreaks or emerging diseases. One example was H5N1 in China, where the WHO was receiving reports from countries neighboring China, but not China itself. The Director General of WHO went to the press and exposed the situation publicly, and within 24 hours, China began reporting.

The question of what constitutes a pandemic was debated. Although more than 30,000 Americans die of influenza each year, it is generally not regarded as a pandemic. However, infections such as West Nile virus or smallpox are considered to be much more serious by the public and receive more attention in the media, but few people have died of these diseases. This contrast needs to be put into perspective for the public and the media, which appears motivated more by diseases that sound exotic and frightening, rather than those that are mundane, common illnesses like the flu but may cause more morbidity and mortality.

Scientific opportunities and challenges

Horizontal programs such as hand washing do not discriminate or target a specific strain or illness, and it has been proven that hand washing reduces transmission of multiple pathogens. One success story was at Virginia Commonwealth University (VCU), where hand-washing compliance was historically at 40%. Placing soap and disinfectant gel in more convenient places throughout the hospital raised compliance to 60%. After instituting a policy of direct observation and reporting the statistics to departments, compliance rose to more than 90%. Hand washing is

relatively inexpensive and quick to implement, and it does not require highly educated workers to document compliance, leaving nurses and doctors to concentrate on patient care instead of paperwork. Once compliance is up to 90%, the program sustains itself. Another example of a horizontal program is daily chlorhexadine baths, which has shown an 87% reduction in VRE bloodstream infection and 70% reduction in MRSA in hospital intensive care units (ICUs).

There are additional horizontal approaches, aside from hand washing and antibacterial baths, that can be used in acute-care settings. Gathering intelligence from a local region can provide helpful information for guiding treatment. For example, awareness that patients from a certain nursing home have had high incidence of VRE or MRSA infections would lead to immediately placing all new patients from that home in isolation upon admission to a nearby hospital. Expanding this kind of regional knowledge to a database within a community of hospitals, allowing broader access and recognition of patterns, is the next step.

The Clean the World project was also mentioned as an excellent example of a horizontal program. This program collects and recycles soap from hotels in popular tourist destinations (e.g., Las Vegas, Orlando) and sanitizes and redistributes the soap to less-wealthy countries. This idea could be expanded to other regions or products. Often in countries like the U.S., vaccines and other drugs are discarded immediately after the expiration date. However, the expiration date does not necessarily mean that these drugs are no longer effective, and these products could still be used effectively elsewhere. Similarly, this concept could also be applied to used medical equipment.

For the general population, a substantial advance for combating many pathogens would be the development of a vaccine. So far, research has focused on diseases that are "easy" to control as a target for vaccines. For example, a salmonella vaccine exists that is 60% to 70% effective. However, it was agreed that further research was critical, and that an additional goal should be developing vaccines for pathogens such as *Staphylococcus aureus* that affect hospital patients and vulnerable populations.

The horizontal approach has already gained some traction in the marketplace, with companies employing microbial-resistant materials that can be integrated into hard surfaces, including walls, tables, and intravenous (IV) poles. Some materials are proprietary, while others include known substances such silver, which is a natural antibiotic. There has also been success in deploying antimicrobial fabrics that have been proven to be resistant to MRSA in hospital curtains and medical garb, such as ICU and operating room scrubs.

A global monitoring system or international surveillance system was discussed as a way to track and reduce the spread of diseases and pandemics. Although it was agreed that such a system is an achievable goal, it would require a global effort by many countries and hospitals to report critical data in a timely and transparent manner. Policies to promote the sharing of this data would be a critical step in ensuring the effectiveness of such a program.

Hospitals need not only report infection rates, but also basic information such as the amount and type of drugs being administered, without tying their dispensing to a certain illness. Many hospitals track this information on an internal basis, but it is not shared publicly. It was argued that it is possible to establish criteria to identify spikes in dispensing of specific drug types, but not necessarily for a specific illness or pathogen. Such criteria have worked in the past, when the CDC saw a spike of drugs generally used for pneumonia in Haiti, but discovered that the actual outbreak was of pneumocystis. The prophylactic use of antibiotics in both humans and animals, and their contribution to both effective treatment and expansion of resistance, need to also be considered.

In the U.S., pharmacists could take a larger role in tracking infection and antibiotic use. Even if prescribers are unsupervised, pharmacists have been helpful not only in determining the right drug for the right duration, but also in identifying more complicated drug interactions that required multiple treatment options. This teamwork and communication within the medical community have been effective, but it would be useful if guidelines for proper use and duration of antibiotics could be simplified and implemented more widely.

The possibility of reintroducing "healthy" flora back into hospital settings was discussed. This has been performed successfully with fecal transplants involving patients with c-diff, but it has also been proposed to introduce bacteria onto hard surfaces in hospitals to outcompete pathogenic and resistant organisms. It was agreed that having a nonpathogenic or antibiotic-sensitive bacterium on a surface is preferable to a resistant strain, but deliberately introducing such bacteria in hospital settings would be extremely difficult, particularly in ICUs where patients have many exposed orifices, tubes, and stents, and where patients are already in a vulnerable and immune-suppressed state.

Policy issues

The measure of success for an international surveillance data-sharing system would be the absence or reduction in disease transmission, but it is difficult to prove that the absence of diseases can be traced to a specific action, (i.e., an averted pandemic or the nontransmission of a pathogen). It was questioned how it would be possible

to prove or assess results that did not occur, particularly for the purposes of allocating funding and resources for a specific policy.

An existing model for a successful notification system is the Program for Monitoring Emerging Diseases (ProMED-Mail), which has been operated for more than a decade by the International Society for Infectious Diseases. ProMED-Mail is a vetted international surveillance program that was faster than the WHO in reporting the outbreak of SARS in 2003. ProMED-Mail receives some funding from the Gates Foundation, and it was argued that collaboration with the WHO could lead to increased data sharing and faster response times.

The WHO does have protocols for pandemics, and the possibility of invoking the WHO's International Health Regulations (IHR) was raised. The IHR requires the 180 member countries of the United Nations to ramp up international surveillance and infection controls under certain conditions. Historically, this was only done once, for H1N1, and some have proposed that the threshold for invoking the IHR be lowered, or used more frequently. This proposal was noted as being controversial within the UN, but it was suggested that a country like the U.S. use its political influence to advance the issue on the UN agenda. The IHR already has scheduled some regulations to be implemented by 2015, but more than 100 member states have already asked for extensions or are not meeting their requirements to report. It was agreed that the CDC has significant influence to make this an important issue, but the WHO also has gained political capital, especially after the SARS outbreak. The WHO has the ability to pressure specific ministers and departments of health, and has been successful at doing so in the past.

Even if new IHR protocols were instituted, it was argued that there would be issues with countries such as India and China, which may be unwilling to comply, or with other less-affluent countries lacking the resources to implement new requirements. However, some less-wealthy countries are encouraging the growing industry of medical tourism, which can improve health care overall and bring badly needed funding into these countries. It was argued that instituting more stringent surveillance requirements could hamper the medical tourism market. Without the proper incentives, some countries would simply choose not to comply.

To incentivize countries to comply with international standards, the costs of responding to a pandemic need to be made clear. For example, the total economic burden of SARS is estimated to be in the billions of dollars. Some suggestions for incentives included economic rewards for early recognition and reporting, and making rapid response teams available. Countries need to be shown that regions reporting outbreaks will not be punished, and that if information was withheld, the goal would be to keep financial punishment from affecting poorer citizens.

The possibility of banning a country from participation in the Olympics was suggested. Rewards could also come in the form of extra money for laboratories and new medical staff, but need to also be congratulatory. Public recognition of good work goes a long way in gaining the trust needed for voluntary sharing of critical information.

A global monitoring system would have to maintain access to unprecedented amounts of data, with a diverse user base. Professionals from many different fields would be looking at different data and different patterns. There would also be significant competition for hiring technical experts to build and maintain the database, and such an exercise will be expensive. To promote the implementation of a global monitoring system, adopting an economic perspective was suggested. Questions were raised about how much is currently spent on controlling pandemics and if it could be proven that instituting a surveillance database could reduce disease spread by 50%. In the long term, investing in surveillance may save money, and combining resources from the CDC, WHO, and private companies (e.g., Google) could make a robust system a reality.

It was agreed that there is currently an economic incentive to keep data incompatible. In part, this stems from the economic interests of private companies that sell and install proprietary systems, but it is also from hospitals that do not want to make their data available for fear of being graded or penalized. These financial issues were explicitly shown in the March 2013 Steven Brill article in *Time* magazine.

Building a true global surveillance system requires solutions to a number of challenges. Better ways to collect and store data are needed. New software tools will also be needed to analyze and model this information. The question of who could have access to these data needs to be addressed (i.e., whether only professionals or should there be a public channel?). It was argued that global surveillance systems require open access, with tools for public interaction.

Market-driven interest could also help promote public awareness of horizontal programs and improved sharing of information. Currently, consumers of health care are not aware of what programs are in place and what initiatives could be implemented. The concept of "unionizing" the public was suggested. Is there a way to give people access to data to raise awareness, and move the sole responsibility for controlling disease resistance from regulatory agencies to include the public? Having celebrities embrace a topic (e.g., a football player with MRSA, or an actor with AIDS) can help raise public awareness. Incentivizing patients to be actively interested in what happens in the hospital (e.g., a patient would not pay for a visit

if a health care provider does not wash his/her hands) could put pressure on community hospitals to maintain higher levels of infection control.

Using social media to share information and stories could also be an effective tool to involve the community. Although reviews of facilities or caregivers already occur, more mundane information can be culled from social media to identify scientific patterns. If a thousand people from a region or community post reports online of a respiratory ailment that is unusually persistent or harsh, ProMED-Mail or another monitoring system may be able to recognize this and lead to further investigation. Reporting and pattern identification no longer needs to be limited solely to health care providers.

