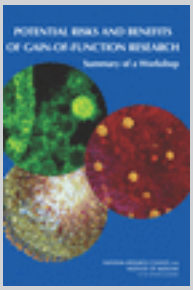

Potential Risks and Benefits of Gain-of-Function Research: Summary of a Workshop

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POTENTIAL RISKS AND BENEFITS OF GAIN-OF-FUNCTION RESEARCH

Summary of a Workshop

Frances Sharples, Jo Husbands, Anne-Marie Mazza,
Audrey Thevenon, and India Hook-Barnard, *Rapporteurs*

Board on Life Sciences
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This workshop summary has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published summary as sound as possible and to ensure that the summary meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process.

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the workshop summary before its release. The review of this summary was overseen by Stephen Fienberg, Carnegie Mellon University. Appointed by

the National Research Council, he was responsible for making certain that an independent examination of this summary was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this summary rests entirely with the authors and the institution.

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1

Introduction

On October 17, 2014, spurred by incidents at U.S. government laboratories that raised serious biosafety concerns, the U.S. government launched a 1-year deliberative process to address the continuing controversy surrounding so-called "gain-of-function" (GoF) research on respiratory pathogens with pandemic potential (White House, 2014a).[1] GoF research is the latest example of U.S. efforts to develop oversight mechanisms for dual use research in the life sciences that can "reliably identify, and where necessary, mitigate risks while protecting scientific autonomy, discovery and innovation, public health, national security, and other critical interests" (Hebbeler, 2014).[2]

[1] As discussed in Chapter 3, in virology "gain of function" refers to a type of mutation that results in an altered gene product that possesses a new molecular function or a new pattern of gene expression. A loss-of-function mutation is a type of mutation in which the altered gene product lacks the molecular function of the wild-type gene (Mouse Genome Informatics, http://www.informatics.jax.org/). The specific definition applied in the U.S. government policy is discussed in the text.

[2] A 2004 report from the National Research Council, *Biotechnology Research in an Age of Terrorism*, argued that biotechnology posed a "dual use dilemma" because "the same technologies can be used legitimately for human betterment and misused for bioterrorism" (NRC, 2004:1). Most policy discussions have focused on efforts to address a subset of "dual use research of concern" (DURC), which was defined by the National Science Advisory Board for Biosecurity in 2007 as research that, "based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or materiel" (NSABB, 2007:17). Examples of U.S. policy initiatives stimulated by the controversy over GoF research that began in late

The GoF controversy began in late 2011 with the question of whether to publish the results of two experiments involving H5N1 avian influenza and continued to focus on certain research with highly pathogenic avian influenza over the next 3 years.[3] The new U.S. policy expanded the scope to include experiments with the coronaviruses that cause Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). The heart of the U.S. process is an evaluation of the potential risks and benefits of certain types of GoF experiments with influenza, SARS, and MERS viruses that would "inform the development and adoption of a new U.S. Government policy governing the funding and conduct of gain-of-function research" (White House, 2014a:3). As part of the process, the government also instituted a pause in both new and current funding for some GoF research projects while the evaluation was carried out.

> New USG funding will not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. The research funding pause would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity. In parallel, we will encourage the currently-funded USG and non-USG funded research community to join in adopting a voluntary pause on research that meets the stated definition. (White House, 2014a:2)

Initially, 18 research projects funded by the National Institutes of Health (NIH) were halted, although several involving the effort to develop an animal model for studying MERS were later exempted (Kaiser, 2014).

Two entities were given special responsibilities for supporting the deliberative process. The National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee established in 2004, is to "(1) advise on the design, development, and conduct of risk and benefit assessment studies" and "(2) provide recommendations to the USG [sic]

2011 include the *USG Policy for Oversight of Life Sciences Dual Use Research of Concern* (March 29, 2012), the *HHS Framework for Highly Pathogenic Avian Influenza Research* (2012), the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (November 2013), and the *USG Policy for Institutional Oversight of Life Sciences Dual Use Research of Concern* (September, 2014). In addition, in response to the laboratory incidents revealed in July 2014, White House Science Advisor John Holdren and Homeland Security Advisor Lisa Monaco issued a memorandum in August 2014 on *Enhancing Biosafety and Biosecurity in the United States* that "urged departments and agencies to take specific steps to strengthen safety and security" in federal laboratories (Hebbeler, 2014).

[3] Information about the initial controversy may be found in NRC (2013).

on a conceptual approach to the evaluation of proposed GOF studies" (Stanley, 2014). The formal assessment of the potential risks and benefits would be commissioned by the NIH and carried out by private contractors.[4] The National Research Council (NRC) and Institute of Medicine (IOM) of the National Academies[5] were asked to "provide a forum for broad public debate, which will inform the NSABB's deliberations and the development of USG [sic] policy on GOF research" by carrying out two public conferences (Groesch, 2014). The first conference would offer the opportunity for input from a wide range of stakeholders about both general principles that should guide the assessments of benefits and risks and what specific issues should be considered, while the second would provide an opportunity for comments on the NSABB's draft policy recommendations once the assessments were completed. In each case, a summary report of the meeting would be provided to the NIH within 1 month. The formal statement of task from the NIH for the first meeting may be found in Box 1-1. This document was prepared as a factual summary of that first meeting. The timeline for the entire deliberative process may be found in Figure 1-1.

The first public symposium was organized by a planning committee under the chairmanship of Dr. Harvey Fineberg, Gordon and Betty Moore Foundation. Biographies of the planning committee members may be found in Appendix B. The agenda for the meeting, which was held December 15-16 at the National Academies, may be found in Appendix C. Biographies of the speakers may be found in Appendix D. The symposium was attended by 140 individuals; a list of attendees may be found in Appendix E. In addition, the event was webcast and attracted approximately 300 viewers; an archived version may be found at https://www.youtube.com/playlist?list=PLuTGMA3A_-16HWJ6smsx4w1Bh_2TKf40V.

In his welcoming remarks IOM President Dr. Victor Dzau commented that the symposium was an example of one of the major roles played by the National Academies: providing a neutral forum for the discussion of complex and controversial issues in which science is an essential component. Both he and National Academy of Science (NAS) President Dr. Ralph Cicerone acknowledged the support for the symposium from the NIH as well as several foundations and underscored the importance

[4] The "Sources Sought Notice" from the NIH for the project may be found at https://www.fbo.gov/?s=opportunity&mode=form&id=c134018fd1d008c582b7755be1fc1c06&tab=core&_cview=0.

[5] The National Academies is the collective name of the National Academy of Sciences, the National Academy of Engineering, the Institute of Medicine, and the National Research Council.

BOX 1-1
Statement of Task

An ad hoc committee established by the National Research Council and the Institute of Medicine will organize two public symposia on Gain of function (GOF) research. The first symposium, which will be held in the middle of December 2015, will examine the underlying scientific and technical questions that are the source of current discussion and debate over GOF research involving pathogens with pandemic potential. The topics to be addressed include: Principles important for, and key considerations in, the design of risk and benefit assessments of GOF research. This will be informed by discussion of the following topics: Potential benefits of the research, including whether, in addition to generating new scientific knowledge about biological organisms, it will:

1. Inform public health responses to a potential pandemic, in particular by supporting surveillance efforts to identify possible pandemic strains and provide more time for preparedness; and
2. Facilitate the development of vaccines and antiviral therapeutics.

- Potential risks associated with the research, in particular those related to biosafety and biosecurity.
- Alternative methods that may be employed to yield similar scientific insights and/or potential benefits, while reducing potential risks.

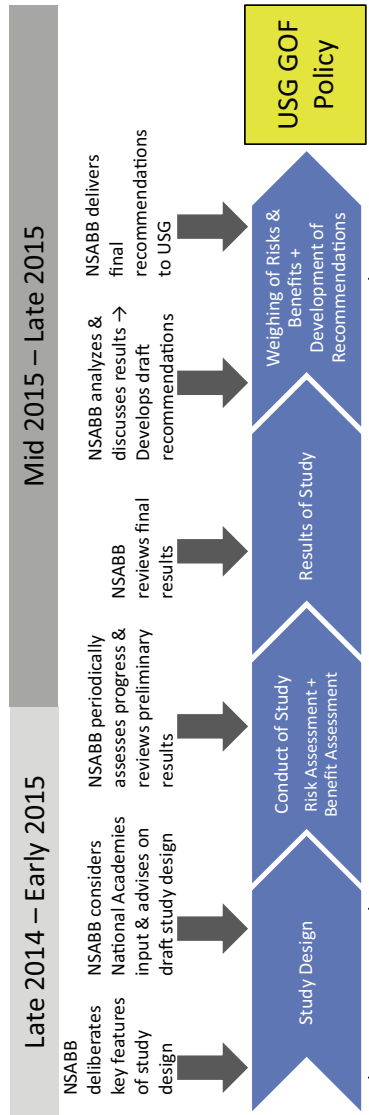
The two-day symposium will invite participants with a wide range of perspectives and expertise, including public health, biosafety, public health surveillance, research, security, drug and vaccine development, and experts from regions of the world where pathogens with pandemic potential are endemic. The symposium will be webcast and the presentations and background materials will be archived online.

SOURCE: NIH, 2014.

of finding a way to allow science to move forward while addressing the concerns that were raised about GoF research.[6]

In his introduction to the symposium, Fineberg stressed that the event was intended to provide an opportunity for fundamental reflection and reconsideration, with no attempt to reach consensus or force agreement. There are widely divergent views from many areas of expertise about the potential risks and benefits of GoF research, and the debate, like the research, is international. This had been reinforced for him the previous

[6] In addition to the NIH, support for the symposium came from the John D. and Catherine T. MacArthur Foundation, the Alfred P. Sloan Foundation, the Wellcome Trust, and internal National Academies' funds.



*The USG intends for these efforts to occur as expeditiously as possible, and dates are subjects to change based on the deliberative process.

FIGURE 1-1 Flow chart showing timeline for deliberative process regarding monitoring and regulation of GoF research.

week when he took part in a major meeting in Hannover, Germany, organized by the Volkswagen Foundation and the Max Planck Society that reflected the extensive European engagement with GoF issues.[7] Although U.S. policy was the focus of this symposium, the issues are not restricted to the interests, programs, or funding of any one nation. Science is universal, and the possibilities of both the benefits and risks from GoF research are not limited to any country. So the question of how the world can proceed to develop a consensus about a way forward was an essential part of the backdrop.

The symposium was designed to offer an opportunity to explore what issues should be included in the risk and benefit assessments, "to systematically expose, explain, and identify those elements of consideration that should be brought to bear on the question of proceeding or not proceeding with what types of gain-of-function research. . . . We will have done our job in this next 36 hours if by the end of our conversation we have been able to enumerate in a more systematic way the questions, the points of potential agreement, the points of difference, and what differences would matter the most to the ultimate decisions that would need to be made" (Fineberg, 2014).

This report has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. The planning committee's role was limited to planning and convening the workshop. The views contained in the report are those of individual workshop participants and do not necessarily represent the views of all workshop participants, the planning committee, or the National Research Council. It offers a summary of the key issues and ideas identified during the symposium, but offers no consensus conclusions or recommendations and is intended to reflect the discussions during the meeting. In order to be as responsive to the charge as possible, it is organized thematically rather than chronologically, so that ideas raised at various points in the symposium are grouped together. Chapter 2 begins with an overview of risk and benefit analysis. It is followed by an overview in Chapter 3 of the science associated with GoF research, the particular characteristics of the experiments that are the subject of the U.S. funding pause and the earlier controversy over influenza, and some of the ideas that were suggested as alternative experimental approaches. Chapter 4 describes the discussions of the major potential benefits claimed for GoF research, while Chapter 5 describes the discussions about potential biosafety and biosecurity risks. Chapter 6 offers a summary of the presentation and discussions of policy issues.

[7] Further information about the Hannover meeting, "Dual Use Research: Biosafety, Biosecurity, Responsibility," may be found at http://www.volkswagenstiftung.de/dualuseresearch.

2

Assessing Risks and Benefits

Dr. Charles Haas, Drexel University, a member of the symposium planning committee, summarized the standard risk assessment process. The major steps in risk assessment were first articulated in a National Research Council report titled *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983), otherwise known as the "Red Book." This report has been updated several times (see NRC 1994, 1996, and 2009). The basic framework laid out for risk assessment consists of the steps in Box 2-1.

However, there are also other considerations besides following these technical steps, and Drs. Baruch Fischhoff (Carnegie Mellon University), Gavin Huntley-Fenner (Huntley-Fenner Advisors, Inc.), and Monica Schoch-Spana (University of Pittsburgh Medical Center [UPMC] Center for Health Security) elaborated on these and provided further details about crucial considerations that need to be taken into account in risk assessments. These comments are summarized later in this chapter.

Haas noted that the major focus of attention with regard to Gain-of-Function (GoF) research has been on hazard assessment. This encompasses occupational health risks, but needs to go beyond this to risks to the members of the public near research sites as well as global risks for pandemic organisms. A number of questions in this arena need to be addressed in a risk assessment, stated Haas. Do the safety records of high containment laboratories provide an appropriate basis for quantifying the risks of lab accidents that lead to worker or public exposures or are there more systematic approaches that need to be incorporated into a

BOX 2-1
Basic Steps in the Risk Assessment Process

- Hazard Assessment: Determining whether a particular chemical (or microbiological agent) is or is not causally linked to particular health effects.
- Exposure Assessment: Determining the extent of human exposure and the probability of occurrence of the health effects in question.
- Dose-response Assessment: Determining the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
- Risk Characterization: Decscribing the nature and magnitude of human risk, including attendant uncertainty.
- Risk Management: Reducing risks and increasing expected benefits.
- Risk Communication and Appropriate Involvement of Stakeholders

SOURCE: Modified from NRC, 1983; Haas presentation, 2014 symposium.

risk assessment? Are there finer gradations of lab capabilities that must be considered that go beyond the BSL/ABSL (biosafety level/animal biosafety level) framework, for example, the competence of the laboratory staff and the steps taken by the host institution for community preparedness (see comments by Dr. Rebecca Moritz of the University of Wisconsin's Biosecurity Task Force in Chapter 5)? And how is deliberate misuse of either the pathogens themselves or the information obtained through the research on these pathogens to be incorporated into the risk assessment?

Haas noted that the debate on GoF research has paid scant attention to either exposure assessment or dose response assessment. Both are crucial components of a risk assessment, although it is likely that at least for dose response, there is little information available, particularly for Middle East Respiratory Syndrome (MERS) virus and possibly also for Severe Acute Respiratory Syndrome (SARS) virus. As a consequence, the GoF research debate has jumped directly into the risk characterization stage without the benefit of the missing intermediate analyses and the dissection of the exposure and dose response issues that may make considerable differences in how the risk characterization is framed. It was Haas's view that the current risk characterization picture contains too many lumped parameters, combining factors dealing with environmental effects, host properties, and infectious agents. All of these need to be taken into account when estimating outcomes and require more attention, as does the role of uncertainty. Very often we do not necessarily know that

we have incorporated all of the factors that may influence uncertainty. Similarly, the full fundamental basis of risk assessment is missing for the risk management considerations for GoF research, although it is still possible to discuss to what degree biological and methodological modifications can reduce or obviate risk. The risks of not doing the proposed work, highlighted in several talks and comments during the symposium, also should be considered and balanced against the risks of doing the research. Finally, Haas noted that a risk assessment can *inform* decisions, but is not determinate per se. The concept of "acceptable" risk is a trans-scientific issue that will be more appropriately addressed in the policy arena.

In Session 8 of the symposium, Baruch Fischhoff, another member of the symposium planning committee, gave an overview of what risk/benefit assessment can and cannot do, as well as what has been learned from past attempts to conduct risk/benefit assessments. He recommended a book, *Risk: A Very Short Introduction* (Fischhoff and Kadvany, 2011), in which the authors use simple conceptual frameworks from decision theory and behavioral research to explain the science and practice of creating measures of risk, how scientists address risks using historical records, scientific theories, probability, and expert judgment, and what cognitive scientists have learned about how people deal with risks and how these lessons apply to diverse examples and demonstrate how understanding risk can improve making choices in everyday life and public policy.

