
# *Emerging and Persistent Infectious Diseases: Focus on Prevention*

Conference convened by the ISGP June 5-8, 2011
at the Estancia La Jolla Hotel, San Diego, California

**Institute on Science for Global Policy (ISGP)**

# Emerging and Persistent Infectious Diseases:
## *Focus on Prevention*

Conference convened by the ISGP at the Estancia La Jolla Hotel
San Diego, California, USA
June 5–8, 2011

*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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## 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 and convene the invitation-only ISGP conference on *EPID: Focus on Prevention* held at the Estancia La Jolla Hotel in San Diego, California, June 5–8, 2011. Other contributions aided the ISGP in preparing the material presented in this book, including not only the eight invited policy position papers, but a record, without attribution, of the views presented in the discussions, critical debates and caucuses that ensued.

The process began with the early recognition that EPID and related aspects of Food Safety and Security (FSS) and Synthetic Biology (SB) are topics that deserved significantly greater attention from both domestic and international policy makers. The willingness of those in the scientific and policy communities who have expertise and experience with EPID, FSS, and SB to be interviewed by the ISGP staff was a critical early step in creating and updating the Strategic Roadmap on EPID. The resultant Strategic Roadmap describes the two-year series of ISGP conferences focused on different policy aspects of EPID, FSS, and SB. The endorsement of and support for the EPID Strategic Roadmap by the governments engaged with the ISGP facilitated the launching of the EPID conference series and the convening by the ISGP of the *EPID: Focus on Prevention* conference.

The efforts of the scientific presenters invited by the ISGP in both preparing policy position papers and engaging policy makers in vigorous debates were especially appreciated. Their biographies are provided in this book.

No less critical to the success of the program were the often-intense debates that originated between the scientific presenters and the subject-matter experts and policy makers in the audience who, following consultations with the participating governments, were invited to attend the June 2011 conference. The exchange of strongly held views, innovative proposals, and critiques generated from questions and debates fostered an unusual, even unique, environment focused on clarifying understanding for the non-specialist and addressing specific questions related to formulating and implementing effective public policy pertaining to EPID.

The ISGP is greatly indebted to all those who participated in these vigorous, not-for-attribution debates and caucuses.

The energetic, highly professional work of the ISGP staff merits special acknowledgment. Their outstanding interviewing, organizing, and writing skills were essential to recording the often-diverse views and perspectives expressed in the critical debates, capturing the areas of consensus and next steps from the caucuses, and persevering through the extensive editing process needed to assure the accuracy of the material published here. All of their work is gratefully acknowledged. Their biographies are provided in the book.

Finally, the ISGP expresses sincere appreciation for the advice and financial support of agencies and departments of the U.S. federal government including the National Intelligence Council, the Department of State, the Department of Homeland Security, and the Department of Health and Human Services. In addition, major scientific and financial support was provided by the Istituto Regionale di Ricerca in Milan, Italy. The ISGP also benefited from the recommendations and generous gifts provided by the MARS Corp., Novartis, and Mr. Edward Bessey. The ISGP gratefully acknowledges the ongoing support provided by the Critical Path Institute, the University of Arizona, and the University of Minnesota.

Dr. George H. Atkinson
Founder and Executive Director
Institute on Science for Global Policy
August 15, 2011

## Table of contents

# Introduction

Dr. George H. Atkinson
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**Preface**

The contents of this book are taken from the policy position papers, discussions, debates, and caucuses that were part of an international conference convened by the Institute on Science for Global Policy (ISGP). This ISGP conference, held June 5–8, 2011, at the Estancia La Jolla Hotel in San Diego, California, addressed topics involving prevention issues related to Emerging and Persistent Infectious Diseases (EPID) as well as aspects of Food Safety and Security (FSS) and Synthetic Biology (SB) related to infectious diseases. 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.

**Current realities**

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 based on science and technology (S&T) necessarily involve both domestic and international policy decisions. 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, are now fundamental governmental responsibilities. These responsibilities are especially complex since policy makers must consider the demands of different segments of society often having 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 communicate effectively. With a seemingly unlimited number of urgent S&T challenges, both developed and developing societies need the most accomplished members of these communities to focus on effective, real-world solutions. Some of the most prominent challenges involve infectious diseases and pandemics, environmentally compatible energy sources, the consequences of climate change, food safety and security, the cultural impact of stem cell applications, nanotechnology and human health, cybersecurity for advanced telecommunication, the security implications of quantum computing, and 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 non-experts directly engaged in decisions. Such discussions, sequestered away 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 implement any decision.

**The ISGP mission**

The Institute on Science for Global Policy (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 period, these ISGP conferences are convened on different aspects (e.g., surveillance, prevention, or mitigation) of a broad, overarching topic (currently, EPID and related aspects of FSS and SB). The format used emphasizes written and oral, policy-oriented S&T presentations and extensive debates led by an international cross section of the policy community.

The current realities, relevant S&T-based options, and policy issues are debated among a few scientists selected by the ISGP and an international group of government, private sector, and societal leaders selected following consultations with the participating governments. ISGP conferences reflect global perspectives and seek to provide government 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. The value of ensuring that science-based understanding is closely linked to realistic policy decisions made by societal leaders, and endorsed and supported by the public.

2. The importance of venues where internationally distinguished scientists candidly debate policy makers concerning scientifically credible options, and associated risks, available to effectively address the major challenges facing 21st century societies worldwide.

**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 developed 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, over-hyped 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 found in ISGP 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**

The ISGP conference convened on June 5–8, 2011, addressed EPID and related aspects of FSS and SB with a focus on prevention issues.

Prior to the EPID/FSS/SB conference, the ISGP invited eight internationally recognized, subject-matter experts to prepare concise (three pages) policy position papers describing their views on current realities, scientifically credible opportunities now available together with the associated risks, and the domestic and international policy issues involved. These individuals were chosen to represent a broad cross section of viewpoints and an international perspective. Several weeks before the conference convened, these policy position papers were distributed to representatives from governments, societal institutions, and international organizations engaged with the ISGP. For the June 5–8, 2011 conference, this included representatives from the United States, Italy, the United Kingdom, Japan, Canada, Germany, France, Singapore, Hong Kong, Switzerland, Mexico, the Food and Agricultural Organization of the United Nations, and the European Commission. Individuals from several private sector and philanthropic organizations also were invited to participate and, therefore, to receive the papers. All participants had responsibilities and/or made major contributions to the formulation and implementation of domestic and international policies related to EPID, FSS, and SB.

The conference agenda was comprised of eight, 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 there can be no attribution of any remark to any participant). In each 90-minute 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 the clarity of understanding among the non-specialists and identifying areas of consensus and actionable policy decisions supported by scientifically credible information. With active participation from North America, Europe, Australia, and Asia, these candid debates reflected international perspectives on real-world problems.

The ISGP staff attended the debates of all eight 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 eight debates, caucuses were held by small groups 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. The ISGP has no preconceived opinions nor do members of the ISGP staff 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 found in the 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 non-specialists 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 non-specialists, but also in which the debates and caucuses identify realistic policy options for serious consideration by governmental and societal leaders. With success, these new ISGP programs can 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 challenges of preventing and controlling infectious diseases in humans and in animals, as well as the diseases themselves, are deeply intertwined and are critically influenced by diverse factors, including those that characterize ecological and social environments. Therefore, it is paramount that efforts to prevent and control infectious diseases use a comprehensive approach that considers human, animal, and wildlife health and is based on multi-disciplinary understanding, including input from social and behavioral sciences and from economics. While the concepts underlying the "One Health" initiative were developed to forge such multidisciplinary collaborations, there are few examples of the One Health approach effectively being implemented.

**Actionable next steps:**

1. A separate unit, with global coordinating responsibilities and unified leadership, perhaps located within the United Nations (UN), needs to be created to promote the implementation of the One Health concept within specific countries and regions. To be operationally effective, national One Health initiatives must coordinate efforts across all in-country human health, animal health, and wildlife management agencies and collect meaningful data to be shared with the regional and international One Health organizations responsible for global health issues.

2. To effectively share infectious disease data across disciplines, significant improvements to existing information networks must be made, starting with the creation of a unified reporting system with common core data requirements. A coordinated database can enable infectious disease-management policies and programs to appropriately consider information from a wide range of disciplines, including information from those traditionally omitted from disease prevention strategies (e.g., ecology, economics, and social sciences).

3. To educate One Health practitioners who are effective in developing and sustaining long-term initiatives, university curricula with internationally recognized standards must integrate concepts from the numerous academic disciplines that examine human and animal health, including the social and behavioral sciences, ecology, and economics.

4. Significant policy-level changes are required to ensure that agencies and departments across governments fully cooperate in implementing necessary improvements in disease prevention and control. The sharing of work plans and strategies as well as the coordination of budgetary requests and expenditures are fundamentally important first steps. While many in government recognize the importance of the One Health approach, the *status quo* is routinely maintained in an effort to prevent budget reductions, loss of responsibilities, and personnel cutbacks. Intragovernmental coordination, as well as international cooperation, must be driven by the highest level of national and global leadership to correct the *status quo*.

**Area of consensus 2:**

The demonstrated worldwide success and cost effectiveness of vaccines in minimizing, and in some cases preventing, the acquisition and spread of infectious diseases strongly supports the

conclusion that vaccine use must be significantly increased globally. Specifically, all individuals for whom specific, existing vaccinations are indicated need to be immunized. Recent experience demonstrates that a variety of socially complex obstacles to universal immunization exist, including economic barriers that restrict the distribution of and access to vaccines and a growing tendency of the public to refuse vaccines based on mistrust of vaccines and/or perceived low risk of contracting disease. Scientifically credible evidence suggests that effective new strategies are needed to accurately inform policy makers and the public about the advantages and rational risks associated with vaccines and to minimize the impact of the unwarranted obstacles to universal vaccine use.

**Actionable next steps:**

1. Substantially improved societal and governmental leadership, among scientists, physicians, academics, and others who help shape public opinion, is needed to develop a consistent, "one voice" view committed to universal vaccine coverage. Such a one voice approach requires all stakeholders have timely access to detailed, credible information about the logistics, feasibility, degree of potential risks, and uncertainty concerning effectiveness and benefits associated with the use of vaccines for specific diseases. The communication skills of those engaged in such messaging (e.g., scientists, public health officials, and celebrities) need to be improved and the information and messages must focus on fostering rational understanding and accurate instructions that promote confidence in the lay citizen.

2. Given the general perception that vaccine research and development (R&D) is directly dependent on the anticipated profits accruing to the pharmaceutical industry, a new type of public-private partnership is needed to promote the public benefits from vaccine R&D while motivating pharmaceutical companies to invest in innovative vaccine R&D. Long-term corporate tax breaks, first-in-line privileges, and guaranteed numbers of vaccine purchases by governments are incentives that might foster innovative vaccine R&D within such new public-private partnerships.

3. The pace at which regulatory decisions are made concerning new vaccines needs to accelerate if the global demand for vaccines is to be met. Extreme caution must be exercised to ensure that safety standards are not lowered and that such a streamlined regulatory process does not inappropriately lead the public to view these practices as risky. Entrenched attitudes within the regulatory agencies responsible for vaccines often constrain changes in the regulatory process, especially those that accelerate approvals. Enhancing the professional and educational experiences of regulatory agency employees may help clarify the advantages of altering the *status quo* and supporting changes that accelerate approvals while preserving public safety.

**Area of consensus 3:**

Drug resistance in infectious diseases has emerged as a significant issue for the protection of human and animal health. Notably, drug-resistant tuberculosis (DR-TB) has become a major concern worldwide, particularly in light of the global proliferation of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) during the past decade. Improvements in monitoring, treatment, and control strategies are urgently needed to reduce morbidity and mortality from all forms of TB, especially from DR-TB, as well as to prevent new infections.

**Actionable next steps:**

1. Although global surveillance of DR-TB is currently conducted, the accuracy of the data collected, especially with respect to its prevalence, incidence, geographic, and demographic distribution, must be improved if prevention and control efforts are to be successful. In addition to improving the quality of these data, it is critical to accurately characterize adherence rates for Directly Observed Therapy (DOT) and Directly Observed Therapy — Short Course (DOTS) programs worldwide. Adherence data for both DOT and DOTS need to be coupled with an evaluation of the effectiveness of both programs to determine whether modifications and/or significant changes in these strategies are required.

2. Currently accepted treatment protocols have come under scrutiny with respect to their effectiveness. New drug treatment options for DR-TB must be developed, especially for TB that is resistant to more than one first-line drug. In the interim, it is necessary for guidelines on the treatment and management of DR-TB to be regularly updated and/or modified to reflect new research on drug combinations and best practices.

3. It is essential for TB control strategies to focus on preventing new cases of secondary DR-TB (i.e., drug resistant TB that develops from the use of inappropriate drugs or poor adherence). The robust implementation of these strategies must focus on improving treatment completion rates by ensuring the appropriate drug regimen is used until drug-sensitive TB patients are fully cured. Given the prolonged treatment times required and the disproportionate impact TB has on individuals of lower socio-economic status, such strategies must incorporate practical social assistance appropriate for specific societal environments.

**Area of consensus 4:**

Food safety is a rapidly growing challenge worldwide due to the global nature of the food supply chain, rising morbidity and mortality caused by increased outbreaks of foodborne diseases, the continued impact of endemic foodborne diseases, and the growing health care costs associated with foodborne diseases in general. Preventing transmission of the foodborne disease burden requires action at local, national, regional, and international levels. Currently available technologies (e.g., DNA sequencing, risk-based assessments, and source attribution) can be effective in improving food safety systems and need to be employed more widely.

**Actionable next steps:**

1. To accurately attribute a foodborne disease to a source, it is critical to develop a comprehensive and global source attribution system that correctly identifies and characterizes not only known pathogens, but also microbes that are not yet classified as pathogens. Including data on as many microbes as possible would aid in identifying sources not only of foodborne diseases, but also pathogens for other types of infectious diseases. Such multiple uses would garner greater returns on the investment in a source attribution system. The use of DNA sequencing technology, which allows for the identification of specific strains of microbes, needs to be incorporated into a global source attribution system to enhance prevention and mitigation strategies. Capacity building in resource-poor regions of the world (e.g., training in the use of existing DNA technology and provision of necessary equipment) will also be necessary to ensure a truly global system is created.

2. Strategies to ensure food safety need to shift from hazard-based to risk-based approaches to optimize the allocation of resources and to maximize the use of recent advances in risk assessment tools. Government and industry stakeholders need to gain enough confidence in the concepts underlying advanced risk assessment to use them in their decisions.

3. Public messages provided by scientists and public health officials concerning foodborne diseases (including accurate and useful risk assessments) must be significantly improved. Training opportunities to enhance the communication skills within these communities are necessary if rapidly emerging information on foodborne diseases is to be effectively shared with other stakeholders and with the lay public.

4. While the food safety standards, regulations, and guidelines of the World Trade Organization (WTO) and Codex Alimentarius (CA) are generally based on scientifically credible information, precedence in the trade of food products is routinely given to the analogous food safety rules developed by the private food sector, at times without scientific credibility. Global food safety can be ensured only if these rules are harmonized by agreement between the regulatory organizations and the private food sector. The present variability in the rules casts doubt on the safety of food and undermines the fair trade of food.

5. Ensuring food safety worldwide requires that the private food sector be included in the development of policies and tools affecting the production and distribution of food (e.g., a source attribution system). Such new public-private partnerships would strengthen working relationships between the private sector and government and help effectively implement the adoption of emerging tools, technologies, and policies. The sharing of data between the food industry and governments is also critical to improved food safety and infectious disease management.

**Area of consensus 5:**

Advancements in recombinant DNA technology and genomics have created both great optimism and uncertainty concerning how rapidly emerging research, collectively labeled synthetic biology, might transform the prevention, control, and treatment of infectious diseases. Research within synthetic biology seeks to protect human health not only by developing more effective vaccines, pharmaceuticals, and other treatments, but also by altering the course of disease through modifications in biological vectors (e.g., genetically re-engineering mosquitoes that transmit malaria). The prospect of synthetic biology creating opportunities for transformational changes causes major public concern regarding potential risks to human health from the genomic manipulation of organisms. Such concerns have intensified due to the possibility that synthetic biology could be used to cause harm as part of an "insider threat," coordinated bioterrorism, and/or the activities of amateur, "Do It Yourself" (DIY) scientists who often work without formal training and in home-grown, unsupervised laboratories. Potential risks from all such sources, both deliberate and accidental, must be well understood and limited through improved biosafety measures.

**Actionable next steps:**

1. Since the broadly interpreted definition and rapid evolution of synthetic biology have contributed to growing confusion and mistrust concerning the goals and practical applications of research in this field, scientists and policy makers need to identify credible options for monitoring formal and informal research and create rational policies

that protect the public interest. Such responsibilities need to begin with a collective effort to articulate clear and coherent definitions of synthetic biology activities that are socially acceptable as well as those activities that constitute a threat to public safety.

2. A balance between mandatory and voluntary regulations must be developed to diminish the possibility of both deliberate and accidental harm stemming from research in and the application of synthetic biology concepts. While mandatory regulations, including the creation of a central intelligence database and licensure of all scientists manipulating organisms, must be seriously considered, caution also must be exercised to ensure that over-regulation does not stifle innovation. Self-regulation must be endorsed by the research and private-sector communities engaged in synthetic biology to encourage conscientious scientific practices and to motivate the prompt reporting to law enforcement of suspected threats.

3. Training for all professional and amateur scientists working in synthetic biology must be considered an integral element of efforts to prevent intentional or accidental harm to humans and/or the environment. Such training on biosafety, biosecurity, codes of conduct, and ethics requires more development and publicity.

**Area of Consensus 6:**

Scientists and policy makers must more effectively communicate scientific information concerning the risks and benefits of infectious disease prevention methods, such as vaccines, among both their respective communities and to the public. Misleading communication leads to confusion among experts and the lay public, and thereby hampers the implementation of policies designed to prevent the acquisition and spread of infectious diseases.

**Actionable next steps:**

1. Joint training programs need to be implemented to improve the communication skills of scientists, public health officials, and policy makers. Opportunities to conduct proactive communication with the public before infectious diseases become an urgent issue need to be encouraged.

2. Greater focus needs to be placed on employing novel, evidenced-based approaches in communicating often complex scientific information to public health officials, policy makers, and lay audiences who do not have specific scientific or technical experience.

3. International sharing of best practices and lessons learned regarding the prevention of infectious diseases (e.g., successful programs, effective methodologies, and challenges in program implementation) is needed to enable policy makers to adapt and replicate successful prevention strategies as well as avoid those that failed.

# ISGP conference program

**Sunday, June 5**

| | |
|---|---|
| 12:00 – 17:00 | **Arrival and Registration: Estancia La Jolla Hotel** |
| 17:00 – 18:00 | *Reception* |
| 18:00 – 19:00 | *Dinner* |
| 19:00 – 19:30 | **Welcome and Opening Remarks**<br>**Dr. George Atkinson, Founder and Executive Director, ISGP, and Conference Moderator** |
| 19:30 – 20:00 | **Evening Remarks and Q&A**<br>**Dr. Carole Heilman, Director, Division of Microbiology and Infectious Diseases, the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, United States** |

**Monday, June 6**

| | |
|---|---|
| 07:00 – 08:00 | *Breakfast* |

**Presentations and Debates: Session 1**

| | |
|---|---|
| 08:00 – 09:30 | **Prof. Martyn Jeggo, Commonwealth Scientific and Industrial Research Organisation and Deakin University, Australia**<br>*Managing the Risks From New and Emerging Infectious Disease: the 'One Health' Paradigm* |
| 09:30 – 10:00 | *Break* |
| 10:00 – 11:30 | **Dr. David Fisman, University of Toronto, Canada**<br>*Bugs and Bucks: Infectious Disease Persistence is a Matter of Economics* |
| 11:30 – 12:30 | *Lunch* |
| 12:30 – 13:30 | *Informal discussions* |
| 13:30 – 14:00 | **Afternoon Remarks and Q&A**<br>**Dr. Peter Biggins, Head of International Research Strategy, Defence Science and Technology Laboratory, United Kingdom** |

**Presentations and Debates: Session 2**

| | |
|---|---|
| 14:00 – 15:30 | **Dr. David Markovitz, University of Michigan, United States**<br>*Vaccines: Very Successful, Strangely Controversial* |
| 15:30 – 16:00 | *Break* |

16:00 – 17:30 **Dr. Timothy Rodwell, University of California, San Diego, Refugee Health Assessment Program, and Utopia Scientific, United States**
*Preventing the Untreatable: Why Drug-resistant Tuberculosis Must Be Prevented*

17:30 – 18:30 *Reception*

18:30 – 19:30 *Dinner*

19:30 – 20:00 **Evening Remarks and Q&A**
**Dr. Sergio Pecorelli, President, Italian Medicines Agency, and Chancellor, the University of Brescia, Italy**

**Tuesday, June 7**

07:00 – 08:00 *Breakfast*

**Presentations and Debates: Session 3**

08:00 – 09:30 **Dr. Robert Buchanan, University of Maryland, United States**
*Moving from Hazard-based to Risk-based Microbial Food Safety Systems to Promote Public Health and Foster Fair Trade Practices*

09:30 – 10:00 *Break*

10:00 – 11:30 **Dr. Jørgen Schlundt, Technical University of Denmark, Denmark**
*The Use of Farm-to-Fork Surveillance and New Genome Sequencing Techniques to Prevent and Control Foodborne Disease Globally*

11:30 – 12:30 *Lunch*

12:30 – 13:30 *Informal discussions*

**Presentations and Debates: Session 4**

13:30 – 15:00 **Dr. Sergio Abrignani, National Institute of Molecular Genetics and University of Siena, Italy**
*Would You Ever Recommend Driving a Motorbike Without a Helmet?*

15:00 – 15:30 *Break*

15:30 – 17:00 **Dr. Bruce Hay, California Institute of Technology, United States**
*Synthetic Biology and Infectious Disease: Challenges and Opportunities*

**Caucuses**

17:00 – 18:30 **Focused group sessions**

18:30 – 19:30 *Dinner*

**Wednesday, June 8**

| | |
|---|---|
| 07:00 – 08:00 | *Breakfast* |
| **Caucuses** | |
| 08:00 – 09:30 | **Focused group sessions** |
| 09:30 – 10:00 | *Break* |
| 10:00 – 12:00 | **Plenary session**<br>Dr. George Atkinson, Moderator |
| 12:00 – 12:10 | **Closing remarks**<br>Dr. George Atkinson |
| 12:10 – 13:00 | *Lunch* |
| 13:00 | *Adjournment* |

# Managing the Risks From New and Emerging Infectious Disease: the "One Health" Paradigm**

Martyn Jeggo, B. Vet. Med., MSc., Ph.D., FAICD, M.R.C.V.S.
Director, Australian Animal Health Laboratory

**Summary**

The global risk from new and emerging infectious diseases continues to grow with recognition that, for the most part, the pathogens involved emerge from animals to infect humans. Recognizing the complexity of these interactions and the need for a strong interdisciplinary approach to effectively manage these risks, new partnerships are being forged under the general umbrella of "One Health." Involving human health, animal health, and environmental health exponents, solutions are sought for how to prevent as well as respond to the threats. But is this approach working? Whilst a number of key meetings continue to be held under the One Health umbrella, are we really seeing measurable progress in risk prevention and mitigation? Focusing research on the drivers for emergence, on modeling the risks, on improved diagnostics, and on targeted vaccines could considerably enhance our ability to prevent and respond. Ensuring the uptake and applications of new diagnostics and vaccines will be the key to prevention and response, but achieving this will require policies that drive further the One Health collaborations. Such policies should ensure that scant available resources are targeted toward the identified outcomes through research delivery and uptake, and that we genuinely work as "one world" in tackling the very real risks we face.

**Current realities**

New and emerging infectious diseases are now seen as a major global threat. Much of this realization has arisen as a result of the perceived threat of a global influenza pandemic, but other events such as the outbreaks of severe acute respiratory syndrome (SARS), Nipah virus infections in Southeast Asia, and foot and mouth disease in Korea have focused attention on the impacts of these diseases on humans, livestock production, the environment, and on food security in general. Studies have clearly shown that more than 70% of new infectious diseases in humans arise from animals, and several papers at the recent 1st International One Health Congress, held in February 2011 in Australia, highlighted the emergence of disease from wildlife through farmed species to humans. To better manage these risks, and in recognition of the multidisciplinary needs to tackle them, a One Health approach has been advocated for some time. This approach is cognizant that to effectively manage all the issues, those working in human health, animal health, and environmental health need to collaborate and coordinate in ways that they have not done before. Importantly, the transboundary nature of many of these infectious diseases clearly indicates a need to tackle the situation at the international as well as national levels. Acknowledgment of this need has resulted in, for example, new partnerships among the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the World Organisation for Animal Health (OIE). The risks of a global influenza pandemic, through the emergence of the highly pathogenic H5N1 strain of influenza from poultry to humans, catalyzed these approaches. Many meetings have been held in recent years to further develop One Health partnerships, enhance collaborations, mobilize resources, and identify deliverables. Recent meetings on One Health have gone to great lengths to document these achievements and to focus on "doables" and deliverable outcomes.