Mitigating Antibiotic Resistance with DNA Sequence Information**

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Summary

Antibiotic resistance is a growing problem, particularly among gram-negative bacteria (a distinct class of bacteria distinguished by differences in the cell wall) from hospital-acquired infections. There is a clear need for new drugs. However, the pipeline for new drugs, and especially novel molecular entities, is low. Since an outpouring of new drugs is not going to occur in the near future, it will be important to manage the development of resistance to currently available drugs. A possible way to control the spread of resistance is to take advantage of the tremendous improvements in DNA sequencing technology to identify resistance genes in real time in the clinical setting. With real-time information on what genes are present in an infecting bacterium, an informed decision on which antibiotic to use for treatment could be made. DNA sequencing is becoming a feasible tool for use in clinical microbiology laboratories and its widespread use as a diagnostic and surveillance tool is a reasonable expectation in the next several years. The successful use of DNA sequencing will release a vast amount of information on antibiotic resistance genes. To take advantage of this information to slow the evolution and spread of antibiotic resistance, it will be critical to have well-designed databases of resistance sequence determinants.

Current realities

Bacterial resistance to antibiotics is increasing and presents a threat to public health. Two major problems that currently restrict antibiotic therapy are infections caused by methicillin resistant *Staphylococcus aureus* (MRSA) and those associated with multidrug-resistant gram-negative bacteria. Among gram-positive organisms, MRSA has become widespread in both hospital and community settings and by 2003, greater than 50% of *S. aureus* strains isolated in hospitals were MRSA. Due to the acquisition of a new target enzyme that is not efficiently inactivated by the

available drugs, MRSA bacterial strains are resistant to nearly all penicillin-style antibiotics.

The current situation with hospital-associated (nosocomial) infections with gram-negative bacteria is equally critical in that no new drugs are expected in the near future to effectively treat these infections. Resistance rates have been increasing for certain problematic species such as *Pseudomonas aeruginosa*, *Acinetobacter* spp. and Enterobacteriaceae including *Klebsiella pneumoniae*. Not surprisingly, the presence of multidrug-resistant strains of gram-negative organisms has been associated with prolonged hospital stays, higher health care costs, and increased mortality.

The emergence and spread of the New Delhi metallo-â-lactamase (NDM-1), which destroys many penicillin-style antibiotics, to many gram-negative bacterial species and multiple countries, is an example of how quickly resistance can emerge and become a threat to public health.

The rapid emergence of resistance reveals a need for monitoring the spread of antibiotic resistance genes. DNA sequence information provides unambiguous identification of antibiotic resistance genes and thus is the most rigorous means of tracking the spread of these genes. With thousands of unique resistance genes known, only DNA sequencing can provide the level of detailed genetic information required for a precise conclusion on the presence of a given resistance mechanism.

The above examples also highlight the need for new antibiotics and particularly for novel molecules with unique mechanisms of action. Unfavorable economic and regulatory environments, however, have led to a reduction of investments by the pharmaceutical industry in antibiotic research and development. There are several economic factors involved, but the limited duration of antibiotic use for any given treatment relative to treatments for chronic disease, as well as the rise of resistance, make them less-profitable drugs. Regulatory issues for antibiotic approval, including stringent requirements for limiting adverse side effects, as well as uncertainty with regard to criteria acceptable to demonstrate safety and efficacy of a candidate antibiotic, have reduced antimicrobial development efforts.

Scientific opportunities and challenges

While antibacterial drug discovery and development activities within the pharmaceutical industry have decreased, our knowledge of the nature and abundance of antibiotic resistance determinants has steadily increased. This is partially because of tremendous increases in throughput from DNA sequencing technologies whereby sequencing of large bacterial plasmids and genomes has become routine for research purposes. This has led to information on the

constellation of antibiotic resistance genes within resistant bacterial isolates as well as knowledge of the genetic mechanisms by which these genes can spread to other bacteria.

Based on the DNA sequencing technology recently made available as well as new technologies in development, there is a promise of maintaining the large increases in sequencing capacity while continuing to decrease the cost. This has led to the beginnings of the use of DNA sequencing as a diagnostic tool for clinical microbiology in addition to its widespread use as a microbiology research tool. In turn, the amount of genomic and plasmid sequence information has been rapidly expanding. The end result is that there is a great deal of molecular information in the form of gene sequences and lists of mutations that are available to describe and diagnose a resistance mechanism.

As DNA sequencing technologies continue to improve, it is likely that sequencing will become a routine diagnostic tool in clinical microbiology laboratories to identify bacterial species as well as possible antibiotic resistance mechanisms. This will lead to an opportunity to use DNA sequence information to guide treatment. As DNA sequencing is incorporated as a clinical microbiology tool, it will greatly increase information on which antibiotic resistance genes (or mutations) are most common in a certain bacteria, as well as the geographical location of where bacterial infections associated with resistance genes occur. On a national and international scale, this would present information on the distribution and abundance of antibiotic resistance genes at any moment in time as well as dynamic information on how the distributions change over time. A DNA sequence of a cultured bacterium from a patient would provide obvious information with regard to treatment choice because one would avoid giving an antibiotic for which resistance genes are clearly present. However, widespread sequencing and rapid dissemination of the information could also guide treatment when the sequence of the organism causing illness was not known. In this case, the distribution of resistance genes among bacteria in a geographic region or specific hospital could be used to determine the probability that such a resistance gene would be present in the organism at hand. Information-based, targeted therapies could decrease inappropriate antibiotic use and thereby decrease the spread of antibiotic resistance.

A key element for harvesting information from the application of high throughput sequencing as a clinical microbiology diagnostic tool is a database containing known DNA sequence information on antibiotic resistance genes and mutations associated with resistance. As DNA sequence data is obtained on an organism, the method to determine the resistance mechanism involved is to search databases for sequence matches to known resistance determinants. If a resistance

determinant is not present in the database, no knowledge will be obtained from sequencing. Therefore, the quality and completeness of the database is crucial to success in using sequence information to guide treatment. DNA sequence databases that can be used for sequence matching to resistance genes exist. However, ideally the databases should also contain information on location (i.e., city, state, and hospital) and frequency of occurrence of the resistance determinant. An open source database whereby clinical microbiology laboratories deposit all sequence information obtained as well as information on the organism, location, and date would allow the database to contain current information on the state of resistance gene frequency at any point in time.

Policy Issues

Policy formulation to foster the development of new antibiotics and management of resistance of currently available antibiotics will depend on several issues:

- Policies will need to be developed for participation in data sharing in the form of depositing sequences into a common, international database. The construction and operation of the database should be funded by governments but be independent of any one government.
- As new technologies become established, particularly the adoption of low-cost DNA sequencing as a diagnostic tool for antibiotic susceptibility, it will be critical that an infrastructure for data management and sharing be in place.
- DNA sequencing as a routine diagnostic tool would release a flood of sequence information that needs to be captured to enable its use as guide for treatment. Development of a common database of antibiotic resistance gene information is a large bioinformatics challenge that will need to be undertaken soon to keep pace with information flow from the technology. Automation in data submission would facilitate database development.
- If such a database were to be used for diagnostic purposes there would need to be approval and monitoring of the database by regulatory agencies of participating countries.
- Efficient use of DNA sequence information and databases requires detailed knowledge of the antibiotic resistance mechanism. Therefore, basic research on the genetics and biochemistry of antibiotic resistance should be supported.

- Management of antibiotic use via sequence information should be coupled with increased efforts at development of new antibiotics that act on novel targets in bacteria. A combination of effective management of resistance to current antibiotics and the development of entirely new antibiotics could work in synergy to provide improved treatment options.

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Debate Summary

The following summary is based on notes recorded by the ISGP staff during the not-for-attribution debate of the policy position paper prepared by Dr. Timothy Palzkill (see above). Dr. Palzkill initiated the debate with a 5-minute statement of his views and then actively engaged the conference participants, including other authors, throughout the remainder of the 90-minute period. This Debate Summary represents the ISGP's best effort to accurately capture the comments offered and questions posed by all participants, as well as those responses made by Dr. Palzkill. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Palzkill, as evidenced by his policy position paper. Rather, it is, and should be read as, an overview of the areas of agreement and disagreement that emerged from all those participating in the critical debate.

Debate conclusions

- Because antibiotic resistance is a growing problem, new, rapid diagnostic tools are needed to identify and prevent the spread of resistant pathogens.

- While routine DNA sequencing will become commonplace in the near future, a major challenge will be managing the massive amount of data DNA sequencing produces. Consequently, a database of globally acquired DNA sequencing results, accessible worldwide, needs to be established to help organize and analyze genomic information to optimize its use.
- Although DNA diagnostics will be an invaluable tool, traditional tests such as microbiological culturing will remain invaluable to establish a more complete understanding of antibiotic resistance.

Current realities

The future of rapid diagnosis lies with DNA sequencing, which will continue to increase in speed and decrease in cost as the technology progresses. Although this expansion of DNA sequencing as a common tool has great potential, it will also produce massive amounts of data that need to be effectively stored, managed, and analyzed as a precursor to maximizing the impact of DNA sequencing. It was agreed that as costs decrease during the next five to 10 years, DNA sequencing will become a major tool in diagnostics, but only if a system to share these data widely is designed and implemented.

The National Library of Medicine, a division of the U.S. National Institutes of Health (NIH), has already begun coordinating data obtained from DNA sequencing. Rather than creating a new, independent database in the U.S. just for rapid diagnostics, it was suggested that such new DNA sequencing data needs to be integrated into the storage/retrieval system already being developed. During this development, it is essential that plans to accommodate massive quantities of DNA sequencing data be implemented in preparation for the time when such data become available.

The history of DNA sequencing has traditionally been built around decoding the human genome, but the technology does not adapt easily for smaller genomes such as bacteria. This finer subdivision of focus will need to be considered when building a new system to handle bacterial genome data. The previous goal was "jackpot"-oriented (i.e., looking for large payoffs by identifying single resistance genes), but the real opportunities will come from more routine analyses that will identify subtle additive effects and contribute smaller pieces of knowledge to the detection and overall understanding of identifiers for antibiotic resistance.