Fischhoff outlined the key considerations related to the risk assessment paradigm above. These considerations include:

1. Defining "risk" and "benefit"
2. Assessing risks and expected benefits
3. Communicating risks and expected benefits
4. Organizing to reduce risks and increase expected benefits

For the last item, he noted that for GoF research, the expected benefits are potentially reduced risks. For this reason, the same methodologies apply to assessing risks and expected benefits.

DEFINING "RISK" AND "BENEFIT"

Fischhoff stated that the terms of all analyses embody values that favor some interests above others. Thus, when transparent, the underlying assumptions can be controversial and, therefore, an analytical and deliberative process is required to create *socially acceptable* definitions. Such analyses utilize science to inform estimates, but they also depend on subjective value judgments about what metrics to include and how much weight to put on each. One commonly used metric is risk of death,

which can be defined as the risk that somebody dies, or in terms of the probability that someone exposed to a hazard dies prematurely, or the number of years of life that are expected to be lost with each death. A further refinement of this metric may assign higher value to deaths of particular groups, for example, young people. Other bases for evaluating the value of death as an outcome of risk include whether the deaths are equitably distributed, voluntarily assumed, well understood, controllable, or borne by future generations. Echoing Haas, Fischhoff noted that choosing among these and other alternatives require making value judgments, which is a role for the policy makers.

ASSESSING RISKS AND (EXPECTED) BENEFITS

Fischhoff noted these key needs for risk assessments:

- Socially acceptable outcomes defined
- Factors that are believed to affect outcomes identified
- Factors and interdependencies assessed based on observation and expert judgment
- Quality of the evidence assessed

Fischhoff urged policy makers to have a clear idea of what the purpose of a particular risk/benefit analysis is so that the analysis suits its purpose. He noted that risk analyses can be either for purposes of "design" or to inform decisions. Analyses for purposes of design identify better options to improve understanding of complex systems. Analyses to inform decisions focus on the acceptability of risks (given the expected benefits) by predicting outcomes. As an example of the former, Fischhoff cited a 1975 Reactor Safety Study known as "WASH-1400" (USNRC, 1975) that attempted to assess the risk of accidents at commercial nuclear power plants in the United States. The study was later critiqued by an ad hoc review group that stated the following:

> We find that WASH-1400 was a conscientious and honest effort to apply the methods of fault-tree/event-tree analysis to an extremely complex system . . . in order to determine the overall probability and consequences of an accident. . .
>
> We have found a number of sources of both conservativism and nonconservatism in the probability calculations of WASH-1400. . . . Among the former are inability to quantify human adaptability during the course of an accident . . ., while among the latter are nagging issues about completeness, and an inadequate treatment of common cause failure.

> We are unable to define whether the overall probability of a core melt given in WASH-1400 is high or low, but we are certain that the error bands are understated. We cannot say by how much. (USNRC, 1975)

This example illustrates two notable things. First, risk assessments on low probability/high consequence events are not new. Second, the roles of uncertainty as well as human factors (see more below) are crucial in risk assessment. As also pointed out by Haas, risk assessments generally are forced to deal with considerable uncertainty, which needs to be acknowledged and dealt with. As Huntley-Fenner added later during the discussion, the fact that certain types of accidents, fatalities, and injuries are rare and we do not often see them is interpreted as a sign that things are going well. But the absence of such rare events may not necessarily be a positive sign; it may be that we are just missing the right indicators. If we do not see the data relevant to what accounts for safety, then maybe we are not looking in the right places or in the right way.

HUMAN BEHAVIOR AS A SOURCE OF VULNERABILITY AND RESILIENCE

Fischhoff noted that the contribution of human factors to understanding industrial and other processes has been studied for a very long time, referencing, for example, a study by H.M. Vernon (1921), a member of the English Industrial Fatigue Research Board, on Industrial Fatigue and Efficiency. He also noted that the literature from nuclear power and other sectors makes clear that human behavior must be taken into account as both a source of vulnerability and a source of resilience. Although human error is clearly a problem, human innovation can also rescue difficult situations.

Gavin Huntley-Fenner elaborated on the topic of human factors in his presentation. He defined human factors as "the study of the interrelationships between humans, the tools they use, and the environment in which they live and work." He provided some data on the role of human error in various accident scenarios: 80 percent of motor vehicle accidents, 80 percent of medical errors, and 60-80 percent of aviation accidents are estimated to be attributable to human factors. He stated that studies have shown that physical (e.g., working in personal protective equipment) and cognitive (e.g., working under conditions of fatigue) stresses undermine human reliability. Not only can human error not be eliminated, but it also has actually increased as a contributor to accidents in some arenas, such as traffic accidents. Analyses of human reliability and errors must identify the critical areas that are incompatible with human capabilities and the areas where a system is vulnerable to human error. He cited a 2009 Gov-

ernment Accountability Office (GAO, 2009) report that found that role of human error is unappreciated.

Huntley-Fenner provided a list of characteristics to guide hazard analysis processes (Box 2-2). He added some key questions to be asked:

- Are task demands compatible with human capabilities and characteristics?
- Has the system been designed to cope with the inevitability of human error?
- Does the system take advantage of unique human capabilities?

BOX 2-2
Best Hazards Analysis Processes

1. Include multi-disciplinary teams
2. Incorporate qualitative and quantitative data
3. Use both structured and unstructured approaches to developing scenarios
4. Consider human capabilities as well as limitations
5. Expect disproportionate number of human factor scenarios vs. environment or mechanical

SOURCE: Huntley-Fenner, G. 2014 presentation to Gain-of-Function symposium.

BOX 2-3

- Enhanced preparedness
- Prevention of significant accidents
- Mitigated consequences
- Improved problem solving after adverse events
- Data needed to support rigorous analysis identified
- Decisions regarding allocation of limited resources supported
- Implicit risks adopted by a team are highlighted
- Hidden or underappreciated benefits of existing practice are highlighted
- A robust biosafety environment can “harden” a biosecurity target

SOURCE: Huntley-Fenner, G. 2014 presentation to Gain-of-Function symposium.

According to Huntley-Fenner, the benefits of a risk assessment guided by consideration of human factors are summarized in Box 2-3.

Huntley-Fenner cautioned the audience about our limited capacity to understand and manage risk. He noted that we tend to underestimate risk, are optimistic about our capacity to control local risk, and need to be aware of the potential to accrue benefits (science) and externalize risks (public health). He also, however, highlighted the fact that establishing simple, consistent routines can yield significant reductions in errors, referencing, for example, a paper by Haynes et al. (2009) that reported the use of a simple surgical safety checklist that resulted in a significant decline in errors related to anesthesia in surgical procedures.

Fischhoff further elaborated on the general area of limitations in risk assessment and noted that the limits include variability among observations, the quality of the studies on which the analysis is based (internal validity), whether these studies are generalizable (external validity), and how good the underlying science is ("pedigree"). "These are the standard considerations that a policy maker needs to know in order to make responsible judgments about the risks and benefits of a technology. . ." said Fischhoff. He stressed the importance of risk communication and taking account of behavioral research that demonstrates how humans tend to make faulty intuitive judgments. He cited two special issues of the *Proceedings of the National Academy of Sciences (PNAS)*[1], one in 2013 and another in 2014, devoted to "The Science of Science Communication" as well as a Food and Drug Administration *Strategic Plan for Risk Communication* (USFDA 2009) as good sources of additional information on risk communication. The topic was also elaborated on by Schoch-Spana in her presentation in Session 8.

PUBLIC ENGAGEMENT

Monica Schoch-Spana framed her presentation with four questions: Who is the public? What do we mean by engagement? Why is engaging the public valuable? And what are some take away considerations for the National Science Advisory Board for Biosecurity (NSABB), National Institutes of Health (NIH), and workshop attendees?

Who Is "the Public"?

Schoch-Spana defined "the public" in the broadest sense as all the people who are interested in or affected by GoF research governance decisions. However, who is in that group depends on political jurisdiction

[1]PNAS 2013. vol. 110 Supplement 3 and PNAS 2014 Vol. III Supplement 4.

and many other factors that complicate definitions. Global, national, and local publics are all relevant to this particular debate. In the pandemic context the population at risk is global. Anyone in the world, at least in the abstract, can be equally in danger of infection and equally in need of medical countermeasures potentially informed by GoF research.

In a U.S. context, Schoch-Spana referenced a study by Sandra Quinn and colleagues (Quinn et al., 2011) who proposed that U.S. racial and ethnic minorities were at a threefold disadvantage during the 2009 H1N1 influenza pandemic. These subgroups faced enhanced exposure to the H1N1 virus because of social, economic, and behavioral elements. They faced greater susceptibility to influenza because of the high prevalence of chronic disease and immunosuppression, and they had impaired access to timely and trusted health information, vaccination, and treatment. There are also other "national" publics that come to mind in the United States. Ultimately, the U.S. taxpayer underwrites the cost of government-sponsored research and confers authority and operating budgets on federal bodies implicated in the biosafety systems that have been created and continue to be refined to keep researchers and the larger public safe in the context of GoF and other research of concern.

Schoch-Spana also noted that at the local level there also is another potentially relevant public—the communities that actually host the facilities in which GoF research is conducted. In the case of a laboratory release they could be on the front end of an emerging pandemic. As a result, they have a strong and direct interest in the biosecurity and biosafety systems designed to avert any release and, should prevention fail, they also have a direct interest in locally robust systems to treat the sick and interrupt transmission.

What Do We Mean by "Engagement"?

Schoch-Spana stated that "engagement" usually refers to the processes by which citizens influence the policies and programs that affect them. In a democracy people have a variety of means to make their voices heard. They can vote, write letters, lobby, demonstrate, and take other collective actions. Over the past 50 years more direct means of public participation in the decision-making process itself have developed as citizens have become less deferential toward authorities and public policy issues have become more complicated.

The theories of deliberative democracies have flourished and practical experience in participatory approaches has accumulated. Scholars and practitioners usually talk about public engagement as a flow of influence and information between authorities and constituents. Very simplistically,

there are three different modes of public engagement: communication, consultation, and collaboration.

In the communication mode, an official or an agency conveys information to members of the public in a one-way fashion, often with the intent of educating and informing the public. Public feedback is not required and not necessarily sought (Schoch-Spana, 2007). In the case of the GoF research debate, this could take the shape of press releases, educational websites, and reports, such as the proceedings of meeting such as this one.

The consultation mode is an interaction in which authorities solicit opinions through surveys, polls, and focus groups or during public comment periods. Again this communication is one-way, but it is *from* the citizens *to* the authorities. The public's points of view, criticisms, and constructive advice can inform policy options, but this input is just one of many that decision-makers take into consideration.

The third mode, collaboration, is considered to be a two-way flow of information and influence between citizens and authorities; it is about dialogue fostering better understanding of very complex problems from all sides and perspectives. Collaboration allows an opportunity for collective learning as part of honest and respectful interaction among the authorities and diverse constituents (Schoch-Spana, 2007). Such iterative exchanges, as Fischhoff indicated earlier, are necessary to approach policy concerns that are technically and ethically complex.

Why Is Engaging the Public Valuable?

Schoch-Spana noted that there is a valuable summary in the 2008 NRC report *Public Participation in Environmental Assessment and Decision Making*, which identified three important justifications for deliberative processes: improving product quality, enhancing legitimacy, and building capacity.

- **Improving product quality:** Collaboration enhances decision quality by helping to get the science right. People who are not typically considered experts may nonetheless have relevant local knowledge that is sensitive to context. Their input has often been able to correct technical analyses that have been misapplied to local conditions. The public can also bring fresh eyes not encumbered by technical presuppositions that in the end can improve the technical competence of policy decisions.
- **Enhancing legitimacy:** Participation can serve as a means to inform and elicit the consent of the governed on complex issues in ways that traditional methods such as elections cannot provide. Participatory forms of engagement, when performed in good

faith, can help build trust between officials and the public and enable officials to consider different points of view, including those of otherwise disenfranchised people. They can also provide evidence even to dissenting participants and nonparticipants that officials have indeed acted in a fair and accountable manner.

- **Building capacity:** Well-executed public participation builds a foundation of trust and mutual understanding as well as practical experience with dialogue, which can benefit future policy formulation implementation and evaluation. The public can derive greater facility with the science and the political process, and scientists and governing officials can develop a better understanding of public concerns. Such an exchange helps scientists, citizens, and governing officials understand the aspects of a problem that go beyond their immediate circumstances and provides the opportunity for refinement and even the changing of opinion.

Schoch-Spana reiterated a fourth cross-cutting justification for public engagement—navigating uncertainty—which Fischhoff, Huntley-Fenner, and Haas had also mentioned. Involving the public can strengthen the capacity of civil society and technical experts, industry, and government for analysis and reflection on the uncertain and ambiguous nature of many scientific and technological developments. Judgments informed using scientific fact *and* social values are necessary in the context of unforeseen consequences that can be good or bad or in between and can unfold over decades or more. The benefits of public participation are not merely aspirations. The 2008 NRC report that Schoch-Spana referenced provides information on a large number of studies from across the social sciences that demonstrate these benefits.

Considerations for the NIH and the NSABB

Schoch-Spana concluded with two points that she believes merit further attention for broad public engagement in the proposed GoF assessment—nested engagement and enduring structures. Broader publics at local, national, and global levels could participate in public engagement exercises that are national in scope, diversely populated, and involve technically and ethically complex health security matters, for example, how does one distribute scarce medical resources in an influenza pandemic? Policy makers could consider holding deliberations in communities hosting GoF research laboratories and populating the national conversation to address the health disparities aspects of risks and benefits. Federal agencies and partners such as the National Academies and other interested entities could also encourage their counterparts internationally

to develop comparable deliberative processes. She noted that in 2009 a citizen consultation on climate policy was conducted simultaneously in 38 countries. Transnational consideration of a transnational public health problem seems to Schoch-Spana a reasonable goal to at least consider.

On enduring structures, public engagement on GoF should not be limited to a "one and done" performance. Engagement mechanisms on this issue could serve as a foundation for the development of deliberative systems to tackle analogous dilemmas that are certain to emerge in the future. Participatory endeavors and the diffusion of well-crafted communication products emanating from them are investments in democratic governance. Such efforts would enhance the scientific literacy of citizens as well as the capacity of scientists, their sponsors, and their regulators to represent their work in broadly meaningful ways. Her final takeaway message was "How a decision is made is just as important for many people as the outcome of that decision."

SUMMARY OF RISK AND BENEFIT OVERVIEW

Fischhoff summarized as follows the tasks to be accomplished by the risk/benefit assessment that the NIH plans to conduct:

- Define the risks and benefits;
- Assess the risks and expected benefits;
- Communicate the risks and expected benefits; and
- Organize to reduce the risks and increase the expected benefits.

The bottom line, he stressed, is that a credible risk benefit analysis must be both technically sound and socially acceptable. There should be a strategic decision on whether to focus on design or decision. There should be proper disciplinary breadth and proper treatment of uncertainty. An ongoing two-way communication with stakeholders is needed to ensure that the assessment receives the credibility it deserves. The process should be organized for transparency and learning.

For this particular endeavor, it is Fischhoff's view that the NIH would do best to focus on design and on determining how to reduce the risks and increase the expected benefits. He pointed out that the structure of risk analysis is well known and has been used many times. But the benefits side of the equation is more difficult and poses more interesting problems that require an investment in formalizing the benefit arguments as well as formalizing the arguments for those who see alternative paths. It is necessary to know which numbers are really important and whether they are even relevant to an analysis. He noted that the NIH could consult with people who have some experience with these issues, for example,

Michael Gorham and Kevin Dunbar at the University of Virginia; both study scientific discovery processes, at the individual and laboratory levels, and know something about this. It is possible to take advantage of such people who have already studied the world of scientific innovation in quantitative or qualitative terms.

Fischhoff reiterated that the assessment should seek to inform decisions, not presume to make them. "Anybody who thinks that putting out a contract for a risk/benefit analysis will tell the country what to do on this topic is just deluding themselves." The subjectivities that inevitably exist in setting the terms of any analysis also need to be acknowledged. When taking a multi-attribute approach to things, somebody needs to decide which attributes are the outstanding ones and whether mortality will be measured in terms of probability of premature death or in terms of expected lives saved. In addition, how should the externalized costs and benefits to the rest of the world, i.e., those that can take advantage of breakthroughs in this country if our sociopolitical and economic systems allow, be weighed? There is a need for some socially acceptable way to resolve the subjectivity in scientific judgment, which must be explicitly acknowledged. As scientists we know that all analyses are incomplete. We can do a better job of quantifying things that are often left out, such as human factors, but there are certain things, such as the quality of the underlying research, that will remain matters of judgment. Similarly, the associated uncertainties in the analysis must be elicited and expressed.