The recent 1st International One Health Congress, however, clearly indicated that much needs to be done. Patchy engagement by the international organizations (e.g., FAO, WHO, and OIE), the "silo" mentality of many governmental departments and ministries, and the protectionism of

resources and mandates by national agencies hamper the impact of proposed policy changes. The paucity of research outcomes in key areas, such as drivers for emergence and effective vaccines, and a number of examples of research duplication, suggest ineffective use and a lack of research resources. With the scant resources currently available at both national and international levels, practical, on-the-ground preventive actions to mitigate these threats seem few and far between. There is a considerable amount of highly constructive talk taking place at all levels. Yet, where are the targeted activities that are needed to bridge the gap between the current dialogue and future solutions? The gains so eagerly sought from a One Health approach remain an enigma.

**Scientific opportunities and challenges**

To develop effective prevention and mitigation strategies, some basic science is required. It is necessary to understand the pathogenesis of the disease, host-pathogen interactions, drivers for pathogen emergence, and processes underpinning host switching (i.e., pathogens switching from one host to another). For effective disease surveillance, modeling the likelihood of outbreaks using information both on the drivers for emergence and the basic pathogenesis of the disease becomes critical. Linked to this is the use of effective diagnostic procedures that provide both sensitivity and specificity to the surveillance system. Finally, whilst a number of approaches can be utilized for prevention and mitigation, (e.g., prophylactic treatment, slaughter of infected animals, and draconian trade restriction), effective vaccines remain the most potent weapons for prevention, mitigation, and even eradication of disease (e.g., the recent eradication of rinderpest through mass vaccination).

Fortunately, current research is poised to deliver significant insight into a number of these areas. Whole genome sequencing, whether at the cellular, host, or pathogen level, is providing exquisite insight into the host-pathogen relationship and underlying mechanisms of host and pathogen adaptation. High throughput systems for rapid and large-scale sequencing and data management processes are allowing rapid discovery to take place. Due to the use of complex science modeling systems, drivers of emergence and the emergent process, particularly around host switching, are becoming clearer. This in itself will lead to alternative preventive approaches and to targeted preventive actions. Equally, new systems of field-based assays (e.g., penside/bedside tests) linked to multiplexed assays can considerably enhance the predictive capabilities of surveillance systems and approaches. Finally, new approaches to vaccine construction, and new processes for fast tracking vaccine-use approval (e.g., those agreed to for influenza vaccine production in Australia) suggest the potential for greater use of vaccines in both prevention and mitigation. That science can deliver in the short term is not the key challenge. But targeting resources to drive this delivery, as well as directing additional resources to ensure vaccine uptake and widespread use, remain the key goals for effective risk reduction from new and emerging diseases in the short to medium term.

The underlying challenges remain — an appreciation of the risks, an understanding that science can deliver solutions to manage these risks, and that resources are required from those who control the purse strings. We are all aware of the current fiscal challenges, but when there is a problem with available solutions it must merit serious prioritization for resource allocation.

**Policy issues**

- First and foremost, build on what is already being undertaken at both national and international levels. The CDC initiative on “operationalizing One Health;” the establishment of working groups following the U.S. Centers for Disease Control and Prevention (CDC) One Health meeting at Stone Mountain, U.S.; and the identification of

"doable" activities are all under way and will be continued during the proposed November 2011 meeting in Mexico. Building on these initiatives should be a key focus for all involved in One Health.

- Continue to build genuine One Health partnerships at the national level among governmental departments and agencies, with real organizational change, to avert "business as usual." Also, ensure the incorporation of wildlife surveillance activities into mainstream disease reporting.

- Given the difficulties reported by many countries in gaining real traction at the national level across agricultural, health, and environmental sectors, it could be valuable for countries to consider the development of "One Health Divisions" or equivalents that can act as a national focal point for specific activities in the One Health area.

- Accept the transboundary nature of the risks and establish a global system for disease reporting that transcends the activities already undertaken separately by WHO, FAO, and OIE. Create, within either WHO or FAO, a staffed One Health Division with responsibilities for international disease reporting of new and emerging diseases, for monitoring of national One Health surveillance systems, and for the identification and implementation of key researchable areas.

- International reporting needs to recognize existing reporting systems, such as those under the FAO Emergency Prevention Systems (EMPRES) program, the OIE formal disease reporting processes, and more informal systems such as the Program to Monitor Emerging Diseases (ProMED). In reporting as a single definitive source of information from this WHO or FAO One Health Division, the reports would draw on and recognize these currently fragmented but valuable information sources.

- In taking on the issues of research needs in this area, the "One Health Division" should develop a structured process for: the identification of the research required, the identification of the key deliverables in a time-bound process, the determination of the resources required, and the funding sources. The division should seek proposals for undertaking this research through an international process seeking competitive bids. Once approved, the division would oversee the completion of the research and facilitate the uptake of the findings both through international and national One Health activities.

- The key research areas to be considered under the aforementioned process would be: (i) identifying drivers for emergence and the basis for host switching; (ii) developing disease-targeted penside tests and multiplexed assays; (iii) further enhancing modeling tools to underpin targeted and general national and international disease surveillance; and (iv) improving vaccines for new and emerging diseases based on rapid production and utilizing licensed vaccine processes.

- Create an International Society for One Health (ISOH) to foster collaboration between and among researchers and policy makers, through the convening of biannual meetings, a specialized journal, and the establishment of networks to facilitate further collaboration and coordination of research in this area. A meeting to further consider the development of ISOH is planned by the committee of the recently held One Health Congress in Melbourne (2011), to take place in London (June 2011).

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*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP) June 5–8, 2011, at Estancia La Jolla Hotel, San Diego, California.*

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## Debate conclusions

- The "siloization" of activities for responding to infectious diseases threats is a key problem. The One Health approach addresses this challenge by encouraging cooperation among various bodies (e.g., intergovernmental agencies, national governments, academia) concerned with human, domestic animal, and wildlife health. The appropriate degree of leadership that international organizations should assume in the One Health process is a key question yet to be resolved. However, existing international reporting structures need to be harmonized to be more effective.

- Despite much encouraging discourse by international organizations and governments, securing more widespread support is required if the One Health approach is to be made operational. The research arena is an obvious starting point for generating the collaboration needed to support One Health. Successful implementation at the research level should encourage policy-level reform and integration within national government organizational structures.

- There are significant challenges to the full and transparent implementation of One Health principles, including economic and budgetary concerns, intragovernmental power struggles, and trade and tourism implications. Economic and social factors must be taken into consideration when developing prevention plans for emerging and persistent infectious diseases, and therefore must be studied in conjunction with the biological components of disease control. Economists and social scientists need to be included in designing One Health approaches if they are to be practical.

- The One Health approach is a useful framework for responding to *both* emerging and persistent infectious diseases. Yet, emerging diseases (e.g., pandemic influenza) have received disproportionate attention because they are a priority of affluent countries. Less-wealthy countries shoulder the majority of the world's infectious disease burden and are primarily concerned with persistent diseases. Hence, ensuring that persistent infectious diseases are adequately integrated into One Health approaches is a priority.

- Successful adoption of One Health principles may require the introduction of legal frameworks and requirements, along with either voluntary or imposed methods of enforcement to ensure compliance.

**Current realities**

It was acknowledged that the One Health agenda has been extensively discussed by many countries and organizations, yet questions were raised as to how supportive these groups are in practical terms (e.g., with financial and/or logistical support). It was further recognized that, despite ongoing dialogues, there has been limited international implementation of One Health objectives.

There was extended debate about the role of economics for driving how organizations respond to the appearance of infectious diseases, and it was agreed that economics as a discipline has not been adequately incorporated within the One Health framework. At the microeconomic level, not all drivers involved in disease emergence can be understood in biological terms (e.g., interactions among wildlife, domestic animals, and humans). Economic issues must be considered together with biological interactions, particularly given that increased biological contact among species is driven by the economics of production and the overall domestic and international economic environments. Consensus was reached that economic factors play a large role in determining how governments respond to infectious disease threats.

A pervading theme of the debate was the problem of siloization of human, animal, and environmental health issues. Siloization routinely occurs at international, national, and sub-national levels. This compartmentalization is largely due to the current division of responsibility and competing budgets among intergovernmental organizations, government agencies, jurisdictions, the private sector, and/or academia that address various aspects of the infectious disease response.

Success stories for the integrated One Health approach do exist, such as the collaboration between the Red Cross and animal health agencies to concurrently deliver rinderpest vaccines to cattle and a range of vaccines to young children in southern Sudan.

**Scientific opportunities and challenges**

Education and training of the next generation of wildlife, domestic animal, and human health professionals that encourages them to work cooperatively and to approach infectious disease issues with a One Health mentality was deemed critical to improving future responses to these issues. However, concern was raised that although courses specifically focused on One Health concepts have recently been developed, it will take many years to train people in this transdisciplinary approach and for them to develop their careers based on cooperation among disciplines. In the meantime, the infectious disease community should continue to explore organizational changes that can be made in the immediate future to enhance transdisciplinary activities.

It was recognized that mentalities that support siloization in national and international organizations will be challenging to overcome. There are multiple vested interests in terms of territorial control and/or budgets that will need to be changed toward a more integrated One Health approach at all levels (e.g., local, regional, national, and international).

Questions were raised as to the appropriate priority to be given to One Health efforts with respect to emerging and persistent infectious diseases. Some suggested that it should move quickly beyond the current concentration on *emerging* infectious diseases to encompass *persistent* infectious diseases as well. It was asserted that the recent focus predominantly on emerging infectious diseases has been too narrow. Many of the emerging disease issues considered under One Health (e.g., pandemic influenza) were dictated by affluent country concerns despite disproportionately impacting less-wealthy countries. Moreover, although less-wealthy nations must contend with emerging diseases, it was argued that persistent diseases frequently pose an equal — if not greater — threat to those less-wealthy areas. It was further suggested that the One Health approach is particularly useful for those less-wealthy countries with a disproportionate risk of both emerging and persistent infectious diseases. Such an integrated approach could offset the effects of limited resources and help to counter imprecise reporting in these countries.

It was widely asserted that gaining a better understanding of the drivers for new infectious disease emergence must begin with an expanded view of biological factors (e.g., host switching), but that this work also must include the economic and social drivers that lead to increased interactions between animals and humans. Establishing a more robust picture of these drivers may potentially provide new opportunities for preventing and mitigating infectious diseases.

The importance of crises (e.g., H5N1 and H1N1 influenza) in changing attitudes toward One Health approaches was extensively discussed. Many felt that organizational and attitudinal changes are catalyzed only by global disease crises. However, it was suggested that being too effective in driving the One Health approach (i.e., by reducing catastrophic disease outbreaks) may perversely prevent the very crisis environment needed to bring about wide-ranging changes. There was general agreement that the current reactionary approach — wherein public policy change and financial support are largely driven by infectious disease crises — is a barrier to long-term solutions.

The role of economics in internationally implementing a One Health approach was discussed. It was noted that trade implications, both positive and negative, would directly affect uptake of the One Health model. For example, it was contended that the detrimental effect of a hypothetical foot-and-mouth disease outbreak in Australia on the Australian cattle export trade would be considered a significant impetus to participate in a One Health approach that could reduce chances of importing the pathogen. Conversely, the fear of negative trade or tourism impacts as a result of reporting disease outbreaks was considered a significant barrier for countries to report accurately or expeditiously.

**Policy issues**

There were divergent opinions as to whether moving toward a One Health approach requires a legal framework. Some argued that the creation of a One Health structure would necessitate legal instruments to combat entrenched systems with vested interests that are resistant to change. Among those who supported legal action, it was questioned whether the International Health Regulations (IHR) would provide a suitable model. Others, however, disputed proposals for legal intervention and suggested that the self-interest of relevant organizations would be enough to promote a voluntary system. No consensus was reached on the best way forward,

although some improvements were viewed as essential to fostering an effective One Health system.

It was acknowledged that mentalities that support siloization among different professions are highly unproductive. This led to discussions regarding how to integrate diverse disciplines, institutions, and individuals into more cooperative approaches to One Health. Proponents of a legal One Health framework contended that cooperation is unlikely unless required by a higher authority and/or international agreements. Others, however, asserted that siloization should be addressed by building trust and managing competing interests.

It was suggested that, as an incremental step toward wider reform, the research arena is the obvious starting point for adapting international attitudes, programs, and organizations to a One Health approach. It was generally agreed that the existence of established research collaborations among different sectors and countries, and the system of mostly external funding sources for such research (which lessens concerns about permanent budget reductions), makes a One Health research agenda more achievable in the near term than wholesale change to institutions. It was contended that the second stage of reform should occur at the policy level, although no specific action items were identified. Lastly, it was proposed that a third stage of reform should take place at the national government level. National reforms were viewed as the most challenging area for One Health operational change to be implemented due to the common siloization mentality that pervades departmental structures (e.g., wildlife, agriculture, and health departments).

The current priorities of wildlife and agricultural agencies are typically focused on areas outside the realm of human health, such as tourism or farmers' interests. It was accordingly proposed that providing political support, which encourages the consideration of human health outcomes, to officials and bureaucrats in these agencies will be key to advancing these wildlife and agricultural institutions toward a One Health approach for infectious disease prevention, mitigation, and control.

During a related discussion on the influence of policy makers, a question was raised as to whether change required direction from above (i.e., from the head of a government), or whether change could be driven organically from within the relevant organizations. Considerable support was given to focusing the attentions of the higher levels of government on implementing effective One Health systems.

Much discussion was focused on the role of incentives for voluntary adherence versus the imposition of penalties for non-compliance with the One Health structure. The incentives for moving toward the One Health approach are apparent, but the consequences for failure to do so are much more difficult to identify (e.g., preventing a negative outcome remains largely unrecognized). The potential compliance issues involved were debated, and it was questioned whether inspections or binding regulations are required. It was agreed that more detailed discussions are needed before specific methods for enforcement are implemented.

A significant part of the debate surrounded the appropriate role, scope, and mandate of international organizations (e.g., UN agencies). It was suggested that these organizations should exert a greater leadership role in setting agendas and coordinating domestic and international activities. Counter arguments were made by those familiar with these organizations suggesting that they are already overloaded with responsibilities, financial pressures, and workloads. Moreover, widespread (though not unanimous) views were expressed that there is a specific lack of cooperation among international bodies regarding One Health initiatives and, to be successful, any proposals to make significant changes in One Health initiatives must come from the member states. The member states have the ultimate decision-making power in these international bodies.

There was general agreement that the aim of disease-response structures should move away from the current reactionary approach to specific incidents or crises, to a predictive or anticipatory model. This will require improved coordination of international surveillance systems, which include biomodeling and whole genome sequencing, to reveal outbreak indicators and consequently allow early risk mitigation.

There was general agreement that, in addition to animal and human health experts, the One Health process should include economists and social scientists to help understand and manage the responses of both governments and individuals to this new approach.

There was substantial debate about the extent to which international reporting structures (e.g., those maintained by the World Health Organization [WHO], the Food and Agriculture Organization [FAO], and the World Organisation for Animal Health [OIE]), could be harmonized or aligned to promote more efficient and timely responses. It was proposed that a single reporting portal be established. Although agreement was not reached with respect to the creation of a unified reporting portal, there was consensus that greater harmonization among reporting structures is highly desirable. It was also recommended that the positive aspects (e.g., flexibility and agility) of other existing structures, such as ProMED-Mail (a notification service operated by the International Society for Infectious Diseases), be considered when reshaping international organization reporting structures. It was further noted, however, that ProMED (the nonprofit international Program to Monitor Emerging Diseases) is not a perfect model — it is significantly underfunded and some concerns do exist about the reliability of ProMED's reports.

# Bugs and Bucks: Infectious Disease Persistence is a Matter of Economics**

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## Summary

We live at a moment in history unprecedented with respect to both the breadth and quantity of resources available for the prevention and control of infectious diseases. Many communicable diseases of public health importance have exclusively human reservoirs, and can be made nontransmissible using readily available tools (e.g., vaccines, antimicrobials, and improved water and sewage treatment). In other words, we live in a time when it is (theoretically) within our power to actually eliminate or eradicate several infectious diseases of public health importance, and yet these diseases persist. It is proposed that the reasons for disease persistence in such situations relate primarily to phenomena that fall easily into frameworks already well studied and understood by economists. In this paper, "economics" is defined in its broad sense, as a discipline that seeks to understand the behaviors and choices of individuals and societies as they attempt to maximize their well-being through the production and distribution of "goods." The "good" in question is the absence of morbidity and mortality from persistent infectious diseases. The failure to incorporate economic considerations into disease-control policy will result in suboptimal policy. Policy-relevant concepts include: (i) the concept of public goods (e.g., clean water, widespread vaccination) that produce environments and herd effects that benefit all members of a community and cannot be denied to anyone; (ii) the related concept of transmissibility of infection, and prevention of disease transmission, as key economic "externalities" that cannot be ignored when disease-policy decisions are made; and (iii) the fact that individuals with infectious disease, or at risk of infectious disease, are rational actors, and will behave and engage with one another in ways that can be described as economic "games." Dissemination of knowledge related to these concepts, and tools and data that permit their incorporation into disease-control policy, represent a valuable opportunity to reduce the burden of persistent infectious diseases at local, national, and global levels.

## Current realities

It is evident, from even a cursory evaluation of global statistics, there is a powerful economic undercurrent that must inform any discussion of the persistence of infectious diseases. Life expectancy, infant mortality, and the proportion of deaths attributable to infection all exhibit linear or log-linear relationships with per-capita gross domestic product (GDP). For example, as GDP increases, on average, there is a corresponding rise in life expectancy and a decrease in mortality rates (see Figure 1). While the mechanisms underlying this relationship are incompletely understood, it is clear that wealth translates into health at the national level, partly through elimination of infectious-disease threats.

Several key correlates of improved health and longevity include availability of infrastructure (e.g., to provide clean water and treat sewage), provision of basic health care and immunization, and development of systems to limit transmission of disease from animals to humans (e.g., via rabies prevention, and food-safety regulations/food inspection). All of these factors likely contributed to the epidemiological transition from infectious to chronic diseases as major drivers of mortality that occurred approximately a century ago in wealthy countries — with recent research suggesting that the largest single impact may have derived from reduced death from waterborne infection. However, successes in eliminating or markedly reducing morbidity from waterborne disease have not been replicated in many middle- and low-income countries, and

indeed waterborne threats such as cholera have emerged in countries where they have not occurred previously. Similar observations can be made regarding vector-borne diseases such as malaria, once endemic but now rare in many high-income countries, including the United States. These diseases persist in low-income countries where the promise associated with control programs has been eroded by antimalarial-drug and pesticide resistance, and perhaps by climate change. In high-income countries, recent resurgences in vaccine-preventable diseases (including measles, mumps, rubella, and pertussis) have occurred, spurred in part by reduced vaccination levels that reflect public concerns about vaccine-adverse effects.

All of the aforementioned occurrences are driven, in part, by systems that have strong "economic" components. They have been facilitated by the failure of disease-control policy to consider such components, which include externalities (i.e., indirect effects that accrue due to the communicable nature of many infections), public goods (e.g., the "herd immunity" derived from vaccinating a sufficiently large proportion of the population), and "game behavior" (i.e., the tendency of members of the population to change their behavior based on their expectations of what others will do).

**Scientific opportunities and challenges**

Mathematical modeling approaches that are commonly employed with "complex systems" have been in relatively wide use for the study of infectious diseases since the 1920s. Such models are useful tools for explaining and predicting the response of epidemics to control efforts, and explicitly treat disease transmission effects as economic externalities. Such models represent the risk of infection in an individual in a population as a function of infection prevalence in contacts, but also as a function of the population's "immune status" and herd immunity. Herd immunity becomes a "public good" because it is shared by all individuals in the population. However, the application of disease models to public health policy is a fairly recent development, and there is relatively limited understanding of the concepts that underlie these models among front-line public health professionals. This results in a misdirected focus and suboptimal programmatic approaches. For example, the public health community focuses on the role of vaccines in protecting the vaccinated individual rather than the "herd." In the context of disease resurgence (e.g., the recent mumps epidemics that have struck North America and Europe), public health messaging recommends that young adults should be boosted for their own protection. With endemic diseases, such as influenza, public health messages focus on direct protection by immunization, rather than the (often more substantial) indirect protections produced by wide-scale immunization coverage. Models project that immunization of younger individuals, at less risk of severe outcomes from influenza but more likely to spread the disease as well as respond to vaccination, is actually a far superior influenza-vaccination strategy than the targeting of older individuals currently advocated by North American public health authorities. Such model projections have more recently been validated by randomized trials. As such, enhancing the understanding of such concepts as externalities and public goods, as well as improving the availability and acceptance of tools for system-dynamic modeling in public health, could provide innovative and more successful approaches to disease prevention and control policy.

However, although system dynamics models do explicitly capture externalities and public goods such as herd immunity, such models have only more recently begun to capture behavioral responses to disease risk (e.g., hiding, fleeing, and engaging in risky behavior due to a decrease in perceived risk). Recent work suggests that behaviors and associated changes in movement and contact patterns may provide the key to persistence of diseases (e.g., syphilis)

and to the "waves" characteristics of epidemics and pandemics. Furthermore, rational actors, whether individuals, institutions, or governments, will behave in a manner that anticipates the actions of others (whether by free riding on herd immunity, or failing to invest in disease control due to concerns that others will not do the same), leading to suboptimal "Nash equilibria." In the context of immunization, Nash equilibrium refers to the phenomenon whereby as a disease approaches elimination due to high vaccine coverage, the (near-term) risk associated with the vaccine itself will inevitably begin to outweigh the (near-term) risk of infection and illness. This will lead rational parents to pull back from immunization of their children, on the assumption that other parents will continue to immunize (i.e., creating a free ridership problem). Nash equilibria can also be identified for systems in which neighboring jurisdictions or hospitals must invest to control disease; actors may free ride on successful neighbors, while high-performing countries may defund their efforts if disease is simply reimported from poorly performing neighbors. A key and as-yet-unanswered question is the degree to which changing risk perception by policy makers drives increases or decreases in disease-control funding, which could result in oscillation in disease prevalence independent of other systematic changes. Thus, there are emerging scientific opportunities related to the measurement of such changes in behavior, risk perception, and motivation in response to epidemics, both at the level of individuals and at the level of governments and decision makers. Furthermore, emerging social media and telecommunications technologies make it possible to measure and anticipate behavioral drivers of disease persistence (via mining of Twitter feeds, or by using cell-phone towers to measure movement patterns in epidemic regions).

**Policy issues**

- Public health and disease-control experts need to understand that issues of free ridership and Nash equilibria appear frequently as a consequence of the success of programs. Training programs for epidemiologists and public health physicians need to teach adaptability and responsiveness as core components of disease-control programs; a corollary is that disease-control programs need to be conceptualized and taught as works in progress that are not static over time. **Proposed leads:** Many of these concepts are already taught in economics curricula. Universities, schools of public health, and training programs (e.g., U.S. Centers for Disease Control and Prevention [CDC] Epidemic Intelligence Service) need to establish trans-disciplinary links necessary to integrate such concepts into training activities.

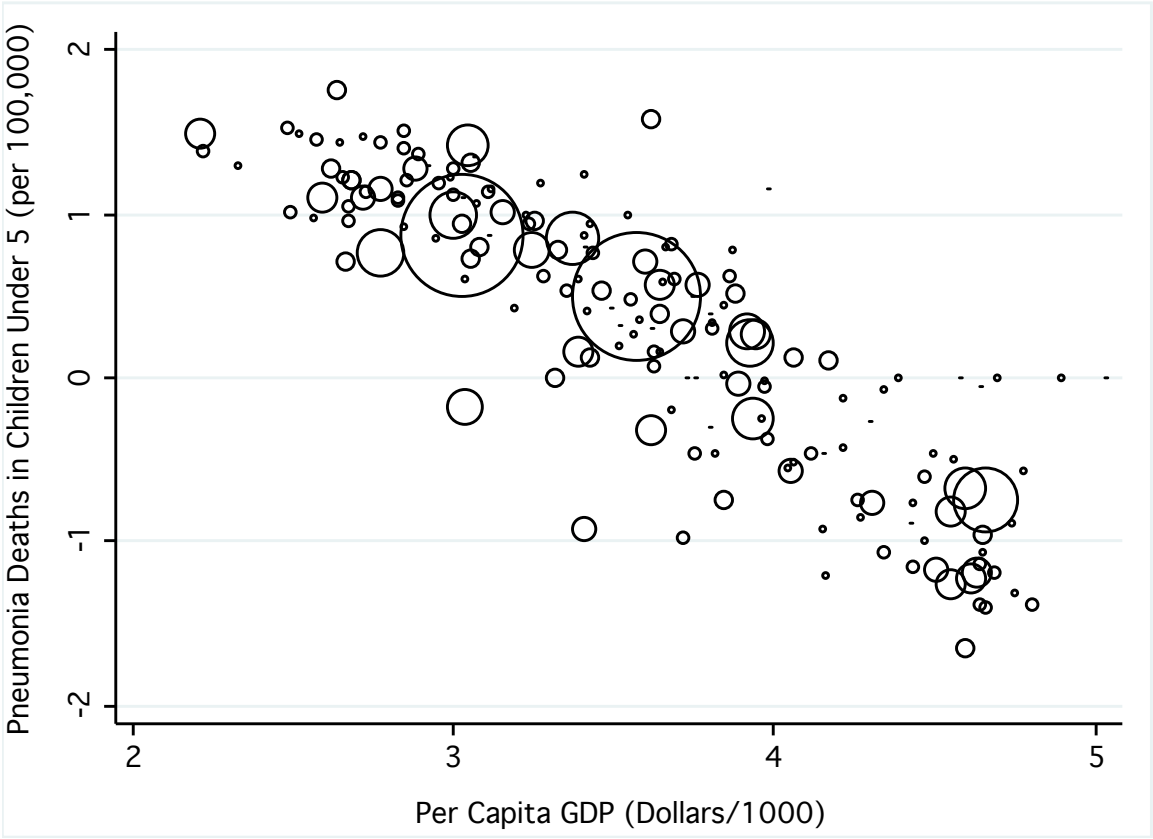
- Tools for modeling, interpretation, and analysis of infectious disease-control programs as complex systems must be made more readily accessible and user-friendly to front-line public health personnel. **Proposed leads:** Universities can foster training as part and parcel of core public health teaching; industry can work to meet the need for user-friendly software resources designed for use in the field. Such software resources also need to have graphical interfaces that facilitate the translation of model projections into easy-to-understand applets and graphs. Government agencies should adopt these tools.