Hospitals in both more- and less-wealthy countries are beginning to invest in DNA sequencing technologies. A comparison was made to the adoption of MRI machines, which were rare and expensive during the 1980s but are now

commonplace. DNA sequencing will also inevitably become widespread even though the timeline for adoption will vary geographically. The questions that must be addressed are associated with the flood of data that will come with routine DNA sequencing. It is valid to assume that the genomic revolution is rapidly approaching, and although computational challenges will likely be addressed by the continued and often exponential expansion of computing power, establishing the storage analysis infrastructure commensurate with the amount and complexity of data is an imminent need.

Currently, there is a bottleneck in creating a usable product from the information gained through genomic sequencing. The assembly and adaptation stages have not kept up with the speed of sequencing itself. While DNA sequencing is not yet a diagnostic tool for antibiotic resistance, there was agreement that sequencing will become such a tool, although there was not agreement on the scale of the real cost or the timeline over which it would be developed.

Sequencing is not yet cheap or easy, and often encounters resistance from institutions of all sizes (e.g., the U.S. Centers for Disease Control and Prevention [CDC]), which prefer simpler, less expensive options when available. The CDC has questioned the need for expansion of sequencing if simpler diagnostics could be effective, and noted that there are no current global standards. It was argued that the amount of data that comes from DNA sequencing is exceptional, but may be excessive for effective use within the current clinical environment.

Many laboratories have already abandoned microbiological culturing, relying on other more advanced tools, even though sequencing by itself is not yet capable of tracking the spread of disease. The CDC was three weeks slower in announcing an influenza pandemic when compared to the search engine Google, which can analyze popular searches (e.g., complaints, prescriptions, other keywords) for spikes in requests. Therefore, tools that rely more on traditional observation, reporting, and culturing (e.g., antibiograms testing the sensitivity of isolated bacterial strains for different antibiotics) will not become extinct, but will probably remain an important diagnostic component in the future.

A compromise was offered to combine some simpler methodology for international surveillance based on direct observation of syndromes as a first step, rather than sequencing every pathogen that comes through a clinic. If an epidemic emerges, a move to sequencing more extensively could then be made. It was agreed that medicine is not yet at a stage where sequencing every patient sample is possible, but the technology can serve as an adjunct to other tools in the immediate future.

Scientific opportunities and challenges

It is unlikely that antibiograms will ever be as fast as DNA sequencing because of the time taken to culture samples. Consequently, physicians put patients on broad-spectrum antibiotics as a precautionary measure before having all the information, even when there might be a more targeted choice of drugs. The challenge is to combine more traditional practices with rapid diagnostics. Questions were raised about limiting sequencing to certain patients, (i.e., targeting patients with defined symptoms) or adopting a blanket approach in which samples from every patient would be added to the database. It was agreed that a good database would contain other information for more thorough comparisons. Because DNA sequencing will be faster, it was recommended that blanket sequencing be done to obtain the widest sample possible of spreading microbes, both pathogenic and harmless. Adding as much information as possible to the central database will eventually make rapid diagnostics the first choice when making decisions regarding specific drugs to prescribe.

By combining sequencing and antibiograms, there is a better chance of pinpointing types of pathogens and their spread. While sequencing will become invaluable, it will be limited by the information in the database and may be able to determine only that a new organism has been identified. Medicine will still need to look beyond genomics by utilizing approaches such as transcriptomics (i.e., identifying genes that are expressed by an organism) to build more complete data sets.

Making information more useful to physicians (i.e., designing rapid diagnostic tools) needs to be the goal for improved DNA screenings and databases. Currently, only a small percentage of doctors know where to find sequencing information and what to do with it. A new international database and surveillance system would have to be "smart" and present data in an understandable way. It would probably need to be updated in real time as new information is added to the system. Also envisioned are devices and software that even nonspecialists could use to interact with the data. Phones or other mobile devices could provide limited rapid diagnostic capabilities, or applications that track conditions within a certain region, community, or hospital.

The "normal," nonpathogenic microbes humans and animals encounter must also be considered. Constant surveillance for pandemic-level pathogens need not overshadow genetic sequencing of common flora and fauna. Having a wider spectrum of knowledge of the overall microbial environment will provide more information about the origins of resistance.

Because the information provided by any database is only as good as the information that is submitted, issues regarding quality control were also raised. Poor data quality was acknowledged as a real concern, especially in the early stages of establishing the database when only limited sources are available. There are ways to achieve certain quality standards that can be built into the technology, such as requiring a certain number of nucleotides to be sequenced before a sample would be accepted by the system. However, there are also factors that cannot be controlled at the sample source level when the submission choice is made by a person (e.g., submitting old samples, or choosing one patient who seems sicker than another).

Ultimately, the DNA sequencing database would be a discovery tool because even when a definitive diagnostic answer cannot be provided, new information can still be obtained to inform research efforts. A new, slightly related microbial strain may be identified and cataloged in the database, which can provide useful information for a subsequent user. The next step is to turn this knowledge into something useful and practical in clinical settings.

Policy issues

Although it was agreed that the creation of standards for data input and access is critical to make sharing of data and their usability as efficient as possible, there was some disagreement about what policies are needed to set these standards. For example, some argued that no standards are needed initially, and that data need to be collected without restrictions. This would provide opportunity for standards to emerge rather than having government bodies act too early and thereby create inefficient and restrictive regulations or standards.

Even if genomic sequencing identifies a new, potentially dangerous strain, this information on its own may not satisfy current regulatory requirements as a basis on which to make clinical decisions. The rapid diagnostics envisioned may be too rapid to fit within the current clinical framework. Genomic sequencing will need to be considered in future policy decisions by many agencies that use different tests for defining critical clinical or regulatory thresholds.

Others argued that standards for universal formats and data access must be in place before databases are developed. Standardized formatting should be an integral part of creating a useful and universally accessible system. For example, the NIH requires standard file formats and data deposition to receive grants. Similarly, scientific papers are not published unless the data are correctly formatted, thereby incentivizing authors to comply with standards. The Genomics Standards Consortium (GSC) in the United Kingdom aims to set baseline standards for

sequencing data. The goal of the GSC is to promote mechanisms for standardizing the description of genomes, including the exchange and integration of genomic data.

Specific policies targeted at stopping the spread of antibiotic resistance or managing sequencing data were not explicitly stated, but general questions were raised about priorities that governance bodies might take into account. Should pharmacies have more power to control the distribution of antibiotics? Who would police regulations if a sequence database were truly to become a global effort? It was agreed that the goal needs to be a two-part strategy: first, addressing overall use of antibiotics, and then, coordinating an international surveillance system that integrates and adds data for global use.

Questions were also raised regarding the incentives for less-wealthy countries to contribute to a global database. Many in less-wealthy countries feel that the data are primarily being used to help people in wealthier countries. One example was given from Indonesia, where the health minister held a sample "ransom" until there were assurances that treatments generated from the sample would be accessible to those in Indonesia. It was suggested that "the global good" needs to be the motivating factor because every country benefits from an increased understanding of antimicrobial resistance. The database envisioned needs to be globally egalitarian and data need not be limited or censored according to region or individual.

More DNA sequencing machines exist in developing counties than is commonly thought, but this is because the technology manufacturers sell the equipment at discounts, knowing that practice will lead to continued opportunities to sell the consumables required to use the machines. At the same time, many less-affluent countries see the inevitable move toward reliance on sequencing technology and are concerned about missing opportunities to be included. Decisions to invest in sequencing technologies are often made without fully understanding that further purchases will be required and that a communications infrastructure (i.e., full-time Internet connection) is needed to benefit from the information that a global database could provide. Less-wealthy countries are interested in participating in global sequencing networks, but are limited not by the lack of availability of DNA sequencing technology, but rather by the inability to access and manage the data.

It was argued that investments need to be made in a global database from the governmental level. Policies will be needed to address enforcement issues that arise when such a database suggests that a certain antibiotic is not indicated for a particular pathogen. This was countered by the suggestion that legislation is not needed because it is already in the best interest of the health care providers to heed

the recommendations that such a database could provide. In addition, it was argued that legal sanctions would be too slow to effectively prevent the spread of antimicrobial resistance once identified by the database.

It was agreed that to secure funding, the proposed international database must emphasize potential national security and global public health benefits. For example, researchers are investigating the use of microbiome data in forensic science, and creating a large microbial database could be useful for such approaches. Emphasizing national security benefits of microbial DNA sequencing networks may also help to ensure sustained, long-term funding.

Surveillance of Antibiotic Resistance Gene Epidemics**

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Summary

Initially, each new antibiotic cured almost all bacterial infections. However, infecting bacteria then began to acquire genes that blocked the antibiotic's action. Such resistance genes arose somewhere by mutation or by transfer from obscure bacteria to an infecting strain, and were then driven from their origin by antibiotic use through genetic elements, bacterial strains, animals, and people, to different hospitals and continents. Such epidemics of resistance genes and the bacteria that carry them have spread resistant strains throughout the world. As these genes have spread through the global population of infecting bacteria, successive antibiotics have become ineffective and patients have died as a result.

Efforts to control antibiotic resistance have not adapted to its epidemic spread. While caregivers at the local level make efforts to track and contain resistance in the hospital as a component of infection control, there is little tracking at state, national, or international levels. Hospitals do not know what can be expected from another local hospital or from hospitals elsewhere in the country. Public health agencies, traditionally responsible for detecting and minimizing epidemics, lack data for tracking resistance. Yet, abundant data is already collected at the clinical level that could be utilized for surveillance of resistance.