Fischhoff also reiterated the importance of considering and evaluating human factors in scientifically sound ways and that public engagement should be treated as an opportunity to increase the public's literacy and to build trust in a community. This means reaching out, pulling the community into the process, and taking its opinion seriously. It means accommodating the concerns, which are easier to deal with at the beginning than at the end. A good design process is one that does not need some kind of patchwork at the end. Finally, the appropriate level of aggregation for making decisions needs to be determined while considering the variability in the research and the resolution of the decision-making processes. If it is appropriate to evaluate research proposals on a case-by-case basis, then bodies that are properly staffed and resourced and that have credibility with the public to make those case-by-case decisions will be needed.

In the discussion following the end of the Session 8 presentations, Harvey Fineberg noted that Haas included on one of his slides the question "When should the precautionary principle be invoked?" This slide referenced a 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management. In this report, the following comments were provided on the question of use of the "precautionary principle:"

> Decision-makers must balance the value of obtaining additional information against the need for a decision, however uncertain. Sometimes a decision must be made under the precautionary principle. Every effort should be made to avoid "paralysis by analysis" where the need for additional information is used as an excuse to avoid or postpone decision-making. When sufficient information is available to make a risk management decision or when additional information or analysis would not contribute significantly to the quality of the decision, the decision should not be postponed. (Presidential/Congressional Commission, 1997:39)

Several participants, including Haas himself, noted that there may be a dearth of information for quantifying many aspects of the GoF research risk assessment. Dr. Michael Imperiale of the University of Michigan commented that there is a lot of debate about how one quantifies the risks and benefits and that there are different ways to look at this question. People can come up with different numbers depending on what is fed into the equation. In addition, benefits, as many people noted, may be intangible or difficult to predict. Some outcomes may not be evident until 20 years in the future. He stated that we should not kid ourselves into thinking we can come up with some formula to plug in all the variables and produce something that shows that the risks outweigh the benefits or vice versa. It needs to be acknowledged that it will be difficult to quantify the equation and, in addition, if we were able to determine exact numbers, then different individuals would place different values on different variables. Some may believe that the advancement of knowledge is much more important than whether risky research is going to inform vaccine preparedness. He believes that one of the best things to come out of the risk assessment would be to convince ourselves and the public that we considered the issues in depth and that whatever decision we made was not pulled out of thin air, but rather the result of a careful deliberative process.

Fineberg also asked Fischhoff whether there are special issues that should be considered in a situation such as that posed by GoF research where there is a very small likelihood of a catastrophic possible outcome. Fischhoff replied that there are people who say that the public is incapable of understanding small risks or making difficult decisions, but that he does not believe that the evidence supports that. He said he would not give up on the public on the basis of a glib meme about public incompetence. People respond in ways seemingly contrary to the evidence because the evidence has not been presented in a credible way. The precautionary principle is brought into play when the people who are uncomfortable with technologies are analytically outgunned by the officials in charge of those technologies. Proposers of projects, such as new power plants, are often well financed and reluctant to modify their proposals, which are

often assembled without listening to other people or incorporating other concerns. This can produce an either/or situation, and the people who object are simply outgunned. The precautionary principle may be the only arrow in their quiver, but it may make objectors appear to be demanding zero risk and unwilling to accept any kind of trade-off.

3

Gain-of-Function Research: Background and Alternatives

The field of virology, and to some extent the broader field of microbiology, widely relies on studies that involve gain or loss of function. In order to understand the role of such studies in virology, Dr. Kanta Subbarao from the Laboratory of Infectious Disease at the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) gave an overview of the current scientific and technical approaches to the research on pandemic strains of influenza and Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) coronaviruses (CoV). As discussed in greater detail later in this chapter, many participants argued that the word choice of "gain-of-function" to describe the limited type of experiments covered by the U.S. deliberative process, particularly when coupled with a pause on even a smaller number of research projects, had generated concern that the policy would affect much broader areas of virology research.

TYPES OF GAIN-OF-FUNCTION (GOF) RESEARCH

Subbarao explained that routine virological methods involve experiments that aim to produce a gain of a desired function, such as higher yields for vaccine strains, but often also lead to loss of function, such as loss of the ability for a virus to replicate well, as a consequence. In other words, any selection process involving an alteration of genotypes and their resulting phenotypes is considered a type of Gain-of-Function (GoF)

research, even if the U.S. policy is intended to apply to only a small subset of such work.

Subbarao emphasized that such experiments in virology are fundamental to understanding the biology, ecology, and pathogenesis of viruses and added that much basic knowledge is still lacking for SARS-CoV and MERS-CoV. Subbarao introduced the key questions that virologists ask at all stages of research on the emergence or re-emergence of a virus and specifically adapted these general questions to the three viruses of interest in the symposium (see Box 3-1). To answer these questions, virologists use gain- and loss-of-function experiments to understand the genetic make-up of viruses and the specifics of virus-host interaction. For instance, researchers now have advanced molecular technologies, such as reverse genetics, which allow them to produce de novo recombinant viruses from

BOX 3-1
General Virology Questions and Questions Specific to Influenza, SARS, and MERS Research

- Why/how does the virus infect and kill mammals?
  - What are the critical host range and virulence determinants of MERS-CoV?
  - Why are some influenza strains more virulent than others?
- Do antiviral drugs work, and how does the virus become resistant?
  - Can we identify antiviral drugs that are safe and effective for MERS-/SARS-CoV?
  - What drives the evolution of influenza antigenic change and antiviral resistance?
- Do current or novel vaccines or monoclonal antibodies provide protection, and can the virus escape?
  - Can we develop a SARS-/MERS-CoV candidate vaccine that is safe, immunogenic, and efficacious?
  - Can monoclonal antibodies be used safely for prevention and treatment?
  - Are there some influenza viral targets that will not allow escape from the immune system?
- How does the virus spread within animals or between animals?
  - Why do some influenza strains spread efficiently while others do not?
- Could the virus cause a pandemic?
- What is the likelihood of (re)emergence?
  - Will SARS or a SARS-like CoV re-emerge from bats or other animal hosts?

SOURCE: Subbarao's list of general and influenza/SARS/MERS specific questions in virology, symposium presentation, 2014.

cloned cDNA, and deep sequencing that are critical for studying how viruses escape the host immune system and antiviral controls. Researchers also use targeted host or viral genome modification using small interfering RNA or the bacterial CRISPR-associated protein-9 nuclease as an editing tool.

During Session 3 of the symposium, Dr. Yoshihiro Kawaoka, from the University of Wisconsin-Madison, classified types of GoF research depending on the outcome of the experiments. The first category, which he called "gain of function research of concern," includes the generation of viruses with properties that do not exist in nature. The now famous example he gave is the production of H5N1 influenza A viruses that are airborne-transmissible among ferrets, compared to the non-airborne transmissible wild type. The second category deals with the generation of viruses that may be more pathogenic and/or transmissible than the wild type viruses but are still comparable to or less problematic than those existing in nature. Kawaoka argued that the majority of strains studied have low pathogenicity, but mutations found in natural isolates will improve their replication in mammalian cells. Finally, the third category, which is somewhere in between the two first categories, includes the generation of highly pathogenic and/or transmissible viruses in animal models that nevertheless do not appear to be a major public health concern. An example is the high-growth A/PR/8/34 influenza strain found to have increased pathogenicity in mice but not in humans. During the discussion, Dr. Thomas Briese, Columbia University, further described GoF research done in the laboratory as being a "proactive" approach to understand what will eventually happen in nature.

In Session 8 of the symposium, Dr. Ralph Baric, University of North Carolina and a member of the symposium planning committee, explained that GoF experiments for CoV research encompass a very diverse set of experiments that are critical to the development of broad-based vaccines and therapeutics. Like Subbarao and Kawaoka, Baric listed experiments important for the identification of determinants of pathogenesis and virulence, defined the virus-host interaction networks, and described the alleles responsible for susceptibility and the host response patterns that drive a pathogenic or protective responses. However, he specifically noted that transmissibility studies for SARS and MERS-CoV actually fall in a different category than influenza research because of fundamental biological differences between these viruses. He first explained that the SARS-CoV has evolved over the past ~800 years to efficiently infect human cells that expressed the ACE2 viral receptor. To illustrate this, he shared sequencing results obtained from the Chinese during the 2003 SARS-CoV pandemic that show the gradual changes in the amino acid sequence across the genome associated with the expending epidemic.

Among the 16 mutations found at the end of the pandemic, two were associated with the increased efficiency of the civets' strains to use the ACE2 receptor to invade human cells. In vitro experiments on human airway epithelial (HAE) cells and in vivo experiments on transgenic mice showed that while the human strain can efficiently infect and replicate in cells expressing the human, bat, and civet ACE2 receptor, the civet strain cannot use the human ACE2 receptor. This demonstrates the human SARS-CoV strain evolved to maintain its capacity to replicate and cause expanding epidemics while keeping its capacity to cycle through civets and most likely retreat into the bat reservoir following the control of the epidemic. In most instances, GoF experiments looking at receptor interactions with SARS-CoV and MERS-CoV showed that in in vitro or in vivo models with a civet strain gain human ACE2 receptors but also lose the civet ACE2 receptor. Cell receptors for influenza viruses are relatively similar across different species, and this prompts a concern about possible increased transmission in humans from an influenza virus that is adapted for readier transmission in other mammals. By contrast, the ACE2 orthologue receptor interface for coronaviruses varies more markedly across different species.

APPLICATIONS OF GOF RESEARCH

Subbarao emphasized that current medical countermeasures are often insufficient largely because of resistance mechanisms that lead to "escape mutants," that is, drug-resistant strains. There is, therefore, a continual need to develop new antiviral drugs and additional options, such as immunotherapy, based on neutralizing monoclonal antibodies. Ultimately, GoF studies, which enhance viral yield and immunogenicity, are required for vaccine development. Molecular methods help with the characterization of antigenic variants, elucidate the biological basis for adverse outcomes associated with vaccine candidates, and determine the basis for attenuation and stability of vaccine candidates.

Subbarao also explained that one of the important applications of GoF research is the development of animal models, especially in the case of pathogens with pandemic potential, because to get approval to study a countermeasure compound in humans, the Food and Drug Administration's animal rule requires the presence of disease that mimics the human disease in an animal model. Influenza virus is unique in that its genome is fragmented; therefore, mouse models can be used to specifically identify viral determinants of virulence using single gene reassortment. Another type of GoF experiment, where the influenza virus is administered to ferrets and passaged a certain number of times, can lead to the characterization of molecular determinants of transmissibility. Subbarao reiterated

that there are currently no small animal models to study MERS-CoV virulence factors or transmissibility and that lab strains of SARS-CoV need to be adapted to specific animal models to induce clinical signs of disease.

Baric, in Session 8 of the symposium, expanded on the complexity to use and optimize animal models for studying SARS- and MERS-CoV transmissibility and virulence. He referred to a study done in Subbarao's lab where a SARS-CoV strain was adapted by serial passages into a mouse model. As described earlier, the adaptation of the virus to the mouse ACE2 receptor decreases its interaction fitness with the human receptor but also does not induce a lethal phenotype in mice because supplemental mutations need to occur. Further experiments demonstrated that increased virulence and replication efficiency do not correlate with increased transmissibility in the mouse model, making the use of GoF research safe in these models.

GOF RESEARCH AS DEFINED BY THE U.S. GOVERNMENT

Many participants pointed out during the course of the meeting that the broad term "gain-of-function" needs some refinement that will differentiate the type of experiments typically performed for basic virological research from experiments that clearly raise concerns. When asked to define where virological research crosses the line into GoF research as defined by the U.S. government (White House, 2014a), Subbarao responded that "the term gain-of-function is used by geneticists and is a vague and unsatisfactory term for microbiologists." This statement was echoed by Imperiale and many others during the discussion. Subbarao presented a list of experiments that encompass all influenza viruses, SARS-CoV, and MERS-CoV that can be reasonably anticipated to increase pathogenicity or transmissibility in mammalian species (see Box 3-2). Reflecting on this list, Dr. David Relman, Stanford University, and the panelists of Session 2 expressed the view that GoF experiments generating viruses with increased virulence, transmissibility, and pathogenicity would clearly define the line that would prompt the use of alternatives.

Imperiale explained that, with respect to the GoF terminology, whenever researchers are working with RNA viruses, GoF mutations are naturally arising all the time and escape mutants isolated in the laboratory appear "every time someone is infected with influenza." He also commented that the term GoF was understood a certain way by attendees of this symposium, but when the public hears this term "they can't make that sort of nuanced distinction that we can make here" so the terminology should be revisited. Fineberg, the session moderator, after listening to this set of talks, asked whether proposed GoF experiments should be individually reviewed to make a better judgment. Subbarao proposed

BOX 3-2
Where Does Virological Research Cross the Line into GoF Research as Defined by the U.S. Government?

- Adaptation of MERS-CoV to animal models
- Elucidating the molecular determinants of transmissibility by the airborne route (influenza)
- Elucidating the biological basis for adverse outcomes associated with candidate SARS vaccines
- Conclusive experiments to demonstrate the biological significance of
  - novel gene products
  - genetic differences between isolates from animals and/or humans for newly emerged viruses, e.g., H7N9, H5N8, H5N2, H10N7, and H10N8 influenza and MERS-CoV
  - Virulence determinants of newly emerged viruses, e.g., H7N9, H5N8, H5N2, H10N7, and H10N8 influenza and MERS-CoV
- Molecular basis for resistance to antiviral drugs and MAbs
- Viral evolution under immune pressure
- Viral evolution in the presence of antiviral drugs

SOURCE: Subbarao's ideas on when she believes virological research crosses the line into GoF as defined by the U.S. government, symposium presentation, 2014.

to first redefine the line because she is concerned that the pause in the current research "has swept far too many aspects of virologic research into the definition." Dr. Mark Denison, Vanderbilt University, suggested that a case-based approach should be considered for coronaviruses, for which a better understanding of the biology is needed. Along the same lines, Imperiale added that we should "take each individual case and call it what it is rather than try to come up with some acronym or two- or three-word term that can easily be misinterpreted." Baric reminded the audience during his talks that because there are currently no small animal models to study MERS-CoV, restrictions on this coronavirus should be lifted immediately.

Throughout the symposium, particularly in the final discussion session, there were calls for a clearer definition of precisely what types of experiments are really of concern. Dr. Tom Inglesby of the UPMC Center for Health Security noted that he thought that the origin of the term "gain-of-function" goes back to a 2012 meeting that he convened for the NIH on this topic. The term was used to replace more descriptive terms that indicated concerns about research that generates strains of respiratory viruses that are highly transmissible and highly pathogenic. According to Inglesby, this was the provenance of the term, and he suggested that it could be retired with something more descriptive. Dr. Gerald Epstein

of the Department of Homeland Security also called for clarifying which experiments are of most concern. GoF is clearly not the right descriptor, and he stated that it would be a tremendous service to have terminology that accurately describes those things about which we are most concerned. The same point was made by others at various times during the workshop (see in particular the summary of Relman's talk in Chapter 5).

ALTERNATIVES TO GOF RESEARCH

The essence of the debate around the risks and benefits of GoF research and the concerns it raises have naturally encouraged virologists on both sides of the debate to consider alternative methodological approaches. During his talk, Kawaoka discussed alternatives to GoF research mostly applicable to influenza research, such as loss-of-function research, use of low pathogenicity viruses, and phenotypic analyses. He further cited a review paper in which Lipsitch and Galvani (2014) stated that "alternative scientific approaches are not only less risky, but also more likely to generate results that can be readily translated into public health benefits." However, Kawaoka argued through specific examples that alternatives do not always provide the full answer to key questions. For instance, he cited work by Tumpey et al. (2007) and Imai et al. (2012) on mutations responsible for the loss of transmission capabilities of the 1918 influenza strain between ferrets and noted that this work required GoF research because a loss-of-function approach did not provide the complete picture. In addition, although working with low pathogenic avian influenza viruses provides a safer approach, Kawaoka explained that "highly pathogenic avian influenza differ from low pathogenic viruses in their kinetics of virus replication and tropism" and therefore the data can be misleading. Other alternatives discussed by Kawaoka and Dr. Robert Lamb, Northwestern University, in Session 8 of the symposium were cited from the recent review paper by Lipsitch and Galvani (Box 3.3). Kawaoka concluded that even if these approaches offer safer alternatives to GoF research of concern, for some questions researchers cannot rely solely on them because the phenotype of and the molecular basis for these new traits have been identified by GoF research but not by alternative approaches.