- There needs to be improved understanding of how changes in disease prevalence drive downstream changes in the funding of disease-control programs, and to what extent such changes might be important drivers of disease persistence. **Proposed lead:** As this represents an informational need that lies at the intersection of social-science research and applied public health, partnerships between agencies that fund social science and health-policy research and agencies that would be the beneficiaries of such knowledge should be explored.

- Issues of personal privacy and confidentiality need to be reconciled with public good so that emerging electronic-data sources can be used to capture information on human migration, contact networks, and behavioral responses to epidemics and outbreaks. **Proposed leads:** National and regional governments need to review appropriate uses of extant electronic-data resources for protection of public health, and consider legislative and regulatory changes that balance privacy rights against potential contributions to population health.

Figure 1:

Incidence of pneumonia-related death in children as a function of per-capita gross domestic product, 2008–2009 data. Bubble sizes are proportional to countries' populations.




*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP June 5–8, 2011, at the Estancia La Jolla Hotel, San Diego, California.*

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**Debate conclusions**

- Mathematical models are important tools for researchers and policy makers addressing infectious diseases since they can help explain the spread of disease, clarify the impact of public health interventions, and aid in conveying complex ideas to lay audiences. Obviously, however, given their dependence on the quality of the input data and creativity of the models themselves, their predictions do not come with absolute certainty. Regulation, peer review, and the sharing of best practices should be instigated to increase the accuracy of models and the confidence in their usage.

- Researchers and policy makers within mainstream public health need to include models in their infectious disease control efforts. Incorporating training and courses into the curricula of public health schools, and for those already working in public health fields, can strengthen both the effectiveness of research and policy decisions.

- It is necessary to communicate to policy makers and public health professionals not only the general benefits of mathematical models, but also specific examples of economic concepts such as "Nash equilibria" and "free ridership " for use in modeling of infectious diseases. At present, these economic concepts are insufficiently taken into account in infectious disease control strategies and policies.

- Mobile phones and social media provide innovative ways to more accurately predict and track infectious disease spread. Researchers need to harness the data driven by such emerging technologies to construct mathematical models for disease prediction, including accounting for sociobehavioral factors. Efforts to collect and incorporate sociobehavioral data should be expanded.

- The challenges facing policy makers to continually balance the public good derived from controlling infectious diseases *writ large* against protecting the rights of individuals to accept or reject vaccination, and to maintain personal anonymity requires a greater understanding of the relative importance of societal factors influencing the appearance and spread of infectious diseases.

**Current realities**

In the study of infectious diseases, mathematical models are valuable tools for (i) understanding their scientific basis, (ii) predicting how they spread, (iii) demonstrating the impact of interventions, and (iv) aiding in communicating complex concepts among scientists, policy makers, and the public (e.g., through illustrative charts and diagrams). It was agreed that models are not crystal balls that foretell the future (i.e., they cannot predict what will occur with absolute confidence). It was strongly argued that, despite inherent imperfections, models can be effective tools for managing risk and uncertainty. However, it was also argued that the practical application of models to real-world scenarios is limited by their inability to provide

wholesale assurances. Examples were presented where mathematical models failed to accurately predict an event and were used to convey a false level of certainty.

There was consensus that mathematical models, used in public health and other disciplines, vary in quality. Such variations are due to differences in the accuracy and availability of data inputs, as well as the precision of the models themselves. As a result, the application of models has resulted in both positive and negative consequences.

Minor disagreement was voiced concerning the simplicity of models. While some contended that models are too complicated to be useful to a lay audience, others countered that models can be conveyed with varying degrees of complexity appropriate for different audiences. For example, it was asserted that analogies and illustrations can be used to distill and convey the outcomes of models so that they can be comprehended by non-experts. It was further argued that only knowledge of simple math (e.g., addition and subtraction) is needed to understand most mathematical models.

There was considerable debate regarding the extent to which mathematical models are currently being used in infectious disease research and public health efforts. On one side, it was argued that models have been regarded as exotic or unusual, are not widely available, and are rarely taken into account in public health decisions. Others, however, suggested that their usage is actually fairly common. The debate concluded that the use of mathematical models varies considerably across fields of study. In human health, for instance, models have been employed more routinely than in disease ecology. It was also noted that models may be used for research and decision-making within some countries more than others, although no specific examples were provided.

There was strong agreement that economic concepts such as Nash equilibria and free ridership are insufficiently taken into account in infectious disease control strategies and policies. These concepts may have negative implications for the effectiveness of certain interventions (e.g., vaccination strategies). The concept of Nash equilibria was illustrated by the fact that public attitudes toward vaccines are related not only to perceived risks associated with the targeted disease, but also to the perceived risk of the vaccine itself; an individual is therefore more likely to accept the risks accompanying a specific vaccine when the risks associated with the corresponding disease are perceived to be high. For example, because of the devastating effects of polio in the 1950s, many societies were willing to be vaccinated with a new polio vaccine even though the vaccine sometimes produced negative side effects (e.g., paralysis). In terms of free ridership, it was noted that this problem becomes most apparent as vaccine uptake for a specific disease increases and the risks of contracting that disease correspondingly decrease. In this situation, individuals may feel that the risks associated with the vaccine outweigh the benefits and therefore choose to capitalize on the herd immunity that is provided by the large number of people who do receive the vaccine.

It was recognized that individual- and country-level responses to problems associated with infectious diseases are influenced by factors such as culture and socioeconomic status. Despite growing acceptance of the importance of these factors in shaping disease control strategies and outcomes, sociobehavioral responses to infectious disease risks have been underutilized as data for mathematical models. Moreover, it was noted that there is a deficiency in wider understanding and research related to why variations in sociobehavioral responses exist.

Surveillance was widely recognized as a crucial component of infectious disease prevention. However, it was asserted that current surveillance techniques are insufficiently multimodal because they do not take into account enough data sources and some types of data are heavily underrepresented (e.g., there is a dearth of information related to behavioral responses within

data collection efforts). Reliance on only one information source was purported to increase the likelihood of erroneous models. For example, the modeling program Google Flu Trends was noted to have limited success when used in isolation of additional data because it does not take into account changes in behavior associated with disease threat.

Debate took place over the suggestion that individuals, governments, and institutions must be regarded as rational actors in relation to disease control and response. The premise underpinning this view was that individuals will behave in ways that anticipate how they expect others to behave. The question arose as to whether behavior in response to infectious diseases can always be regarded as strictly rational.

The relationship between a country's health and a country's wealth was also discussed in detail. There was consensus that, with a few exceptions (e.g., in the 1950s, China experienced a rapid rise in life expectancy while wealth remained low), there is a tight link between a country's level of wealth and health outcomes. However, this link encompasses complex factors and it is challenging to determine causality from any one factor. Differing views were expressed as to whether wealth translates into health or vice versa. It was contended that whether wealth leads to health or health leads to wealth is an important distinction to more carefully understand since it has implications for policy decisions.

**Scientific opportunities and challenges**

A significant challenge to increasing the uptake of mathematical models for use in infectious disease research and policy decisions is the difficulty in ensuring the accuracy of the results. There was consensus that the development of a robust system for peer review and validation of models, as well as setting guidelines and sharing best practices among modelers, would provide the requisite substantiation necessary to establish better confidence in models. For example, it was argued that policy makers would likely feel more secure in relying on the recommendations generated by models if they were better evaluated in terms of the risk of unexpected outcomes. Policy makers are obviously concerned that they, rather than the modelers, are likely to be blamed for unexpected outcomes.

There was consensus that the increasing utilization and availability of technologies (e.g., mobile phones and social media) provide important opportunities for the use and improvement of mathematical models in disease control. In Haiti, for example, mobile phone data were used to predict the spread of cholera far more accurately than traditional projection methods. However, it was argued that existing technologies have not been leveraged to their potential. Opportunities to incorporate technologies from other disciplines (e.g., oil drilling and hedge funds) into infectious disease modeling were also highlighted.

Although technologies offer new opportunities, other data obstacles remain. Problems in accessing data (e.g., privacy issues) that are most useful for mathematical models were highlighted as a continuing challenge. Additionally, data integration issues were purported to decrease model efficacy. For example, it was recognized that the ability of Google Flu Trends to accurately model influenza disease spread has been limited by an insufficient variety of data inputs.

It was contended that the resurgence of a number of preventable diseases in more-wealthy countries caused by increased vaccination refusal (e.g., pertussis and measles) has presented an opportunity for concepts such as free ridership and herd immunity to be incorporated into infectious disease control strategies. It was strongly emphasized that, as a starting point, a considerable amount of work will need to be done to improve how such ideas are communicated to policy makers, the public health community, and the public.

**Policy issues**

Confidence in models for infectious diseases would be enhanced by the current efforts to improve the quality of the data input, to identify the best practices for the use of results, and to establish minimal acceptable standards for creation. There was strong agreement that it is necessary to establish a formal process for the peer review of models to ensure all models adhere to certain standards.

There was a call for mathematical models to be employed by researchers and policy makers in a variety of fields so that models are not solely the domain of a narrow group of mathematically centered individuals. It was recommended that rigor, as well as training in the development and application of models as tools for infectious disease control, should be widely instituted among researchers and policy makers. Success stories were used to highlight the feasibility of this approach. For example, grant requirements compelled a group of disease ecology experts to create a predictive model. This led to positive and transformational results for the team and the project.

Given the acknowledged importance of training researchers and policy makers to appropriately create and interpret models, it was suggested that public health degree programs include courses on models as part of their curricula. Additionally, it was emphasized that an informal educational process must be developed through which those working in public health can learn how to appropriately apply modeling and its results to their activities. Reaching out to individuals who are already in public health fields is of particular importance because public health agencies are currently uncertain about how to utilize models and their outcomes (particularly in areas such as resource allocation across departments and budgets).

There was general agreement that improving messaging concerning the value and limitation of models is imperative, both for promoting the use of mathematical modeling and for increasing vaccine uptake. The key messaging issues are: (i) that non-mathematicians can and should be trained to better use models, (ii) that carefully constructed models can be successfully used to manage disease risk, and (iii) that models can be effective tools for communicating with lay audiences when their outcomes are simplified (e.g., via visual images or analogies). On the topic of vaccines, it was contended that the public does not understand the concept of herd immunity as an externality. It was asserted that the public looks for credible messengers to guide them, but has not been adequately provided with the intellectual tools to make decisions about vaccine usage. It was conceded that it may be challenging to effectively convey the concepts and values underlying collective action, especially in countries that are guided by a credo of rugged individualism (e.g., the United States and Canada). However, the resurgence of diseases such as measles in more-wealthy countries may provide a window of opportunity for messaging related to the importance of vaccine uptake.

It was argued that social and attitudinal changes related to protecting the public good may sometimes be more effective than mandating rigid policies. For example, problems enforcing coercive laws (e.g. compulsory vaccination) were highlighted. It was argued that education (i.e., to change mindsets) is not only a better route to disease control but also preserves individual liberties.

The debate highlighted the need for policy makers to address potential conflicts between the public and private good. For example, it was noted that coercive public health policies may benefit the public (e.g., by lowering disease rates through mandatory vaccinations) while simultaneously infringing upon the decision-making rights of individuals. It was similarly noted that there is a fine line between the public and private good that must be navigated in the

selection of data inputs for models. This is because the inclusion of sensitive data could improve the accuracy of models while concurrently infringing upon the privacy of individuals to maintain their anonymity.

Specific diseases should be targeted in the development and implementation of mathematical models because it is difficult, and generally less effective, to make recommendations that simultaneously address all infectious diseases. Influenza models were used to illustrate the potential success of a singular disease approach. Such models have demonstrated that there is a high likelihood that influenza mortality would decrease if children were given preferential vaccination treatment over the elderly. Using this model outcome, it was suggested that children should be the primary focus of the next influenza vaccination drive.

# Vaccines: Very Successful, Strangely Controversial**

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**Summary**

Vaccines prevent disease before individuals can become infected and thus, along with economic development, represent the greatest hope to alleviate the burden of infectious diseases and save lives worldwide. Many vaccines also offer the advantage of primarily targeting the young, hence not only saving lives in general, but particularly preserving the prime years of life. Development of vaccines requires a partnership among academia, industry, and government. However, there are multiple hurdles to maximizing the use of vaccines globally. While there are a host of scientific issues that are beyond the scope of this discussion, in this paper I specifically address some of the issues for which the intersection of policy makers, academics, and industry plays a vital role: combating the anti-vaccine movement, improving influenza vaccines, and strengthening the ability of regulatory agencies to efficiently evaluate vaccines.

## Current realities

Not only do vaccines save millions of lives every year, they also prevent the cruelly disabling effects of infectious diseases.[1] The use of vaccines, primarily starting in the 20th century, has greatly ameliorated the historically widespread infectious disease burden. Perhaps the most stunning success was the global elimination of smallpox. Childhood diseases that once crippled and killed millions, such as polio, measles, mumps, rubella, and tetanus, have also been greatly reduced worldwide.[2] Recently, immunization efforts have also reduced the rate of diarrheal disease (through the rotavirus vaccine) and childhood meningitis (through the *Haemophilus* influenza type b vaccine). Some vaccines also protect against cancers caused by infectious diseases. For example, introduction of a hepatitis B vaccine in 1981 has prevented liver failure and liver cancer, thus becoming the first "anti-cancer" vaccine. Unfortunately, the World Health Organization (WHO) estimates that 1.7 million children will die annually from vaccine-preventable diseases. Obstacles, including social and economic barriers, still hinder the maximal use of effective vaccines in both poor and rich countries.

In spite of the remarkable efficacy and safety of vaccines, an anti-vaccine movement has arisen in the United States and Europe, paradoxically led by people who are well connected (such as celebrities) and/or well educated. This campaign originally centered on the unfounded fear that the measles, mumps, and rubella (MMR) vaccine causes autism — a link put forward by Dr. Andrew Wakefield in a 1998 *Lancet* paper that was recently discredited due to flawed scientific methods and financial conflicts of interest (*The Lancet*, 2010). The anti-vaccine movement is also comprised of individuals who believe that the purpose of vaccines is to develop "herd immunity" and who are unwilling to have their children be vaccinated for the common good. This idea puts the public, especially unvaccinated children, at risk. Of note, due to concerns surrounding the safety of the MMR vaccine, parents began to withhold vaccination from their children, coinciding with a number of large measles outbreaks (Jansen *et al*., 2003).

[1] When the great vaccinologist Dr. Maurice Hilleman died in 2005, Dr. Anthony Fauci, head of the National Institutes of Allergy and Infectious Diseases, and Dr. Paul Offit, chief of Infectious Diseases at the Children's Hospital in Philadelphia, noted in a New York Times article that he had likely saved more human lives than any other scientist in the 20th century.

[2] WHO estimates that immunization currently averts 2.5 million deaths every year in all age groups from diphtheria, tetanus, pertussis (whooping cough), and measles. The WHO also estimates that "more than 5 million people who would otherwise have been paralyzed are walking today because they have been immunized since the [polio eradication] initiative began in 1988," let alone the lives saved and paralysis averted since polio vaccines became widely available in the 1950s.

Influenza, which causes extensive morbidity and mortality and is a target of annual vaccination campaigns, presents a somewhat unique challenge.[3] Because of the variable nature of the influenza virus, a new vaccine — the composition of which is determined by educated guess — must be administered annually. Not only is seasonal influenza a major public health concern, but so too is the possibility of a pandemic that would evolve from a new or re-emerging type of virus. The 1918 influenza pandemic killed approximately 20 million people. Such a pandemic would again have the potential to kill many millions of people, despite our advanced technology, and undoubtedly overwhelm the health care system. The current technology used to produce influenza vaccines involves the use of eggs, thus growing the virus in an antiquated system. Modern genetic ways to generate influenza vaccines are now available but, due to regulatory hurdles, have not yet been put into place in the U.S. and are only beginning to make headway in Europe. These new recombinant DNA and cell-culture techniques could help us to respond in a more nimble fashion to annual changes in the makeup of influenza viruses. The Food and Drug Administration (FDA) and its European counterpart (European Medicines Agency) play active roles in assessing and approving new vaccine technologies. Unfortunately, the FDA is markedly underfunded and can be bureaucratic, thus slowing progress considerably. In addition, the need to protect industry secrets can make the decision-making process less than transparent. The agency is also in the unenviable position of being criticized for moving ahead too slowly, while at the same time being criticized by others for being less than careful.

**Scientific opportunities and challenges**

A major challenge facing scientists (in both academia and industry) and policy makers is how to overcome the current anti-vaccine sentiment in the U.S. and Europe. Vaccine manufacturers will need to continue to closely monitor vaccine safety both in preclinical trials and after vaccine implementation. Ongoing safety surveillance by the FDA and manufacturers already takes place (e.g., removing thimerosal from vaccines in 2001). However, there is often a disconnect between the data and the anti-vaccine advocates that no amount of research can overcome (e.g., many individuals continue to believe that thimerosal is linked to autism even though its removal had no effect on autism rates in subsequent years). While the science is presently clear that vaccines generally are safe, the court of public opinion and the corresponding realm of public policy are where the current challenges to the effective use of existing vaccines lie.

While the influenza vaccine has been reasonably successful (approximately 50% efficacy), a number of key scientific and policy challenges have emerged. These challenges also raise significant opportunities for improvement in influenza vaccination. First, as previously noted, influenza vaccine virus strains classically have been grown in eggs. However, recent advances allow production of these viruses in a more controlled, modern environment that permits more effective vaccine production. Specifically, genetic engineering now allows scientists to make different types of influenza virus in the laboratory using animal cells. Because this is being done using recombinant DNA methodology (cloning), the viruses can be more readily and rapidly made to reflect the makeup of the influenza viruses that are circulating in a given year. These types of technologies would also be particularly useful when applied to rapidly emerging epidemic strains of virus such as H5N1 or H1N1 influenza. The primary hurdle is assuring safety and swift implementation of these methods through regulatory mechanisms. The ultimate key to success in fighting influenza is the development of a vaccine that is effective against almost all strains of influenza, yet the development of a "universal vaccine" remains a major scientific challenge.

[3] The WHO estimates that influenza causes 3 million to 5 million cases of severe disease and 250,000 to 500,000 deaths every year.

Another issue that affects all vaccines is the current lack of clinically useful and available adjuvants, which are substances that potentiate the immune response to a given virus or bacteria that is being vaccinated against. Developing adjuvants is a major scientific challenge and also a regulatory one, as safety must be clearly delineated. Improvement in adjuvants has the potential to benefit the development of all vaccines.

**Policy issues**

- To not lose the battle to the vaccine deniers, policy makers must initiate a vigorous campaign to encourage vaccine uptake and combat vaccine misinformation. A vigorous public campaign that includes well-known political figures and celebrity volunteers (and their children) receiving vaccines is in order. Public health officials should appear on radio and TV "talk shows" to promote vaccine usage.

- Policy makers should support improved efforts to develop vaccines by funding university and industry partnerships, since substantial industry involvement is imperative. Industry is now finding that vaccines can be profitable in addition to their remarkable public health benefits. As in all other vaccine endeavors, public/industry cooperation is needed to ensure original thinking and translation of interesting ideas into clinical utility.

- The FDA must be empowered to improve its performance by being given a mandate that is compatible with progress, as well as substantially more funding from taxpayer and industry dollars. This would also improve the ability to attract more talented individuals to the FDA and similar agencies in other countries. Unfortunately, the present FDA budget, which already is insufficient, is facing a US$200 million cut by Congress. If we want both efficient progress and attention to safety, we must be willing to pay for it.

- In view of their life-saving potential, vaccine regulatory decisions should be made on a "fast-track" system. This would also apply to new methods of making vaccines, such as molecular technology for making new influenza vaccines.

- The focus of much influenza vaccine research should be the development of a universal influenza vaccine and better adjuvants.

- Governments should invest heavily in vaccination campaigns and should actively seek support and cooperation from nongovernmental organizations to implement the use of vaccines, many of which are available at a reduced price for use in poor countries.

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*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP) June 5–8, 2011, at the Estancia La Jolla Hotel, San Diego, California.*

**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. David Markovitz (see above). Dr. Markovitz 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. Markovitz. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Markovitz, 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**

- Vaccines save lives from infectious diseases. Yet, an anti-vaccine movement has emerged that has increased vaccination refusal among the public. The issues associated with accurately communicating the benefits and risks of vaccines must be more vigorously addressed jointly by scientists and policy makers.

- Since successful public messaging campaigns are critical to improving vaccine uptake, scientists and policy makers must improve their communication skills (e.g., via training programs). Novel approaches to conveying such reliable information must be considered (e.g., employing celebrities or other public figures to act as appropriate spokespersons).

- Because vaccine research and development is greatly dependent on perceived profitability within the pharmaceutical industry, public-private partnerships are a useful mechanism for stimulating vaccine innovation. New public-private partnerships must be created and existing partnerships among government, academia, and the private sector must be strengthened.

- Fostering a culture where all sectors view public-private partnerships as collaborative and mutually beneficial will bolster these collective efforts to improve research and development and, thereby, improve the appropriate use of vaccines. Incentives to pharmaceutical companies for establishing public-private partnerships (e.g., tax breaks, first-in-line privileges, and guaranteed number of buy-ins) are needed to encourage participation. Problems associated with the short-term (generally annual) government budgets and longer-term interests of the private sector's research efforts also need to be reconciled.

- The pace of regulatory decisions concerning vaccines should be accelerated without lowering safety standards. However, caution must be exercised in how a faster regulatory process is explained to the public to prevent such changes from being viewed as unsafe or risky. Entrenched attitudes within the regulatory agencies responsible for vaccine review are a barrier to transforming regulatory processes. It is critical that misplaced confidence in oversight and issues of self-interest within regulatory agencies be avoided by enhancing the professional experience and standing of their employees (e.g., by increasing the number of staff, creating more stimulating roles for talented scientific regulators, and providing new opportunities for scientific education and advancement).

**Current realities**

There was general consensus throughout the discussion that vaccines have been remarkably effective tools for saving many lives worldwide from infectious diseases. However, it was also agreed that, despite the demonstrated efficacy of vaccines, vocal and popular critics have instigated an effective anti-vaccine movement that has exaggerated the risks associated with vaccines. The anti-vaccine movement has been successful in increasing vaccination refusal among the public, despite the fact that there is still widespread acceptance within the public health community that vaccines offer a favorable benefit/risk profile. This disparity between the views of health care professionals devoted to examining the scientifically credible information and a small but vocal part of the public underscores the gap between scientific understanding and public acceptance. This topic became a central issue throughout the debate.

Vaccine research and development is largely dependent on perceived profitability within the pharmaceutical industry. While it was acknowledged that vaccines do not have the same profit margins as drugs for chronic health issues, public initiatives and funding have helped create public-private partnerships that have offset industry's economic concerns and have encouraged increased vaccine innovation. Additionally, it was noted that the public likely does not fully understand how vaccine research and development is supported. Issues regarding vaccine uptake among the public were also raised. The example of the significant amount of government financial support for an influenza vaccine and the public reluctance to use the vaccine was noted.

During the discussion of the effectiveness of market forces as catalysts for vaccine development and distribution, it was suggested that the concept of trickle-down economics has influenced the increased dissemination of some vaccines. This influence has been especially effective when vaccines were created in wealthier countries to address not only infectious diseases domestically, but also major needs in less-wealthy regions of the world. Although it was recognized that trickle-down economics can provide benefits in promoting both vaccine research and dissemination, there was substantial disagreement regarding the policy role that trickle-down economics should play in disease control. In particular, concern was voiced that wholesale reliance on market forces is not sufficient to ensure access to the quantity of life-saving vaccines needed to address worldwide needs.