Tens of thousands of laboratories worldwide distinguish phenotypes of infecting bacteria daily with biochemical and antibiotic tests and are now genotyping more strains, but the reports only go to the requesting clinical staff. New informatics now enable us to translate the reports from diverse file codes, extract them with confidential/secure protocols, aggregate, integrate, and search them on Web servers continuously to find events, trends, and epidemics in real time and alert predesignated responders automatically. We should do all of these things now. The current method of using publication to disseminate resistance

data obscures actionable information and delays its effective use to protect the effectiveness of the antibiotics.

Current realities

The world's bacteria evolved and diversified over billions of years into massive populations. Only a tiny fraction of these bacteria can infect people, but these infecting bacteria shortened human lives more than any other cause. Then, 80 years ago, we began making antibiotics. These small molecules could diffuse through tissues of infected patients, kill any bacteria within the tissue and, astonishingly, cure any infections caused by the bacteria. No drug is ever likely to save as much life as penicillin did in 1943. However, the miracle did not last. Antibiotics failed to cure more and more infections because infecting bacteria became resistant to the antibiotics. New antibiotics were then discovered and also cured most infections, until bacteria became resistant to them too. However, few new antibiotics are being discovered now.

An antibiotic kills a bacterium by binding to a target site within the bacterium to block an essential function at that site. A strain of bacteria becomes resistant to the agent by acquiring a resistance gene expressing a product that keeps an antibiotic from blocking its target site. A strain of bacteria may get a resistance gene from a mutation in one of its own genes or from a gene transferred to it from another strain. However, the antibiotic resistance conferred by these resistance genes is only beneficial if selective pressure is applied by exposure to antibiotics. Many such resistance genes would thus previously have disappeared or stayed too rare to notice, until they began to be enormously amplified because of selection by widespread use of antibiotics 70 years ago. A gene expressing resistance to an antibiotic has often been first noticed only after the antibiotic was used for years or even decades, and then only in one or a few parts of the world, from which it eventually spread widely.

The resistance gene that makes a patient's treatment fail today may have thus emerged years earlier on another continent and traveled to this patient in a strain of bacteria, or a genetic element moving between strains, through a long chain of hosts colonized or infected by the bacterium. Such travel is driven mostly by antibiotic selection. When a resistant bacterium lands on a host, it is a tiny part of that host's total bacteria and has only a tiny chance of being among those that the host transfers to the next potential host. But, if an antimicrobial kills the host's other bacteria, the resistant bacterium will multiply exponentially, as will its chances of getting to the next host.

The antibiotic resistance genes that cause the most treatment failure, morbidity, and mortality today, and the genetic elements and strains of bacteria carrying them, can now be seen to have emerged and spread through a succession of antibiotic-driven global epidemics. Penicillin-insensitive pneumococci first appeared in South Africa and began to spread in Europe a decade later with derivative strains being spread from Spain, one to Iceland, and others to the Americas. Methicillin-resistant *Staphylococcus aureus* (MRSA) circulated for a decade in Europe before first being seen in a few United States hospitals and then moving into the community more widely. Vancomycin-resistant enterococci (VRE) appeared in animals in Europe and then became widespread in intensive care units in the U.S., and later in many other countries.

Genotyping and now genome sequencing have enabled precise identification of different genes expressing resistance to one antibiotic, and as a result have enabled more precise tracking of the epidemics of each gene. A gentamicin resistance gene (*aad2"*) first seen in Paris was thus shown to have spread on an epidemic plasmid (a transferable DNA element) through hospitals in Venezuela and the U.S. over the following decade and, after a single entry, to have converted a hospital with no resistance to gentamicin to ones with it prevalent in many infections by many bacterial species. Reports are now growing of single incursions into multiple countries from an apparent base in India of the recently discovered New Delhi M1 (NDM1) gene, which is now making infecting bacteria resistant to all effective antibiotics.

Scientific opportunities and challenges

Recognition of such successive epidemics of antibiotic resistance genes has been delayed. Thus, chances for early detection and containment have been lost because the potential observers, mostly based in separate hospitals and with few surveillance tools, see only parts of the epidemics and communicate primarily through publications in scientific journals. Genotyping of resistant bacteria is increasingly being reported but rarely related to the context of local resistance phenotypes. What is most needed to fill these gaps is the traditional surveillance for epidemics by public health agencies, overseeing and responding to all information across laboratories, hospitals, and communities and coordinating containment for their regions. Until now, these agencies have lacked data for such surveillance and response, but newer informatics can now provide this data.

Modern informatics has enormous potential to track and focus containment of the global spread of antibiotic resistance. Tens of thousands of microbiology laboratories around the world each day issue millions of reports of richly detailed

identification and antibiotic resistance phenotypes of bacteria infecting patients. These reports, which already are paid for, contain everything we can know about the kinds of bacteria, their antibiotic resistance, which patients they are infecting and where, and where this information suggests these bacteria may be heading next. Informatics technology for accessing, aggregating, and analyzing such reports has been lacking, but is now increasingly available. In addition to antibiotic resistance tests, the reports include other tests valuable to public health epidemiology (e.g., *Clostridium difficile*, HIV viral load, viral influenza), that could be accessed as well.

While these reports are primarily produced to guide care of individual infected patients, their reuse for overview across regions for trend discernment, epidemic detection, and containment can be seen as a new and under-recognized public health opportunity. Networks for such surveillance of antibiotic resistance exist in several regions of the world but underutilize newer informatics and gather only a tiny fraction of the available reports that could enrich these networks. A systematic effort to enhance, extend, integrate, and fully analyze and use such surveillance would be the most cost-effective component of any initiative to control antibiotic resistance.

Policy Issues

Since all levels of public health, infection control, and patient care should coordinate their responses to global resistance epidemics, there is a need for global public health funding to develop and deploy shared, automated informatics to speed and integrate the surveillance and alerting required by health care organizations. Policies are needed to:

- Implement the translation, extraction, secure transmission, and aggregation of reports from multiple clinical microbiology laboratories onto dedicated Web servers.
- Develop and solicit statistical and other algorithms to search these aggregated Web databases continuously for events, trends, and epidemics in antibiotic resistance.
- Develop automated, prompt alerting of preselected public health and local responders to detected events, trends, and epidemics for which they can begin containment measures.
- Extend automated searches of aggregated Web databases beyond antibiotic resistance to findings of other reported pathogens

(e.g., *Clostridium difficile,* HIV viral load, viral influenza) and for links with other data (e.g. genome sequences).

There is also concurrent need to encourage and prepare public health, infection control, and patient caregivers to utilize this new level of surveillance information with skilled responses to alerts generated by such information.

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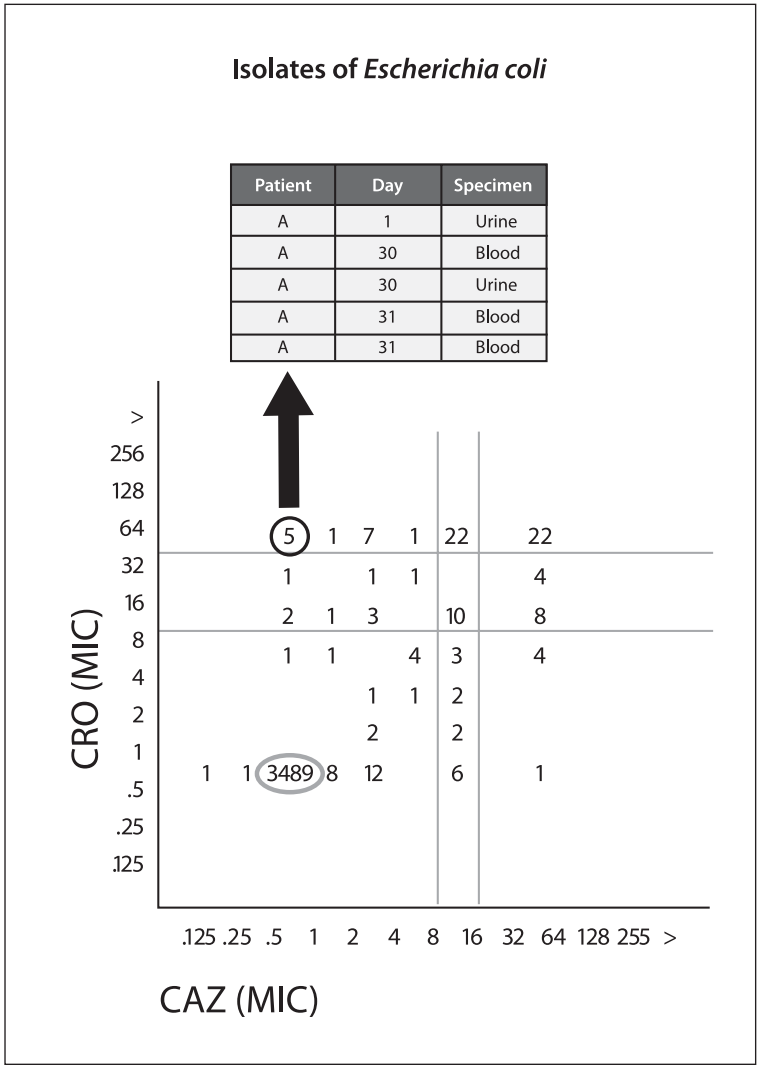
Figure 1: Routine clinical laboratory results detect incursion of a distinctive resistance phenotype.



Scatterplot (by WHONET) of minimal inhibitory concentrations (MICs) of ceftriaxone (CRO) and of cefazidime (CAZ) for all isolates of E. coli at one hospital during one year.

The **gray** circle encloses the 3,489 isolates that had MICs of 0.5 ìgm/ml for both agents. Scattered single or double digits falling on intercepts representing varied other MICs of the two agents indicate the numbers of isolates with each of those sets of MICs. The

black circle encloses the five isolates that had an MIC of 0.5 ìgm/ml for ceftazidime and an MIC of 64 ìgm/ml for ceftriaxone.