Alternatives to in vivo models have also been attempted to study SARS-CoV. Baric presented the work by Deng et al. (2014), who proposed to optimize a safer mouse model for in vivo drug screening using the non-pathogenic recombinant Sindbis virus (alphavirus) expressing a SARS proteinase. Although the investigators succeeded in enhancing mouse survival when the virus was mutated in the protease site, targeting the engineered virus with protease inhibitor failed to protect the mice. A few reasons might explain the results and constitute challenges of using alternative viral strains such as virus tropism, bioavailability of the drug,

BOX 3-3
Alternative Research Methods with Potentially Less Risk

- Molecular dynamical modeling of influenza proteins and interactions with inhibitors and receptor
- In vitro studies of specific properties required for human adaptation, using single proteins
- In vitro studies of genetic interactions between loci in one or several viral proteins using replication-incompetent viruses – epistatic interactions
- Sequence database comparisons of genetic properties of human and avian adapted viruses
- Comparisons of human seasonal isolates and zoonotic isolates from infected humans and avian isolates

SOURCE: Lipsitch and Galvani, PLoS Med included in Kawaoka's symposium presentation, 2014.

and virus titer in the targeted organ. Baric concluded that this type of indirect model can lead to misinformation that can complicate downstream development of treatment.

When discussing risk mitigation, Imperiale said he believed that "you can develop safer approaches to do these types of experiments; it just needs a little bit of imagination on the part of researchers." An example that was cited several times during the symposium is the work by Garcia-Sastre and others (Langlois et al., 2013). The group exploited species-specific endogenous small RNAs, which can shut down some basic functions, such as replication, found in the human and mouse respiratory tract but not in the ferret. Its engineered influenza A strain, which contained this specific microRNA target site, did not prevent influenza replication and transmissibility in ferrets, but it did attenuate influenza pathogenicity in mice and presumably in humans. Imperiale and later Kawaoka agreed that it constitutes a promising approach. During his talk in Session 8, Lamb also listed some mitigation and reversibility approaches, such as the use of:

- Viruses with drug sensitivity (if not studying drug resistance)
- Vaccinations for strains used as genetic backbone, if possible
- Existing virus where immunity is widespread
- Mutation that confers acid stability (Zaraket et al., 2013)
- Mutation in HA multi-basic cleavage site (depends on GOF sought)

4

Potential Benefits of Gain-of-Function Research

The benefits that have resulted from the billions of dollars invested in biomedical research over the past several decades are seldom disputed. Biomedical research has made enormous contributions to the understanding of disease and the development of cures through the creation of countless innovations for improving and protecting human health, including new animal models and more effective vaccines and drugs. However, as pointed out by Dr. Ronald Atlas, from the University of Louisville and one of the symposium planning committee members, the benefits of basic biomedical research for medical practice and public health may be long term and their value not immediately evident. The results of particular types of research cannot always be predicted, and benefits are often serendipitous. Because it is not possible to predict what breakthroughs may occur as a result of fundamental research, it is impossible to quantify the benefits of fundamental research for risk/benefit analyses. Long-term research benefits are achievable, but it is not possible to specify what these are when the research is initiated.

Research using Gain-of-Function (GoF) techniques is no different with respect to what it can achieve in the long term, at least according to many of the symposium participants. Atlas noted that, although there was no attempt to achieve a consensus, no disagreement was voiced to the repeated claims of various presenters that in the short term GoF research is helpful for adapting viruses to growth in culture and for developing essential animal models for emerging pathogens, such as Middle East Respiratory Syndrome coronavirus (MERS-CoV), and escape mutations

to understand drug resistance and viral evasion of the immune system. In the long-term it may also allow the generation of information that is not obtainable through other methods, but whether all the long-term benefits envisioned for GoF research will actually be realized is still unclear. Vaccine producers in particular disagree on whether GoF methods are essential for vaccine development, so the contributions of GoF research to vaccine development need careful evaluation. Increasing reliance on gene sequences to predict phenotypes may increase GoF research's importance over time. As was clear from the presentations in Session 4 of the symposium, there is wide recognition that it is not yet possible to predict phenotype from genotype, but Dr. Philip Dormitzer, from Novartis Vaccines and a member of the symposium planning committee, noted that as more genotype-phenotype linkages are established, it may enable keeping certain viral characteristics out of vaccine strains.

Two symposium sessions were devoted to presentations on the potential benefits of GoF research, one focusing on the role of GoF in surveillance, detection, and prediction and the other on its role in treatment and response.

SURVEILLANCE, DETECTION, AND PREDICTION

The first presentation in Session 4 was given by Dr. Stacey Schultz-Cherry, St. Jude Children's Research Hospital, who discussed the information garnered from GoF studies about what she believes are its public health implications. Her home institution is one of five National Institute of Allergy and Infectious Diseases (NIAID) Centers of Excellence for Influenza Research and Surveillance in the United States and focuses on the animal-human interface. St. Jude is also a World Health Organization (WHO) collaborating center for studies on the ecology of influenza and is part of a global influenza surveillance and response system that includes six WHO collaborating centers and 144 national influenza centers throughout the world. St. Jude collaborates with colleagues in the animal health sector and their main role is to decide on the influenza strains that are incorporated into the seasonal flu vaccines. They also decide whether vaccines or candidate vaccine viruses are needed for emerging zoonotic threats.

The national influenza centers conduct viral strain surveillance throughout the year, looking at the genetic information from human as well as emerging zoonotic viruses. Every February and September, representatives from the WHO centers and central regulatory laboratories as well as animal health experts go through the surveillance data to decide on which viruses to choose as vaccine strains. This information is given to the vaccine manufacturers and regulatory agencies, and 6-9 months later

the vaccines become available. She described many of the complexities of the process. She noted, in particular, that determining the function of amino acid changes in the viruses circulating in the field is one of the key tasks. As an example, she discussed an ongoing outbreak of H5 viruses in Cambodia. Through GoF research, it has been determined that the presence of certain genetic markers in the outbreak strain suggested that this particular virus could be more readily transmitted, at least in ferrets. This information has provided the persuasive factor to move forward with the development of a vaccine.

Schultz-Cherry noted that GoF research-derived information is also used for risk assessment. The U.S. Centers for Disease Control and Prevention has developed a risk assessment tool, the Influenza Risk Assessment Tool, to rank the risk associated with particular viruses. She stated that the result of using the Tool is not a prediction of the next pandemic, but rather an objective means of prioritizing viruses for future risk management. The Tool looks at the properties of a virus. What kind of receptors does it bind to? Is it more mammalian or avian? Does it transmit in animal models, or does it have molecular signatures that would suggest transmissibility? What is its genomic variation? She stated that all of this information, especially the molecular determinants of transmissibility, has been generated through GoF studies at some point, perhaps even as far back as the 1970s. She stated that the ability to prioritize is important because of limited resources; vaccines cannot be made for every new emerging virus.

Schultz-Cherry's final points dealt with the limitations of these studies. Phenotype still cannot be predicted from genotype. We may know a lot from studies of particular amino acid changes in one strain of virus that may not apply to another strain. She noted that opponents of GoF research have said that this is a reason to not continue this work. She would argue, however, that inability to predict phenotype is precisely why GoF studies must continue so that eventually this inability can be overcome.

During the discussion following the presentations, Schultz-Cherry was asked what is the trajectory of the information being used for vaccine candidate selection? She explained that the risk assessment tool is continually updated to add new information about molecular determinants of virulence and transmissibility. She believes that the more information we have, the better we will be able to predict the risk of a pandemic and then use that prediction to prioritize vaccine strain selections and make the vaccines available.

Dr. Christophe Fraser of Imperial College, London next spoke about potential pandemics. He began by stating that he would scrutinize the benefits of GoF experiments using a narrow definition of GoF as dealing

with the transmissibility of the highest risk potential pandemic pathogens (PPPs). He is the Deputy Director of the Center for Outbreak Analysis and Modeling, which is also a WHO Collaborating Centre for Infectious Disease Modelling, located in London. He and his colleagues at the Centre have worked on the Severe Acute Respiratory Syndrome (SARS) outbreak, the initial response to the 2009 influenza pandemic, and have synthesized a variety of surveillance, neurological, and epidemiological information. In 2014, their work turned to both MERS, for which they were trying to quantify its transmissibility to humans, and Ebola as part of the WHO response team. He noted that, on a global scale, the interventions in the event of an outbreak are quite simple—well-organized classical public health tools. The key aspect is timeliness, and the classical tools are diagnostics, social distancing, and risk communication. Probably the area most lacking at the moment on a global scale is rapid diagnostics to allowed triaging of people, which has been made very clear with Ebola. Data systems, multidisciplinary validation, and sharing of data and samples are all required. There is also a huge role for basic science, but once an epidemic has started, the value of information from this limited realm of GoF work on transmissibility is unclear. The role of such work is clearly going to be in predicting pandemics. He stated, however, that H5N1, H7N9, MERS, and Ebola had all clearly been identified as threats prior to any GoF-PPP experiments, although this is less the case for the 2009 H1N1 outbreak and SARS. Nevertheless, the failure to predict outbreaks of the first four pathogens he listed was due to surveillance gaps, not a lack of understanding. Of the viruses that emerged in 2009, there were no closely related viruses found by surveillance in any swine populations for 12 years prior to the emergence of H1N1. MERS also emerged from a complete surveillance gap.

The next utility that has been claimed for GoF research-derived data is for predicting emergence. The data from the two experiments on H5N1 transmissibility were plugged into a model by Colin Russell and Derek Smith (Russell et al., 2012), who concluded that it is not possible to calculate the level of pandemic risk precisely because of uncertainties in some aspects of the biology. Fraser stated that he very much endorses that statement; it is not possible to calculate the level of risk from the mutational landscape. The aim in Russell et al. (2012) was to conduct basic science to understand the factors that increase or decrease risk, not to assess the actual risk. Russell's work built on earlier work that attempted to predict pandemics. The earlier work from Jamie Lloyd Smith tried to establish a general rule, which is that infection begets transmission and transmission begets epidemics. Things that can cause transmission are much more likely to result in epidemics than things that are not already transmissible.

The WHO uses an empirical, rather than a theoretical, approach,

meaning that alarm bells should be based on human cases and clusters and the key is surveillance and sharing of data. However, as Fraser had previously noted, there are limitations, especially given that for many years there was reluctance to acknowledge clusters of infections because of the fear of escalating the WHO alert levels and the resulting consequences. In terms of surveillance and response, it is of course very useful to know what viruses are out there, but it is promptness that is critical. To contain an epidemic at its source, there is a window of days in which to intervene. Once the epidemic gets going, the scale of the problem will double every week. The most suitable response would be based on the timely reporting of cases.

Fraser believes that pre-pandemic vaccine strain selection is the crux of the argument. Timely development of vaccines could be transformative. Vaccine seed stocks can speed this up, but there are other rate-limiting steps, especially international agreements on the regulation and conduct of human trials. He also believes that the objectives should be to:

- prioritize strains with evidence of infection and transmission;
- cover antigen space, and monitor antigenic drift;
- plug gaps in surveillance;
- make more/faster seed stocks (Dormitzer et al., 2013)?

Fraser concluded with the following:

- The direct benefits for enhanced surveillance and model-based prediction of GoF experiments with PPP should not be overstated.
- The indirect benefits of basic science are likely huge, but the rationale for working with dangerous pathogens requires benefits that outweigh risks and opportunity costs.
- The benefits of GoF with PPP for pre-pandemic vaccine production should be probed in depth.
- The risks are real and present (Lipsitch and Inglesby, 2014).

A participant asked Fraser about what he would require to be confident about using data from GoF or other experiments in his modeling? He responded that the tools required for this lengthy, although worthwhile, journey must be available. The issue centers on the risk taken at the beginning of the journey. Earlier in the morning, Fineberg mentioned that, by their nature, pandemics provide many years to think about the tools but only infrequent and limited time to acutally test them. Weather forecasting has improved dramatically because weather forecasters can test their models daily and receive many complaints when they are wrong. The situation with pandemics is not like that.

Dr. Colin Russell of Cambridge University Infectious Diseases responded to the two previous presentations as the last speaker of Session 4. He noted that both of the previous speakers touched on the ability to predict risks for pandemic viruses and on the ability to produce vaccines in a timely manner, and to ensure that there are enough vaccines to go around and provide a chance to mitigate the early spread of disease. However, the more we learn about nature, the more we understand that there are a vast number of undescribed viruses out there, many known only through sequence data. He stated that genotype to phenotype prediction is one of the holy grails of influenza biology research. However, much more research is required to reach this goal. He referred to a National Institutes of Health workshop for which he was lead organizer in the fall of 2013 that brought together experts in virology, epidemiology, and other fields. It included participants from both sides of the GoF debate, and a key focus of the meeting was to rectify the limitations in the ability to make inferences about the phenotype of influenza viruses from genetic sequence data alone. A full report of this workshop was published in October (Russell et al., 2014). A key question in the discussions was whether the effects of mutations are dependent on the viruses in which they occur. A variety of studies suggest that the effects of particular mutations are strongly likely to depend on the genetic context in which they appear. First, in 2006 Jane Stevens, Ian Wilson, and others published a paper in the journal *Science* (Stevens et al., 2006) about GoF research, investigating the potential for a virus to switch receptor binding from avian-like to human-like. This work was among the first to demonstrate that single amino acid substitutions could cause such a switch. But the authors concluded that knowledge of genetic changes in circulating virus isolates by themselves obviously cannot be used to predict the impact of receptor binding specificity, let alone affect the results of future mutations (Stevens et al., 2006). It is worth bearing in mind, Russell stated, that there is a great degree of genetic diversity in the H5 virus. Other studies have found that the effects of mutations in other H5 viruses depend on the clade of H5 viruses in which the substitutions were produced. These residues alone cannot be used as reference points with respect to specificity in H5N1 strains, but when combined with other data, the presence or absence of these mutations can be informative. None of this should be in any way construed to undermine the value of the studies, but highlight the impressive need for further work. In short, Russell believes that, given the incomplete state of knowledge, there is a risk of overestimating what is known based on sequence data alone. Focusing too much attention on the presence or absence of particular mutations may cause other mutations or even other traits yet to be identified to be overlooked.

Gavin Huntley-Fenner asked the panel members what sort of public

health system would be needed to justify the status quo and whether the risks and benefits of GoF research are balanced from this public health perspective. Fraser answered that transmissible viruses makes GoF research a very special case. In terms of general basic science, we never have to justify that to the same degree, luckily, because otherwise we would find it difficult to move forward. Basic science is a much broader portfolio where the risks are very small. The real crux of the GoF issue is separating out that very small number of experiments. We need a much wider frame for all experiments, where occupational health risks are not an order of magnitude higher than public health risks.

Laurie Garrett of the Council on Foreign Relations commented to Schultz-Cherry that her statement that the risk assessment model would be adjusted differently if H5 was in Canada speaks to the core of the whole problem. Risk is about rich people, which is about 5 percent of the global population, if that. She stated that we have never once delivered vaccine to poor people around the world for any epidemic/pandemic situation in the history of the planet, have never delivered clinical tools, and have never delivered diagnostic tools. Garrett had just come out of quarantine for Ebola, and there is nothing that can possibly be called a rapid diagnostic available for Ebola. So when the Council on Foreign Relations reviewed the whole question of GoF use and issued its memorandum to the White House (available at www.CFR.org), it concluded that the most fundamental problem is that the International Health Regulations have never been fully implemented. Garrett stated that none of the wealthy nations has assisted poor nations to raise them to capacity and that "none of the benefits will ever be available to the majority of planet Earth and none of them are getting the toolkit to minimize or mitigate risk. We are having a very American conversation that excludes the rest of the planet."

Schultz-Cherry responded that her remark about having H5 in Canada was designed to make people think about risk versus benefit and to reflect that doing more work can democratize the surveillance process. With more work, it could become cheap and easy to assess the threat of viruses. If this could be done, we could radically change the way we do surveillance worldwide and we would not have the same sort of geographic distributional issues that are of concern now.