The procedures and funding for the United States Food and Drug Administration (FDA) were identified as major sources of delay in the approval process for vaccines. As an example, the FDA vaccine review group does not currently have enough employees to conduct internal research both thoroughly and quickly. As a result, the timeline required for vaccine market approval remains far too long. A similar situation exists in Europe. Many regulators within the FDA and its European counterpart, the European Medicines Agency (EMA), may be comfortable with the status quo related to vaccine review because they benefit from the security associated with the current detailed and cumbersome process.

The liability and litigation procedures relating to vaccines approvals have historically also been major barriers to innovation and progress. The promotion of serious tort reform was identified as a critical step to improving the approval process while protecting public rights.

**Scientific opportunities and challenges**

It was widely agreed that confirming the scientific validity of evaluations of vaccine safety and efficacy, as well as communicating the benefit/risk information to the public, are ongoing challenges for both the scientific and governmental communities. Scientists must first be able to

validate the safety and value of a particular vaccine and then, in turn, to effectively convey this information to public health officials. While it was agreed that the scientific community is generally capable of confirming vaccine safety, it was argued that its members are less skilled in providing clear and informative messages to policy makers. These scientific and policy groups must jointly take responsibility for conveying the resultant understanding to the public in a fashion that reassures the lay person and encourages appropriate vaccine uptake. There was strong support that these communication skills must be significantly improved in both the scientific and policy communities that deal with infectious diseases and the use of vaccines.

There was general consensus that the anti-vaccine movement is a serious barrier to the appropriate use of vaccines and requires more attention from the scientific and policy communities. Discussion centered on the need for more effective public messaging campaigns to appropriately counter the influence of those who question the value and safety of vaccines. Some advocated for the scientific community to take the lead in carrying out the message against the anti-vaccine movement and that, to do so effectively, scientific leaders must develop better communication skills.

Although public-private partnerships for vaccines do exist among government, academia, and the private sector, there was consensus that such partnerships need to be strengthened. Embracing opportunities to enhance such partnerships through both financial and regulatory avenues was strongly endorsed. In addition, the importance of fostering a culture where all sectors view the process as collaborative and mutually beneficial was emphasized.

Vaccine research and development is a protracted process that requires substantial investment over long periods of time. It was widely noted this has been a continued challenge for public-private partnerships between government and the pharmaceutical industry due to the misalignment of short-term (generally annual) government budgets and the longer-term interests of industry's research efforts.

It was emphasized that the current FDA organizational structure related to vaccine approval needs to be altered to accelerate the pace of regulatory decisions. Within this, it was noted that regulators and manufacturers have adapted to the current process and, therefore, may resist any substantive changes. There was also consensus that any regulatory improvement should not lower safety standards, and that the public perception that the process is being unduly accelerated should be avoided. Currently, user fees (i.e., fees paid by industry to the FDA at the time of product review) play a significant funding role for FDA review activities, and any structural funding changes must consider the size and use of these fees.

There was general agreement that the creation of a universal influenza vaccine would provide a significant opportunity to improve human health globally. However, the issue of whether this type of vaccine can in reality be created was raised. Consensus was reached that the concept of a universal influenza vaccine must be evaluated in a multidisciplinary review. In addition, there was agreement that other new ideas should also be reviewed from the outset to avoid the repetition of past missteps (i.e., attempts to implement initiatives that were never properly reviewed and later deemed scientifically unsound).

**Policy issues**

It is critical that a realistic mechanism be found that provides formal communication training for those scientific and policy leaders who are increasingly responsible for effectively communicating the risks and benefits of vaccines to the public. Public understanding and confidence in the safety and efficacy of vaccines remain an essential step for increasing vaccine uptake. The public and scientists would also benefit from a better understanding of how the

government works to establish the safety and efficacy of vaccines. Several different fellowship programs were discussed for scientists, which provide an opportunity to work in government offices on a short-term (e.g., two weeks) or longer-term (e.g., one or more years) basis. It was noted, however, that there is no one optimal track for all scientific leaders.

It was strongly recommended that tactics to combat the anti-vaccine movement center on providing messages to the public that are credible, clear, and appropriate for a lay audience. It was further proposed that celebrities and/or other public figures be engaged in the process to present the information through the media.

There was agreement that the wide variety of stakeholders associated with vaccine research, development, and delivery must be involved in any public-private partnership. Government, academia, and the private sector all have significant roles to fulfill. It was also noted that some less-traditional areas of government should be included in these partnerships. For example, it was suggested that the U.S. Department of Defense (DoD) be included since it has been successful in integrating the views of stakeholders from academia, government, and the private sector.

Incentives to establish public-private partnerships are important to facilitating cooperative efforts. Incentives from government to industry could include direct financial support through contracts and grants, tax breaks, regulatory consultations during the research and development process, first-in-line privileges, and guaranteed number of buy-ins. Incentives from government to academia could include new grant funding targeting vaccine research and technology and employment opportunities for qualified graduates trained in vaccine research and development.

In addition, the regulatory process related to vaccine development and approval needs to improve. While only regulatory agencies are positioned to implement such changes, discussions with the private sector are needed to facilitate reasonable outcomes. Entrenched attitudes and wholesale acceptance of the status quo were consequently deemed counterproductive to the improvement of regulatory practices. As part of these efforts, increased staffing within the FDA was endorsed. It was proposed that, in addition to funding for supplementary positions, attracting talented scientific regulators is imperative. Expanding opportunities for FDA employees to be engaged in more creative activities (e.g., promoting grant opportunities and encouraging research/publication) was cited as a valuable tactic that should be considered to improve the culture of the FDA working environment and attract new scientific talent.

It was repeatedly mentioned that the existing regulatory bottlenecks for vaccine approval must be removed. This issue was considered of particular importance in the event that efficacious vaccines are developed for high-burden diseases, such as HIV/AIDS. While it was suggested that the establishment of regulatory reciprocity networks might decrease vaccine approval delays by pooling resources and reducing duplication of efforts, it was agreed that such an approach required further study on its viability and efficiency.

There was general agreement that vaccine approval acceleration should be pursued, but it was asserted that caution must be exercised in how a quicker process is marketed to prevent the public from viewing these changes as unsafe or risky. For example, it was proposed that such acceleration should not be characterized as fast track.

From a policy perspective, vaccines can be viewed as victims of their own success. As the prevalence of a disease controlled by a vaccine diminishes, political interest in the disease wanes and the public develops a skewed view of the benefit/risk profile. Lessened public and political interest in existing vaccines can narrow the market for a particular vaccine, which can reduce manufacturer interest in producing it. When this occurs, supplies often diminish, access

may be negatively impacted, and support/funding for research into new vaccines is frequently impaired.

The comparative value of high-impact, low-cost public health measures (e.g., clean water) versus vaccines was discussed. While it was questioned whether funds would be better spent on improving general public health, no complete agreement was reached on this point. It was argued, however, that even with rising, global economic pressures, it should not be necessary to choose between basic public health measures and vaccines. In part, this is because their funding sources often differ. Public health measures are generally funded through governments and international organizations. Conversely, vaccine development is substantially funded by for-profit companies in affluent countries, potentially benefiting all world sectors. While it was agreed that these investments should be carefully scrutinized, it was also noted that investment in both areas are fundamentally important for infectious disease prevention worldwide.

# Preventing the Untreatable: Why Drug-resistant Tuberculosis Must Be Prevented

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**Summary**

There were more than 9 million new cases of tuberculosis (TB) worldwide in 2009 (WHO, 2010). It takes at least six months of daily drug therapy to treat just one case of TB, thus the global TB burden represents more than 4 million person-years of treatment from the 2009 cases alone. While this represents an almost incomprehensible drain on public health resources, evidence of decreasing TB incidence over the last few years suggests that it is at least possible to impact this disease on a global scale. For more than a quarter million of these new TB cases, however, treatment will be unsuccessful due to the drug-resistant nature of their infections, and they will join the ranks of almost 2 million people who die of TB each year. Most countries outside of North America and Europe do not routinely test TB patients for drug resistance, nor do they have access to the correct drugs for drug-resistant TB; accordingly, fewer than 10% of the patients with drug-resistant TB worldwide receive appropriate treatment (WHO, 2011). While it is critical to build the global capacity to diagnose and treat drug-resistant TB patients appropriately, it is clear that for many low-income, high-burden countries, preventing the development of drug-resistant TB should be the primary means of tackling this problem.

**Current realities**

TB is a persistent infectious disease that has been a part of human history for thousands of years. Drug-resistant TB, however, is considered an emerging disease that has developed in the last few decades. While drug-sensitive TB is a treatable disease, the emergence of multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), and totally drug-resistant TB (TDR-TB) is "threatening to destabilize global TB control" (Sharma & Mohan, 2006) and has rapidly turned TB into a lethal disease again, even in high-income countries. TB in humans is caused primarily by the pathogen *Mycobacterium tuberculosis* (*Mtb*). Most strains of *Mtb* are sensitive to the critical antituberculous drugs, isoniazid (INH) and rifampin (RIF), which have been the foundation of effective "first-line" drug therapy for TB since the 1960s. MDR-TB is caused by *Mtb* strains that are resistant to INH and RIF and is either "acquired" when TB treatment is not completed correctly or it is directly transmitted from one person to another ("primary" MDR-TB).

MDR-TB has a significant impact on the clinical course and outcome of TB disease as none of the so-called "second-line" drugs used to treat MDR-TB are as effective as the first-line drugs, INH and RIF. Treating MDR-TB is also more complicated than treating drug-sensitive TB, as second-line TB drugs are costlier, often require intravenous administration, and are more toxic than first-line TB drugs. Furthermore, many countries do not have access to second-line drugs and an often-underappreciated aspect of MDR-TB is that even if the second-line drugs are available it can take two years or more to treat, resulting in social isolation, loss of employment, and long-term socioeconomic and psychological effects.

The World Health Organization (WHO) and the International Union Against TB and Lung Disease (IUATLD) began global drug-resistance TB surveillance in 1994. By 2002, MDR-TB had been found in all world regions. In 2006, a cluster of lethal TB cases (greater than 95% mortality), caused by MDR-TB strains resistant to both first-line *and* second-line drugs, was

reported in South Africa. These XDR-TB strains have since been found all over the world. Given that MDR-TB and XDR-TB are resistant to the drugs available in most developing countries, both are considered "virtually untreatable" in those regions. Consequently, patients with these diseases have either been isolated indefinitely or simply released into the community where they continue to transmit the disease.

**Scientific opportunities and challenges**

Acquired MDR-TB is prevented by ensuring appropriate and consistent treatment of drug-sensitive TB cases, and primary MDR-TB is prevented by identifying and treating/quarantining patients to avoid person-to-person transmission. If we know what needs to be done, why is this so difficult to achieve?

TB-treatment failures occur primarily because therapy requires daily ingestion of four different drugs for six months — a challenge for even the most self-sufficient and adherent patient. While initially the supply of first-line TB drugs was a significant hurdle for many countries, it appears that medication availability and cost no longer are major impediments to effective treatment of drug-sensitive TB in most parts of the world. Completing six months of TB treatment, however, requires more than drugs and supply chains; it requires complex social interactions between patient and care providers, and is almost impossible to maintain without significant social support for the patient. It has been demonstrated that the only reliable way to ensure effective TB therapy is through Directly Observed Therapy (DOT), a heavily supervised form of treatment in which patients are observed taking each and every dose of their medication. WHO reports show that a large proportion of TB patients are on DOT, but the truth on the ground contradicts such reports. It is clear from observations in Mexico, Africa, and Southeast Asia that very few countries are actually observing more than a small percentage of the daily medication events. Yet each country dutifully records a large proportion of its patients on DOT each year in reports to WHO. We will be able to minimize acquired drug resistance only when we are able and willing to acknowledge that DOT is not being implemented as reported; only with this acknowledgment will there be an impetus to develop new solutions, incentives, and appropriate social-support resources to ensure treatment adherence. Commitment to social services during TB treatment, together with creative operational solutions, is an area of opportunity that could bring in untapped funding as well as new expertise from the social sciences.

Regardless of how well TB treatment is managed, there will always be drug-resistant TB cases that can be directly transmitted as primary infections. It is critical that these cases be quickly identified and treated appropriately. This challenge is currently complicated by limitations in diagnostic technologies, availability and cost of drugs for treating drug-resistant TB, and severe social/adherence problems resulting from the minimum of 24 months of treatment needed to cure MDR-TB.

Until recently, MDR-TB diagnosis was a significant laboratory challenge. *Mtb* is a slow-growing organism requiring a sophisticated biosafety laboratory environment and eight to 12 weeks for culture and drug-sensitivity testing. Within the last three years, there have been major advances in the development of new molecular-based diagnostics that can detect drug-resistant TB in a matter of hours. While there is still some basic science needed to verify and validate these technologies, it is critical that funding bodies also recognize the need to start shifting from an almost exclusive focus on diagnostic innovation toward the broader aim of implementation and scale-up of existing technologies.

Regarding treatment, global TB organizations such as STOP TB and Green Light Committee have taken bold leadership roles in delivering and controlling low-cost second-line drugs for treating drug-resistant TB. Many nations are, however, moving too slowly to take advantage of

these opportunities and most countries are treating far fewer than 10% of the estimated number of MDR-TB cases.

**Policy Issues**

- *Acknowledging and characterizing the limitations of DOT*: This will require a transparent field evaluation of DOT worldwide to determine what is really happening on the ground and what level of treatment supervision actually is being conducted. Such an evaluation will need leadership buy-in from global TB control bodies, such as WHO and STOP TB, to ensure the national TB-control bodies are encouraged to report accurately.

- *DOT alternatives*: It is time for a paradigm shift. If DOT is not practical or feasible in most high-burden, low-income countries, alternatives must be elucidated. Many innovative treatment supervision models have been proposed (community involvement, incentives, and cell phone applications). An ideal first step is a world conference on alternatives to DOT. The purpose of this conference would be to provide the groundwork for new WHO recommendations for "Enhanced Adherence TB Treatment" guidelines instead of one-size fits-all DOT.

- *Social support for TB patients*: TB is a social disease. It is expensive and complicated to maintain the human networks necessary to support TB patients through their treatment. Global and national TB control and funding bodies need to acknowledge the social complexities of TB control and take some responsibility for the financial burden of this element of TB treatment. National and international TB organizations have shown great leadership in funding and maintaining new diagnostic laboratories and medication supply lines across the globe. The social programs supporting TB treatment require the same level of attention.

- *Diagnosis of drug-resistant TB — Technology*: Over the next five years, global TB funding and control organizations need to have an intense focus on development, implementation, and scale-up of the most promising rapid TB diagnostics.

- *Diagnosis of drug-resistant TB — National guidelines*: Within five years, rapid diagnosis of TB and drug-resistant TB will be cost effective and no longer require sophisticated laboratories. National TB programs worldwide need to start adapting their guidelines to shift from a strategy of using treatment failure to detect MDR-TB cases, to detecting drug-resistant TB cases early and rapidly using low-cost, next-generation diagnostics.

- *Treatment of drug-resistant TB*: Most national TB-control programs are not scaling up their drug-resistant treatment programs to keep pace with the treatment resources that are being made available through global TB programs, such as the Green Light Committee, STOP TB and U.S. President's Emergency Plan for AIDS Relief (PEPFAR). It is important for the national organizations crafting TB guidelines to develop into more nimble and adaptable bodies to take advantage of the rapidly evolving diagnostic and treatment landscape. It appears, in many cases, that conflicting government regulations and competing departmental priorities are obstructing progress. The global funding bodies should consider including legal and policy experts in existing TB program implementation teams to help smooth the way.

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## Debate conclusions

- Tuberculosis (TB), in particular drug-resistant TB (DR-TB), continues to be a global public health issue of significant concern. However, more complete data is needed to adequately understand the depth of the problem and to pinpoint areas where increased attention is required. Thus, expanded research is needed to accurately determine the prevalence, incidence, and geographic distribution of all forms of TB.

- Current treatment options for DR-TB are limited and of unproven efficacy, especially when the disease is resistant to more than one first-line drug. Additional research on treatments for DR-TB and new guidelines for treatment regimens are needed to reduce TB mortality.

- While Directly Observed Therapy (DOT) and Directly Observed Therapy — Short Course (DOTS) have been heralded as successful strategies for TB control, current reported rates do not accurately reflect the true adherence rates in many countries. More data on this discrepancy, a complete evaluation of DOT(S) strategies, and a potential overhaul of the strategy are needed.

- Increasing drug completion adherence to drug-sensitive TB (i.e., non-drug-resistant TB or standard TB) regimens, including treatment completion and cure, will prevent many new cases of secondary DR-TB from developing. However, there is currently a gap in

existing TB control programs that should be filled by social support strategies. More social support programs are essential for this approach to succeed.

**Current realities**

Despite conflicting viewpoints on whether TB drug shortages exist throughout much of the world, it was generally agreed that significant strides have been made in acquiring drugs for drug-sensitive TB. It was further contended that most countries currently maintain adequate drug supplies for standard TB, but that drugs for treating all forms of drug-resistant TB (DR-TB) — including single drug-resistant TB (mono-DR-TB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB) — remain scarce.

DR-TB is a problem of escalating global public health significance. In addition to increased costs and time associated with treatment, DR-TB infection significantly increases the likelihood of mortality. There was strong consensus that there is a pressing need to halt the progression of DR-TB in all of its forms (e.g., mono-DR-TB, MDR-TB, and XDR-TB). It was argued that, presently, the best method for decreasing the incidence of DR-TB is to ensure treatment adherence/completion for drug-sensitive TB patients, thus significantly reducing the probability that they would develop resistant strains of the bacterium.

Although it was widely acknowledged that DR-TB is a significant public health dilemma, difficulties in adequately understanding the extent of global DR-TB prevalence and incidence were recognized. Currently, data do not accurately reflect the number of individuals affected by DR-TB or the geographical distribution of such infections. Consensus was reached that data on the current cases of DR-TB and the risk associated with emerging cases is presently inadequate.

It was also generally acknowledged that TB is a sociopolitical disease. Social support was seen as a critical element that often dictates the success of an individual's treatment regimen. Current research suggests that making more social support available to patients leads to increased treatment completion rates for all types of TB. Consequently, it was agreed that any proposals for programs to combat TB would need to incorporate major commitments for social support into their designs.

Following an extended discussion, general agreement was reached that adherence rates of DOT and/or DOTS, which are reported to the World Health Organization (WHO), do not accurately reflect the actual rates in-country.

**Scientific opportunities and challenges**

There was consensus that effective drugs and treatment protocols exist for drug-sensitive TB. It was equally clear that treating drug-sensitive TB until the patient is cured would significantly lessen the global burden of DR-TB by preventing the development of secondary drug resistance (i.e., resistance that develops via erratic and/or inappropriate drug therapies). However, many argued that even if drug-sensitive cure rates dramatically improved, substantial barriers to lowering DR-TB rates would remain. It was asserted that this is because curing drug-sensitive TB only tackles part of the problem: It does not take into account primary DR-TB infections (i.e., resistance that is spread from person to person).

Although drugs do exist for the treatment of most forms of DR-TB, skepticism was expressed regarding whether the right drug combinations have been clinically established (particularly for MDR-TB and XDR-TB) and whether current treatment protocols are universally accepted. It

was subsequently agreed that more data is required to address both the issue of drug combination efficacy and treatment guidelines for DR-TB.

It was acknowledged that significant improvements in TB diagnostics are on the horizon, and that rapid diagnostic tests will be available within the next five years. There was general consensus that these improved diagnostics are needed to address the present lack of accurate information related to the prevalence, incidence, and geographical distribution of DR-TB. Additionally, some discussion emerged regarding the challenges of sample quality and sample heterogeneity that are inherent in current TB testing procedures. While the question was raised whether sample heterogeneity could limit the validity of TB test results, it was generally viewed as not being a significant problem.

The social dimension of TB treatment was repeatedly highlighted as a major barrier to treatment adherence and increased inclusion of social support programs is required for more effective therapy. While there is a growing body of research on the utility and implementation of social interventions for individuals infected with TB, more attention to the effectiveness and practical role of social interventions is needed. Despite growing recognition of social barriers, the financial support for social programs remains too small.

The collective view was that more information is also needed to assess the extent of the problems found with DOT(S) implementation, uptake, and adherence. Some participants suggested that DOT(S) should be adapted to reflect a more realistic approach that would involve keeping the name but changing the protocol to be more consistent with what is feasible in a given country. This suggestion led to a discussion about what metrics should be considered for reorganizing DOT(S). It was repeatedly stated that the key indicator for any treatment method should be resolution of infection with continued negative status, rather than adherence to the method.

Questions were raised regarding the potential for a new TB vaccine and the efficacy of the current Bacille Calmette-Guérin (BCG) vaccine. The variable efficacy of the BCG vaccine was discussed, and it was contended that the principal gain from BCG vaccination is the prevention of TB meningitis in young children. A consensus emerged that a new vaccine for TB is desirable; however, it was also recognized that this is not a short-term solution given that vaccine development is a long and often arduous process.

**Policy issues**

The extent of the public health impact of TB was debated. It was recognized that while the true extent of the global TB burden remains unknown, approaches to communicating the degree of importance and the degree of uncertainty concerning how TB affects public health (i.e., TB risk), vary greatly. On one hand, some recommended a guarded assessment and a more judicious communication approach to avoid alarmism and panic. Others, however, argued that this tactic would downplay the fact that TB could become a future pandemic and that it would therefore discourage policy makers from acting in a timely fashion. No consensus was reached on the optimal way to move forward, but it was generally agreed these issues need urgent attention and clear decisions.

The opinion was expressed that current funding schemes are primarily targeted toward developing innovative, new diagnostics for TB, rather than implementing existing interventions already proven to be successful, including social support programs. The participants were in agreement that social programs would require increased political will to be more effectively implemented. Parallels were drawn between social approaches to HIV therapy and those that could be employed for TB. For example, it was proposed that lessons could be learned from

the United States President's Emergency Plan for AIDS Relief (PEPFAR), which only provides funding for implementation of proven existing interventions.

A significant portion of the discussion was focused on whether DOT(S) is effective in its current iteration and, if so, whether it needs to be replaced, renamed, or otherwise altered. It was agreed that the focus of any treatment should be on the resolution of infection via the completion of well-defined treatment protocols.

The discussion on the effectiveness of DOT(S) led to questions about why disparities exist between DOT(S) reporting rates and actual adherence observed within countries. A two-fold explanation was presented. First, it was asserted that the pressure for countries to conform to expected coverage rates is too strong, and therefore leads to misreporting. It was recommended that some flexibility should exist in the reporting benchmarks to allow for a more accurate assessment of the true treatment adherence rates. Second, it was suggested that confusion exists with respect to the definition of DOT(S), with some following the original WHO definition of DOT (i.e., strictly directly observed therapy) and others following the revised definition known as DOTS (i.e., directly observed therapy plus a series of other requirements). While it was agreed that a unified understanding of DOT versus DOTS is needed, it was also recognized that these terms are so ingrained in the treatment communities that it is a difficult problem to ameliorate. No firm solutions were presented.

In a continuation of the conversation on DOT(S), the role of WHO was extensively debated, primarily in relation to setting the guidelines for DOT(S) or other therapies. Agreement was reached that better data are needed before a strong case could be made that WHO must reassess DOT(S) protocols. However, it was also pointed out that a 2009 Cochrane Review suggested that the routine use of DOT(S) in low- and middle-income countries does not improve treatment outcomes. It was asserted that this study was largely ignored by WHO. Doubt was expressed as to WHO's ability to objectively consider contradictory data on DOT(S) effectiveness if the outcome would be unlikely to change accepted practices. The discussion concerning changes in DOT(S) protocol acknowledged that altering WHO practices would need to be driven by member states rather than the WHO Secretariat.

Forward-looking discussions considered the resource allocation implications of the proposals presented. Some participants asked what would be the contingency plan should the proposed policy recommendations fail to reduce the spread of DR-TB. This discussion was underscored by concern that only 10% of DR-TB patients worldwide are estimated to receive appropriate treatment, which leaves most infected individuals requiring therapy. Scaling up treatment to include more DR-TB infected individuals could be problematic if the recommended drugs are expensive and/or in short supply. While no consensus was reached as to how much the proposed recommendations in the policy position paper would prevent or eliminate DR-TB, support was given for several specific recommendations, including the need to increase social support programs and the need to identify and scale up programs to treat DR-TB.

Because foreign-born residents comprise approximately 50% of all U.S. TB cases, the topic of U.S. TB screening policies was discussed. Although some overseas screening does occur (based on risk from the country of origin), it was suggested that this policy could be improved by extending overseas screening requirements to additional countries.

Despite growing recognition that social barriers limit the effectiveness of protocols for TB treatment, the financial support for social programs has not caught up with the financial support for research. Without adequate funding for social programs, it was agreed that ensuring infected individuals are compliant with treatment will remain problematic.