All five isolates were from patient A, who, as shown in the inserted table, had a urine isolate and a month later urine and blood isolates with that unique-for-the-year combination of MICs. The patient had received a kidney transplant three months earlier on another continent. Analyses of routine laboratory tests could thus detect incursion of an epidemic foreign resistance gene.

The distinctive phenotype of this patient's five isolates was generated by measurements of its susceptibility to two antibiotics. Each isolate's file, however, has measurements to 15 other antibiotics as well as results of an additional 48 biochemical tests - indicating their potential in combination to discriminate distinctive phenotypes.

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Debate conclusions

- A Web-based, centralized global surveillance system created to allow sharing of microbiological data would provide many advantages, including automatic software updates, automatic aggregation of data, and more rapid output. Using informatics, tracking the spread of infectious diseases can be improved at an exponential pace.
- While a sizable amount of data already exists in the internal, distributed information systems of microbiology laboratories, these data are underutilized. Consequently, storing these data in a centralized database

with basic formatting standards would improve disease tracking by allowing more data to be stored and analyzed.

- The effectiveness of any centralized surveillance system depends on the receptiveness of the intended audiences, especially if its results are presented in ways that appropriately recognize the wants and needs of specific audiences.
- Although sharing data and analysis information among countries (e.g., on epidemic diseases) has proven problematic due to economic and security concerns, the sharing of such information is critical to the success of any disease surveillance system. Practical incentives, mandates, and policing policies are essential components in the design of any successful system for global disease surveillance.

Current realities

The spread of diverse antibiotic resistance has been observed in many different parts of the world. Faster methods of transportation, more people traveling, and medical tourism, have all increased the spread of bacterial resistance. Types of resistance that were regionally isolated are now appearing around the globe. As one example, a patient with a resistant strain of *Escherichia coli (E. coli),* who traveled to an Asian country for a kidney transplant, transported this exotic strain to the United States. It was agreed that if there were a networked central database, data on exotic phenotypes could be distributed more widely and serve as an early warning system for such cases.

Microbiology laboratories have routinely been collecting phenotype data (e.g., resistance profiles or antibiograms) for many years. While some laboratories produce 40,000 reports a year, these reports are rarely shared and are primarily used for individual patient treatment and occasionally for internal infection control purposes. These recorded data are already valuable when they can be accessed, but are underutilized since they are often stored on systems that are incompatible for sharing with other institutions.

Although there has been limited success with retrieving information from separate databases using a software tool that homogenizes and converts these data, the current situation in health care informatics in the United States is dominated by proprietary software programs that are needlessly incompatible with each other. If standards had been established earlier, this lack of compatibility would not be the problem it is at present. For example, faculty at the Baylor College of Medicine, (part of Texas Medical Center, the largest medical complex in the world), serve five

different hospitals and two outpatient centers. All of the institutions use a common software program, but each institution has a different version that requires different mandatory training sessions. These systems are unable to be networked together. Likewise, the Veterans' Administration hospitals use a different software program, which only shares data within its own system.

One advantage of microbiology laboratories is that the file contents are basically uniform all over the globe. It would be expected that integrating such microbiological data would be easier than for other data types (e.g., individual patient data that may be collected under different parameters at each hospital). Current standards for laboratories require measuring biochemical activity using approximately 70 tests, including susceptibility to 17 different commonly used antibiotics. The combination of currently available data and the uniformity of such data make microbiology reports in a shared network an excellent place to establish a global surveillance system.

While existing microbiology laboratory networks were cited as examples, none share or integrate data outside an individual system. WHONET is a free-to-use, shared software platform for recording microbiology reports and is used in approximately 1,700 laboratories. However, it is distributed on local computers that are not networked for data sharing. Many machines running WHONET are in less-affluent nations. These combined factors mean that WHONET data, although abundant, are not stored in a central system for easy analysis.

Although The Surveillance Network (TSN) has collected valuable microbiological data from about 300 laboratories across the U.S. during the past several years at a regional level, data are delivered retrospectively only about once a year (i.e., the system does not include potential for live updating). Clinicians expressed a desire to see a centralized, rapidly updating system instead, even if it was only available internally (i.e., not on an open system).

Likewise, the Pan American Health Organization (PAHO) operates a system with approximately 720 labs in 10 countries, and although the information is publicly available, the system does not frequently update. It was argued that large governmental organizations need to establish the proposed global database to ensure that it remains open. For example, the U.S. Centers for Disease Control and Prevention (CDC) has been helpful in the past with distributing WHONET, and could again act as a proponent of a new system.

Scientific opportunities and challenges

It was agreed that the intended audiences must be considered when developing a database: (i) patient care at the level of individual physicians or clinicians dealing

with individual patients; (ii) infection control at a hospital level; and (iii) public health at local, regional, and national levels. These varied audiences have different needs for the type and presentation of data to conduct useful analyses. A large database would likely produce too much data for individual mining, but the probable solution would be to create algorithms for the builders of the architecture, in addition to scientific professionals and clinicians. Algorithms might be able to reduce the complexity of the data so users can make informed decisions without needing a detailed knowledge of the intricacy of the statistical models.

A possible pilot program of a global networked system, with an ideal goal of 100 laboratories participating initially, was proposed as a proof-of-concept. With live updating as an open source, such a system would offer not only proof-of-concept value, but would also be able to foster collegial incremental growth of analytical methodologies as different users prompted the system for alerts and reports. Database observers could also learn what kind of data users regularly demand to provide more automatic algorithms. Individual users at all levels could add different types of rule-based analysis queries.

Concerns arose regarding the intended use of the proposed global database. Many agreed that an element of direct benefit for patient care needed to exist, in addition to the global surveillance aspect that was emphasized. If a system did not benefit individual patients, what would be the incentive for physicians to share? In some cases, it has been mandatory for clinicians to report laboratory results to infection control organizations or other oversight institutions. It was argued that these mandates were the only reason a clinician would be compelled to report findings. In addition what would be the benefit to microbiologists from participating in the system?

Ideally, reporting would be automatic: the software would deliver the pathology report to the clinician and the server at the same time. If there were other similar specimens already in the system, software would alert the designated person or people (physician, infection-control personnel). With the proper algorithms, patterns would emerge and help trace the movement of a particular strain from laboratory to laboratory or country to country. This tracking approach has already worked in the PAHO system where NDM1 was identified in a Nicaraguan hospital and both contained and eventually eradicated.

It was also noted that individual patient care would require experienced analysts, of which there are currently few. The ultimate goal would be a highly automated system. It was argued that the proposed system is not initially intended to be an element of individual patient treatment, but rather for international surveillance purposes designed to prevent the spread of resistant (and nonresistant)

pathogens by observing patterns in distribution. However, this does not preclude these data from being mined for different types of analysis at an individual level. With the proposed database, it is possible to set a threshold that would send an alert when a certain trigger has been reached by including rule-based analysis at a large and small scale. For example, a user could instruct the software to provide an alert when a particular bacterium that is resistant to a certain type of pharmaceutical is observed in Central America.

There was debate about whether the different types of analysis would be determined by the operators or users of the database. A definition is needed for the term "informatics". Is it just acquisition and storage of data, or will analysis also be involved? While there was agreement that analysis ideally must be included in the system design, at the initial stage storing data would be given priority. There is already a strong consensus among microbiologists regarding what information they would typically seek in a report. However, the opportunity for future analysis of value propositions must become parts of new systems. Even if certain fields initially are not included because of cost and/or time factors, new fields need to be created for data acquisition that reflect changing demographics and societal priorities as well as for self-analysis.

It is essential that any model must demonstrate its value, and contain built-in mechanisms to show efficacy and adherence. Because the system probably would not offer self-analysis initially, it would begin primarily as a warehouse for data. The types of analyses would be proposed by individual clinicians, organizations, or countries to reflect their needs and priorities. While analysis would probably start at an infection-control or hospital level, clinicians could still introduce their own parameters for certain types of notifications.

A global surveillance system needs to be broadened beyond phenotype data to include DNA sequencing data as part of an integrated approach. The current system at WHONET allows DNA sequencing information as an attachment, but the individual DNA data must be downloaded and input to another piece of software for analysis. Although the current focus of WHONET is to maintain phenotype data, a future system needs to be developed focusing on certain goals (e.g., phenotype data only) while allowing for the integration of a broader array of data. This type of system may also help scientists conducting research in specific areas.

Policy issues

Concern was expressed about selective reporting and open data exchange among countries. A global system would need to be run in accordance with the existing

International Health Regulations, although it was noted that regulations would likely need to be modified to remain competitive with advancing technology. Policy in this regard needs to evolve from a working model established first to prove the worth and effectiveness of the system. The PAHO system, which has demonstrated that open sharing can work, could be viewed as an example. While the PAHO system has operated in a collegial manner with yearly meetings, it did take time and work to build confidence among users. The technology needs to come first, and a condition of benefiting from any system must be the requirement to share data.

For the U.S. government, there are already at least two networked systems that have been deployed in multiple countries. These systems only gather data on biothreat agents (e.g., plague, anthrax). These systems do include data from animals and other organic samples in addition to humans, and also include GPS data. The problem has been that countries are reluctant to share this type of data with neighboring regions for fear of economic and security consequences or sanctions. From this experience, it was proposed that mandates would be required to establish a policing system, either through the World Health Organization (WHO) or another United Nations agency.

Mandates and incentives might not solve data-sharing issues, especially in less-affluent countries where many systems are paper-based. It was proposed that more-wealthy nations need to set the tone, and less-wealthy nations will follow — even if not for the right reasons. It is essential to convince more-affluent nations of the value of this type of network for all countries concerned with the spread of antibiotic resistance.

Alternatively, opinions were expressed that less-wealthy countries already have an interest in sharing data. The Gates Foundation established a program to build microbiological capacity in less-affluent countries through developing basic capabilities and providing training for operators. Many countries observe what the U.S. does and view these approaches as too complex or costly to implement in their settings (e.g., a massive networked database of pathology reports). As a consequence, these countries might choose a simpler model that can provide laboratory reports at an individual level or case-by-case basis, while still serving as a sentinel for global resistance surveillance. These simpler methods and systems could perhaps later be included in the larger proposed surveillance network.