Dr. Gregory Koblentz, George Mason University, asked Schultz-Cherry about the proven accuracy of the risk assessment tool used for selecting flu strains for yearly vaccines. She, in turn, called on Dr. Ruben Donis of the CDC to comment more about the risk assessment tool. Donis noted that the risk assessment tool is a product of the global community of scientists working on both human and animal health. It is a product of the realization of the gaps in surveillance that were noted in Fraser's presentation. It was developed to ensure that we have a comprehensive

way of evaluating all the possible viruses that are circulating in animals that could reassort, recombine, and change the phenotype and eventually emerge as pandemic viruses. The tool attempts to develop a comprehensive review of all of the potential threats.

Via the web, Dr. Daniel Perez, University of Maryland, asked whether the potential of strains that resulted in past pandemics to affect humans would have been moderated if we had had the opportunity to sequence them. Fraser stated that understanding how a virus expands its host range from swine to humans requires a lot of information. The validation of the genotype to phenotype prediction tools really should address that question. Russell added that he did not think that having sequence information at the time of earlier pandemics would have forewarned of the emergence of those viruses, which again speaks to the incomplete nature of knowledge and the critical need for further work.

Another participant pointed out that there is probably a very large number of variables involved in understanding viral pathogenicity. Given the number of variables, is there much chance of doing anything useful? Russell and Fraser both agreed that this is a very complicated problem, which is why more experimental work is needed to help reduce the dimensionality. But what we currently know cannot help us very much in understanding what will occur in the next 5 years. However, science is an incremental process. The increases in understanding that have been achieved from the work that has been done so far have been helpful. In terms of translating directly into public health improvements, that is a pretty substantial leap to make. But saying we will not get there will not undermine science. Nevertheless, tools that can deal with perhaps thousands of genetic traits and phenotypes are needed. It is not about the mutations but rather about the function of the mutations. We could reach the state where we sufficiently understand the traits that a virus needs to adapt to humans and identify ways to test for those that are either independent of sequence or a metalevel of sequences.

Another participant made the point that had the 2009 pandemic strain been seen in animals instead of humans, it might have been falsely viewed as having low virulence and transmissibility and would have been discounted. Fraser agreed that the fact that our knowledge is incomplete right now creates a risk of discounting viruses that lack a certain number of substitutions when in fact we should be concerned about the risk.

Dr. Ron Fouchier, Erasmus MC, commented that he believes a lot is being asked of papers that were only published in 2012 and for which the follow-up work has been shut down twice for extended periods. This is work in which the phenotypes, not just the genotypes, are being studied. He agreed with Fraser that although he cannot yet predict phenotypes from genotypes, the assays produced by his work are being used to look

at phenotypes in surveillance, which means a better job is already being done. He made a plea for more basic science to follow up on his work, which is still in the early stage. Fraser responded that the basic science is not under question. The question is: Should we be starting with experiments that have orders of magnitude higher risk than other work in the area?

TREATMENT AND RESPONSE

Session 5, moderated by Baruch Fischhoff, consisted of a panel discussion with four speakers. Each panelist was given about 5 minutes and then the session was opened up for discussion.

The first speaker was Philip Dormitzer, who described how GoF research and the regulation around research affect the real-world case of trying to apply virology to a public health situation. For the purpose of his talk, Dormitzer described the chronology for the production and delivery of the 2009 H1N1 influenza pandemic vaccine, an "historical reminder," for which the response was the "fastest ever, but still came after the disease peaked" (Borse et al., 2013). In fact, an estimate published in *Emerging Infectious Diseases* (EID) showed that for every week of acceleration of vaccine supply, an additional 300,000 to 430,000 U.S. cases could have been prevented. Dormitzer explained that Novartis, in collaboration with the J. Craig Venter Institute (JCVI) and Synthetic Genomics Vaccines (SGVI), are now working together to establish a process for rapid generation of synthetic influenza viruses that includes GoF studies based on sequence motif data to guide the genetic assembly of the vaccine. For instance, the Novartis research team routinely screens for phenotypic traits of interest and can specifically remove or mutate strains with either polybasic cleavage sites in the hemagglutinins (HA) (found in highly pathogenic avian influenza viruses [HPAIV]) or neuraminidase (NA) gene markers of resistance. For that specific example, Dormitzer explained that the process from the identification of the relevant HA and NA sequences for the new influenza strain to the genetic identity confirmation of the vaccine virus lasted about 1 week. However, the next phase leading to the first large-scale clinical trial took months because of various well-intentioned regulations and policies to protect the food supply in the United States. Notably, because Novartis could not obtain a U.S. Department of Agriculture permit, this phase involved international research collaboration with Germany before taking the vaccine back to the United States, which unintentionally slowed down the human vaccine development. Under U.S. government regulations on select agents, vaccine development against HPAIV is counter-productive because "you can't really put an entire manufacturing facility under select agent conditions and

still have a factory that can produce seasonal vaccines in an economically competitive way" and in a timely manner. Also, as Dormitzer pointed out, he "couldn't apply any of this [GoF research] technology." Therefore, if adaptation of vaccine virus to increase yield or more modern synthetic biology were captured by GoF regulations, then additional unintended impediments to timely vaccine supply could be created.

Next, Ralph Baric presented his view on the impact of GoF restrictions to the emerging coronavirus vaccine and therapeutic research. Baric started his talk by reiterating that no vaccine has been approved for MERS-CoV or SARS-CoV in the midst of an ongoing MERS-CoV outbreak. Baric explained how new restrictions reduce public health preparedness to respond to future SARS-like CoV outbreaks. He explained that the original vaccine target for the SARS-CoV outbreak 2002-2004 strain was 99 percent identical between human and civet (Ge et al., 2013). However, metagenomic sequencing showed that bat SARS-like CoV (SL-CoV) with 65 percent to 95 percent sequence homology, can constitute a large pool of strains with pandemic potential against which countermeasures need to be developed. To evaluate whether the existing vaccine and drugs work on these strains, Baric's team and others used two types of approaches. The first was based on the production of CoV pseudotypes coated with virus spike-like proteins that can potentially engage the human angiotensin converting enzyme II (ACE2), which is the SARS-CoV cellular receptor molecule. This method constitutes a safe and ethical research alternative approach. Similarly, chimeric recombinant viruses that encode spike-like proteins as part of the virus particle can also be used. While studies using pseudotypes and structure-based prediction confirmed the existence of a bat SL-CoV that can infect human cells, only studies using GoF chimeric virus identified an additional bat SL-CoV as a potential threat. Baric noted that both bat SL-CoV were less virulent in a mouse model. Importantly for public health implications, data further showed that existing vaccine and human monoclonal antibody therapy failed to protect against these two newly identified bat SL-CoVs, leading Baric to point out that "we are vulnerable" to SL-CoV bat strains that currently exist in nature. The second part of Baric's talk described how robust animal models are essential for vaccine/drug design, safety testing, and performance outcomes. He explained that SARS-CoV replicates poorly in mice (Frieman et al., 2012) and although his team and Subbarao's lab have developed mouse-adapted strains, the in vivo correlates of infection vary widely depending on the model used. For example, he described some collaborative work done on inbred and outbred mice demonstrating that in some cases the vaccine could have caused increased mortality in some individuals and emphasized the need for better animal models for SARS-CoV vaccine research. In the case of MERS-CoV, the epidemic is ongoing and no robust

animal model exists because routine GOF studies, including passage in small animal models, have failed. Baric called for an immediate lifting of the restrictions on MERS-CoV research on animal model development. This was echoed by other participants during the final discussion. For example, Peter Hale of the Foundation for Vaccine Research stated that he thought the inclusion of the coronaviruses in the "pause" was "muddying the waters" and that he did not detect any enthusiasm among SARS and MERS investigators to increase their transmissibility. This point was also made strongly during the discussion following the session.

The next speaker was Dr. Jerry Weir from the Food and Drug Administration's Center for Biologics Evaluation and Research, whose team participates in the selection of strains for the yearly influenza vaccines and regulates viral vaccines to ensure that they are safe and efficacious for human use. Weir offered some comments about how the regulatory process views some of the experiments and techniques addressed by the symposium speakers. He stated that there are actually not very many, if any, regulatory issues associated with the type of virus manipulations that were under discussion (i.e., improved types of seed development, reverse genetics, manipulation of virus genomes to improve vaccine virus stability or performance). Manufacturers already licensed can submit a supplement to the license that is evaluated for using a fairly standard process. In lieu of giving examples of how GoF research can influence a process, Weir mentioned a few challenges that still remain in vaccine development for the influenza virus. In general, for the seasonal strain selection and the preparation of pandemic vaccine strains, the major challenge is the existence of very large gaps in our knowledge of how genotype sequences relate to phenotypic changes. Weir stated that strain prediction and selection remain a "guessing game . . . for which improvements are desperately needed." In addition, for other factors such as transmissibility or virulence, a lot is not known and improvements are also needed there. To complicate the matter, the incorporation of four, instead of three influenza strains in the seasonal vaccine is a challenge every year for the different players in the global community that pick the vaccine strains as well as the manufacturers who need to deliver the vaccines in a timely manner. For them the yields of vaccine viruses need to be improved with the challenge of limiting factors such as poorly growing strains among the four chosen. In his view, Weir believes that, as broadly defined, "GoF studies have had an enormous influence on how we develop vaccines over the years . . . and can help improve the process with the challenges that we still face."

The final speaker was Mark Denison, who explained his view of GoF studies in MERS-CoV and SARS-CoV countermeasure development and how oversight or regulation might be limiting. Denison reminded the

audience about the basic research and ongoing challenges that remain in the development of therapeutics to SARS and MERS-CoVs, emphasizing, like other speakers, the need for in vivo and in vitro models to identify common mechanisms and determinants of resistance. He then moved to a case study involving GoF research and asked the audience whether they would consider giving or taking "a live vaccine with a virus that has an engineered increased mutation rate," for which only a few people raised their hands. The question was an introduction to a series of studies showing that CoVs, contrary to other viruses, express a proofreading exonuclease (ExoN) normally only found in bacteria and eukaryotes. When this ExoN was inactivated, the CoV mutation rate was increased by 20-fold. Normally, mutations allow tremendous variation in viral populations and presumably increase adaptation, fitness, virulence, and therefore public health risks. However, GoF studies demonstrated that SARS-CoV with the inactivated ExoN were less fit, attenuated in a mouse model of lethal SARS-CoV, could not compete with the wild-type virus, and could therefore be used as a target for therapeutics development. This work was also adapted to other RNA viruses with encouraging results. Denison used this case study to reflect on the implications of new regulations and guidelines if he wanted to create a mutated strain of a virus and test it in an animal model. In conclusion, Denison stated that he believes that because assumptions are usually wrong, GoF research that includes "passage for adaptation and resistance in in vitro and animal models are essential components of therapeutics development" and that to his knowledge no bioinformatics or predictive safer alternative approaches are effective to develop new countermeasures.

Following the panel member's presentations, there was discussion with the audience. Fraser asked Dormitzer how he would propose to reconcile, practically, the need to conduct very dangerous research without casting the net too wide. Dormitzer responded that what is first needed is a very clear and limited definition of the sorts of research that require particular attention. As Relman discussed, experiments that combine increased transmissibility, virulence, and and lack available countermeasures are very concerning. But we have to make sure that the definitions are not too broad so that they do not capture a lot of other work. Second, there needs to be a distinction between the highly diverse work performed for basic research and the much more restricted, but more urgent, work needed for vaccine development. A classic example is H5N1 vaccine development. There have been at least 26 H5N1 strains that have been attenuated all in the same way. But for the 27th one, the often months-long routine must be goone through again. We need clearly established, well-defined pathways to get vaccines quickly and not encumber the process with regulations.

Relman also stated that he does not think that there is a major question about the value of MERS and SARS research, even that research that currently falls under the rubric of GoF. Restrictions do, in fact, hamper the quest to develop countermeasures, etc. What he thinks is a more interesting question is whether there is a very discreet and specific set of experiments with MERS and SARS that you might not want to see undertaken. For example, would it be appropriate to deliberately start with a highly virulent human isolate of MERS and then attempt to add to that much enhanced human-to-human transmissibility by the respiratory route? Baric responded that he did not know of anyone doing transmissibility studies with the human coronaviruses. Unlike flu, there are currently no small animal models suitable for MERS or SARS transmissibility assays. This is mostly due to receptor incompatibility between the human and any small animal models. Optimization assays to enhance virus transmissibility between ferrets, for instance, would probably decrease the ability of that modified virus to bind to the human ACE2 receptor. Relman reformulated the question to include the possibility of using transgenic ferrets with the human receptor, but Baric explained that the human receptor itself is not sufficient and that other proteins are essential for viral transmissibility and, therefore, the results in transgenic models would not be predictable.

Denison added that nobody would have as a goal or would support trying to increase virulence and transmissibility of MERS or SARS. That is why he recommends the use of a case-based approach that looks at how we really do science. Denison shared his approach when sending a proposal through study sessions or review process at a funding institution. For him, instead of trying to define "boundaries of absolute," the real question should always be, "What is the best approach to answer that question?" Then, depending on the stage of the review process, the response should be iterative to be adequately addressed.

Inglesby asked Dormitzer whether the annual process of production of flu vaccine relies on research using highly transmissible and highly virulent strains. Dormitzer responded that this is not the case and that the goal is quite opposite—to take a strain found in nature and transform it into something that can be manufactured efficiently by increasing its growth rate in cell culture or eggs. Inglesby then asked whether virulence and transmissibility are traits that can be distinguished from increased growth capability. Dormitzer stated that there is precedent that shows that adapting viruses to grow better in cell culture does not, in general, increase their virulence or transmissibility, whereas passaging from animal to animal often does. He stated that we also need to distinguish between two things: the need for very rapid production of new antigenic variants, which should start on the day it is found that there is a new

variant causing disease, and the development of the vaccine backbone, which could be used in multiple variants and which you do not want to take forever. It is not the same issue when facing an emergency.

Dr. Simon Wain-Hobson, Institut Pasteur, echoed Denison's presentation by citing work done on polio by John Holland 15 years ago that showed that when chemical mutagenesis is combined with a rapidly evolving RNA virus such as polio, the fitness of the virus goes down. Several members of the panel agreed. However, Denison raised the issue of perception in the current environment and under the current policy circumstances. Such proposals might not necessarily be vetted even though most of the time we can not know the answers until the experiments are conducted.

Another questioner from the webcast asked Dormitzer whether, in his opinion, GoF research is essential for future development of intervention strategies against various pathogens. Dormitzer responded that he thinks it depends on whether you are talking about the short- or long-term. He stated that GoF research is not going to help pick next year's flu vaccine, but if one is making viruses for use in manufacturing and a certain genetic motif that correlated with high transmissibility is known, then one could make sure that the motif is not included in the vaccine strain. GoF research has utility for such purposes. The other thing is that vaccine manufacturers are increasingly figuring out how to take genetic data and use it to predict what they want to make. That would be a genuine utility if it could be done. The question is whether we can do that kind of science in a way that does not create more problems than it solves. There is potential for GoF research to improve vaccine production, but it is not today except for limited instances; it has long-term potential for this purpose as long as the work can be done without inordinate risk. Denison asked whether any "bad" GoF experiments were performed to discover the polybasic cleavage site associated with high virulence. Dormitzer listed what is believed to have led to this discovery, including studies on correlations between the presence of these sites and clinical observation of virulence in birds; discovery of plausible mechanisms looking at cleavage proteins expressed in different cells; and loss-of-function and GoF studies to make sure that the gene identified is the correct one. Denison's point was that a series of experiment led to that conclusion.

It was clear, however, that there is a substantial disagreement over the value of GoF research for vaccine development. Lamb, in a later session (Session 8), stated that he thought we should modify the mantra that GoF research is useful for vaccine and antiviral drug development. He thinks that this point is overused and oversold. Hale also commented during the final discussion that he agreed with Lamb, we do need to modify the mantra that this research will help develop vaccines and antivirals.

He said that he and his Foundation fully endorse that sentiment. It is an argument that is made over and over again without evidence to substantiate it. He believes that in terms of development of better vaccines, GoF research has little or no benefit, and if there is any benefit, then it is tiny and way down the road. In the meantime, he said, it is not worth the risk and there are other priorities.