# Moving from Hazard-based to Risk-based Microbial Food Safety Systems to Promote Public Health and Foster Fair Trade Practices**

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## Summary

Foods are one of the major vehicles for the transmission of a broad range of infectious diseases. The ability to prevent these diseases is becoming more complex as the world increasingly relies on global marketplaces. National governments have agreed that the best way to prevent food-related infectious diseases is through international trade that safeguards public health while ensuring fair trade practices. However, this goal has not always been realized, in part because of the highly varied approaches to food production, processing, distribution, and marketing used throughout the world. Experts have generally agreed that the framework needed is one that is science-based, risk-based, and flexible, while still ensuring verifiable levels of control.

The need to prevent foodborne infectious diseases is fostering the development of risk analysis approaches for controlling them. Great strides have been made in our ability to conduct microbial food safety risk assessments; however, equivalent gains have not been achieved in microbial food-safety risk management and risk communication. Risk management systems are in the process of moving from being hazard based to risk based, but this is hampered by our ability to define consensus international standards. Harmonization is critical both for consumer confidence and for industry, as well as for less-wealthy countries to have predictable food safety targets.

One key issue is how to take risked-based approaches and adapt them to "Hazard Analysis and Critical Control Points" (HACCP), the primary risk-management system used by the food industry. A second is how the level of stringency can be transparently related to the level of public health protection. These key issues can be overcome by food safety policies and infrastructure investments that foster transparency, improve inter-sector data exchange, develop and quantify alternative food safety approaches, harmonize international standards, and provide objective measures of the level of control currently achieved by our food safety systems.

## Current realities

A predictable, adequate, affordable, and safe food supply is critical for public health, economic development, and political stability worldwide. The transmission of infectious diseases via foods is one of the key factors that erodes confidence in the food supply. While it has long been recognized that foods can be a source of pathogenic microorganisms, we have only recently appreciated the magnitude of the public-health burden. The impact is often greatest for developing countries where there is minimal food safety infrastructure, and the export of agricultural commodities and food is a primary source of hard currency.

There have been concerted international efforts to rationalize and harmonize food safety standards and guidelines, including efforts by national governments through the World Trade Organization's (WTO) Sanitary and Phytosanitary Agreement (SPS), and the UN's Codex Alimentarius Commission (CAC), as well as by industry through the Global Food Safety Initiative (GFSI). These efforts have been accelerated by the WTO's recognition of both the CAC "standards" and the importance of risk assessment. These organizations have emphasized the critical need for consensus standards that promote public health, are based on science and risk

assessment, foster fair-trade practices, and provide flexibility in the methods used to achieve the desired rigor.

Refocusing food safety standards has led to tremendous advances in microbial risk-assessment methods and food safety risk-management metrics concepts. These strengthened capabilities help identify outbreaks, attribute foodborne disease to specific foods, estimate the burden of foodborne disease, and distinguish residual food safety risks from low-frequency system failures. However, many food standards are out of date, nontransparent, poorly justified in relation to food safety risk priorities, not focused on measurable outcomes, and not translatable into actions that can be incorporated into HACCP. These food standards' shortcomings often are reflected by regulatory systems that are hazard based instead of risk based and/or an inability to communicate with stakeholders in a manner that leads to consensus in "tolerable levels of risks," while ensuring continuing improvement.

**Scientific opportunities and challenges**

The past decade witnessed rapid advances in our understanding of the risks related to foodborne infectious diseases. Different classes of microbial risk assessments have been developed to address diverse public health and regulatory questions (e.g., risk ranking, evaluation of risk-mitigation strategies, risk-risk trade-offs, risk-benefit trade-offs, and risk of introduction of new infectious agents). A cadre of highly capable risk assessors and subject-matter experts is emerging internationally as governments begin to use risk assessments in their regulatory deliberations. However, there are significant challenges in the other two components of risk analysis: risk management and risk communication.

Risk management is the process of determining the degree of stringency appropriate for controlling microbial food safety risks and determining which mitigation efforts can provide the desired degree of control. In general, risk managers have placed little emphasis on defining principles for effective risk management (Buchanan, 2011). However, CAC (2007) recently defined a four-step process for microbial risk management that consists of: (i) preliminary management activities, (ii) selection of risk-management options, (iii) implementation of programs, and (iv) monitoring and review. There are significant challenges within this framework such as:

- Developing a library of common metrics to objectively prioritize dissimilar risks,
- Acquiring data on contamination rates in various foods and data that associates foodborne disease with specific foods and commodities,
- Developing informatics systems for sharing data across food-industry sectors and among countries,
- Defining and maintaining "lots" for product identification,
- Distinguishing food systems' residual risks (i.e., frequency of infectious agents when the system is in control) vs. low-frequency systems' failures (i.e., incidents of loss of control), and
- Identifying effective predictors of performance.

A critical bridge in this process is the ability to link the impact of decisions and actions taken within HACCP to the expected public health protection provided by food safety systems.

Perhaps the greatest challenge to improving our food safety systems is how to achieve effective risk communication. A large and diverse group of stakeholders has deep interests in food safety, each with its own perspectives, values, and vocabulary. Communication challenges are further amplified when different countries and cultures are involved. For example, it is difficult to reach consensus on national and international food safety standards if one does not appreciate

that consumers view food safety as a binary state (i.e., safe vs. not safe), whereas food manufacturers view the degree of safety assurance as a continuum that requires a series of trade-offs in terms of public health protection, food quality, and cost of the food to consumers. The ability to achieve multidirectional communication is the foundation upon which consensus food safety standards must be developed.

**Policy issues**

- Advance transparent food policies which articulate the level of risk reduction that will be achieved, including relating it to frequency of risk-management monitoring and review.

- All microbiological standards should articulate the actual risk reduction likely to be achieved.

- Working through an appropriate intergovernmental organization (e.g., the Food and Agricultural Organization [FAO] and the World Health Organization [WHO]), develop and provide guidance on how to link the stringency of HACCP plans to desired public health outcomes.

- Develop policies and informatics systems that foster the inter-sector exchange of data while safeguarding the proprietary interest of the business community.

- National governments and industry should work together to pool existing data to determine baseline levels of microbial contamination in various classes of food, the variability associated with those baselines, the residual risk associated with "in control" food production and processing operations, and the incidence of systems failures.

- As per the WTO's SPS, national governments should be willing to accept international consensus food safety standards to reduce the degree of unpredictability for industry and developing countries.

- National governments and industry should look for approaches to better harmonize regulatory food safety standards and industry-purchase specifications.

- National governments, industry, and intergovernmental organizations should develop risk-based tools that allow food safety systems and approaches to be evaluated objectively, for comparability/equivalence.

- National governments should invest in developing and validating "size-appropriate" microbial food safety prevention and intervention technologies that offer approaches appropriate for small- and medium-sized producers, processors, and distributors of foods, as well as for use in less-wealthy countries.

- National governments and intergovernmental organizations should continue efforts to determine the burden of foodborne disease globally, but must couple this with equivalent information on the extent of microbial contamination in the food supply.

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**Debate conclusions**

- The food supply chain has become increasingly global. Countries currently import significant quantities of goods and products to meet their local consumption demands. Yet, food safety regulations and practices from country to country differ widely, which often leads government authorities and the public to question the safety of imported products.

- The establishment of the World Trade Organization (WTO) and Codex Alimentarius (CA) has helped ensure fair trade. However, less-wealthy countries still face significant challenges when competing in the international food market. This is primarily due to the continued technological and economic gap between wealthy and less-wealthy countries.

- To better prevent foodborne disease outbreaks, the food industry must shift from hazard-based to risk-based systems. Recent advances in risk assessment tools have provided more efficient means for addressing problems related to food safety.

- Many different food safety standards exist globally, some of which have been instituted by the private sector. The general lack of transparency in the development of private-sector standards, particularly in terms of their scientific basis and the determination of acceptable levels of risk, is problematic. Additionally, private-sector standards often place undue pressure on less-wealthy countries, where the capacity to meet them is often absent. Currently, there is no organization that has the authority to address the proliferation of private-sector standards for food trade.

- Communication of risk among all food stakeholders (i.e., intergovernmental organizations, government, the private sector, academia, and the public) must be improved. Ineffective communication leads to poor understanding and implementation of food safety practices (e.g., zero tolerance) and causes confusion related to the degrees of risk associated with food.

- Greater focus and input are needed at the policy level to ensure that food defense receives sufficient attention. Additionally, better integration of available data sources is needed so that the food industry can make informed decisions related to food defense.

**Current realities**

Significant discussion centered on the fact that food production, manufacture, and processing methods, as well as food safety practices, vary greatly worldwide. The contrasting methods by which peanuts are screened were presented as an illustration of these differences. In more-affluent countries, for instance, each peanut is screened by laser. In West Africa, however, the process is much more labor-intensive, with women and children examining every peanut by hand. It was further noted that the great variance in food safety practices, regulations, and standards used worldwide was one factor leading to the creation of the Sanitary and Phytosanitary (SPS) Agreement by the WTO, an international treaty establishing measures for food safety systems to facilitate safe and fair trade. The SPS operates in conjunction with CA, which is intended to protect consumers' health and ensure fair trade practices in food commerce.

The growing capacity gap (e.g., infrastructure and technology) between more-wealthy and less-wealthy countries was repeatedly highlighted. It was asserted that this divide is exacerbated by the substantial economic difficulties that less-wealthy countries routinely contend with, which impact international trade as well as their ability to meet SPS and CA measures. Both SPS and CA were instituted to improve food safety worldwide. However, it was acknowledged that difficulties in complying with the SPS and CA measures often limit the opportunities less-wealthy countries have to export food.

The food industry has been urged to move from a hazard-based (i.e., preventing identified hazards from occurring) to a risk-based (i.e., managing hazards based on acceptable levels of risk) food safety system. Recent advancements have refined risk assessment as a tool that can be applied to food safety, and have concurrently demonstrated the value of a risk-based approach. There was general agreement that this methodological shift is long overdue, and that it would benefit the food industry and public by better targeting potential problems related to food safety. However, it was noted that some stakeholders (e.g., countries and food industries) are reluctant to make this change because of the potential negative consequences for profitability.

The food safety management system called Hazard Analysis and Critical Control Points (HACCP) is a systematic preventive approach that addresses biological, chemical, and physical hazards throughout all stages of the food production and preparation processes. The HACCP system has the flexibility to function as either a hazard-based or risk-based system because it involves planning how to prevent and/or mitigate an identified hazard or risk. It was noted that HACCP is the primary risk management system used by the food industry worldwide and that it is universally accepted.

The retail food industry group has developed standards for the global trade of food products, through avenues such as the Global Food Safety Initiative (GFSI). GFSI methods have been questioned as being less than totally science-based, risk-based, and transparent.

International food-focused treaties have been jointly crafted by the United Nations' Food and Agriculture Organization (FAO) and the World Health Organization (WHO), as well as by the WTO. However, it was contended that not all treaties have been formulated with enough

involvement from the scientific community. For example, it was argued that the SPS Agreement was established with only limited input from scientific food experts.

Significant concern was expressed that both scientists and the government agencies responsible for food policies inadequately communicate levels of risk associated with food to stakeholders (e.g., to the public and each other). It was asserted that insufficient communication has undermined the degree of public confidence required for successfully ensuring food safety.

Zero tolerance is a risk communication term that has been used to express a high level of concern for safeguarding public health. In food safety policy, zero tolerance is the prohibition of a potentially threatening substance (e.g., microbiological or chemical) on or in a product, which thereby renders the product unsuitable for human consumption.

It was asserted that the food safety system is not binary (i.e., safe versus unsafe). The system is one of stringency, wherein the level of control is set based on acceptable levels of risk. Within this, varying degrees of risk are always present. Although part of government's regulatory role is to ensure that the food industry is meeting stringency standards, it was pointed out that when there is a failure within the food industry, such as an infectious disease outbreak, the government is often blamed for industry's failures or shortcomings. It was further argued that the true responsibility for food safety ultimately lies with those in the food industry because they manufacture these products.

It was noted that the top 10 food companies in the world, which are all multinational corporations, produce 90 percent of the world's food. Due to their abundant resources and research capabilities, it was widely agreed that these corporations have significant economic advantages over smaller companies as players in the world market. However, it was asserted that smaller businesses can compete in world markets in some instances, such as the orange juice market, as long as technology costs do not become prohibitive.

**Scientific opportunities and challenges**

Strong support was voiced for moving from hazard-based to risk-based management of food safety issues. It was contended that a risk-based approach will improve public health and food trade practices by more appropriately targeting where risks lie and accordingly mitigating these problems.

It was acknowledged that members of the food industry generally support and adopt international safety standards because regulation uniformity benefits them directly. Such standards not only decrease the burden of interfacing with individual countries' bureaucracies, but also minimize the work the food industry must invest in reconciling differing regulations in areas such as packaging and distribution. This demonstrates that opportunities exist to simultaneously promote the agendas of all stakeholders (e.g., government, food industry, and others).

Due to the high cost of certain technologies that are routinely used to protect food, small- and medium-sized farms and food manufacturers encounter disproportionate economic challenges in complying with many food standards relative to their larger counterparts. Yet, it was noted that this barrier could be overcome with the aid of research and development for lower-priced technologies. This was exemplified by the case of the orange juice industry in the United States, wherein smaller companies faced problems competing and complying with U.S. Food and Drug Administration (FDA) standards due to the high price of flash pasteurization devices

(approximately US$500,000 per device). In this instance, a research project was initiated and a more cost-effective device (approximately US$15,000) that meets FDA requirements was developed and approved.

It was contended that core communication efforts should focus on the intersection of risk and food safety. However, it was also recognized that the divergent interests of the relevant groups complicate effective communication. For example, it was noted that the public generally looks to the government and food industry for clarity on whether foods are safe — yet it is impossible for authorities and industry to promise zero risk with respect to food consumption. While it was agreed that government officials and the food industry should be honest with the public, conflicting viewpoints were voiced regarding how much the general public is capable of understanding and/or applying degrees of risk to everyday decisions. Balancing candor and clarity was accordingly perceived as an ongoing challenge.

Acceptable levels of risk are sometimes based on parameters that are not transparent. It was asserted that this lack of clarity can be problematic because ambiguity concerning the degree of risk can fuel the public's mistrust of the food safety system.

It was argued that while zero tolerance is ideal in principle, it is extremely difficult to implement such practices in real-world settings. The primary obstacle is that for zero tolerance to truly be obtained, every piece of food must be tested (as opposed to employing statistical sampling methods). This approach not only is cost prohibitive from a procedural standpoint, but also impractical given that current testing methods are often destructive to the food itself. It was argued that levels of risk therefore must be set in accordance with the ability of the food industry to effectively meet these requirements.

There was acknowledgment that the food industry needs an effective system for sharing and analyzing the various forms of data it collects on a regular basis. Multiple factors that have become barriers to data sharing were highlighted. For example, to protect themselves from economic repercussions, farmers are reluctant to divulge potentially negative information to food manufacturers or producers. Similarly, to safeguard their proprietary interests, food manufacturers are frequently hesitant to share data with competitors or regulatory agencies.

Although international food safety standards exist, not all countries require that they be adopted. For food product export, manufacturers will frequently follow only the standards necessary for their products to be accepted in a given country. Manufacturers may therefore follow different stringency standards with respect to products intended for local consumption versus those intended for consumption abroad. This is particularly true for manufacturers in less-wealthy countries who continually seek out ways to reduce costs. However, it was stated that encouraging and facilitating less-wealthy countries to export food products meeting international standards frequently motivates these countries to also adopt higher standards for their internal products. This results in safer food in all areas.

**Policy issues**

There was general consensus that a shift from a hazard-based to a risk-based food safety system should be promoted by encouraging the use of available risk assessment tools and increased training for stakeholders in this area (e.g., government, the food industry, and the public). It was argued that support from policy makers is necessary to facilitate the movement toward a risk-based system, including implementation of food safety risk assessments, creating and supporting data sharing mechanisms, and promoting international harmonization of food safety regulations and practices.

While it was contended that risk-based food safety systems should become the primary model implemented worldwide, it was also recognized that some food producers are already instituting scientific risk-based practices. To keep pace with these changes, policy makers must review and revise regulations and policies on both national and international levels so that existing food laws will not lag behind risk-related technological developments. It was noted that such laws currently vary widely by country, and often are outdated. In addition, it was deemed important for countries to review whether their national regulations and standards comply with the SPS agreement, and to update them where needed. Although national government agencies were tasked to review their regulations and standards after the SPS Agreement took effect, it was contended that not many countries (if any) undertook this exercise.

There was agreement that inconsistent food safety standards as well as the problems that variable standards create, particularly related to trade, must be addressed. The food safety standards that have been adopted by industry, especially by multinational food companies, often differ from standards established by intergovernmental organizations, such as the WTO. This divergence creates confusion among exporters, who are unsure of which standard to follow. It was also noted that private-sector standards prevent some smaller countries and/or manufacturers from participating in export trade, even when they are able to meet accepted standards of intergovernmental organizations. A mechanism is needed to manage the various standard-setting bodies. Additionally, to determine whether existing standards are scientifically valid, increased transparency in how standards are derived or developed is of fundamental importance.

It was noted that policies related to food safety practices must take into account the disparate capacities of small and large producers and manufacturers. While both group sizes should be held to equivalent standards, policies should allow producers and manufactures to achieve food safety standards through the creative use of effective, affordable technologies. This means that a greater focus must also be placed on applied research into developing them.

The need to improve communication among government, the food industry, and the public was widely endorsed. It was argued that the level and quality of communication related to food safety issues must be enhanced among all relevant food industry stakeholders. To move forward, communication training must be implemented and other communication mechanisms, such as multidisciplinary meetings where communication can be facilitated, should be developed and/or promoted.

Another critical aspect of communication in which improvements were suggested relates specifically to the public. There is an urgent need for the public to understand and apply levels of risk acceptance to their routine decisions. A fundamental part of a risk-based food safety system rests on decisions that accurately reflect the degree to which the public understands how regulatory agencies and the food industry establish levels of acceptable risk (e.g., the public must decide whether to consume a product, and/or how to cook it, based on decisions made by government and industry on tolerable pathogen levels). As such, the public must be provided with better risk information to make informed decisions. It was recognized, however, that public decisions will likely vary across the world due to differing perceptions of risk related to food safety (e.g., in some areas, hunger abatement may take precedence over perceived risks).

It was strongly asserted that food product testing, as part of import regulation, should occur at the point of production rather than at borders. Proponents of this change contended that point-of-production testing would be more efficacious and economical. The current emphasis on border testing is inefficient because it requires food products to be shipped in advance of testing; when problems arise, these products must then be returned to their point of origin. As such, funds are unnecessarily spent simply moving products from place to place. Additionally, it

was argued that potential problems can be addressed in a more timely and efficient manner when identified at the point of production, which would therefore make better use of the limited resources currently allocated to food testing.

It was recommended that greater attention and input at the policy level be applied to food defense (i.e., protecting the food supply from deliberate or intentional acts of contamination or tampering). For food defense to succeed, a better framework using all available data is critical. The types of data to be included for food defense can often be found in the information collected by law enforcement, regulatory agencies, and the food industry. For example, in the case of data collected by law enforcement agencies, one area of interest would be criminal activities involving the food industry. This information should be made available to agencies engaged in food safety, so it could then be used to make more informed food safety decisions.

# The Use of Farm-to-Fork Surveillance and New Genome Sequencing Techniques to Prevent and Control Foodborne Disease Globally**

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## Summary

In the future, it is likely that all clinical microbiological laboratories will have access to DNA sequencing on a daily basis. The technology will become significantly cheaper and quicker than present bacterial identification systems. Given that human infectious diseases have an increasingly global epidemiology (e.g., severe acute respiratory syndrome [SARS], H5N1 avian influenza, influenza, *Salmonella*, and antimicrobial resistance), rapid identification of microorganisms and timely response are crucial for preventing global spread. It is suggested that new technologies (e.g., DNA sequencing), combined with new methodologies for risk assessment and attribution of human infectious disease to the source (animals and/or food), should be used for science-based reduction of the foodborne disease burden at the global level. Systems to enable real-time detection and prevention of infectious diseases should be based not only on the best available collaborative science, but also must have a clear and transparent governance structure with global reach.

## Current realities

A significant portion of, if not most, infectious diseases in humans is related to animals. The diseases are caused by zoonotic pathogens (i.e., pathogens shared between human and animal populations). Recent major human outbreaks of diseases that stem from animals include bovine spongiform encephalopathy (BSE) and its human counterpart, Creutzfeldt-Jacobs disease, SARS, avian influenza, and the H1N1 pandemic. Such diseases may jump once to the human population and then spread from human to human (e.g., SARS or H1N1), spread in animals and jump to humans multiple times through human-animal contact with live or dead animals (e.g., avian influenza), or spread in animal populations and then to humans via food (e.g., BSE). Efficient early detection and prevention of such diseases will be possible in the future, based on new DNA sequencing techniques.

It should be realized, though, that the most significant part of the zoonotic infectious disease burden is not related to these unusual pathogens, but rather to a small group of pathogens that cause endemic foodborne diseases. These endemic zoonotic pathogens are responsible for a significant number of “ordinary” disease cases year after year. Endemic diseases typically relate to zoonotic pathogens that are constantly present in a large proportion of certain animal populations and, if not controlled, cause an ongoing and often large disease burden. In addition, the use of antimicrobials in

animal populations (to promote growth and treat sick animals) is creating zoonotic strains resistant to the antimicrobials used to save human lives. The occurrence of these resistant zoonotic pathogens exacerbates the foodborne disease burden in humans.

Old food safety systems have failed to control this significant food-related disease burden for a number of reasons, including intuitive reliance on end-product testing and a lack of inter-sectoral collaboration. Safety cannot be achieved by senseless testing alone, including testing of imported food at borders. Monitoring the presence of pathogens in the end product usually is inefficient because it is impractical to test enough samples to obtain the necessary degree of statistical certainty (Havelaar et al., 2010). Silo thinking in the broader food safety system has also significantly contributed to the relatively sorry state of affairs that exists at present. This mentality has resulted in a situation in which surveillance systems for animals are not at all linked to surveillance systems for food or humans. Thus, for example, *Salmonella* cannot be linked among the animal, food, and human domains. Notably, when countries have succeeded in creating integrated systems spanning both agricultural and human sectors, preventive and control efforts have also been more successful (Wegener et al., 2003). Such inter-sectoral systems have been used to monitor the situation and spread of antimicrobial resistance from animals, via food, to humans. However, coordination of data-gathering efforts is presently missing in many food safety systems, leading to a very weak evidence base, uninformed decisions, and ultimately poor implementation. The result is a lack of political support and generally poor financing of systems and efforts.

The new thinking in food safety relies heavily on the farm-to-table concept (i.e., focusing prevention on the full food-production chain from farm to consumer) and the proactive use of risk assessment. Risk assessment presents a science-based and transparent way of evaluating food safety problems as well as the efficacy of solutions along the full food-production chain. The use of risk assessment to deal with microbiological food safety problems primarily began in the United States and Canada, and moved to the rest of the world throughout the 1990s and 2000s. Guidelines and expert committees for this purpose were defined by the World Health Organization (WHO) and the Food and Agricultural Organization (FAO) in 2000.

## Scientific opportunities and challenges

In terms of source attribution, *Salmonella* exemplifies an area where new methods have been created to link the bacteria in animals and food to the infections in humans. In typical food safety systems, *Salmonella* is not compared in animals, food, and humans. Thus, the source of most cases of sporadic human salmonellosis (e.g., pork, chicken, and eggs) cannot be found, ultimately resulting in a lack of upstream prevention (i.e., sporadic cases are not linked together in outbreaks). However, in an effort to relate *Salmonella* in animals/food to the infections in humans, a model was developed to estimate the number of human cases attributable to each of the major animal-food sources (Hald et al., 2004). *Salmonella* subtypes found in animals and food are compared with subtypes found in humans, and annual estimates on the impact of

*Salmonella* through major animal-food sources are accordingly generated. The model has become a powerful decision-support tool for allocating resources to achieve optimal *Salmonella* prevention and control. This is true for both drug-sensitive (i.e., nonresistant) and antimicrobial-resistant *Salmonella*.[4] While the case of *Salmonella* demonstrates a significant opportunity in terms of developing new models for source attribution, this precise model cannot at present be applied to other infections. The model is possible for *Salmonella* because of the specific typing methods available for this bacterial genus, as well as the epidemiology of the pathogen, yet for most other pathogens similar possibilities do not exist.

The rate of total genome sequencing has increased tremendously in the past decade. Whole bacterial genomes can now be sequenced in minutes, creating significant new opportunities (and challenges) in term of monitoring, tracing, and attributing foodborne bacterial infections. In principle, the rate and cost of sequencing will not be the limiting factor. Rather, problems will relate to storing, analyzing, and interpreting the enormous amount of bacterial-sequencing data. The genome-sequencing technology will also enable a globally harmonized system for the identification and characterization of bacterial strains. This information will be easy to share among countries, thus enabling global monitoring and tracing of foodborne pathogens. It also enables significantly quicker, more specific, and less expensive characterization of bacterial strains. When a pure bacterial culture is available, results can be achieved within minutes in the field without specialized laboratories. Likewise, sequencing data can be used as the basis for broader source attribution, enabling specific infectious-disease prevention for most zoonotic pathogens. The major challenges lie in achieving global agreement on the specific sequencing technique and in determining ways to transmit and store data.