It was suggested that a new kind of expert is needed to meet the exceptional data challenge a global surveillance system would create. These experts would need to understand the intricacies of harnessing cooperation among countries and critical biodefense issues. A proposal was offered that as a corollary to receiving

the benefits of the proposed system, free training and education would be offered to create experts from within a country, but only upon agreement to share critical disease surveillance information. Because of the security and training aspects of the proposed compromise, it was argued that this is also a helpful proposal to garner funding for a broader network.

Acknowledgment

Numerous individuals and organizations have made important contributions to the Institute on Science for Global Policy (ISGP) program on Emerging and Persistent Infectious Diseases (EPID). Some of these contributions directly supported the efforts needed to organize the invitation-only ISGP conference, *EPID: Focus on Antimicrobial Resistance,* convened in partnership with the Baylor College of Medicine (BCM) at the BCM in Houston, Texas, March 19–22, 2013. Other contributions aided the ISGP in preparing the material presented in this book, including the seven invited policy position papers and the summary record, without attribution, of the views presented in the discussions, critical debates, and caucuses that ensued.

We would specifically like to thank our colleagues at the Baylor College of Medicine, and especially Dr. Paul Klotman, BCM President, and Shawn Davis, Assistant Vice President for Institutional Strategy & Research Initiatives, for their many, critical contributions toward the success of this conference.

The ISGP greatly appreciates the willingness of those in the scientific and policy communities to be interviewed by the ISGP staff, who organized the content of this ISGP conference. The efforts of the scientific presenters with expertise in Antimicrobial Resistance invited by the ISGP to both prepare the seven policy position papers and engage policy makers in the vigorous debates and caucuses that comprise all ISGP conferences were especially appreciated. The biographies of these authors are provided in this ISGP book. The ISGP would also like to thank the two keynote speakers, Ambassador Thomas Pickering and Texas Medical Center President and CEO Dr. Robin Roberts, for their insights. Their biographies also are provided in this ISGP book.

The success of every ISGP conference critically depends on the active engagement of all invited participants in the often-intense debates and caucuses. The exchange of strongly held views, innovative proposals, and critiques generated from questions and debates fosters an unusual, even unique, environment focused on clarifying understanding for the nonspecialist by addressing specific questions related to formulating and implementing effective public and private sector policies. The ISGP is greatly indebted to all those who participated in these not-for-attribution debates and caucuses.

The members of the ISGP Board of Directors also deserve recognition for their time and efforts in helping to create a vital and growing not-for-profit organization that has relevance to many of the most important societal questions

of our time. Their brief biographical backgrounds are presented at the end of this book.

The energetic, highly professional work of the ISGP staff merits special acknowledgment. The staff's outstanding interviewing, organizing, and writing skills were essential to not only organizing the conference itself, but also to recording the often-diverse views and perspectives expressed in the critical debates, capturing the areas of consensus and actionable next steps from the caucuses, and persevering through the extensive editing process needed to assure the accuracy of the material published here. All of the staff members' work is gratefully acknowledged. Their biographies are provided in this book.

ISGP programs are financially supported by government agencies and departments and through gifts from private-sector entities and philanthropic individuals. Specifically, the ISGP conference on Antimicrobial Resistance convened in Houston, Texas, received funding from the National Intelligence Council (NIC). Funding from the Federal Bureau of Investigation (FBI), the U.S. Department of Health and Human Services (HHS), the U.S. Department of State (DOS), the U.S. Department of Homeland Security (DHS), and the Istituto Regionale di Ricerca in Milan, Italy, has also been provided to the ISGP for its general activities. The ISGP also benefited greatly from generous gifts provided by the MARS Corp., Novartis Pharmaceuticals Corp., GlaxoSmithKline, Cargill Inc., Julian Segal, and Edward and Jill Bessey. Finally, the ISGP gratefully acknowledges the ongoing administrative support provided by the Critical Path Institute.

Dr. George H. Atkinson
Founder and Executive Director
Institute on Science for Global Policy
June 13, 2013

ISGP books from previous ISGP conferences listed below are available to the public and can be downloaded from the ISGP Web site: www.scienceforglobalpolicy.org. Hard copies of these books are available by contacting Jennifer Boice at jboice@scienceforglobalpolicy.org.

ISGP conferences on, or related to, Emerging and Persistent Infectious Diseases:

- *21st Century Borders/Synthetic Biology: Focus on Responsibility and Governance*, convened December 4–7, 2012, in Tucson, Arizona, U.S., in partnership with the University of Arizona.
- *EPID: Focus on Societal and Economic Context*, convened July 8-11, 2012, in Fairfax, Virginia, U.S., in partnership with George Mason University
- *EPID: Focus on Mitigation*, convened Oct. 23–26, 2011, in Edinburgh, Scotland, U.K., in partnership with the University of Edinburgh.
- *EPID: Focus on Prevention*, convened June 5–8, 2011, in San Diego, California, U.S.
- *EPID: Focus on Surveillance*, convened Oct. 17–20, 2010, in Warrenton, Virginia, U.S.
- *EPID: Global Perspectives*, convened Dec. 6–9, 2009, in Tucson, Arizona, U.S.

Biographical information of Scientific Presenters and Keynote Speakers

Scientific Presenters

Dr. Brad Spellberg, M.D.

Dr. Brad Spellberg is an Associate Professor of Medicine at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA) and the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center. He is also the Associate Medical Director for Inpatient Services at Harbor-UCLA Medical Center. His research interests range from basic immunology and vaccinology to pure clinical research and outcomes research. Dr. Spellberg has worked with the Infectious Diseases Society of America (IDSA) to attempt to bring attention to the problems of increasing drug resistance and decreasing new antibiotics. His research regarding new drug development has been a cornerstone of the IDSA's white paper, *Bad Bugs, No Drugs*, and has been cited extensively in medical literature and on Capitol Hill. He is a Fellow in the IDSA and has worked extensively with IDSA and outside of IDSA to address this critical problem. As a member of the Antimicrobial Availability Task Force (AATF), he has first-authored numerous societal position papers and given congressional briefings and testimony relating to public policy of antibiotic resistance and antibiotic development. Dr. Spellberg is the author of *Rising Plague*, which he wrote to educate the public about the crisis in antibiotic-resistant infections and lack of antibiotic development.

Dr. Thomas O'Brien, M.D.

Dr. Thomas O'Brien is an Associate Professor of Medicine and Medical Director of the Microbiology Laboratory at Brigham and Women's Hospital, and Co-director of the World Health Organization (WHO) Collaborating Centre for Surveillance for Resistance to Antimicrobial Agents. Dr. O'Brien has served as an adviser on numerous national and international committees, including the NIH Task Force on Antibiotic Resistance, which he chaired from 1984 to 1986; the WHO Scientific Working Group on Antimicrobial Resistance (AMR) (1981); the Food and Drug Administration's (FDA) Veterinary Medicine Advisory Committee (since 1994); the Office of Technology Assessment Advisory Panel on Impacts of Antibiotic-Resistant Bacteria; the Inter-Agency (FDA, Centers for Disease Control and Prevention [CDC], U.S. Department of Agriculture [USDA]) Working Group on Antimicrobial Resistance; and the CDC Working Group on Drug-Resistant *Streptococcus pneumoniae*. He has also consulted on antimicrobial resistance for

WHO, the Pan-American Health Organization, the British House of Lords, and the National Health Research Institute of Taiwan, and helped develop the WHONET surveillance program. Dr. O'Brien has conducted research on antimicrobial resistance since the 1960s, and is Vice President of the Alliance for the Prudent Use of Antibiotics (APUA).

Prof. Eriko Takano, Ph.D.

Prof. Eriko Takano is Professor of Synthetic Biology at the Manchester Institute of Biotechnology, University of Manchester, in Manchester, United Kingdom. Her research focuses on the use of synthetic biology to produce antibiotics, the systems biology of the metabolic switch from primary to secondary metabolism, and the regulation of antibiotic production through signaling molecules in Streptomyces coelicolor, the model organism of the most important group of commercial antibiotic producers. Prof. Takano has worked in industrial and academic research settings for more than 26 years. After working as a researcher at the Department of Genetics of Meiji Seika Kaisha, Yokohama, Japan, she moved to the John Innes Centre and the University of East Anglia in Norwich, United Kingdom. She has had appointments as an assistant professor at the University of Tübingen, Germany, and the University of Groningen, The Netherlands, followed by a move to the University of Manchester in 2012. Prof. Takano has been awarded the Rosalind Franklin Fellowship from the University of Groningen (2006), Naito Kinen Kaigai Ryigaku Jyoseikin from the Naito Foundation Japan (1994), and the Lepetit Award from Lepetit and the Italian Society for General Microbiology and Microbial Biotechnology (1993). She has held several large grants from German and Dutch research councils, and has published more than 50 peer-reviewed publications on various aspects of Streptomyces biology.

Dr. H. Morgan Scott, D.V.M., Ph.D.

Dr. Morgan Scott is Professor of Epidemiology and E.J. Frick Professor in Veterinary Medicine at Kansas State University. A veterinarian with training in epidemiology and public health, Dr. Scott has worked in private practice, academic, and government (food safety surveillance) settings for more than 20 years. He has represented the United States on several European Union-U.S. food safety initiatives evaluating science policy as related to foodborne pathogens and antimicrobial resistance and currently serves on the WHO's Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR). His research focuses on studying factors impacting antimicrobial resistance among commensal and pathogenic enteric bacteria, with a program spanning the realm from the molecular to the sociological. He is particularly interested in applying epidemiological and

ecological approaches to quantify the emergence, propagation, dissemination, and persistence of resistant enteric bacteria, and to use this knowledge to prevent resistance among enteric pathogens in animal agriculture.