Dormitzer responded to the latter comment and acknowledged that the community of people who make vaccines is divided just as much of the symposium audience was divided. He stated that the basis for that division is informative. Flu vaccines today are still made by very, very old techniques. One looks at what is spreading, sees if it has changed, and then picks the strain. There is not a lot of basic science in this; rather it is 1960s science. In 2009 we were not able to get the H1N1 vaccine out until after the outbreak had peaked, and many people have commented that the current flu vaccines, although somewhat effective, are not good enough. A lot of people who work on vaccines think we need to do things better. One way to do things better is to take advantage of the available information, particularly sequence-based information, so we can do things faster and make vaccines better. Information from GoF research can contribute to identifying risks earlier so countermeasures can be taken earlier. Dormitzer said he does not think it is the case that GoF research is essential to the current vaccine system as it is generally practiced today, but it is not useless. It is clearly part of the trend to understand and predict what can be done better and to help respond quickly. That does not mean it is open season to do what you want and forget the risks. A balance is needed. But he was firm in his statement that the vaccine producers are not universally of the opinion that there is no use for GoF research.

Koblentz asked whether the coronavirus researchers had a sense and could comment on why MERS and SARS were included in the "pause" on GoF along with influenza. Denison believes that, despite the circumstances, the inclusion of SARS- and MERS-CoV in the "pause" demonstrates that this is not about one virus but more about the issue of how we address critical questions in science and what constitutes appropriate review and safety among the different research institutions. He believes that whatever the question asked, whether about replication or virulence and transmissibility, the science should be the same and should follow an iterative process that incorporates risks, milestones, and points to change along the way.

As a follow-up from Relman's question on transmissibility in MERS and SARS animal models, Koblentz asked Baric to clarify which set of experiments he would use to study transmissibility. Baric explained that many variables are needed to make a model to enhance transmissibility, but if he had the perfect model to do these experiments he would not do

them. Later during the discussion, prompted by Inglesby, Baric added that because the CoV interaction barriers are species specific, the only real absolute model that could be used would be human, so he certainly would not do the experiment.

Fraser asked Denison to clarify what he meant when he said that no one would want to increase the pathogenesis or transmissibility of MERS and, therefore, that the regulation should not apply to MERS and SARS research, especially because this is what the debate is about. Denison explained that he thinks that increasing transmissibility of human coronaviruses is not a goal. He then described the importance of research on wild-type or genetically modified animal models or cell cultures to understand determinants of pathogenesis or virulence factors. No one has the goal to increase these characteristics, but researchers need to be able to study the virus or they would need to rely on epidemiology and surveillance, which are not adequate to answer the question. Denison also stated that to his knowledge there is no other approach to develop countermeasures and vaccines.

Richard Roberts, New England Biolabs, asked whether experiments on dangerous traits that exist in highly pathogenic and virulent strains could also be done on strains that have already been incapacitated in some way. Denison agreed that on a case-by-case basis, if it is possible, then a safer approach is always preferred, but that it depends on the genetic background of the strain of interest. As an example, Denison explained that sometimes a certain type of loss- or gain-of-function experiment is undertaken on BSL-2 strains that are 90 percent identical to more virulent strains, but that the small genetic background differences and therefore structure can greatly influence the outcome of the experiment. When one has strains that are not genetically identical or from the same clade, it may not be possible to make the right determination without doing the experiments.

A participant from the Department of State noted that although there may be ways to do the research in a safer manner, Denison had just argued that in a competitive environment the research question should be answered in the best and most direct way to get funding. The participant wondered whether, in this competitive context, a researcher would prefer the safest, but perhaps more indirect, option assuming it would get at the question. Denison commented that sometimes there are safer options such as when he used a mouse model for hepatitis virus to identify determinant proteins such as those for proofreading. This approach is of public health importance because it proves that certain mechanisms might be a useful target across multiple strains, including those we have not yet tested, such as the basic cleavage site. Returning to his earlier comment about the funding, Denison explained that professors not only try to

educate students to do the best science in the best way, but also ask them about finding alternatives that will eventually answer the question in a less direct way. Dormitzer added that although one may get NIH funding through a grant that incorporates safety considerations, institutional safety boards and questionnaires about dual use research of concern are procedures already in place to make sure it is not only the most direct way to a scientific answer taken, but also that safety is considered.

Each of the panel members was then given an opportunity for closing remarks. Dormitzer's closing remarks were that he believes that there is long-term potential in GoF research. He believes that we must be very careful with any sort of restrictions or regulations to make sure we do not inadvertently capture a lot of work that is not only good for basic science, but also a core part of the public health response. He stated that as a practitioner of vaccine development, he has realized that there really are road blocks that were never intended by the people who drafted the restrictions.

Baric agreed with those comments and affirmed the importance of reverse genetics and GoF research in understanding viral pathogenesis as well as vaccine and therapeutic design. NIH should be very careful about delineating the boundaries of the restrictions to be placed on the research community because there could be dire consequences if these restrictions are too broad. Weir affirmed one of his earlier points: if we had great vaccines for all of these agents, we might be having a different discussion, but the fact is that we do not.

Denison closed by proposing an iterative process whereby scientists do a review along the way. For critical pathogens of high human consequence there should be a mechanism that allows for a case-based, iterative approach that identifies problems along the way. Investigators need to have their research supported and be allowed to integrate best practices when doing GoF research.

5

Potential Risks: Biosafety and Biosecurity

KEY CONSIDERATIONS IN RISK ASSESSMENT

In his talk intended to provide an introduction to some of the key considerations that might be included in the risk assessment that the National Institutes of Health plans to commission, Dr. David Relman identified six key considerations, several of which he covered in his presentation and several of which were addressed in other presentations and discussion. These were as follows:

- The properties of newly created strains, their consequences, and alternative approaches;
- Science and technology (S&T) trends over time;
- The global distribution of risks and benefits, their relative weights, and questions of justice;
- The types of possible misuse, in particular safety and security;
- Moral and ethical responsibilities of scientists and issues of public trust; and
- Risk assessment and mitigation

But he began by stressing that he believed there was substantial agreement on a number of points, both by many at the symposium and within the larger scientific community.

Relman emphasized that he believed greater clarity, specificity, and precision were needed in identifying what aspects of Gain-of-Function (GoF) research should be the source of the most concern. In his view, it

was the creation of certain combinations of those properties that relate to high degrees of pathogenicity and high degrees of transmissibility, perhaps with or without properties that would allow the infectious agent to become impervious to currently available countermeasures. He stated that he saw a major difference between deliberately creating agents that are not now believed to exist in nature with these combinations of properties as opposed to research to understand properties that have arisen naturally for particular viruses. He commented that he took to heart the comments that had been made about the importance of being proactive, that he absolutely ascribed to its importance in doing good science, and that he recognized that GoF can result from knockout mutations. Thus, he thought the discussion was about properties and not experimental approaches per se. Powerful selective conditions and screens are frequently applied, for example, that can be reasonably anticipated to yield agents with the properties that these selective conditions and screens are meant to identify.

In his view, risk assessments should be focused on intentional work that can be reasonably anticipated to produce these problematic properties. Such research is consequential because in some cases there are not adequate countermeasures available to thwart or contain these agents, and the results could be used in further research in less secure settings.

He acknowledged that there are also potential risks in not doing experiments, but the question is how large they are and argued that there are ways of trying both to anticipate and address this concern. Relman also stated that, in almost every case, other experimental approaches will provide the knowledge that scientists agree is critical and many of the benefits that they agree are needed without necessarily undertaking this very small subset of experiments to create the specific agents with these combined properties.

These alternative approaches include knockout approaches, GoF experiments in altered genetic backgrounds, as well as much more aggressive surveys of what already exists in nature. Relman accepted that there may be circumstances when these approaches would not yield what has been learned from the more risky GoF experiments, and that Dr. Yoshihiro Kawaoka had clearly described them in his talk (see Chapter 3). There are uncertainties in those results just as there are uncertainties in the results of these alternative approaches. There is always uncertainty about whether or not the results are truly relevant to the circumstance that scientists most wish to understand.

With regard to the future, over time the technology of reverse genetics developed by Peter Palese in the 1990s (e.g., Palese et al., 1996) is becoming increasingly easy to undertake, more efficient, and less expensive. Today, it is not known how many people could download an influenza

virus sequence and remake the pathogen in his or her own laboratory. But one can say with confidence that the number of people with such capabilities will grow as the capacity to do this work continues to expand. This is a good thing, but it has consequences and implications. Not only is the information now in a digital form, but the procedures are also now digitized and rendered into protocols that can be uploaded to robots. Companies are emerging, for example in Silicon Valley, that will do research for money of whatever type and specificity are indicated in the experimental protocol.

For Relman, these trends mean that one cannot simply talk about risk and benefit at the site where the original information is produced or the site at which the original experiment takes place. It is more than a question of biosafety. This means that the work is a distributed effort across the globe and that many people are interested in this work for a wide variety of reasons, some of which the participants in this meeting may not have been able to fathom, and who were not represented in the room. They were not there, nor have they been so far in discussions about both benefits and risk. He argued this also means that governance and oversight should be distributed in the same fashion that the scientific capability is becoming distributed.

Relman regards the potential risk of deliberate misuse of GoF research as a plausible scenario in today's world. In misuse, he also included people willing to do irresponsible, if not deliberately mischievous acts, as well as those who show callous disregard or accidental or benign neglect of proper procedures and mindfulness. The discussion of potential risk is thus about safety *and* security. He underscored the range of motivations in the life sciences beyond a quest for knowledge or to help people. Some people now undertaking life sciences research are just curious, some are interested in fame, and some are interesed in fortune and economic benefit. None of these is bad, but the variety of potential motives and actors has serious implications for how to think and talk about risk.

Relman also noted that part of the diffusion of capacity was the rapid expansion of the capabilities of individuals in life sciences, which are now comparable to those of large organizations 10-20 years ago. In addition, in the current geopolitical climate, individuals and small groups with mal-intent are easier to muster and "radicalize." When added to other new participants in life science research from alternative backgrounds and with different motivations, this suggests that the risks of misuse are increasing and that these issues must be included in the assessments for GoF research.

Relman began his remarks about moral and ethical principles in science with the statement that scientists have an obligation to think about public beneficence, which means maximizing benefits, minimizing harm.

Everyone has a responsibility to be a good steward of the ecosphere of the planet to the betterment of all and especially those without representation who do not have access to the same kinds of routine public health measures available to those in developed countries generally.

Scientists have an important commitment to intellectual freedom and responsibility in science—and the two go hand in hand. This should include support for democratic and deliberative processes of decision-making. Furthermore, modern science, much of which is funded by the public, demands consideration of morality because of the increasingly blurred line between basic and applied science. Scientists have to talk about the common good and, as Joseph Rotblat said, "spend a little bit of time thinking about the consequences of our work" (Mertl, 2000). It is scientists' obligation to society. This leads to the question of whether there are any experiments that ought not to be undertaken because the risks outweigh the benefits or because the benefits will only be realized in the indefinite future. For Relman, the answer is clearly "yes." In addition, it would be possible to triangulate in on exactly what they might be. The experiments should be defined carefully today, mindful that those definitions might have to be altered very quickly.

In summary, Relman offered several points about how to move forward:

- As others have said, we need narrow and specific definitions of what research we are concerned about.
- We need to come to some agreement, if we can, about whether there are experiments that will not be funded and whether there are, morally, experiments that should not be undertaken for now. He thinks these experiments are very few and far between and should not scare anyone away from addressing this question.
- We should also give guidance about which experiments others might view as very closely related but that we think are acceptable and should be funded, perhaps under certain degrees of oversight. But we need to give positive messages as well as negative messages.
- We need standardized reviews, standardized assessment approaches, and flexible mechanisms.
- We need democratic, deliberative, and iterative processes that have neutral sponsors and hosts.
- Finally, as others had already said, this effort must international and must be collaborative.

During the discussion of the papers by Kawaoka and Dr. Ronald Fouchier, Dr. Robert Webster from St. Jude Children's Research Hospital

and a member of the symposium planning committee, asked whether the sequences of pandemic pathogens should continue to be released now that research has moved into the genomic era. Kawaoka answered that before mechanisms to restrict access and keep information only in certain groups are in place, it will be difficult to use that information in a useful way. Relman added that a distinction must be made between information that comes directly from nature or is deliberately created to have a combination of properties that renders them unusually dangerous to humans.

Dr. Harvey Fineberg noticed that Relman's talk stressed the idea of the danger of the combination of creating in the laboratory any agent that is simultaneously transmissible, highly pathogenic, and resistant, and asked whether his conclusion would stop short of considering transmissibility alone. Relman specified that he is not concerned about the deliberate enhancement of only one of the properties cited earlier in an agent and, therefore, he thinks that the broad term GoF does not specify what people are the most concerned about.

Webster stated that in the influenza field, the goal is to predict which influenza viruses in birds have the potential to shift its host range to humans. He then asked whether we can achieve this kind of information without the GoF studies. Kawaoka and Relman agreed that researchers should understand more than what is currently known and that they are just beginning to learn what is involved in transmissibility and how to make predictions about it.

Dr. Susan Wolf, University of Minnesota, made a comment in reaction to Relman's statement that even a careful analysis of the benefits and the risks will not be enough because the analysis will also need to make value judgments about what risks are related to what benefits. She asked how the National Science Advisory Board for Biosecurity could structure a more capacious and robust risk/benefit analysis that would capture some of these additional value considerations. Relman suggested that particular pieces of useful experience from other circumstances where scientists had to deal with difficult to quantify potential risks, such as the nuclear power industry or the creation of airplanes or even variability in the infectious disease community, all are worth capturing.

Dr. Gerald Epstein asked Relman whether there are there meritorious scientific experiments we should not do. Relman thinks there are experiments that would yield interesting information that may have some value, but may fail on the appropriateness and prudence question because of the magnitude of risk (e.g., create a strain of Ebola virus with respiratory transmissibility capability).

BIOSAFETY

Alta Charo, from the University of Wisconsin (UW)-Madison and a member of the symposium planning committee, moderated Session 6 on Biosafety, with four speakers serving on a panel: Dr. Barbara Johnson (Biosafety Biosecurity International), Dr. Rob Weyant (U.S. Centers for Disease Control and Prevention), Rebecca Moritz (UW), and Dr. Marc Lipsitch (Harvard University). Johnson began the session with a presentation that highlighted examples of the kinds of accidents that have occurred recently in the United States as well as in other countries. Some of these accidents involved shipping of incompletely inactivated pathogens that should have been harmless but were not, improper handling of contaminated wastes, and "inventory holdovers," such as the recent discovery of viable smallpox in an NIH storage area. Such incidents can result in Laboratory Acquired Infections (LAIs) among laboratory workers, and these have occurred all over the world. Johnson presented data on LAIs from Europe, Asia, the Middle East, New Zealand, and Africa that occurred between 2000 and 2011. Causes of these accidents included noncompliance with biosafety procedures, human error, and equipment failures. Fortunately among the recent mishaps in the United States, there have been no LAIs, but this is not the case elsewhere in the world.

The causes of LAIs may be difficult to recognize at the time of the exposure. There may be no definitive moment that indicates an LAI potential, such as a needle stick, animal bite, or dropped pipette. It is estimated that only 20 percent of the causes of LAIs are actually recognized. To add to this problem, many countries under-report accidents or may claim to have never had an LAI. Johnson noted that to say that a lab has never had an LAI may mean that the operators have never been able to account for it, that it has never been investigated, or that it has never been reported. Johnson believes that under-reporting is harmful in that it prevents us from learning from our mistakes—we are losing the opportunity to benefit from lessons learned.

Johnson provided information on the actions that had been taken in the United States in response to the recent spate of incidents. At the CDC, these included suspension of activities, review and remediation of all procedures, verification of adequate inactivation procedures, strengthening of biosafety agency-wide, the formation of an external group of experts to review and advise CDC, improvement of management of internal incidents, investigation of root causes and personnel issues, and a new requirement for single point of contact to be established for biosafety issues. At the NIH, "Operation Clean Sweep" was initiated. This was a "top-to-bottom" inventory of all NIH laboratories. The NIH also declared a "National Biosafety Stewardship Month." Finally, on August 18, 2014, the White House issued a memorandum titled "Enhancing Biosafety and

Biosecurity in the United States," urging all federal government agencies that work with pathogens to "take immediate and long-term steps to enhance safety and security in research facilities to minimize the potential for biosafety and biosecurity incidents." Agencies were urged to institute a "Stand-Down" to include an "immediate sweep of their facilities to identify Biological Select Agents and Toxins (BSAT) and ensure proper registration, safe stewardship, and secure storage or disposal."