## Policy issues

To contextualize the salient policy issues, it is imperative to bear in mind the following: (i) globally, up to half a billion microbiological isolates are characterized each year in diverse and expensive typing systems involving serology, all of which could be replaced by total genome sequencing for bacteria and viruses; (ii) human infectious diseases have an increasingly global epidemiology — thus, rapid detection and identification of microbial agents and timely response and control are crucial if we want to prevent or control global spread; and (iii) globally standardized, research-based solutions and technological developments are needed for real-time microbiological identification and analysis of information, and such solutions must be implemented with global access and long-term sustainability.

- A standardized methodology to analyze microbiological genomes should be globally agreed on. Included within this should be a system to report, in real time, microbiological identification data together with antimicrobial-resistance characteristics. Such systems should take diagnostic and surveillance needs for animal, food, and human health sectors into account. Policy-level debate and

[4] For example, in 2005, it was estimated that 60% of all *Salmonella* infections acquired in Denmark came from Danish meat and 40% from imported meat. However, when examining the multiple antimicrobial-resistant isolates or fluoroquinolone-resistant isolates, more than 90% of infections were attributed to imported meat.

decisions are needed in an international forum with much inclusiveness and transparency.

- A capacity to assemble, process, and handle large data quantities over Web-based systems should be developed to create a global database of microbiological strain DNA-sequence data.

- The governance structure for such an interactive global DNA-sequence database and system needs to be transparent, be inclusive, and consider information-sharing constraints. Policy-level consideration of implications and timelines for such constructs is needed.

- Data-gathering efforts related to food contamination and foodborne disease must be coordinated so systems to efficiently prevent foodborne diseases are based on solid evidence. Likewise, monitoring, surveillance, and control efforts should be geared toward enabling common goals.

- Establishment of global source-attribution models should be based on full genome sequencing linking the specific animal and food sources to human infections at national, regional, and global levels. The outcome can be used to track and evaluate the spread of microbial pathogens and antimicrobial resistance, as well as to set and monitor targets for contamination and disease reduction. A clear and transparent global governance system is needed for this to succeed.

- There should be increased standardization of information on microorganisms, including information on the relationship between antibiotic use in agri-/aqua-culture and antibiotic resistance in foodborne pathogenic microorganisms. It is also important to document and evaluate specific intervention strategies for prevention of antibiotic-resistant microorganisms.

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*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP) June 5–8, 2011, at the Estancia La Jolla Hotel, La Jolla, California.*

**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. Jørgen Schlundt (see above). Dr. Schlundt 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. Schlundt. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Schlundt, 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**

- Foodborne diseases are an immediate global concern. They negatively impact societies through associated morbidity, mortality, and substantial health care-related costs. The present foodborne disease burden warrants action at global, national, and local levels to prevent the transmission of these diseases.

- Source attribution is an example of a successful strategy for the prevention and mitigation of foodborne diseases. Source attribution has demonstrated its value in Denmark where, despite being limited in terms of the microbes involved, it led to significant reductions in foodborne illnesses, deaths, and associated health care costs. Accordingly, similar systems should be established worldwide.

- Source attribution systems must draw on the One Health approach by utilizing data from as many sources as possible (e.g., combining data from human health and veterinary systems). While data collected from processing plants, farms, food, and patients are all critical elements of source attribution, more emphasis should be placed on data from the farm because that information allows disease management decisions to be implemented at the primary production stage.

- For a source attribution system to be successful, it must be global in design (i.e., collecting and analyzing data across national borders) and have the participation of both the food industry and regulatory agencies. The system should also be designed to catalog as many microbes as possible to broaden its application to non-foodborne microbial infections.

- Extensive advances in DNA sequencing technology have played a large role in the feasibility of source attribution. A global source attribution system would still take several years to put in place, but would be viable with appropriate political support. Given that the benefits (e.g., reduced morbidity, mortality, and health care expenditures) outweigh the cost of developing and implementing a source attribution system, intergovernmental agencies and governments should encourage and champion the development of such a system.

- Countries must more widely communicate with each other regarding their foodborne disease control strategies. When communication is lacking, successful strategies (e.g., Denmark's source attribution system) go unnoticed and are not replicated in countries where they could have great impact. Additionally, data sharing (e.g., genetic material) should be encouraged to accelerate the development of disease prevention methods, such as vaccines.

**Current realities**

Globally, thousands of people die each year from diseases transmitted to humans through food. While it was suggested that most of the bacteria that are transmitted to humans via the global food supply originate from animals, it was acknowledged that source attribution is not frequently employed to establish a causal link.

A Pew Charitable Trust report recently estimated the health care-related cost of foodborne disease at approximately US$152 billion yearly to the United States alone. There are also tremendous resource expenditures to implement point-of-import testing of food as a safety measure. This procedure was perceived as less useful than point-of-production testing.

It was noted that Denmark has implemented a system of source attribution, which is currently focused on *Salmonella*. The system is based on the premise that, if animals are the suspected cause, microorganisms in food, animals, and humans should be compared to determine the true source. There is a significant amount of data available on *Salmonella* (found in chicken, eggs, pork, etc.) to support a comparison of the strains found at the farm, in food, and in patients. This source attribution allowed Danish authorities to attribute a number of disease outbreaks to a specific source. It was strongly argued that source attribution is only truly successful if testing is performed at the farm level (i.e., the source), alongside testing in food and in affected patients.

Concern was expressed that, currently, common foodborne diseases are not a serious enough priority within public health programs, especially in the United States. Attention was drawn to an announcement made by the U.S. Centers for Disease Control and Prevention (CDC) that *Salmonella* infections in the U.S. have increased during the last 15 years. Meanwhile, the European Union has made significant efforts to reduce *Salmonella* in poultry. Differences between the E.U. and U.S. systems of food safety were also clarified. The E.U. system relies more heavily on measures implemented at primary production stages (e.g., farms), while the U.S. system relies more heavily on measures implemented at the processing stage (e.g., slaughterhouses).

Due to the tremendous progress made in DNA sequencing technology, it has become much easier to decode genomic data. The Smithsonian Institution's "Barcode of Life" initiative was highlighted as a successful application that has emerged from such advanced DNA sequencing technologies. There are numerous collaborative projects focusing on genetic sequencing that have taken place. For instance, the National Institutes of Health (NIH) has worked with the E.U. to fund the International Human Microbiome Project (IHMP), which was recognized as a successful international collaboration. The IHMP aims to characterize the human microbiome and, hopefully, identify its role in disease pathogenesis. It took approximately two years to overcome the ethical and data sharing issues that posed problems for this initiative and to develop the necessary protocols. Ten other organizations have joined the consortium working together on the IHMP, and the project now includes representatives from countries across five continents. Such collaboration was cited as an example of a framework that could be imitated to establish a global source attribution program for foodborne diseases.

It was noted that other international frameworks also help countries negotiate with each other on data sharing. For example, a database of microbes involving approximately 160 countries was favorably discussed. The U.S. Food and Drug Administration (FDA) has made a large investment in a total genome sequencing facility, including spending significant resources on a supercomputer for sequencing purposes. These points underscored the current, worldwide interest in the use of DNA technology and the need for avenues to share the results of such research.

**Scientific opportunities and challenges**

Despite evidence demonstrating endemic diseases comprise the main burden of foodborne diseases, it was recognized that significant resources are reactively expended on managing foodborne disease outbreaks. It was contended that a more anticipatory approach based on an effective attribution system is needed, on both national and international levels, to prevent and mitigate foodborne diseases. Some concerns were raised regarding barriers to such source attribution systems, including the costs of such endeavors and the level of collaboration that could truly be achieved across borders. It was acknowledged that a high level of participation is necessary to achieve a system of global attribution. Such a major commitment can be justified by the associated health care-related cost of foodborne illness in the U.S. alone (i.e., US$152 billion annually).

There was general consensus that a global foodborne disease attribution system is both necessary and feasible. It was agreed that it may be necessary to implement such a system through a tiered approach because each country has differing capacities in infrastructure and human resources. Such a disease attribution system could eventually allow for real-time assessment of global trends related to pathogens and emerging diseases. This would accordingly move the focus beyond epidemics to include management of endemic diseases. It was proposed that, if political will can be garnered, such a system could be established within 10 years. Involving less-wealthy countries in the design and implementation of such a program will not only provide a broader source of data, but the associated training and capacity-building would provide these countries with the opportunity to bypass the mistakes made by wealthier countries in foodborne disease management.

The debate concerning how technological advances (e.g., DNA sequencing) have provided a significant opportunity for greatly improving food safety through extensive source attribution focused on identifying the benefits that could be realized by patients. Considerable enthusiasm was displayed vis-à-vis the possibility of a global source attribution system, which would significantly shorten the diagnosis-to-treatment time of patients by providing real-time data. Such a system would embody the One Health approach to disease management, be applicable to other fields such as environmental health, and provide yet another opportunity for transdisciplinary collaboration. Involving industry in the development and implementation of the source attribution system is imperative, particularly for accelerating the implementation of necessary technologies.

It was argued that an important first step in developing a source attribution system would be to establish the current baseline of microbial prevalence. The baseline information required would need to be gradually accumulated over time as data are collected and analyzed. This proposal stimulated debate on the feasibility and affordability of such a system. It was noted that the resulting long-term savings from reducing foodborne illness costs would more than offset the costs of developing and implementing such a system.

For source attribution to be successful, the data collected must be shared with other countries to increase the value of such information and to allow a global picture of foodborne microbes to emerge. A source attribution system has great potential to move beyond solely addressing foodborne microbes and could be expanded to include other microbes of interest. Such a global database of microbes would be an invaluable tool to the medical community since patients could be treated more easily and quickly, thereby possibly preventing disease outbreaks and loss of life. Human health professionals are often inconsistent in performing or reporting the results of microbial tests, especially since this is not always mandatory. Because of this inconsistency, gaps in essential source attribution data have been routinely identified. Likewise,

there was some disagreement over the feasibility of monitoring and collecting data at the farm level in countries with vast numbers of farms although it was noted that the number of farms is irrelevant when appropriate statistical sampling methods are employed.

While it was suggested that the U.S. should adopt some of the food safety measures employed in the E.U., it was not clear whether comparable efforts would be obtained in the U.S. This difference of opinion was exemplified by concerns that U.S. industries such as those involved with poultry would be reluctant to support the stringent measures necessary to establish an effective model. It was countered that the poultry industry in Denmark was instrumental in establishing the Danish *Salmonella* program. To be successful, direct industry incentives may be needed to promote the degree of participation that is essential to support any successful attribution program. There are, of course, inherent incentives for industry to cooperate, including the reduction of microbial contamination and outbreaks that can be economically damaging to the food industry.

Intellectual property rights issues and social-based controversies (e.g., privacy rights) related to gene typing, which would generate the enormous amount of gene sequencing required by a source attribution system, were extensively discussed during the debate. It was recognized that to effectively address pandemic outbreaks (e.g., the H5N1 influenza outbreak in Southeast Asia), a framework is needed that facilitates easy access to the pathogen strains necessary for research (particularly pertaining to vaccine manufacturing). Several potential barriers were mentioned. For instance, some countries have felt cheated when the genetic material they provided was later used to create vaccines they could not access and/or afford to purchase. Specifically, a case was mentioned where a vaccine was field-tested in a particular country, but once the vaccine was approved and produced it was too expensive to be used within the test country. This example illustrates the ongoing challenges related to corporate and social responsibilities.

It was lamented that countries are unaware of successes such as Denmark's in addressing food safety challenges. It was generally agreed that such successes should be reported and shared, so that others could benefit from them.

**Policy issues**

While the advances made in technology (e.g., DNA sequencing) can have a major impact on improving food safety through extensive source attribution, the political will and policies needed to support and use these advances are generally absent. Nonetheless, a global source attribution system would be a significant benefit to the public worldwide and, therefore, serious efforts to implement it must be made. The magnitude of such an undertaking could be justified when compared with the enormous health care costs of foodborne diseases. As a related proposal, it was also suggested that import testing expenditures could be shifted to point-of-production testing and monitoring for data. Data from testing and monitoring could then be used in the attribution system. Such an undertaking, however, would require support from a given country's political leadership.

For a source attribution system to be truly global, it must include less-wealthy nations. Therefore, greater understanding is needed regarding how to streamline and implement a tiered system that recognizes the differing capacities of various countries. Additionally, it was noted that a global source attribution system would require worldwide harmonization of standards.

Because microbes evolve over time, an effective source attribution system will require a robust surveillance system that is constantly monitoring microbes. A baseline of circulating microbes

must be established and standard protocols for monitoring will be needed to ensure uniformly useful data.

There was some agreement that non-European countries should follow the E.U.'s mandate to reduce food contamination and microbial foodborne diseases, such as *Salmonella*. Discussion on this point indicated that the reduction in microbial contamination in the E.U. occurred as a direct result of the E.U.'s goal-oriented program. While no clear alternative pathways were suggested, it was contended that it is possible for countries to achieve the required contamination reduction through differing mechanisms as long as the same outcome is achieved.

The need for a global initiative to address intellectual property rights and focus on sharing genetic material, was widely expressed. This initiative would provide a framework to share genetic material and data, not only through ongoing research, but also during times of crisis (e.g., the 2009 H1N1 pandemic). The current absence of such a framework delays rapid data dissemination, which is a detriment to protecting the public (e.g., hindering the timely production of vaccines). However, it must be recognized that such information generally originates from resource-poor countries, which are often reluctant to share data or samples because they generally have not garnered direct benefits from data sharing in the past (e.g., sharing genetic material has not regularly stimulated improved access to vaccines via subsidies). To ameliorate obstacles to data sharing and achieve political support for sharing efforts, it was suggested that these types of source attribution and intellectual property issues must be initially addressed at the highest leadership level possible — prime ministers or presidents. It was noted that value would be optimized by communicating data through existing reporting structures and frameworks, such as those managed by the Food and Agriculture Organization (FAO) or the World Health Organization (WHO).

Successes, and especially failures, in dealing with foodborne disease issues must be shared internationally to enable countries to either emulate achievements or avoid mistakes made by others. It was emphasized that information-sharing difficulties underscore the need for a functioning communication system, both regionally and internationally. Some proposed that it may be possible to strengthen existing communication networks within organizations such as FAO or WHO. Others felt that new international organizational efforts are required.

Changing focus from responding to foodborne disease outbreaks to addressing endemic foodborne disease issues was a common suggestion that was strongly supported. By concentrating on endemic foodborne diseases, the occurrence of outbreaks will lessen and treatment time of cases will also be reduced. Thus, it was generally agreed that a narrow focus on outbreak response is not a sound public health strategy.

# Would You Ever Recommend Driving a Motorbike Without a Helmet?

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**Summary**

Vaccines prevent infections by mimicking them and eliciting memory of this event so that our bodies will eradicate the microorganisms once they show up, even decades after vaccination. The eradication and control of diseases such as smallpox are examples of the effectiveness of vaccination. Not only are vaccines effective, but they have proven to be a cost-effective method of disease management and should be further explored in the fight against infectious diseases. The advent and continued development of synthetic biology have contributed significant new avenues to vaccine development and production. These new paths will allow for the quicker, increased, and cheaper production of vaccines — which in turn allow for the wider use of vaccines, especially in resource-poor countries. Recent anti-vaccine movements have threatened the uptake of vaccines across the world, especially in developed countries, and have led many parents to refuse to vaccinate their children. This negative outcome has contributed to the resurgence of diseases that were previously conquered in these countries, such as measles and mumps. Vaccines are an important resource in the toolbox for the prevention of infectious diseases. However, by inadequately championing the development and use of vaccines, policy makers still do not fully take advantage of the disease-prevention opportunities that they provide. In this paper, we discuss two issues relating to vaccines: 1) the use of existing vaccines, and 2) research activities to discover new vaccines. We will expand first on why we do not vaccinate every single person in the world with the available vaccines, and second why we do not increase public and private investment in synthetic biology research aimed at vaccines against all infectious diseases that impact human and animal health.

**Current realities**

Infectious microorganisms are the only living organisms on earth that have succeeded in exploiting man. Yet, vaccines effectively prevent infections by mimicking them and eliciting memory of this event, so that our body will eradicate the microorganisms once they show up, even decades after vaccination. The burden of infectious diseases has been enormously reduced through vaccination, leading to the eradication of some diseases (e.g., smallpox) and near eradication of others (e.g., polio). Diseases such as tetanus and diphtheria are very rare in the developed world, and others (e.g., meningitis due to pneumococcus) would virtually disappear if available vaccines were implemented to cover all pediatric populations. Although infections are mostly regarded as a problem of developing countries or of a small fraction of hospitalized patients in developed countries, it is noteworthy that infections are responsible for many life-threatening diseases and that chronic infections are associated with 10%–15% of all tumors (zur Hausen, 2009). Also of note, vaccines are among the best anti-cancer remedies because they can prevent some infections that cause tumors, such as hepatitis B (HBV) (responsible for liver tumors) and human papilloma virus (HPV) (responsible for cervical cancer).

Because vaccines prevent diseases by avoiding infection onset and disease development, they are the ideal remedy. Furthermore, vaccines are probably the most cost-effective tools we have to avoid infections. The cost-effectiveness of vaccines has been calculated by comparing the cost of a vaccine with the overall cost of therapy, hospitalization, and lost working days. For example, the Centers for Disease Control and Prevention (CDC) estimates that measles, mumps, rubella (MMR) vaccination saves US$16 for every US$1 spent for vaccines. This calculation does not take into account the value of avoiding the disease — the “intangible” value

of being healthy. Vaccines have typically been viewed as low-tech medical remedies that should have low prices. Previously, the cost per vaccine dose was generally less than US$1. Since the introduction of the first recombinant vaccines, however, vaccine-development costs have been on par with cutting-edge, high-tech products. Yet, public health agencies have continued to ask for something that is impossible: high-tech *and* low-price products. The introduction of synthetic biology offers the opportunity to reduce development costs and therefore generate products that are high tech at moderate prices.

A reductive, though widely accepted, definition of synthetic biology is that it is a synthetic science that seeks to construct novel molecules and systems for useful (in our case, medical) purposes. Synthetic biology has already made some significant contributions to therapeutic medicine, such as artemisinin, the most-effective known anti-malarial drug. In preventive medicine, the introduction of genomic approaches to vaccine development has shown there is a gap between the development of technology and tools, and their applications. The difficulty of translating tools into applications is an obstacle for the growth of the vaccine field. So far, applications have focused on individual products rather than on developing a technology base to support many different products.

Although in the past some vaccines had poor safety profiles, mostly due to poor manufacturing, in the past 20 years, vaccine development and production have resulted in biological vaccines with optimal safety profiles. However, anti-vaccine movements (mainly in developed countries) consider vaccination an unnatural practice that can itself cause diseases in healthy individuals. Moreover, a few fraudulent publications have been used to give scientific dignity to the anti-vaccine movement. For example, the MMR (measles, mumps and rubella) vaccine has suffered a violent campaign against its use after an academic publication linked this vaccine to children's autism (Wakefield et al., 1998). This paper resulted in a dramatic decrease in MMR vaccination coverage, leading to the lethal spread of these diseases in countries, such as Canada and Switzerland. This paper was fully retracted in 2010, after it was demonstrated this research was carried out with dishonest and unethical conduct.

**Scientific opportunities and challenges**

The first key question is why do we not vaccinate every single person in the world with the vaccines that are presently available? The answer to this question is twofold, depending on the part of the world to which we refer (i.e., more-affluent or less-affluent countries). In more-affluent countries, the major obstacle to universal vaccine coverage is the anti-vaccine movement. This movement finds strong support among those who perceive recombinant DNA technology (call it molecular, system, or synthetic biology) as a sort of unnatural evil that puts vaccinated individuals at risk of terrible diseases in the future. In less-affluent countries, it is a matter of economic priorities of the governments, as well as of the type of help they receive from more-affluent countries. Not only is donor money needed for less-affluent countries, but proactive educational campaigns need to be promoted in those countries and logistical help needs to be provided for vaccine distribution.

The second key question is why do we not increase investment in research to develop vaccines against all infectious diseases that impact human and animal health? Synthetic biology provides, for the first time, the possibility to develop vaccines against the great majority of infectious diseases. This applies to even the most complex and difficult diseases, as was the case for the meningococcal B vaccine. Increased investment in research depends on the priorities of those making key decisions related to research programs in the public and private sectors. We should provide solid arguments showing how these investments can be rewarding

from economic, social, and political perspectives. For example, infectious diseases can impact economies (including those of more-weathy countries), as recently shown by the economic impacts of severe acute respiratory syndrome (SARS) and pandemic influenza. Research has also found a possible relationship between a country's child death rates due to vaccine-preventable infections and their probability of engagement in armed conflict. Researchers suggest that vaccines, by preventing mortality, can "function as agents of conflict resolution" (Hotez, 2001). Among the challenges that synthetic biology could help to address in the vaccine field is the development of tools to generate more applications. Synthetic biology should help define approaches that promote the implementation of genomic technologies and tools that allow commercially viable scales and time frames for the development of multiple vaccines.

**Policy issues**

- In a time of budget cuts in research and prioritization of programs, a long-term investment in synthetic biology for new vaccines to prevent infectious diseases (that certainly will affect a sizeable fraction of our world) should be considered as an alternative to complex and expensive defense programs to prevent possible bioterrorist attacks (that most likely will never affect anybody). Moreover, synthetic biology could help spread in the private sector the impetus to invest in the development of tools to generate more applications.

- Government funding for infectious-disease research should be restructured to consider a less-expensive passive immunization strategy for microorganisms that have potential interests for bioterrorists (e.g., anthrax). This strategy should be based on zero research activity and the stockpiling of newly produced monoclonal antibodies. However, most of the public research investment should be targeted toward active immunization (i.e., vaccinations).

- Financial investments aimed at achieving full-vaccination coverage in developing countries should be considered a peacekeeping effort and instruments of foreign policy. This visionary use of vaccines should be rewarded by the funding of vaccine research from agencies dedicated to peacekeeping activities, such as the United Nations (UN).

- We should proactively campaign for scientific education that could avoid a society of charlatans denying scientific successes and asserting the danger of vaccines as anti-natural tools that are created only to generate profits at any cost. An appropriate media campaign should be launched by public-health agencies to educate the public on the safety of synthetic biology, the value of vaccines, and the concept of disease prevention rather than treatment

- Consider vaccines as the most solid helmet one can wear that will protect us from collision with infectious microorganisms throughout our fast lives. Finally, ask whether you would ever recommend driving a motorbike without a helmet.

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*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP) June 5–8, 2011, at the Estancia La Jolla Hotel, San Diego, California.*

**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. Sergio Abrignani (see above). Dr. Abrignani 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. Abrignani. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Abrignani, 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

- Vaccines are a cost-effective method of disease prevention, yet children around the world still frequently die from vaccine-preventable diseases. Barriers to vaccine coverage are complex and, in general, are often different in less-wealthy regions (e.g., economic barriers to distribution and theories of conspiracy by the West) than in more-wealthy regions (e.g., anti-vaccine sentiments and low perceived risks of disease due to herd immunity).

- Strategies to promote vaccine uptake must be developed and improved. Such efforts should include messaging which strives to achieve a social consensus that all eligible individuals must be vaccinated. International sharing of best practices and lessons learned in the area of risk communication related to vaccines must also be encouraged. Efforts outside of the realm of messaging also need to be further researched and considered for implementation (e.g., penalties and mandates). Social scientists, such as communication experts, should be included in this work.

- Leadership is needed to develop a consistent, single statement of strong commitment for universal immunization — vaccinating all eligible individuals with all existing vaccines. To obtain a mutually supportive "one voice" for vaccine use, all the stakeholders, including scientists, physicians, academics, societal leaders, and governmental policy makers, must have access to detailed, credible information about logistics, feasibility, and benefits of a universal vaccine coverage effort.

- National and international leaders should consider the value of universal vaccination as an issue related directly to security and social stability. The use of vaccines may also have a role to play in foreign policy and national security.

- Synthetic biology, a relatively new area of biological research, is changing the way that vaccines are designed and manufactured, allowing for the more-rapid and lower-cost

production of vaccines. For scientists and policy makers to accurately discuss credible options and to collectively create effective policies related to synthetic biology, the development of a clear and coherent definition of synthetic biology is necessary.

- Passive immunization using monoclonal antibodies, particularly after an outbreak, is not currently a viable alternative to active immunization due to considerable challenges including logistics, clinical trial problems, storage and shipping issues, and high cost. From a military perspective, ensuring a state of readiness for troops via active immunization is preferable to employing passive immunization after a bioterrorist event.

**Current realities**

There was consensus that vaccines can and do effectively prevent infections; they have saved many lives and have the potential to save many more. In addition to their high degree of efficacy, it was generally agreed that vaccines are a cost-effective method of disease prevention. However, children around the world still frequently die from vaccine-preventable diseases because the appropriate vaccines either are not available or not taken.