Dr. Eili Klein, Ph.D.

Dr. Eili Klein is an Assistant Professor in the Center for Advanced Modeling in the Social, Behavioral, and Health Sciences at Johns Hopkins Medicine. He is also a fellow at the Center for Disease Dynamics, Economics, and Policy in Washington, D.C. Dr. Klein's research focuses on the role of individuals in the spread of infectious disease, working at the nexus of economics and epidemiology. His work has examined the burden caused by infections with antibiotic-resistant pathogens such as MRSA, CRE, and VRE, including modeling the spread of resistance in relation to antibiotic use, the pressures on doctors to prescribe antibiotics, and the regulatory frameworks that discourage the development of new antibiotics but encourage their use. In addition, Dr. Klein has worked on the ecology and epidemiology of antimalarial drug resistance. In particular, he has focused efforts on understanding parasite competition within individuals and policy responses, such as a global subsidy for artemisinin combination therapies, to control the spread of resistance. Dr. Klein is actively involved in research efforts for the Robert Wood Johnson Foundation, Extending the Cure, the Global Fund, the Bill and Melinda Gates Foundation, National Institutes of Health, and Defense Advanced Research Projects Agency.

Dr. Timothy Palzkill, Ph.D.

Dr. Timothy Palzkill is Professor and Chair of the Department of Pharmacology at Baylor College of Medicine. His expertise is in protein engineering, especially as applied to understanding antibiotic-resistance mechanisms. Dr. Palzkill earned his Ph.D. at the University of Iowa, and received his post-doctoral training at Genentech Inc. and Stanford University. His long-term research interest has been in the use of genetic and biochemical approaches to study protein structure and function, focusing on antibiotic resistance enzymes. Specifically, his research includes the role of beta-lactamase mutations in the evolution of antibiotic resistance and analysis of protein and small-molecule inhibitors of beta-lactamases. These studies provide information for the design of new antimicrobials that are less susceptible to the rapid evolution of resistance. He is the recipient of a MERIT Award from the National Institute of Allergy and Infectious Diseases, and a Fellow of the American Academy of Microbiology.

Dr. Richard Wenzel, M.D., M.Sc.

Dr. Richard P. Wenzel is Professor and former Chairman of the Department of Internal Medicine at the Medical College of Virginia, Virginia Commonwealth University, in Richmond, Virginia. For eight years, he was a member of the editorial board of *The New England Journal of Medicine*, and is currently the journal's first Editor-at-Large. He is the author of more than 500 publications, editor of six textbooks, and lead editor of *A Guide for Infection Control in the Hospital*, translated into eight languages for free distribution to health care workers in developing countries. His popular book *Stalking Microbes* was published in the summer of 2005. Dr. Wenzel's research has focused on the prevention and control of hospital-acquired infections, especially bloodstream infections (BSIs) and sepsis. Dr. Wenzel is a member of the American Society of Clinical Investigation (ASCI), the Association of American Physicians (AAP) and a charter member of the Surgical Infections Society. He is also former President of the Society for Healthcare Epidemiology of America (SHEA) and former Councillor of the IDSA. In March 2010, he received the Maxwell Finland Award for Scientific Achievement from the National Foundation of Infectious Diseases. The IDSA gave him the Edward Kass Lectureship and Award in October 2010.

Keynote Speakers

Mr. Thomas Pickering

Mr. Thomas Pickering is Vice Chairman of Hills & Co, international consultants, and Strategic Adviser to NGP Energy Capital Management. He recently co-chaired a State-Department-sponsored panel investigating the September 2012 attack on the U.S. diplomatic mission in Benghazi. He served as U.S. ambassador to the United Nations in New York, the Russian Federation, India, Israel, El Salvador, Nigeria, and the Hashemite Kingdom of Jordan. Ambassador Pickering also served on assignments in Zanzibar and Dar es Salaam, Tanzania. He was U.S. Under Secretary of State for Political Affairs, president of the Eurasia Foundation, and Boeing Senior Vice President for International Relations. He has received the Distinguished Presidential Award and the Department of State's Distinguished Service Award. He graduated from Bowdoin College and received a master's degree from the Fletcher School of Law and Diplomacy at Tufts University.

Dr. Robert Robbins

Dr. Robert Robbins is the Chief Executive Officer and President of Texas Medical Center in Houston. He formerly was a professor and chairman of the Department of Cardiothoracic Surgery at Stanford and director of the Stanford Cardiovascular

Institute. He also directed Stanford's Heart-Lung and Lung Transplantation programs, as well as its Cardiothoracic Transplantation Laboratory. Robbins completed his medical degree, general-surgery internship, and residency at the University of Mississippi and completed a cardiothoracic-surgery residency at Stanford, where he was chief resident. He also completed postdoctoral fellowships in pediatric congenital heart surgery at Emory University in Atlanta, Georgia, and Royal Children's Hospital in Melbourne, Australia, and a fellowship in cardiothoracic transplantation at Columbia Presbyterian Medical Center in New York. He served as a clinical associate at the National Institutes of Health for two years during the late 1980s.

Biographical Information of ISGP Board of Directors

Dr. George Atkinson, Chairman

Dr. George Atkinson founded the Institute on Science for Global Policy (ISGP) and is an Emeritus Professor of Chemistry, Biochemistry, and Optical Science at the University of Arizona. He is former head of the Department of Chemistry at the University of Arizona, the founder of a laser sensor company serving the semiconductor industry, and Science and Technology Adviser (STAS) to U.S. Secretaries of State Colin Powell and Condoleezza Rice. He launched the ISGP in 2008 as a new type of international forum in which credible experts provide governmental and societal leaders with the objective understanding of the science and technology that can be reasonably anticipated to help shape the increasingly global societies of the 21st century. Dr. Atkinson has received National Science Foundation and National Institutes of Health graduate fellowships, a National Academy of Sciences Post Doctoral Fellowship, a Senior Fulbright Award, the SERC Award (U.K.), the Senior Alexander von Humboldt Award (Germany), a Lady Davis Professorship (Israel), the first American Institute of Physics' Scientist Diplomat Award, a Titular Director of the International Union of Pure and Applied Chemistry, the Distinguished Service Award (Indiana University), an Honorary Doctorate (Eckerd College), the Distinguished Achievement Award (University of California, Irvine), and was selected by students as the Outstanding Teacher at the University of Arizona. He received his B.S. (high honors, Phi Beta Kappa) from Eckerd College and his Ph.D. in physical chemistry from Indiana University.

Loretta Peto, Secretary/Treasurer

Loretta Peto is the Founder and Managing Member at Peto & Company CPA's PLLC. She has experience in: consulting on business valuation and litigation, including valuing businesses for buy-sell agreements, estate and gift tax, marital dissolution and employee compensation; consulting with closely held businesses regarding business restructure, cash management, succession planning, performance enhancement and business growth, and managing tax-related projects, including specialty areas in corporate, partnership, estate and gift tax, business reorganizations, and multistate tax reporting. She is a Certified Public Accountant and accredited in Business Valuations. She is a member of the Finance Committee and Chair of the Audit Committee at Tucson Regional Economic Opportunities. She also is a member of the DM50 and Tucson Pima Arts Council. She received a

Master of Accounting - Emphasis in Taxation degree from the University of Arizona in 1984, and was awarded the Outstanding Graduate Student Award.

Dr. Janet Bingham, Member

Dr. Janet Bingham has been President and CEO and a consultant to the Huntsman Cancer Foundation (HCF) since 2006. The foundation is a charitable organization that provides financial support to the Huntsman Cancer Institute, the largest cancer specialty research center and hospital in the Intermountain West. Dr. Bingham also has managed Huntsman Cancer Biotechnology Inc. In addition, she was appointed Executive Vice President and Chief Operating Officer with the Huntsman Foundation in 2008. The Huntsman Foundation is the private charitable foundation established by Jon M. Huntsman Sr. to support education, cancer interests, programs for abused women and children, and programs for the homeless. Before joining the Huntsman philanthropic organizations, Dr. Bingham was the Vice President for External Relations and Advancement at the University of Arizona. Prior to her seven years in that capacity, she served as Assistant Vice President for Health Sciences at the University of Arizona Health Sciences Center. Dr. Bingham was recognized as one of the Ten Most Powerful Women in Arizona.

Dr. Henry Koffler, Member

Dr. Henry Koffler is President Emeritus of the University of Arizona (UA). He served as President of the UA from 1982-1991. From 1982 he also held professorships in the Departments of Biochemistry, Molecular and Cellular Biology, and Microbiology and Immunology, positions from which he retired in 1997 as Professor Emeritus of Biochemistry. His personal research during these years concentrated on the physiology and molecular biology of microorganisms. He was Vice President for Academic Affairs, University of Minnesota, and Chancellor, University of Massachusetts/Amherst, before coming to the UA. He taught at Purdue University, where he was a Hovde Distinguished Professor, and the School of Medicine at Western Reserve University (now Case Western Reserve University). Dr. Koffler served as a founding governor and founding vice-chairman of the American Academy of Microbiology, and as a member of the governing boards of Fermi National Accelerator Laboratory, the Argonne National Laboratory, and the Superconducting Super Collider Laboratory. He was also a board member of the Association of American Colleges and Universities, a member and chairman of the Council of Presidents and a member of the executive committee of the National Association of Land Grant Colleges and Universities. He was also Founder, President and board member of the Arizona Senior Academy, the driving force in the development of the Academy Village, an innovative living and learning community.

Among the honors that Dr. Koffler has received are a Guggenheim Fellowship and the Eli Lilly Award in Bacteriology and Immunology.