Johnson noted that in the United States there are numerous layers of regulation and oversight for pathogen research. At the institutional level, there are Institutional Biosafety Committees (IBCs) and Institutional Animal Care and Use Committees (IACUCs) that must approve proposed research. There are also Environmental, Health, and Safety units that provide oversight of ongoing research at the local level. At the national level, researchers are expected to follow the requirements in the publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL), and there are requirements for the use of appropriate levels of biocontainment for work with pathogens, culminating in the mandatory Select Agent Regulations for the most hazardous infectious organisms. H5N1 avian influenza and SARS-CoV are both classified as Select Agents and are subject to stringent regulation, but MERS-CoV has not yet been brought under this particular regulatory umbrella. Finally there are also the Recombinant DNA Advisory Committee at the NIH, which has oversight for certain kinds of experimental approaches, and the NSABB, which advises the NIH on policy. The NIH has had additional guidelines for certain types of GoF research related to highly pathogenic avian influenza since 2012.

Johnson pointed out, however, that the extensive regulatory framework in the United States is not replicated in many places elsewhere in the world. The World Health Organization's (WHO's) Western Pacific regional office investigated a number of biosafety incidents that occurred in countries under their jurisdiction. They found problems with laboratory management and lack of biosafety policies, procedures, training, Personal Protective Equipment (PPE), and supervision of less experienced lab personnel. Many laboratories do not have occupational health and safety organizations or programs, and there is also a need for greater quality control and assurance. Many nations do not have codified standards for laboratory work on pathogens. The WHO recommended the development of legislation for national biosafety standards, procedures for timely reporting and follow-up of accidents, worker health monitoring and countermeasures, accreditation or certification of Biosafety Level (BSL)-3 labs, and inventories of infectious agents. Johnson has seen many improvements made in the past 5 years following the issuance of the WHO recommendations, mostly in the more advanced of the developing nations, although many developing nations still have work to do.

In global terms, the proliferation of BSL-3 labs has been widespread. The good news, said Johnson, is that the number of biosafety associations globally has recently increased to about 30, quadrupling since 2005. These nascent oversight organizations are, however, struggling to find expertise and volunteers. Most focus only on genetically modified materials, not on the pathogens of interest in this symposium. Even nations that lack codified standards tend to rely on the U.S. BMBL, the WHO standards, or the United Kingdom's Health and Safety Executive guidelines, but the reality is that many labs in developing countries barely meet BSL-2 standards in terms of infrastructure, training, PPE, and supplies. A safety culture is incremental, hard to develop, and takes time. Many senior scientists don't embrace change quickly. Johnson's last presentation slide contained the following quote:

> [M]any accidents are caused not by a lack of physical barriers or regulations, but by the absence of a strong biosafety culture in labs and their oversight bodies.
>
> *Nature* editorial, July 29, 2014

But, as noted by a questioner from the audience later, although many guidance documents suggest that the development of a culture of biosafety and biosecurity is important, there is little practical advice available to implement this suggestion.

Weyant was the next speaker in Session 6. The Federal Select Agent Program is jointly administered by CDC's Division of Select Agents and Toxins and the Agricultural Select Agent Program of the Animal and Plant Health Inspection Service (APHIS). The Program oversees the possession, use, and transfer of biological select agents and toxins, which have the potential to pose a severe threat to public, animal, or plant health or to animal or plant products.[1]

Weyant explained that the Select Agents and Toxins regulations require that any theft, loss, release causing an occupational exposure, or release outside of primary biocontainment barriers must immediately be reported to CDC or APHIS as well as to the appropriate federal, state, or local law enforcement agencies. This reporting requirement provides the CDC with a database on releases of the Select Agents under its jurisdiction. Weyant noted that if a laboratory does not intend to possess a Select Agent but encounters one (e.g., in a sample provided to a hospital), the laboratory is not required to register with CDC but must fulfill the reporting requirement. Between 2005 and 2012, there were 1,059 release reports

[1] See http://www.selectagents.gov/index.html.

with 3,780 potential worker exposures. Of this number only 10 LAIs[2] resulted and there was no evidence of transmission to the general public. These data allow the calculation of an approximate registered entity annual rate of LAIs per worker less than 0.0005 (5 confirmed LAIs per 10,000 workers over 7 years).

Moritz next reported on the processes by which UW reviews and oversees the GoF research of Kawaoka. She noted that "Select Agent research at the University of Wisconsin is considered a privilege, not a right." The UW IBC had a thorough discussion of Kawaoka's research before it was funded and approved the risk mitigation measures he proposed. Since the beginning of 2006, his influenza research protocol has been reviewed more than 40 different times. Following the issuance of the U.S. government's March 2012 dual use of research concern (DURC) policy, UW chose to form an IBC subcommittee to review research for DURC, and this policy has been revised to account for subsequent changes to the regulations. The DURC subcommittee reviews grants, experiments, and manuscripts for DURC and passes its findings on to the full IBC for additional discussion. The IBC's findings are, in turn, passed on to an additional committee, one that is considered a best practice by multiple federal agencies, including the U.S. Federal Bureau of Investigation. This is the Biosecurity Task Force, which is comprised of key individuals and experts from UW's campuses as well as all responsible university officials (e.g., biosafety officer, director of environmental health and safety, communications, health services) and law enforcement. The mission of this broad group is to ensure the highest level of safety and security for UW's Select Agent laboratories. The Biosecurity Task Force, with the IBC and the DURC subcommittee, helps ensure that the facilities, practices, and procedures meet the stringent biosafety and biosecurity standards set by these committees. While the merits of Kawaoka's research are decided by the agencies that fund it, it is imperative that these UW committees evaluate the risks to the institution and the public so as not to jeopardize the institution's $1 billion research enterprise. Moritz stated that the risk assessment performed by UW included extensive risk mitigation measures that have been put in place and sets forth the principles for a culture of safety. Examples of the risk mitigation measures at UW include the following:

- The Influenza Research Institute (IRI) facility is a stand-alone structure that houses only Kawaoka's research group, which

[2] Five of the 10 LAIs were from registered laboratories, and 5 were from labs exempt from registration. The calculation made by Dr. Weyant uses only the figure for the registered laboratories.

allows university officials to control all aspects of the building and the activities inside it. Entry to the building is strictly controlled. Annual preventive maintenance is performed to ensure the IRI is functioning optimally.

- Kawaoka's transmission experiments are done in a BSL-3 agricultural suite, which is essentially a BSL-4 minus the positive pressure suits and chemical shower. Basically BSL-3s are boxes within boxes that allow for open animal holding. But Kawaoka takes this one step further and uses High Efficiency Particulate Arrestance (HEPA) filters for their cages for primary containment of the animals.
- Personnel wear PPE when working inside the high containment facility and follow numerous procedures for entering, exiting, and conducting research in the laboratory. All researchers at IRI must undergo extensive hands-on training with a mentor and must pass proficiency testing before they are allowed to work in the containment laboratories. In addition, they must undergo hands-on laboratory refresher training as well as regular training updates. GoF transmission experiments are only performed by Kawaoka's most senior research staff.
- Like all Select Agent programs, IRI is required to have incident response and security plans for any number of potential events. Kawaoka and his researchers participate in hands-on and scenario drills with a dedicated trainer who runs these programs. They train for security threats and natural and human made disasters, such as a fire in a containment laboratory. Imagine telling the fire department that they cannot fight a fire. That is exactly what had been done when the IRI was being commissioned. If there is a fire inside the facility, the fire department has orders to let it burn and only prevent the fire from spreading beyond the laboratory perimeter. There are also routine drills for an exposure or potential exposure or for researchers who exhibit influenza-like symptoms.
- Kawaoka has an elaborate exposure control plan that was developed in conjunction with UW health services and infection disease physicians and state, county, and city public health agencies. All researchers receive seasonal influenza vaccines as well as thermometers at home. All of the influenza strains used inside the high containment laboratories are sensitive to the antivirus.
- Possibly the most important part of this process is communication. If anything out of the ordinary happens in one of the containment labs or with regard to the building, then the researchers are obligated to notify the responsible official or the alternate

responsible officials, who form a task force to determine whether there is a risk to be addressed.

- Lastly, there have been questions about research transparency. The UW is a public institution that worked hard to engage the local community prior to building the IRI. From the beginning, UW has been clear about the laboratory, its mission, and the research conducted there.

Later in the discussion, Lamb, who spoke at the very end of Session 8, commented that IBCs vary enormously in competence. He noted that while the UW has a highly competent system for oversight of GoF research, many other universities have much less expertise with designing safety protocols for investigators.

Lipsitch presented the final talk in the Biosafety Session, focusing on pandemic strains of influenza and GoF research that increases their transmissibility among mammals. He noted that the safety record for biocontainment lab research is good, but not perfect, and pointed to data from the literature that indicate that there were 1,141 LAIs and 24 deaths worldwide in the 1979-2005 period. He stated that research projects that pose risks to public health, such as those that make pandemic influenza strains more transmissible, appropriately face greater restrictions. He stated that the public health risks of such research affect a broader, potentially global public and that even low accident rates may be unacceptable given the larger number of people who could be affected.

Lipsitch presented data from Henkel et al. (2012) and from an Environmental Impact Statement for the U.S. Department of Homeland Security's National Bio and Agro-Defense Facility (2007) that provide much higher rates of LAIs for Select Agent labs in the United States and for laboratories belonging to the National Institute of Allergy and Infectious Diseases (NIAID). For the former, the rate he presented was 0.2 percent per lab per year, and for the latter it was 1 percent per full-time BSL-3 lab worker per year. He went through a series of calculations that he believes demonstrate that a release of an H5N1 or other pandemic influenza strain enhanced through GoF research to increase its transmissibility among mammals could result in a 0.01 percent to 0.1 percent chance of 2 million to 1.4 billion fatalities, or an expected death toll of 2,000 to 1.4 million per BSL-3 laboratory-year based on the Select Agent data LAI rate. Using the NIAID data, each full-time person-year of GoF research in a BSL-3 lab could produce a death toll of 10,000 to 10 million. (He noted that these calculations have recently been published, see Lipsitch and Inglesby, 2014.) While acknowledging that these numbers represent "a small probability of a very severe outcome" because the most likely outcome is no pandemic from the work at any lab per year, he emphasized that the problem

is that such levels of risk should not be ignored when the consequences of an accident are on such a scale.

Lipsitch went on to argue that the choice should not be viewed as GoF research versus no GoF research, but rather that there are alternative ways to obtain the knowledge needed about PPPs. (He referred the audience to Lipsitch and Galvani [2014] for a list of such alternatives with citations.) He believes that the alternatives he suggests create no significant health risks while maintaining the ability of science to pursue countermeasures to PPPs. This absence of pandemic risk for Lipsitch tips the scales in favor of alternative approaches.

During the question-and-answer period at the end of the session as well as in the final discussion on the second day, Nicholas Evans, University of Pennsylvania, noted that biosafety data are not well collected in the United States or in many other countries. He pointed to a Government Accountability Office (GAO) report (2009) that stated that the number of BSL-3 laboratories in the United States is not known and there is no central data collection point either inside or outside the United States for biosafety data. Jim Welch of the Elizabeth R. Griffin Foundation also agreed that there is a need to develop a repository for biosafety best practices, particularly with regard to LAIs, beyond simply Select Agents, where the option of noncompliance does not exist because you will be shut down by the CDC. Weyant also noted that although the labs that are performing GoF research are well run and overseen, there are only a small number of them at present. He asked what will be needed to ensure that additional work will also be adequately overseen if the number of such labs grows by one or two orders of magnitude. Charo also pointed out that case-by-case evaluations of particularly hazardous experiments require knowing who is going to be executing them and what their capabilities are.

Another topic that was given attention was the presentation of calculations on risk of GoF research by Lipsitch. Fouchier disputed the calculations, stating, "I prefer no numbers rather than ridiculous numbers that make no sense. . . ." Lipsitch's response was that he invites anyone with better information to challenge his numbers and provide better ones so that the calculations on the risks of GoF research can be as realistic and refined as possible. He stated that "we should incorporate all the data available and the more relevant the better." Since the symposium, Fouchier's own calculations, which he described briefly in the final session and which showed a far lower risk of accidents or pandemic outcomes, will be published soon (Fouchier, 2015).

BIOSECURITY

Over the course of the 2-day meeting a number of participants, such as Gregory Koblentz and Koos van der Bruggen of the Royal Netherlands Academy of Arts and Sciences, commented on the apparent shift over the past 3 years in the international discourse regarding the potential risks of GoF studies from one focused on biosecurity to one focused on biosafety. Nonetheless, Carol Linden of the U.S. Biomedical Advanced Research and Development Authority (BARDA) noted that while biosafety and biosecurity are inextricably linked, they remain distinctly different with different legal, policy, and regulatory regimes. Both aim to keep dangerous pathogens safely and securely inside the areas where they are used and stored, yet they mitigate against different risks. Biosafety provides policies and practices to prevent the unintentional or accidental release of specific biological agents and toxins, whereas biosecurity provides policies and practices to prevent the intentional or negligent release of biological materials or the acquisition of knowledge, tools, or techniques that could be used to cause harm. Thus, while providing a foundation upon which to build biosecurity capacity, biosafety measures, in and of themselves, cannot fully address biosecurity risks.

Consequently, some participants, such as Ed You of the Federal Bureau of Investigation, noted that both the biosafety *and* biosecurity environments are important to consider in any risk assessment, taking into account the organism/pathogen and its weaponization potential, capability (including both scientific knowledge, tacit knowledge, and technological know-how) and intent of an adversary, and the potential consequence of intentional release or misuse. It would also require the expertise of scientists and security experts to fully address the range of potential risks.

These components necessarily require additional considerations as well. Some participants noted that current nomenclature, whether dual use, DURC, or GoF, complicates the focus of any assessment. Several argued for definitions for the identification of organisms/agents and experiments that raise substantial concern that would be both more precise and yet flexible enough to adapt as the science advances. (This point is made several times elsewhere in this report.) Gigi Gronvall of the UPMC Center for Health Security and Koblentz also pointed out that the capability of an adversary is equally, if not more, difficult to assess because understanding of who would act in such a manner (e.g., state actors, non-state actors, or lone wolves) and of their capacity for acting is limited. Furthermore, our understanding of the consequences of a deliberate release or use of a biological weapon in any given set of circumstances is also limited. This includes knowledge of the availability and effectiveness of appropriate measures and infrastructure to respond to such an

event, although we know that capacity varies, in some cases quite significantly, from country to country or even within countries.

Peter Hale of the Foundation for Vaccine Research also noted that a one-time risk assessment is not appropriate, calling for periodic review and updating of any assessment based upon scientific advances, technological know-how, improvements in country capacity and infrastructure, and increases in the number of laboratories undertaking research of particular concern on the one hand and the changing security threat environment on the other. Taken together, this means that any assessment of potential biosecurity risks would have to acknowledge and deal with substantial uncertainties across most, if not all, major parameters

SPECIFIC TOPICS FOR CONSIDERATION

Koblentz noted that today's concerns regarding possible biosecurity risks associated with GoF research in the United States are rooted in biosecurity risk discussions that stemmed from several events that occurred in the mid-1990s: the sarin gas attack in the Tokyo subway in 1995; the bombing of the federal building in Oklahoma City in 1995; and the 1995 attempts by Larry Wayne Harris to acquire plague samples through the mail. Koblentz offered an approach for assessing biosecurity risk, stating that risk assessment is a judgment about the likelihood that an event will occur and the consequence of that event:

$$\text{Risk} = \text{Threat (Capability + Intent)} \times \text{Vulnerability} \times \text{Consequences} - \text{Mitigation Countermeasures}$$

Looking at just one component of the risk calculation is not sufficient, Koblentz cautioned.