Although there was general agreement that the use of vaccines should be promoted, it was also recognized that immunizations are often thought of as a privilege and not a right. This distinction is not new and has been previously demonstrated in other social areas. Formal education, for example, used to be a privilege only available to a select few. Now, education is often viewed as a right. In some countries, not only is education mandatory, school nonattendance is a crime.

Individuals, regardless of their intelligence or educational status, often do not base their decisions on rational risk assessment. The reluctance to take available vaccines can often be attributed to an unconfirmed fear of the potential negative consequences. A "negativity bias" frequently causes people to focus on dangers rather than benefits. When individuals perceive a situation as out of their control, they often make decisions that may appear to be irrational, such as ignoring public health recommendations related to vaccination.

Synthetic biology was recognized as a relatively new area of biological research that is changing the way that vaccines are designed and manufactured by reshaping development and production factors such as speed of development, availability, and cost. For example, it was noted that synthetic biology has enabled scientists to create a wide range of new antigens. Synthetic biology has enabled more rapid production of vaccines at lower cost, which was generally perceived as a significant benefit, especially for resource-poor countries.

The differences between passive and active immunization were discussed. Passive immunization was explained as the administration of *in vitro* produced antibodies or *in vitro* primed immune cells. Both can recognize a specific antigen (i.e., a toxin or other foreign substance that induces an immune response) within the body of a non-immune individual. Passive immunization provides only temporary immunity, meaning it must be frequently repeated, but passive immunization is useful because protection is immediate. Active immunization was defined as the administration of antigens, which then causes the body to create its own antibodies. Because the body produces its own antibodies, protection against disease may last anywhere from several years to a lifetime. However, active immunization is not useful in all scenarios (e.g., bioterrorist attacks) because it may take several weeks for protection to take effect.

It was noted that mandates concerning the use of vaccines vary by country, as well as within countries (e.g., vaccine mandates in the United States are a state issue). Mandates have also changed over time in some countries (e.g., in Japan, vaccination is no longer compulsory) due to political and legal factors.

**Scientific opportunities and challenges**

The debate emphasized the significant and complex barriers to vaccine uptake by the public. The lack of a single global voice among scientists, physicians, policy makers, and other interested groups was cited as a key obstacle to the public's view of universal vaccination worldwide. It was also highlighted that barriers to vaccine uptake in less-wealthy regions are different than barriers in more-wealthy parts of the world. While it was suggested that economic factors comprise the principal barrier to vaccine coverage in less-wealthy areas, it was also proposed that non-economic issues can be equally problematic. For example, conspiracy theories, such as polio vaccines from wealthier countries purposely containing anti-fertility agents, have led to low polio vaccine uptake within certain countries during the past decade. In addition, attention was drawn to social, behavioral, and logistical factors as noneconomic barriers to influenza vaccine uptake in less-wealthy regions. In more-wealthy countries, the anti-vaccine movement, based on unconfirmed fears of acquiring secondary diseases, was identified as a major barrier to vaccine uptake. However, other issues were also identified. During the H1N1 influenza pandemic, for example, anti-vaccine groups played only a minor role in vaccine refusal. More influential factors, including risk perception and decision-making theory, were cited as determinants of noncompliance with H1N1 vaccination recommendations. It was also noted that many parents believe herd immunity will protect their children, even if they are unvaccinated.

Negative side effects from vaccination are generally infrequent (e.g., severe measles vaccine side effects are rare, but have been observed), yet the public's perceived risk of side effects was considered a significant barrier to vaccine uptake. When adverse effects do occur among a small group, it can quickly heighten public concern and escalate rates of vaccination refusal — thereby driving up disease incidence. It was suggested that scientists and policy makers must acknowledge that the decision to vaccinate children can be a difficult one for many parents. Overcoming parents' perceptions and concerns about their children's health will likely be a continuing challenge, but one that must be effectively addressed.

There was considerable discussion regarding the definition of synthetic biology. It was pointed out that a simple Google search reveals multiple definitions, and that even experts do not have a universally agreed-upon definition. Although there was no consensus, a proposed definition was, "the science that is producing life." It was further purported that the definition of synthetic biology varies depending on the context of the discussion, since it is comprised of multiple components. One component of synthetic biology, for example, is the manipulation of DNA (or genomes) to make new organisms; another is using biologic parts to perform specific functions. It was also noted that the term systems biology is sometimes used interchangeably with synthetic biology. It was contended that from a policy maker's perspective, it is important to have a clear and coherent definition based on well-defined scientific terms.

Scientists are beginning to achieve new successes in vaccine research due in part to advances made through synthetic biology. As technology has evolved, opportunities to develop vaccines that produce correlative, or sterilizing, immunity (i.e., completely prevent an infection in addition to preventing clinical disease) have expanded. Yet, this type of vaccine is still not possible for many diseases. For example, in recent years, research has focused on vaccines that produce

sterilizing immunity for human immunodeficiency virus (HIV), but such research has not been successful. It was pointed out that some diseases do not, nor ever will, have a "helmet." Some will only have "brakes."

Some research has shown a statistical association between higher vaccine coverage and lower rates of armed conflict in a country. Such findings were used to justify support for promoting vaccines for the purpose of aiding peacekeeping efforts. However, significant questions were raised regarding whether the statistical relationship reflects a true association or is actually the result of other, confounding factors.

**Policy issues**

There was general consensus that a single statement of strong commitment for universal immunization (i.e., vaccinating all eligible individuals with all existing vaccines) is essential — one voice among scientists, physicians, academics, societal organizations, governments, and policy makers. Questions were raised about who would lead such an effort to speak in a single voice. Specifically, the UN was identified as a potential vehicle. However, it was pointed out that the UN may not be an appropriate organization to take the leadership role primarily because it does not conduct vaccine research.

To commit to the idea of one voice, it was argued that policy makers will need more detailed information, including how many vaccines are involved, the logistics of vaccine distribution, the feasibility of a universal coverage effort, and the benefit-risk profile of vaccines. It was urged that additional information and research in these areas be developed to provide policy makers with a clear, positive way forward.

Concern was expressed that public trust could be damaged if problems arose as a result of a universal vaccination promotion effort. It was concluded, however, that published data strongly indicate that the benefits of moving forward outweigh the risks. While some also asserted that a forceful, unified statement about universal vaccination should be made regardless of the availability of funds, others countered that conversations about logistical factors (e.g., how to pay for the effort) should be the first step in the process.

The possibility of using mandates and penalties to boost wider vaccine coverage was debated. It was suggested that instead of making vaccinations compulsory, penalties might be more effective (e.g., prohibiting unvaccinated children from attending public school). However, the feasibility of penalties was questioned and there was disagreement over the effectiveness of such approaches. It was argued that coercive strategies are often counterproductive.

The importance of messaging to promote vaccine uptake was widely expressed. It was agreed that current dialogues with the public about the importance of vaccination are frequently ineffective. There was consensus that messaging or marketing efforts should strive to achieve a social consensus that all eligible individuals must be vaccinated. Such messages need to be articulated in terms that are meaningful to the lay public.

It was generally agreed that the scientific community and policy makers should include social scientists (including communication experts) in efforts to promote the acceptability of vaccines. When moving from the basic science to implementation, the point was raised that researchers who understand the uptake of ideas, namely social scientists, are necessary.

It was suggested that there should be more international sharing of best practices and lessons learned in the area of risk communication related to vaccines. The importance of building on existing success stories was highlighted (e.g., how many lives were saved due to vaccination).

Recent influenza vaccine promotion exemplified a successful messaging effort. Due primarily to H1N1 messaging in the previous year, influenza season vaccination coverage of U.S. children reached its peak in 2010–2011. A suggestion was also made that communication should emphasize the return on investment of vaccines, since numbers often resonate with people. In terms of lessons, learning from failed public health efforts was endorsed. For example, it was purported that the repeal of the motorcycle helmet law in one Virginia county resulted from the framing of helmet use as a personal liberty instead of underscoring societal health implications (e.g., health care costs). It was argued that this scenario demonstrates the importance of exercising caution when developing vaccine and other public health messages.

The importance of communication was not disputed. However, it was argued that education alone may not be sufficient for increasing vaccine compliance. People are typically not good at making risk/benefit assessments, because of the tendency to focus on fear of the unknown and anything that is uncontrollable. It was therefore suggested that other strategies should also be developed.

It was advised that instead of likening the risk of not being vaccinated to riding a motorbike without a helmet, a more appropriate analogy would compare it to driving a Lamborghini without a seatbelt. While there is a small risk associated with wearing a seatbelt, it is still recommended that drivers and passengers wear them.

Based on research linking higher national vaccination rates to lower prevalence of armed conflict, it was recommended that vaccinations should be seen as a defense issue and part of a peacekeeping effort. While it was proposed that an international body (e.g., the UN or the Group of Eight [G-8]) should be convinced to view vaccines as an instrument of foreign policy, it was strongly counterargued that this proposal requires further substantiation based on experience.

There was consensus that vaccination should be viewed as a national priority by governments. Many also argued that vaccination should be considered a defense issue. The point was raised that the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), one of the most successful and well-funded programs, was only brought to action when HIV/AIDS was made a U.S. security issue. This sentiment, however, was not unanimous. In terms of implementation, there was an appeal for using non-security apparatuses (in contrast to national security forces) to achieve vaccination goals.

There was general consensus that universal immunization is important. However, this dominant viewpoint was disputed by an assertion that expanding other public health efforts (e.g., clean water and sanitation) may be a more effective strategy for preventing infectious diseases than increasing vaccination rates. It was argued that because vaccination campaigns have not always been completely successful (e.g., for polio), disease prevention may be better achieved and a greater return on investment maintained through the development of clean water and sanitation systems. This assertion was vigorously debated and much dissent was expressed. It was counterargued that clean water provision is not a fail-safe solution — in the 1950s, more-wealthy countries experienced high levels of morbidity and mortality from polio despite the presence of clean water. The prevailing view was that vaccines and other preventive public health measures are both essential, and therefore should not be considered mutually exclusive.

Because limited funds are available for vaccination efforts, resources must be prioritized. The relative merits of allocating funding for passive versus active immunization were extensively debated. It was proposed that governments should redirect spending to a passive immunization strategy. This view was based on the assertion that passive and active immunization could be equally effective, and for some diseases passive immunization may be more effective. It was further contended that diseases for bioterrorist attacks (e.g., anthrax) should be prevented via

passive immunization because active immunization is generally ineffective post-exposure. However, there was no general agreement on this point. It was counter-argued that passive immunization using monoclonal antibodies, particularly after an outbreak, is not a viable alternative due to considerable challenges including logistics, clinical trial problems, storage and shipping issues, and high cost. Moreover, from a military perspective, it was argued that ensuring a state of readiness for troops via active immunization is preferable to employing passive immunization after a bioterrorist event.

There was disagreement regarding the efficacy of wealthier countries donating vaccines to less-wealthy countries versus helping less-wealthy countries set up the requisite technology for developing their own vaccines. It was pointed out that successful efforts currently exist to help less-wealthy countries develop their own vaccine production (e.g., by the U.S. Department of Health and Human Services' Biomedical Advanced Research and Development Authority [BARDA] and the World Health Organization [WHO]). Additionally, some less-wealthy countries, such as India, are already moving rapidly to produce their own vaccines. It was argued, however, that while sponsoring the building of production plants may be an appropriate strategy in countries such as India and China, technical and infrastructural difficulties may hinder similar efforts elsewhere.

# Synthetic Biology and Infectious Disease: Challenges and Opportunities**

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**Summary**

The tools of molecular biology (e.g., genetic engineering or synthetic biology) have advanced to the point where it is possible to synthesize the genomes of viruses and small organisms without nuclei (prokaryotes) *de novo*, and to carry out significant modifications of the genomes of larger microbes and higher organisms with nuclei (eukaryotes). There is also a potential to create novel organisms that have an origin largely independent of evolution. Our ability to predict the properties that genes, both new and old, will confer on organisms is incomplete. As a result, our understanding of how novel organisms will behave is to some extent unknown. The potential hazards associated with engineering organisms are inherently different from those of other fields because the agents involved have the potential to spread from small numbers, to proliferate outside of human control, and to evolve. These points notwithstanding, synthetic biology offers enormous opportunities to better human life, including preventing infectious disease. However, these same tools also offer opportunities for disease creation either by chance or as forms of economic sabotage or terrorism. The ability of engineered organisms to reproduce and to cross international borders, with potential effects on the environment and human health far from their site of origin, creates a unique set of scientific and regulatory issues that are just beginning to be considered. Research, regulation, and education are needed to promote beneficial uses of this technology in a responsible manner that limits opportunities for harm through ignorance, sloppiness, or design.

**Current realities**

It is now possible to synthesize large DNA molecules at low cost. These and other costs associated with genome engineering will continue to decrease, allowing us to rapidly determine the sequences of pathogens or potential pathogens, and to modify and create templates for entire organisms at will. Genome sequences, including those of known pathogens, are made available through publications and have been used to synthesize the genomes of known pathogens (e.g., 1918 influenza and polio). These synthetic genomes give rise to infectious viruses when introduced into cells, illustrating how information plus reagents can be used to create an infectious agent. The sophisticated genome manipulation and cell culture involved in bringing these pieces of DNA to life currently require a large amount of tacit knowledge, acquired through extended training in academic or industrial settings. However, there is a new community of individuals (the do-it-yourselfers) who conduct genetic engineering in private settings. This community will grow as costs decline and kits become available, making it easier for those with less specialized knowledge and funding to carry out sophisticated manipulations. A parallel increase in our ability to rapidly and cheaply sequence DNA provides a critical method for identifying known or unknown infectious diseases of plants, animals, and humans.

Synthetic biology is used to prevent infectious disease in many ways. First, engineered organisms are used as bioreactors to produce drugs or vaccines. In addition, disease agents that are identified via sequencing and direct isolation are synthesized and/or manipulated through genetic engineering to identify genes needed for essential pathogen functions such as entry, replication, and evasion of the immune system. It is important to note that, as part of this work, viruses have been created that were unexpectedly more harmful than the original virus, highlighting the potential for the creation of organisms with novel properties. Finally, synthetic biology is being used to engineer populations of disease vectors (e.g., mosquitoes), to make them unable to transmit disease or to bring about a vector population reduction, in either case

preventing disease transmission. Genes that prevent mosquitoes from transmitting disease have been identified or created, and genetic tricks for promoting the spread of these genes in wild mosquito populations are under development in the lab, but have not been tested in the field.

In the United States, synthetic biology is regulated through multiple federal agencies. DNA synthesis companies currently screen sequences for similarity to the genomes of known pathogens and the toxins they encode. When sequences of potential concern are identified, these companies also screen customers to confirm their identities, and ensure that customers have a legitimate use for the DNA and have considered safety/biosecurity issues. These actions are voluntary and subject to different levels of scrutiny depending on the company. The purchase of DNA synthesis machines themselves is not subject to regulation or monitoring. Transborder movements of genetically modified (GM) organisms are regulated through national and international mechanisms. Much of this is piecemeal, with different agencies involved depending on the organism. A number of countries, including the U.S., are not party to the Cartegena Protocol on Biosafety, an international agreement that regulates transboundary movement of GM organisms, and which would serve as an obvious framework within which to regulate the movement of other GM organisms. There is no clear, public resource that details regulations governing modified organisms or that outlines the principles and practices of risk analysis as they apply to different kinds of GM organisms.

**Scientific challenges and opportunities**

Dangers to human health from genetically modified or purely synthetic organisms are largely hypothetical. That said, it is important that rules be identified which can be used to predict the potential of an organism to spread and cause disease. Within this work, the synthesis of pathogens is challenging and controversial. While it involves altering known pathogens to make them less able to cause disease, it also mandates that we work to create novel potential disease agents as a way of understanding what the minimal requirements are to make an organism a pathogen. It is also important to study the evolution of engineered organisms. What are the forces that act to change these organisms over generations? How do these forces act on the genes we introduce to maintain, alter, or eliminate function? In a related vein, we must identify methods for engineering organisms that have built-in fail-safe devices that can limit their ability to survive and proliferate outside the relevant environment. It is particularly important to identify methods for making an organism's survival and/or proliferation dependent on laboratory reagents not found in the wild. Such technology, if incorporated into the design of engineered or purely synthetic organisms, would alleviate concerns about the chance creation of pathogens, though it would not prevent their deliberate creation.

Similar considerations apply when the goal is to alter a wild disease-vector population. We need to continue developing methods for spreading genes that prevent disease transmission into wild populations. We also need to identify genetic methods that will: (i) contain the spread of these genes within regions that support the use of genetically engineered organisms for disease prevention, and (ii) allow for elimination of transgenes from the wild, if necessary.

**Policy issues**

- Develop funding mechanisms through the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the World Health Organization (WHO) that promote the identification, synthesis, and study of new and emerging pathogens, and the deposition of information relating to these pathogens in open databases. Private-sector funding is unlikely to be significant given the general lack of

perceived commercial opportunities. Promote the internationalization of this effort through WHO so that expertise in sampling and analysis is developed locally.

- Develop a harmonized, international regulatory structure that requires monitoring of all DNA synthesis orders for human, animal, and plant pathogens or toxins, as well as for customer identity. Information should be saved indefinitely. Sale of other technologies, including DNA synthesizers, sequencers, cell culture equipment, and bioreactors, should also be monitored because of their dual-use capability. In the U.S., the FBI is the lead agency in investigations of possible terrorist threats, including biological weapons.

- Given the specialized nature of the data being examined, a tiered system is needed. Agencies with greater expertise in biology (e.g., the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), CDC, and NIH) should coordinate archiving and analysis of sequences and consumer information from synthesis companies. It is more appropriate for only problematic cases to be referred to the FBI and international counterparts.

- At the international level, the International Health Regulations (IHR) structure should be used to mandate screening for pathogens and possible toxins. Other parties, such as the Food and Agricultural Organization (FAO) and the World Organisation for Animal Health (OIE) should take the lead in screening for agents that may damage the environment and/or plant and animal health. A mandate that synthesis orders be screened and archived for all customers will be challenging to implement since some orders will involve intellectual property; however, if an event occurs, it will be important to have all sequences immediately available to facilitate rapid identification of the pathogen and its creators.

- Develop regulatory guidelines that apply to all parties engaged in genetic engineering of organisms, regardless of funding source. This will require that those carrying out this work become licensed (e.g., requirements for driving, flying, amateur radio, or gun ownership) through training that serves to ensure minimal competency and acquaintance with relevant regulations and sanctions. These guidelines should be based, in part, on those for NIH-funded work, with input from federal agencies (e.g., the U.S. Department of Agriculture (USDA) and its Animal and Plant Health Inspection Service (APHIS), EPA, and FDA) and international organizations (e.g., WHO, FAO, and OIE). These guidelines should specifically address issues related to the potential consequences of release of engineered organisms into the environment. These guidelines should be regularly revisited and updated as new information comes in and risks are identified.

- Regulatory guidelines should be linked to a public clearinghouse that provides descriptions of regulations, contact information, and flow charts that detail paths through the regulatory process. This clearinghouse should also contain descriptions of risk analysis as applied to particular classes of agents, and be updated with information on potential or likely harms associated with genetic engineering using particular organisms and/or parts. It should also provide, or be linked to, unbiased information on the state of genetic engineering technology and regulatory oversight.

- Work with other countries (perhaps through WHO, FAO, OIE) to craft similar regulations and outreach programs. For GM vectors of disease, work with countries with significant levels of vector-borne diseases to create a regulatory structure that promotes the possible use of these tools to enhance human health while minimizing risk and respecting divergent views on the acceptability of GM organisms. These regulatory

structures should be separate from those — such as the Cartagena Protocol — designed around GM crops, because they may not be applicable to all GM organisms.

*** A policy position paper prepared for presentation at the conference on Emerging and Persistent Infectious Diseases (EPID): Focus on Prevention convened by the Institute on Science for Global Policy (ISGP), June 5–8, 2011, at the Estancia La Jolla Hotel, La Jolla, California.*

**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. Bruce Hay (see above). Dr. Hay 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. Hay. Given the not-for-attribution format of the debate, the views comprising this summary do not necessarily represent the views of Dr. Hay, 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**

- Rapid technological advances in the field of synthetic biology (e.g., developments in recombinant DNA technology and genomics) have led to many new discoveries applicable to the prevention and control of infectious diseases. Technological progress and decreased costs have facilitated a substantial increase in the number of amateur scientists, known as "do-it-yourselfers" (DIYers), who design, redesign, and fabricate biological components and systems. Although DIY scientists have made and will continue to make critical discoveries in the field, it is important that this community adheres to the same regulations and receives the same training as professional scientists.

- Because synthetic biology utilizes living organisms that can replicate on their own and evolve, it is critical for potential risks to be identified and addressed. Deliberate or accidental harm to humans (i.e., stemming from bioerror or the unpredicted evolution of designed organisms) may be caused by the engineering or re-engineering of organisms. The potential for harm must be limited through improved biosafety measures, including expanded regulation (mandatory and/or voluntary), as well as training in areas of biosafety, biosecurity, codes of conduct, and ethics.

- While intentional harm (e.g., caused by "lone rangers," rogue DIYers, or coordinated bioterrorists) is a significant concern, it is impossible to entirely eliminate this risk. Mandatory regulations (e.g., licensure requirements and the creation of a centralized intelligence database) will, to some degree, decrease the likelihood of successful illicit conduct, but there will always be ways for individuals to work around such rules. Mandatory regulations are accordingly better for tracing negative events to their source after the fact. Self-regulation should accordingly be employed in concert with mandatory regulation to promote positive practices and to increase the relaying of intelligence knowledge from scientists themselves to law enforcement. Given concerns that over-regulation will stifle innovation, a balance between mandatory and voluntary regulation is needed.

- Training of both professional and DIY scientists currently takes place. In the United States, this is exemplified by the training courses offered and promoted by the Federal Bureau of Investigation (FBI). However, there is a lack of awareness of existing training opportunities among both groups of synthetic biologists. Awareness of existing training programs must be raised through expanded outreach efforts. Additionally, increased training programs are needed.

**Current realities**

In the last decade, there have been significant scientific advances in the burgeoning field of synthetic biology (i.e., in sequencing and manipulating DNA in existing and simple organisms to create novel organisms). It was recognized that such developments have been produced both by highly trained scientists (primarily micro- and molecular biologists) within established academic and private institutions and by DIY scientists. While conventional scientists conduct synthetic biology research in highly supervised, well-resourced laboratories, DIYers commonly conduct their research in makeshift, unsupervised labs set up in kitchens, garages, and small storefronts. Additionally, DIYers do not typically have the same formal training as their conventional counterparts. The emergence of the DIY synthetic biology community has been accelerated by its members' ability to access equipment and materials at affordable costs (e.g., by purchasing secondhand DNA sequencers, synthesizers, or construct incubators online or at garage sales), as well as the online availability of genetic code and sequence data. It was noted that some DIYers will evolve to become registered commercial entities, but others will remain under the radar and avoid corporate registration and legal business formalities.

Advances in synthetic biology have been used for health promotion efforts, including infectious disease prevention, treatment, and control. While much enthusiasm was expressed for the positive discoveries that synthetic biology could produce for health, it was strongly emphasized that there are potentially dangerous elements associated with research in this area. Technologies that have both beneficial and potentially harmful applications are known as "dual use" technologies. There was substantial discussion of individuals whose goals are to use synthetic biology for nefarious purposes. It was noted that these individuals fall into three primary groups: (i) lone rangers who are highly trained biologists, work in established labs, and pose an insider threat, (ii) a handful of rogue DIYers, and (iii) coordinated bioterrorists who work in groups and possess varying degrees of formal training.

Some of the individuals who aim to cause harm may simply be testing the system to see what boundaries they can cross (both legally and scientifically), while others may intend to genetically engineer agents for harmful purposes. One way that synthetic biology could be exploited would be to recreate known pathogens in a lab to circumvent the legal and physical controls that currently limit access to select agents (i.e., agents flagged by the U.S. government as posing a biological risk). Yet, it was also noted that because synthetic biology is an intellectually difficult enterprise, the threat of bioterrorist activities is partially mitigated by the fact that it would be challenging for even the most highly skilled scientists to produce in large quantities and spread the engineered organisms that can cause damage to humans.

It was contended that since the inception of bioengineering in the 1970s, there have been no significant, adverse human events related to the release of genetically modified organisms (GMOs). Although adverse events have not been identified, a large portion of the debate focused on the increased potential for intentional or unintentional harm. Intentional harm was primarily discussed in terms of potential terrorist activities. It was suggested that since much of the genomic data are stored in digital form, and genomic synthesis is now computer driven, the potential for individual- and country-level illicit activity has significantly increased. Terrorists, it

was noted, also have access to much of the same information for gene synthesis as established scientists (e.g., from scientific articles and in publicly available Web sites such as PubMed). However, concerns related to potential harm that could be caused by legitimate synthetic biology-related activities were also expressed. For example, it was questioned what would happen if the deliberate release of genetically modified mosquitoes (for malaria prevention) has unexpected negative side effects. It was argued that credible synthetic biologists should always build fail-safe measures into their work so that it is possible to reverse any new organisms that have been released.