Mr. Jim Kolbe

For 22 years, Mr. Jim Kolbe served in the United States House of Representatives, elected in Arizona for 11 consecutive terms, from 1985 to 2007. Mr. Kolbe is currently serving as a Senior Transatlantic Fellow at the German Marshall Fund of the United States, and as a Senior Adviser to McLarty Associates, a strategic consulting firm. He advises on trade matters as well as issues of effectiveness of U.S. assistance to foreign countries, on U.S.-European Union relationships, and on migration and its relationship to development. He is also co-chair of the Transatlantic Taskforce on Development with Gunilla Carlsson, the Swedish Minister for International Development Cooperation. He also is an adjunct Professor in the College of Business at the University of Arizona. While in Congress, he served for 20 years on the Appropriations Committee of the House of Representatives, was chairman of the Treasury, Post Office and Related Agencies subcommittee for four years, and for his final six years in Congress, he chaired the Foreign Operations, Export Financing and Related Agencies subcommittee. He graduated from Northwestern University with a B.A. degree in Political Science and then from Stanford University with an M.B.A. and a concentration in economics.

Dr. Charles Parmenter, Member

Dr. Charles Parmenter is a Distinguished Professor Emeritus of Chemistry at Indiana University. He also served as Professor and Assistant and Associate Professor at Indiana University in a career there that spanned nearly half a century (1964-2010). He earned his bachelor's degree from the University of Pennsylvania and served as a Lieutenant in the U.S. Air Force from 1955-57. He worked at DuPont after serving in the military and received his Ph.D. from the University of Rochester and was a Postdoctoral Fellow at Harvard University. He has been elected a Member of the National Academy of Sciences and the American Academy of Arts and Sciences; and a Fellow of the American Physical Society and the American Association for the Advancement of Science. He was a Guggenheim Fellow, a Fulbright Senior Scholar, and received the Senior Alexander von Humboldt Award in 1984. He has received the Earle K. Plyler Prize, was a Spiers Medalist and Lecturer at the Faraday Society, and served as Chair of the Division of Physical Chemistry of the American Chemical Society, Co-Chair of the First Gordon Conference on Molecular Energy Transfer, Co-organizer of the Telluride Workshop on Large

Amplitude Motion and Molecular Dynamics, and Councilor of Division of Chemical Physics, American Physical Society.

Dr. Eugene Sander, Member

Dr. Eugene G. Sander served as the 20th president of the University of Arizona (UA), stepping down in 2012. He formerly was vice provost and dean of the UA's College of Agriculture and Life Sciences, overseeing 11 academic departments and two schools, with research stations and offices throughout Arizona. He also served as UA executive vice president and provost, vice president for University Outreach and director of the Agricultural Experiment Station and acting director of Cooperative Extension Service. Prior to his move to Arizona, Sander served as the deputy chancellor for biotechnology development, director of the Institute of Biosciences and Technology, and head of the department of biochemistry and biophysics for the Texas A&M University system. He was chairman of the department of biochemistry at West Virginia University Medical Center and associate chairman of the department of biochemistry and molecular biology at the College of Medicine, University of Florida. As an officer in the United States Air Force, he was the assistant chief of the biospecialties section at the Aerospace Medical Research Laboratory. He graduated with a bachelor's degree from the University of Minnesota, received his master's degree and Ph.D. from Cornell University and completed postdoctoral study at Brandeis University. As a biochemist, Sander worked in the field of mechanisms by which enzymes catalyze reactions.

Biographical information of staff

Dr. George Atkinson, Executive Director

Dr. George Atkinson is the founder and Executive Director of the Institute on Science for Global Policy (ISGP) and is an Emeritus Professor of Chemistry, Biochemistry, and Optical Science at the University of Arizona. His professional career has involved academic teaching, research, and administration, roles as a corporate founder and executive, and public service at the federal level. He is former head of the Department of Chemistry at the University of Arizona, the founder of a laser sensor company serving the semiconductor industry, and Science and Technology Adviser (STAS) to U.S. Secretaries of State Colin Powell and Condoleezza Rice. In 2013, he became the president-elect of the Sigma Xi Society. Based on principles derived from his personal experiences, he launched the ISGP in 2008 as a new type of international forum in which credible experts provide governmental and societal leaders with the objective understanding of the science and technology that can be reasonably anticipated to help shape the increasingly global societies of the 21st century.

Jessica Appert, M.S.P.H.

Jessica Appert is a Fellow with the ISGP. She graduated with a B.S. in Biology and an M.S. in Public Health from the University of Minnesota, where she is currently a Ph.D. candidate. Her graduate research focused on the role of airborne particles in spreading infectious diseases in human health settings and animal agriculture. Ms. Appert has previously worked with the Global Initiative for Food Systems Leadership and the National Center for Food Protection and Defense in roles examining zoonotic disease risks, food safety, and global food systems leadership.

Jennifer Boice, M.B.A.

Jennifer Boice is the Program Coordinator of the ISGP. Ms. Boice worked for 25 years in the newspaper industry, primarily at the Tucson Citizen and briefly at USA Today. She was the Editor of the Tucson Citizen when it was closed in 2009. Additional appointments at the Tucson Citizen included Business News Editor, Editor of the Online Department, and Senior Editor. She also was a business columnist. Ms. Boice received an M.B.A. from the University of Arizona and graduated from Pomona College in California with a degree in economics.

Sweta Chakraborty, Ph.D.
Sweta Chakraborty is a Senior Fellow with the ISGP. She recently completed post-doctoral research on pharmaceutical regulation and product liability at Oxford University's Centre for Socio-Legal Studies and remains an active member of Wolfson College. Dr. Chakraborty received her doctorate in Risk Management from King's College London and has helped to design and co-teach a summer course in London on Managing Hazards in Europe and the United States with Indiana University's School of Public and Environmental Affairs. Her undergraduate degrees are in Decision Science and International Relations from Carnegie Mellon University.

Anna Isaacs, M.Sc.
Anna Isaacs is a Senior Fellow with the ISGP. She has previously focused on minority health issues and is experienced in field- and desk-based qualitative research. She has interned as a researcher at a variety of nonprofit institutions and also at the House of Commons in London. Ms. Isaacs received her M.Sc. with distinction in Medical Anthropology from University College London and a B.Sc. in Political Science from the University of Bristol.

Paul Lewis, J.D.
Paul Lewis is a Fellow with the ISGP. He worked as a Congressional Aide in Washington, D.C., and as a Legal Associate specializing in Federal Immigration Law before working with Google on Maps and Local Search products. Mr. Lewis came to Google through Immersive Media, the company behind Street View camera technology. He was involved in the rollout of Google Street View, and has managed projects involving 360-degree GPS embedded data worldwide. Mr. Lewis earned his Juris Doctor at the University of Arizona and graduated Magna Cum Laude with degrees in journalism and political science from Northern Arizona University.

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David Miller is a Scientific/Program Consultant with the ISGP. Previously, he was Director, Medical Advocacy, Policy, and Patient Programs at GlaxoSmithKline, where he led the company's U.S. efforts relating to science policy. In this role, he advised senior management on policy issues, and was the primary liaison between the company and the national trade associations, Pharmaceutical Research and Manufacturers of America (PhRMA) and Biotechnology Industry Organization (BIO). He also held management positions in business development and quality assurance operations. Mr. Miller received his B.S. in Chemistry and his M.B.A. from the University of North Carolina at Chapel Hill.

Harvey Morris, Ph.D.

Harvey Morris is a Fellow with the ISGP. As a Licensed Psychologist, he began his work on staff at the New York Health and Hospitals Corporation, and eventually became Director of Clinical Services at a private 100-bed hospital. In the late 1970s he founded and managed a midsized specialty consulting firm that assisted major global corporations and national governmental agencies in accelerating strategy implementation. After retiring, he founded and served as Executive Director of a not-for-profit foundation, and served on an advisory board at the University of Arizona. Dr. Morris received a B.A. in Psychology from the City University of New York, and a Ph.D. in Clinical Psychology from the University of Nebraska.

Arthur Rotstein, M.S.J.

Arthur Rotstein is Copy Editor with the ISGP. Prior to joining the ISGP, Mr. Rotstein worked for the Washington (D.C.) Daily News, held a fellowship at the University of Chicago, and spent more than 35 years working as a journalist with The Associated Press. His writings have covered diverse topics that include politics, immigration, border issues, heart transplant and artificial heart developments, Biosphere 2, college athletics, features, papal visits, and the Mexico City earthquake. Mr. Rotstein received his bachelor in journalism degree from the University of Missouri and holds a M.S.J. from Northwestern University's Medill School of Journalism.

Raymond Schmidt, Ph.D.

Ray Schmidt is a Senior Fellow with the ISGP. In addition, he is a physical chemist/chemical engineer with a strong interest in organizational effectiveness and community health care outcomes. While teaching at the university level, his research focused on using laser light scattering to study liquids, polymer flow, and biological transport phenomena. Upon moving to the upstream petroleum industry, he

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Ramiro Soto

Ramiro Soto is a Fellow at the ISGP. He currently is an undergraduate student at the University of Arizona College of Science seeking a Bachelor of Science degree in General Applied Mathematics. Beyond his academic curriculum, Mr. Soto is an active member of the Pride of Arizona marching band since 2010 and a member of the athletic pep band. He completed an internship with the Walt Disney Company Parks and Resorts segment in 2011. After completing his undergraduate education, he plans to apply for a doctoral program furthering his studies in mathematics.

Matt Wenham, D.Phil.

Matt Wenham is Associate Director of the ISGP. He formerly was a postdoctoral research fellow at the National Institutes of Health in Bethesda, Maryland. His research involved studying the interaction of protein toxins produced by pathogenic E. coli strains with human cells. Dr. Wenham received his D. Phil. from the Sir William Dunn School of Pathology, University of Oxford, United Kingdom, where he was a Rhodes Scholar. Prior to this, he worked in research positions at universities in Adelaide and Melbourne, Australia. Dr. Wenham received his bachelor's and honours degrees in biochemistry from the University of Adelaide, South Australia, and holds a Graduate Diploma of Education from Monash University, Victoria.