In addition to biosecurity, biosafety (i.e., the safe transfer, handling, and use of any living modified organism) was highlighted as a major concern. It was noted that biosafety efforts related to synthetic biology are globally diverse. Although some countries have implemented national regulations and monitoring efforts (e.g., lab inspections) for work related to GMOs, there is a lack of uniformity in their regulatory approaches (e.g., mandatory regulations that apply to both professional and amateur scientists, mandatory regulations that apply only to professional scientists, and/or voluntary regulations). There was no agreement on which method is most effective. Proponents of a mandatory approach cited a need for improved oversight, while advocates for a voluntary approach argued that laws would need to change too frequently to be useful for this rapidly evolving technology.

Although mandatory and voluntary regulatory efforts do exist, there was general agreement that many researchers, as well as some government agencies, are not aware of these initiatives. To illustrate this point, it was contended that 85% of researchers are not familiar with the U.S. National Science Advisory Board for Biosecurity (NSABB). The NSABB is charged with speaking on behalf of and guiding scientific researchers on biosecurity issues. Also of note, data are currently collected and screened in the context of commercial trade of manufactured genomic sequence building blocks. The data include the contents of purchase orders, as well as the identity of sellers and purchasers (i.e., the individuals, academic institutions, and private companies procuring genomic information). Yet, there was a general lack of understanding as to who currently collects the data and how they are subsequently used to investigate potential terrorist threats.

It was noted that most existing data collection and screening efforts are based on self-regulation in the field, are voluntary, and solely focus on select agents or parts of select agents. Several international consortia, composed of research and commercial biotech companies, have been organized to address bioethics, biosafety, and security concerns associated with synthetic biology and develop best practices and codes of conduct. Specifically, the Germany-based International Association Synthetic Biology (IASB) and the U.S.-based International Gene Synthesis Consortium (IGSC) address issues related to the creation of databases to assess the validity of clients, recordkeeping of purchasers for tracking purposes, and the development of contacts with law enforcement.

Using examples and hypothetical situations, the debate clarified the procedures used by U.S. law enforcement for monitoring, investigating, and prosecuting the potentially illicit purchase and use of biological material. The process combines voluntary measures with governmental oversight. U.S. companies are expected to contact their local FBI Weapons of Mass Destruction (WMD) coordinator if they receive suspicious orders (e.g., neurotoxin genes from a dubious point of origin) from other companies or individuals based in the U.S. The case may also be referred to the U.S. Department of Commerce. Questionable requests from a suspicious country and threats on the control list are referred to the U.S. Department of Commerce. Other relevant agencies (e.g., Centers for Disease Control and Prevention [CDC] and U.S. Food and Drug Administration [FDA]) may also be consulted to provide an assessment. If the assessment determines that a pathogen or biological agent is on the “select agents” control list, the Department of State may be brought in to investigate the case. Concern

was expressed that this process may cost businesses time and money. However, it was pointed out that the FBI has an expedited process for legitimate orders (i.e., they can clear the order by next business day). If everything meets the requirements, the individuals are informed of necessary import/export documentation.

In addition to providing oversight, it was highlighted that the FBI is heavily engaged in training activities within the synthetic biology community. The FBI provides training to scientists within academia, the private sector, and the DIY communities to explain the laws and regulations that govern synthetic biology practice, provide education on performing research safely and securely, and identify opportunities for improving biosecurity by working with stakeholders to determine risks.

**Scientific opportunities and challenges**

There was general consensus that the scientific advances in DNA sequencing and manipulation of existing organisms that have transpired during the past decade have created new opportunities for health promotion by allowing agents to be created much more easily than in the past. Such advances have not only enhanced the synthetic biology research opportunities for professional scientists, but have also facilitated the growth of ideas generated within the DIY scientific community. Recognition of DIYers as accepted players in the field is rapidly growing. However, it was also noted that the disparate training and oversight levels among these amateur researchers have intensified the need for a balance between safety and scientific discovery within synthetic biology.

Global protection against the malicious use of DNA sequences (e.g., bioterrorism and experiments by “mad geniuses”) was recognized as a significant challenge during the debate. It was argued that laws and regulations are imperfect solutions because individuals with harmful intentions may either completely disregard such rules or work around them (e.g., employing genetic elements that are not on the select agents lists). It was also noted that it is often difficult for the intelligence community to identify groups such as lone rangers, rogue DIYers, and coordinated terrorists. Detecting lone rangers is problematic because they frequently work under the auspices of credible research in established universities or institutions. As such, they have the ability to purchase dual-use equipment and other materials through unsuspected channels. DIYers, on the other hand, pose a challenge because they often work in isolation. Both DIYers and coordinated terrorists conduct their research without oversight from universities or corporations.

It was contended that it is also extremely difficult to protect against potential biological mistakes that endanger public health and human safety (i.e., bioerror). Such unintentional harm could be caused by the *accidental* release of genetically-engineered plant, animal, or human organisms. Inadvertent damage may also result from the *purposeful* release of freely reproducing, novel modified organisms when unforeseen (or even unimaginable) outcomes occur. Although few major bioerror problems have been reported to date, it was argued that minimizing risk through improved biosafety mechanisms will be of critical importance.

It was proposed that a centralized intelligence database should be created to catalog the purchase and sale of genetic material at national and international levels. The primary purpose of such a database would be to protect against individuals who intend to produce modified organisms for intentional harm. However, numerous obstacles and prerequisites to the success of such a database were outlined during the debate: (i) it would be challenging to keep a centralized database up to date, especially in real time; (ii) currently, formal channels to collect data on non-select agents do not exist and cunning individuals who intend to cause harm may try to stay under the radar by genetically engineering non-select agents; (iii) if data on non-

select agents were included in such a database, the size of the database might make it too difficult to detect red flags (it was also argued that the size of the database does not matter and therefore there was no agreement on this point); (iv) intelligence databases may be able to more accurately trace the chain of events leading to a realized event than they can predict insider threats or other bioterrorist activities, and thus, the end-goal of a database should be clarified from the outset; and (v) it would be imperative for such a database to be screened on a regular basis by an agency assigned this responsibility. These issues must be reconciled before efforts to create a centralized intelligence database can move forward.

There was general agreement that regulating synthetic biology without stifling innovation is a tremendously difficult task. Different viewpoints on the intersection of regulation and scientific discovery were expressed. Some argued that loosening mandatory regulatory controls (e.g., fewer limitations on select agents) would help ensure that opportunities for biological advancement are not overly constrained. Proponents of limiting the scope and number of formal mandates contended that increased self-regulation should be encouraged instead. Conversely, those in favor of formal oversight maintained that conducting synthetic biology research is a privilege and not a right. They further asserted that compulsory regulations related to licensure and continuing educational credentialing would not counter innovation and that there are successful models (e.g., Australia) that can be emulated.

**Policy issues**

A large part of the discussion centered on the need to limit intentional or unintentional harm that may be caused by the design/redesign and construction of biological parts, devices, and systems through synthetic biology. There was general agreement that enhanced training of professional scientists and DIYers engaging in synthetic biology is necessary. It was asserted that training is essential for laws to be effective. There is currently a lack of clarity concerning legal demarcations in what activities are permissible within synthetic biology research, as well as in the proper protocols that must be followed. Moreover, it was contended that training also benefits self-regulation by teaching professional and DIY scientists how to deter bioterrorist activities. Specifically, it was suggested that education, training, and outreach are needed in the areas of biosafety, biosecurity, codes of conduct, and ethical aspects of genetic engineering. It was cautioned, however, that training programs will need to be regularly updated because of the rapid evolution of synthetic biology technologies and regulations.

It was asserted that, in the U.S., training is already being conducted: The FBI plays a large role in training efforts aimed at both the professional and DIY synthetic biology communities. It was generally agreed, however, that many scientists are not aware of existing training. Although it was noted that the FBI has made a concerted effort to raise awareness of its training programs (e.g., via outreach at the International Genetically Engineered Machine (iGEM) competition), it was strongly recommended that additional outreach and advertising is needed by all agencies conducting training.

It was suggested that solutions for addressing potential harm caused by the misuse of synthetic biology also need to take into account the possibility of insider threat (i.e., professional scientists in academic institutions or private companies who aim to use synthetic biology for injurious purposes). It was generally agreed that there is no fail-safe solution to insider threat, and that zero risk is impossible to achieve. For example, proposed solutions, such as a central intelligence database, were believed to be unable to ensure the detection of insider threats before the execution of a harmful event. However, despite limitations to insider threat prevention, certain activities should nevertheless be performed. In particular, promotion of self-governance and the existence of codes of conduct were stressed as areas where improvements are needed. This form of threat should be countered by intelligence activities, such as

interviews by FBI agents, who are heavily engaged in averting insider threats and engaged in surveillance oversight and biosecurity outreach to specifically address this issue (e.g., ethics training and scientist education on how to identify and report suspected insider threats).

It was proposed that governments should implement knowledge-based licensing of all scientists who genetically manipulate organisms that could accidentally or purposefully be released. Synthetic biology licensing should be akin to other forms of professional licensing (e.g., medicine and law) or operational licenses (e.g. motor vehicles) and only licensed individuals could obtain reagents to conduct their work. To further induce licensure, it was suggested that patent offices could be advised to recognize only the ideas of those who are licensed. Synthetic biology licensing could be carried out by the government, professional associations (e.g., American Medical Association), or through community self-regulation. The development of acceptable licensing standards would facilitate the work of law enforcement, and accordingly, threat prevention. There was no agreement, however, over whether such licensing is necessary, and some argued that it could be counterproductive.

It was suggested that over-regulation may stifle innovation. Some questioned why those engaging in synthetic biology activities should be singled out for restrictive regulations (e.g., licensing or mandates to register in a database). Other fields, such as computer programming, may also pose significant threats to individuals and societies (e.g., via computer hacking). It was counter argued, however, that because this unique aspect of biology deals with living organisms that can replicate on their own and evolve, it constitutes a special case and necessitates such measures.

Although it was stated that the regulation of synthetic biology is a subject of recent concern, it was countered that the Organization of Economic Cooperation and Development (OECD) has been engaged in efforts to regulate genetically modified foods since 1985. Furthermore, it was noted that the Cartagena Protocol on Biosafety is an existing international agreement that is focused on addressing the risks posed by genetically modified organisms. Approximately 30 countries have not ratified the Cartagena Protocol, including the U.S. It was accordingly questioned why the U.S. is unwilling to become a party to the Protocol as a policy-level solution to some of these regulatory issues. There was agreement that trade implications are the reason that the U.S has yet to ratify the Cartagena Protocol, which therefore is unlikely to be a realistic policy solution.

## Biographical information of scientific presenters

**Dr. Sergio Abrignani, M.D., Ph.D.**

Dr. Sergio Abrignani is the Chief Scientific Officer of the National Institute of Molecular Genetics in Milan, Italy, and is Professor of Immunology of the Gastrointestinal Tract at the University of Siena School of Medicine. Previously he was Vice President for Immunology and Infectious Diseases Research at Chiron Corp. (Emeryville, CA, U.S.), headed the Immunology and Virology Research Unit at Chiron Vaccines (Siena, Italy), and headed a lab in the Immunology and Inflammation Unit at the Ciba-Grigny Research Centre (Basel, Switzerland). Dr. Abrignani's research interests have focused chiefly on cellular interactions among immune cells and on the effects of viral infections (mainly hepatitis C [HCV]) on the immune system. The major scientific achievements of his research activities have been the identification of the HCV receptor on human cells and the development of a HCV vaccine that currently is in clinical development. In 2004, Dr. Abrignani received the Public Health Gold Medal of Merit for his studies on HCV. He is also affiliated with the European Society of Virology, the Henry Kunkel Society of New York, the American Association for the Study of Liver Diseases, and the Italian Society of Immunology, among other organizations.

**Dr. Robert Buchanan, Ph.D., M.Phil., M.S.**

Dr. Robert Buchanan is Professor and Director of the Center for Food Safety and Security Systems at the College of Agricultural and Natural Resources, University of Maryland (UMD). He has more than 35 years of experience teaching, conducting research in food safety, and working at the interface between science and public health policy. Additionally, Dr. Buchanan is a co-developer of the widely used USDA Pathogen Modeling Program. Previously, he spent nine years as Senior Science Advisor at the U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition (FDA CFSAN) and was Director of the CFSAN Office of Science until 2006. His scientific interests are diverse, and include extensive experience in predictive microbiology, quantitative microbial risk assessment, microbial physiology, mycotoxicology, and food safety systems. Dr. Buchanan has served on numerous national and international advisory bodies, including serving as a permanent member of the International Commission on Microbiological Specification for Foods, as a six-term member of the National Advisory Committee for Microbiological Criteria for Foods, and as the U.S. Delegate to the Codex Alimentarius Committee on Food Hygiene for a decade. Dr. Buchanan is a fellow of the American Society of Microbiology, and the Institute of Food Technologists.

**Dr. David Fisman, M.D., M.P.H.**

Dr. David Fisman is an Associate Professor in the Division of Epidemiology at the Dalla Lana School of Public Health, University of Toronto. Additionally, he is Associate Professor of Health Policy, Management and Evaluation, and Adjunct Associate Professor of Medicine at the University. Previously he held academic positions at Princeton, Drexel, and McMaster Universities. Dr. Fisman's research interests involve the application of novel epidemiologic methods to the study of infectious diseases, including vaccine-preventable diseases, sexually transmitted infections, and bacterial respiratory pathogens. He is Principal Investigator on a Canadian Institutes for Health Research-funded study exploring interactions among influenza, invasive bacterial disease, and the environment in 16 cities in Canada, the U.S., France, Australia, and South Africa. He has also provided testimony to the Institutes of Medicine panel

on climate change and indoor air quality related to environmental influences on disease transmission. Dr. Fisman is a member of the Canadian Institutes of Health Research-supported Canadian Consortium for Pandemic Preparedness Modeling (CanPan) and Pandemic Influenza Outbreak Research Modeling Team (PanINFORM). He was the recipient of a 2010 Ontario Ministry of Research and Innovation "Early Researcher Award." In addition, he received a 2003 GlaxoSmithKline Elion Young Investigator Award and a 2005 "Golden Apple" teaching award.

**Dr. Bruce Hay, Ph.D.**

Dr. Bruce Hay is Professor of Biology at the California Institute of Technology. His research focuses on using genetic and developmental tools to understand and manipulate the biology and genetics of wild populations. In 2008, Dr. Hay was named an NIH Director's Pioneer Award recipient for his innovative malaria prevention research related to genetically modified mosquitoes, which he continues to investigate. Within this, Dr. Hay and his team are pursuing a strategy for preventing malaria in humans by introducing genes that block transmission of the disease into populations of wild mosquitoes. Dr. Hay's work to eliminate mosquito-borne diseases was named as one of the top 50 technological developments of 2007 by *Scientific American.* Additional honors he has received include awards from the Burroughs Wellcome Fund and the Ellison Medical Foundation, as well as the Searle Scholar Award.

**Prof. Martyn Jeggo, B.Vet.Med., M.Sc., Ph.D.**

Prof. Martyn Jeggo is the Director of The Commonwealth Scientific and Industrial Research Organisation's (CSIRO) Australian Animal Health Laboratory (AAHL) and Adjunct Professor at Deakin University, Australia. In his role at AAHL, he promotes a "One Health" approach toward the diagnosis and surveillance of new and emerging diseases. Prior to this position, Prof. Jeggo was the Head of the Animal Production and Health Science Section of the Joint Food and Agricultural Organization/International Atomic Energy Agency (FAO/IAEA) Division of Agriculture, in Vienna, Austria (1996–2002). Additionally, he has held posts as Director of Veterinary Diagnostic Laboratories in Yemen and Head of the Department of Immunology at the United Kingdom's Institute of Animal Health Pirbright Laboratories. Among his professional achievements, Prof. Jeggo was responsible for developing an international external quality assurance program for veterinary laboratories. He is a founding member of the Foot and Mouth Disease Global Research Alliance, and a member of both the Royal College of Veterinary Surgeons and the Australian Institute of Company Directors.

**Dr. David Markovitz, M.D.**

Dr. David Markovitz is a Professor of Internal Medicine in the Division of Infectious Diseases at the University of Michigan, where he also has appointments in Cellular and Molecular Biology, Cancer Biology, and Immunology programs. Dr. Markovitz, who has been a faculty member at the University since 1988, has also practiced at both the University Hospital and the Veterans Administration Hospital Infectious Diseases Service. He currently runs a multidisciplinary research laboratory that studies the interactions between retroviruses and human cells. Specific projects examine the following issues: (1) the mechanism of action of the DEK protein, which has been linked to the pathogenesis of HIV-2, leukemia, solid tumors, and autoimmune disease; (2) the pathogenic effects of human endogenous retroviruses; (3) anti-HIV microbicides; and (4) the role of vimentin in immunity. Dr. Markovitz has been the recipient of numerous awards, including a Burroughs Wellcome Fund Clinical Scientist Award in Translational Research and most recently a National Institutes of Health Director's Transformative R01 Award to study replication of human endogenous retroviruses. Dr. Markovitz has previously served on the FDA

Vaccines and related Biological Products Advisory Committee and is a member of the American Society for Clinical Investigation and the Association of American Physicians.

**Dr. Timothy Rodwell, M.D., Ph.D., M.P.H.**

Dr. Timothy Rodwell is Assistant Professor in the Division of Global Public Health at the University of California, San Diego School of Medicine. Additionally, he is an attending physician at the Refugee Health Assessment Program, and co-founder of Utopia Scientific, a nonprofit organization focusing on promoting awareness of the importance of science, public health, and education through research, education, and community development. Dr. Rodwell has been studying tuberculosis (TB) and emerging zoonotic disease epidemiology since 1995. He specializes in global health with an emphasis on TB monitoring, control, and treatment in resource-poor settings. His work currently involves research on the molecular epidemiology of global drug resistance and TB infection control in Ethiopia, as well as a project looking at multidrug-resistant TB on both sides of the California-Mexico border. Previously, he has investigated anthrax in elephants in Namibia and bovine tuberculosis control in African buffalo in South Africa. Dr. Rodwell also acts as a consultant to UCSD projects funded by the U.S. President's Emergency Fund for AIDS Relief (PEPFAR) in Ethiopia.

**Dr. Jørgen Schlundt, D.V.M., Ph.D.**

Dr. Jørgen Schlundt is Deputy Director at the National Food Institute at Technical University of Denmark. Previously, he was Director of the Department of Food Safety and Zoonoses at the World Health Organization (WHO), Geneva (1999–2010). Before his work at the WHO, he participated in a number of international bodies, including Organisation for Economic Co-operation and Development (OECD) expert groups, WHO and Food and Agricultural Organization (FAO) Expert Consultations, European Union Scientific Committees, and the FAO/WHO Codex Alimentarius Commission. Dr. Schlundt has contributed to the international development of risk analysis principles, including the use of scientific risk assessment as the basis for food safety management decisions. As part of this, he has overseen new international initiatives, including the creation of the Joint WHO/FAO Expert Meetings on Microbiological Risk Assessment and the International Food Safety Authorities Network, the buildup of the Global Foodborne Infections Network, the initiation of the first-ever estimation of the global burden of foodborne diseases, and the development of a major consumer education program on the Five Keys to Safer Food. Dr. Schlundt also worked at the national level on environmental and food safety issues from 1983 to 1999, and headed the Bacteriology Department at the Veterinary Research Laboratory in Harare, Zimbabwe, in this period.

# Biographical Information of ISGP Staff

**George Atkinson, Ph.D.**

Dr. George Atkinson is the Founder and the Executive Director of the ISGP and remains Professor of Chemistry, Biochemistry, and Optical Science at the University of Arizona. His professional career spans several diverse arenas: academic teaching, research and administration, 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 high-technology laser sensor company serving the semiconductor industry, and Science and Technology Adviser (STAS) to U.S. Secretaries of State Colin Powell and Condoleezza Rice. Notably, Dr. Atkinson also launched the Institute on Science for Global Policy (ISGP) in January 2008. The concepts and principles used by Dr. Atkinson to develop the ISGP derived from his personal experiences in domestic and international science policy. He seeks to guide the ISGP in creating a new type of international forum in which credible global experts provide governmental and societal leaders with the objective understanding of the science and technology (existing, emerging, and "at-the-horizon") now critically needed to formulate sound policy decisions. These are the S&T issues that can be reasonably anticipated to shape the increasingly global societies of the 21st century. His academic and professional achievements have been recognized in numerous ways including a National Academy of Sciences (NAS) Post Doctoral Fellowship at the National Bureau of Standards, Senior Fulbright Fellowship, an 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, the Distinguished Service Award (Indiana University), an Honorary Doctorate (Eckerd College), the Distinguished Achievement Award (University of California, Irvine), and selection 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.

**Jennifer Boice, M.B.A.**

Jennifer Boice is the Program Manager of the ISGP. Prior to this role, Ms. Boice worked 25 years in the newspaper industry, primarily at the Tucson Citizen and briefly at USAToday. She was the Editor of the Tucson Citizen when it was closed in 2009 by its parent company, Gannett Corp. Additional appointments at the Tucson Citizen included Business News Editor, Online Department head and Senior Editor. She also was a 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.

**Alexis Boyd, M.Sc.**

Alexis Boyd is a Senior Fellow with the ISGP. In addition, she is currently pursuing her Ph.D. in the Institute of Biomedical Sciences, Department of Microbiology and Immunology at The George Washington University. Her research is focused on the immune response to helminth parasites. Previously, Ms. Boyd was an Infectious Disease Training Fellow at the Centers for Disease Control and Prevention in the Division of Parasitology. She received her M.Sc. in Public Health Microbiology from the The George Washington University and majored in biotechnology at Rutgers University.

**Christine Boyd, M.Sc.**

Christine Boyd is a Senior Fellow with the ISGP, as well as a teacher. Previously, Ms. Boyd was an intern at Roche in the Biochemistry and Drug Metabolism Department working on specificity studies for cytochrome-P450. As a graduate fellow at the National Institutes of Health (NIH), she worked on the development of a high-pressure liquid chromatographic system for the separation of polycyclic aromatic hydrocarbons. She also worked with DNA repair and cell cultures at both the University of California, Irvine and at the University of Cincinnati. Ms. Boyd holds a M.Sc. in zoology.

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**Melanie Brickman Stynes, Ph.D., M.Sc.**

Melanie Brickman Stynes is a Senior Scientist with the ISGP. As a researcher focused on the juncture of public health, demography, policy, and geography, she bridges multiple fields in her emerging and persistent infectious diseases research. Her work has paid particular attention to issues surrounding tuberculosis control (historic and contemporary). She is also an Adjunct Professor at Baruch College's School of Public Affairs. Additionally, Dr. Brickman Stynes spent nearly a decade as a Research Associate for the Center for International Earth Science Information Network (CIESIN) of Columbia University where she worked on a range of projects related to health, disease, poverty, urbanization, and population issues. She received her Ph.D. in medical geography from University College London and her M.Sc. in medical demography from the London School of Hygiene and Tropical Medicine.

**Jill Fromewick, Sc.D., M.S.**

Jill Fromewick is a Senior Fellow with the ISGP. A social epidemiologist by training, Dr. Fromewick maintains a dual focus on quantitative and qualitative methods. Her research spans a broad range of public health topics, primarily focused on investigating the impact of state and local policy on health and health disparities. She is the founder and Executive Director of Sparrow Research Group, a global public health consulting firm specializing in program design, evaluation, and social science research. Dr. Fromewick holds Master's and Doctor of Science degrees from the Department of Society, Human Development, and Health at the Harvard School of Public Health.

**Anna Isaacs, M.Sc.**

Anna Isaacs is a Fellow with the ISGP. She has previously focused on minority health issues and is experienced in primary and secondary qualitative research. Anna has interned as a researcher at a variety of nonprofit institutions and also at the House of Commons in London. She 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.

B**rendan Lee, D.V.M, M.Sc., M.P.H., D.A.C.V.P.M.**

Brendan Lee is a Senior Fellow with the ISGP and a Research Fellow with the National Center for Food Protection and Defense at the University of Minnesota. After practicing clinical veterinary medicine for several years, he turned his focus to public health and food safety. Currently, his primary focus is on issues surrounding food safety, global food systems, and zoonotic diseases, with an emphasis on developing countries. He received his D.V.M. from the University of The West Indies, his M.Sc. in Veterinary Epidemiology and Public Health from the University of London, and his M.P.H. from the University of Minnesota.

**David Miller, M.B.A.**

David Miller is a Senior Fellow 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.

**Arthur Rotstein, M.S.J.**

Arthur Rotstein is the Media Coordinator for 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 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 healthcare 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 concentrated on research and development (R&D) and leading multidisciplinary multi-company teams to investigate future enhanced oil recovery ideas and to pilot/commercialize innovative recovery methods in domestic and foreign locations. Dr. Schmidt received his Ph.D. in chemistry from Emory University.

**Matt Wenham, D.Phil.**

Matt Wenham is a Fellow with the ISGP and a postdoctoral research fellow at the National Institutes of Health in Bethesda, Maryland. His research involves 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.