One of the similarities between the current debate and the debate of the late 1990s is the lack of good data, meaning there are very few incidents. While this is good news, the lack of data leaves room for speculation and uncertainty, creating three distinct schools of thought about the nature of the threat: Optimists, Pessimists, and Pragmatists. Koblentz elaborated on each of these as follows:

Optimists: Individuals who adhere to this school of thought generally believe that the risks of bioterrorism are exaggerated. They note several factors:

1. The number of attempts by terrorists to acquire and use biological weapons has been miniscule compared to the overall number of terrorist attacks, which for Optimists implies that terrorists sim-

ply do not want or need these types of weapons to achieve their goals;
2. Terrorists tend to be conservative and choose weapons that are readily available and have a proven track record, such as guns and bombs;
3. There is a stigma against the use of biological weapons and groups that are capable of pursuing such weapons have not; and
4. Technical hurdles are significant. Dual use research requires a set of skills and tacit knowledge that is acquired through hands-on-training and trial and error.

Pessimists: Individuals who hold this perspective believe that it is a matter of when, not if, a biological attack will occur and the consequences will be catastrophic. Pessimists hold this view because:

1. the small number of incidents is a harbinger of the future and provide evidence that terrorists are innovative and not averse to failure;
2. terrorists take risks and experiment with new ways to cause harm and death;
3. terrorists have employed increasingly lethal measures over time;
4. terrorists are motivated by a rise in religious conviction, which tends to place less constraints on causing mass casualties; and
5. advances in science and technology are decreasing technical hurdles, while diffusion of knowledge and technologies are increasing global access.

Pragmatists: Individuals who adhere to this view believe that bioterrorism is a low-probability, low-consequence event. Pragmatists worry about the emergence of terrorists groups with the intent and capability to acquire and use biological weapons but they consider the likelihood of such groups emerging to be quite rare. Pragmatists pay less attention to probability and consequence and focus more on understanding how and why terrorists groups pursue these types of weapons. Instead of thinking that the past is a predictor of the future as do the Optimists, or predicting the future based on current trends, Pragmatists focus on the conditions or variables that might lead certain groups to seek such weapons. Finally, Pragmatists share the Pessimists' view of the growing capability of certain groups to acquire biological materials and resources but at the same time share the Optimists' perspective that it takes substantially more knowledge and know-how and skill to pull off such an attack than these groups have or will soon acquire.

These three perspectives lead to risk assessments that would weigh

benefits and risk quite differently. And while a risk assessment may not explicitly state which of these views is driving the analysis, the values embedded in these perspectives will nonetheless find their way into the process. Koblentz thus argued it was essential to surface these assumptions early in any risk assessment process.

Gronvall offered six key points to consider in any assessment of biosecurity risks stemming from GoF research:

1. There are few big surprises in life sciences research—science is incremental and rarely presents a clear dividing line that, if crossed, triggers an immediate biosecurity concern;
2. It cannot be denied that publishing sequences of new, potentially pandemic-causing strains of any pathogen lowers barriers to weaponization;
3. While the current debate is focused on flu viruses, SARS, and MERS, these join a host of other pathogens that could be misused;
4. With a plethora of pathogens available for misuse, many paths can be pursued toward weaponization that do not require GoF experiments;
5. Assessing who would likely take steps to weaponize pathogens is incredibly difficult and dependent upon experts with widely diverging views; and
6. Assessing GoF research must include not only the biosecurity risks but also the biosecurity benefits for countermeasures that new knowledge acquired from such research may provide.

Linden expanded the discussion of biosecurity to include the public health aspect of biosecurity. She noted that over the past few decades there has been a growing understanding within the federal government that biosafety will not address all of the biosecurity concerns. Yet, in the end concerns about both biosafety and biosecurity lead to a discussion of the need for a strong and sustained culture of responsibility in science that involves both individuals and institutions and that includes federal laws and regulations. Through a series of education and training protocols efforts have been made to enhance the understanding of biosecurity by laboratory personnel so that work is done safely and securely. Similarly, facilities have been assessed and requirements have been implemented to enhance the physical security of laboratories. Additionally, regulations governing transportation of pathogens contribute to the overall soundness of laboratory and personnel handling of dangerous materials. While this web of education, training, regulations, and requirements contribute to overall improvements, we must be mindful that these efforts do not have unintended consequences. A measured approach that recognizes

that zero risk is not achievable can provide layers of protection to address legitimate safety and security concerns while allowing continued scientific progress.

Several participants and webcast viewers offered additional comments during the final session of the symposium. Van der Bruggen commented on the shift in the GoF debate from security to biosafety. To some this implies that, if the biosafety issues are solved, which they believe is not difficult, then the biosecurity issues are solved as well. He did not agree. He is convinced that the biosecurity risk is very small but still exists. Laboratory biosecurity certainly overlaps with biosafety. However, there are possible biosecurity threats that call for separate attention and often the inclusion of other experts to give advice on these issues. That makes regulating and decision-making more complicated, but it is essential.

Epstein offered an observation about the different ways in which different communities will look at this problem. One difference in these communities' perceptions should be highlighted and that is the difference between what is considered tangible and what is considered speculative or hypothetical. He said he was exaggerating for effect, but for the scientific community the benefits of fundamental research are tangible, while the risks of bioterrorism are speculative. But the security community comes at this the other way around: for many in this group, human intent to do harm is very tangible and real, even if the risk of bioterrorism might be uncertain, while the benefits of fundamental research are seen as speculative.

Piers Millett, Biosecure Ltd., commented that, while he was impressed with the discussion of bioterrorism, he thought that in moving forward consideration should be given to the history of state-level activities and whether something as sophisticated as GoF research was more likely to be misused by a state or a non-state actor. He also suggested looking beyond the WHO to consider the convening capacity of the Biological Weapons Convention and the relevance of the Convention on Biological Diversity for some issues.

Evans commented that any deliberative process going forward would need to recognize the possibility of incommensurate values regarding the bounds of public health value, the value of innovation, and the value of security. All three have to be weighed against each other, and there may be fundamental disagreements about all of them. He believed that the symposium had not adequately discussed the distinction between the restrictions on GoF studies that are proposed or the funding of other research that may offer more or different benefits to society. Those are two different types of regulatory effects, and different considerations apply in each case. This dovetails with the larger issue of the importance of insti-

tutional memory. This controversy over GoF research is not a new issue, and although the dual use aspects of GoF have dropped off the agenda to a certain extent, considerable progress has been made in the discussions regarding the issue, and that should be remembered.

Kavita Berger, American Association for the Advancement of Science, offered a comment that the types of risks being discussed had not been well defined. There had been general discussions of biosafety, laboratory biosecurity, personnel security, and bioterrorism, but almost nothing, for example, about the issue that someone might use information that is publicly available. Going forward, it would be important to be clear about what specific risks are the major concerns. She also commented that, although not perfect, guidance, regulation, and infrastructure are in place dealing with security and biosafety from a laboratory perspective. Too often much of the focus is on the scientist who is actually following the rules, as opposed to the individual who will not follow the rules, which should be of greatest concern. The core of the GoF issue is that someone might use the results to cause harm, and how to include that risk in the overall risk assessment. Her other comment was that in the 10 years since the dual use issue emerged, institutions in the United States, Europe, Canada, and a growing number in other parts of the world have gained experience in reviewing and overseeing research. Again, these efforts are not perfect, but there are best practices that can be shared and examples and models that can be highlighted as ways to start.

6

Policy Implications

The symposium focused on identifying the principles and key issues that the assessments of potential risks and benefits would need to address (see Appendix A for a list of points made by individuals or during group discussions taken from the relevant chapters). In addition, policy implications were discussed at many points in the symposium, which Alta Charo, University of Wisconsin (UW)-Madison summarized in Session 9. She commented that in some cases the policy implications that one might draw from the discussions at the meeting are very specific to Gain-of-Function (GoF) research, while in other cases the implications are common to policy problems regardless of the substantive area.

Charo stated that to reduce risk with regard to biosafety requires a systems approach, which is very complex and requires representation and contributions from a very wide range of stakeholders, including people not ordinarily considered. For example, the presentation by Rebecca Moritz (UW), referenced the need to train the fire department to let the building burn. The discussion of the UW's very complex and thorough system illustrates that. There are also other things not really focused on during the meeting, such as the need to be attentive to protecting nonhuman animals, the flora and fauna in the environment, and so on. This very complicated process is also expensive and resource intensive if the research continues while trying to optimize the mitigation of risks.

One question that falls out of that is, in light of the range and intensity of the necessary investments, do we really want to spend limited resources that way? Charo noted that some commenters spoke about how

it might be better to spend the money on more conventional public health interventions because the goal at the end of the day is to improve public health by preventing disease. In that vein participants heard that perhaps we should be looking at budgetary trade-offs. How much is being spent on this research and the protections it requires in comparison to how much it would cost to move that money into public health?

She stated that in this particular discussion (i.e., of GoF research) there is "lots of room for being a little bit more nuanced in trying to see how trade-offs would or could be made." She also reminded the audience that the benefits and risks are not distributed in the same way. The risks of this research, to the extent it involves potential pandemics, will affect everybody, and yet the benefits will disproportionately go to people who are either personally better off or in wealthier countries because that is often where the healthcare system or economic access to healthcare is better. We need to pay more attention to making sure that the benefits are justly distributed and the science is beneficial for everybody. This is not something scientists can do by themselves, but it is something that is important to keep in mind to maintain public support. The "entire" public has to feel as though it has a stake in both the risks and the benefits.

Charo said that she was struck by the way in which the discussion would shift unpredictably between looking at the value of GoF research overall versus looking at its net benefit or its marginal increase in value when viewed as an addition to all the other types of research or public health efforts that are being done to address the same problem. For example, this appears in the discussions around whether GoF research would help make new vaccines versus GoF research as helpful—in addition to everything done in terms of monitoring—in making more precise predictions of which influenza strain should be worked on next year. The same applies to the discussion of risks. Pandemic potential is not something that is exclusive to GoF research, so the risks that are raised, such as Laboratory Acquired Infections (LAIs), are present for research with many other pathogens. Understanding the policy trade-offs might be helped if one could be clear about whether the discussion is about potential GoF-specific risks and benefits or marginal possible benefits as opposed to marginal increase in risks.

Charo noted that the policy options being discussed were basically in two camps: prohibition, with the fundamental question of which research should be banned, or regulation, with the fundamental question of how to regulate and whether control should be strict or light. The choice between the options will be heavily influenced by the presumptions one brings to the problem. Given that many of the experiments will inevitably fall in a "grey zone," where there can be disagreements about whether their

potential benefits outweigh their potential risks, the chosen default position will determine whether they go forward. If the presumption is that one must prove that an experiment is needed, then anything in the grey zone is going to be prohibited. If the presumption is that research is free to proceed until the government or some other authoritative body has determined that it is unacceptable for some reason, then everything in the grey zone will proceed because the burden of proof will be on the government. Whoever has the burden of proof of making the case will have the more difficult task, and that is a fundamental issue for any policy.

In his opening remarks to the symposium, Dr. Harvey Fineberg had also addressed the burden of proof issue. When the original debate about publication of GoF research to make H5N1 transmissible between ferrets occurred in 2011, the burden of proof was clearly on the National Science Advisory Board for Biosecurity to limit or restrict or modify publication of those findings. With the new U.S. government pause, he thought the burden had shifted more emphatically than in the 2012 policy guidance toward those who would proceed with research to demonstrate that the safety and the potential benefits are such that the research is worthwhile.

Given the importance of the default for policy choices, it is not surprising that so much attention is being given to terminology and finding precise ways to describe what should clearly be prohibited or allowed. Charo stated that ambiguity in policy might very well yield a chilling effect, for example on the pipeline of young researchers entering a field if there is doubt about whether certain lines of work will be permitted. This is not an unfamiliar problem, but it is one to which one should always be attentive.

Charo set out three approaches she heard from the discussions during the symposium about how a policy for GoF research might operate. One possibility would be to create a threshold beyond which experiments are either prohibited or given special attention. Depending on one's point of view, this approach can raise concerns about categories that are either too inclusive or not inclusive enough. Another would be a pure case-by-case approach, probably at the funding stage, with each of the factors considered important to making the choice of whether to allow the experiment to proceed reviewed independently, and then the overall project assessed holistically. The third approach would be "risk-based" regulation that reflects experience with a particular type of research, agent, or setting. The U.S. Select Agent program reflects this sort of approach.

Charo commented that the continuing diffusion and decentralization of science noted by Dr. David Relman and others posed challenges for the choice of approach. Most of the policy options that had been discussed were what she called a "point source" approach, such as that found in environmental law. For example, a factory might send pollutants

into a river. This is the point source of the pollution, and environmental laws will regulate the factory. It is a very detailed, hands-on regulatory approach, which is possible because there are a limited number of sites releasing a limited number of pollutants. "Non-point source" effluent has its own entirely different regulatory and policy challenges. The pollution of rivers and lakes from fertilizer runoff is an example of non-point source pollution. Many individual settings each add only a small amount of damage that collectively creates the pollution, and it is much more difficult to devise policies to regulate such problems.

Charo suggested that it will be essential for GoF research policy to figure out how much the challenge of decentralization is a realistic current problem. This is relevant for GoF research because there are continuing arguments about how readily someone could use the results to carry out bioterrorism or create biological weapons. As Relman's talk and the discussions in Session 7 illustrated, this in turn depends on judgments about the security implications of greater dissemination of scientific information, such as through increasing international research collaboration and the growth of do-it-yourself biology and amateur science versus the barriers posed by the need for tacit knowledge and specialized equipment on the other.

Charo concluded her remarks with a series of special challenges posed by the global nature of GoF research.

- **National cultures**—to what extent is there agreement about the general balance between risk avoidance and innovation/research support?
- **Governmental powers**—which powers are traditionally used to regulate or prohibit research? Is it accomplished by placing conditions on receipt of funds, directly regulating personal activity, licensing institutions, etc.? Or is it done primarily through rules with force of law or by advice and voluntary actions?
- **Relative resources**—given that protective measures can be resource intensive (both equipment and personnel), and countries vary in their capacity, how much should be spent in order to achieve a minimum level of safety? Optimal level of safety?
- **International governance**—how should regulation or prohibition be managed in cases of research collaborations that cross borders?

In the discussions following various sessions and at the end of the symposium, additional points were made. Laurie Garrett, Council on Foreign Relations, commented that the symposium's purpose of providing information for the NSABB made it difficult to consider the international context of the GoF issue, but it should not be ignored. In some less developed countries, there is general suspicion of certain types of research

carried out in Europe, the United States, and other developed countries. The World Health Organization is the only body that has the capacity to bring all the players together in a neutral format that recognizes the various perspectives of all cultures. But Garrett stated that it was her view that the Ebola epidemic has undermined the credibility of the WHO, so any governance effort for GoF research may require increased U.S. government attention to try to assist WHO.

A participant commented on the experience that had already accumulated through the first, voluntary moratorium by influenza researchers in early 2012 and beyond that through the debates and discussions of GoF research. One should take into account what has already been considered and tried as part of the policy process.

One person from the webcast reminded the meeting participants that regardless of what the United States ultimately decides to do or not do, it is important to be mindful that not all research is a global enterprise in other countries, some of which may be less well positioned than the United States and European countries in terms of sophisticated science and adequate investment to be able to carry out this research. Two other viewers raised questions about the roles of scientists and nonscientists, not only in the deliberative discussions that have been described as an important part of public engagement, but also ultimately among the panel or others who will be given the responsibility to make decisions. They questioned whether the scientific community alone is actually in a position to render the necessary judgments to create public confidence without participation from nonscientists.

Dr. Mark Denison commented on the importance of considering the regulatory burden that universities are already carrying when discussing options for GoF research policy. He stressed the need for alternatives to regulation. If there is agreement that pandemic pathogens or potential ones are in and of themselves significant and will continue to appear, then there is a need to think about resources within the laboratories and to supplement those resources to enable them to develop and share best practices within and across institutions that perform research. He also called for policies and resources to facilitate and encourage the development of scientists who are transdisciplinary in their understanding of pathogens, pathogenesis, social sciences, risk analysis, and biosafety.

Dr. Christophe Fraser echoed Denison's comment about the importance of avoiding an increased regulatory burden or hindering the development of good animal models for SARS and MERS. At the same time he acknowledged what he considered a widely shared concern about a very small number of experiments that develop pathogens that are highly transmissible and highly pathogenic and where empirical evidence suggests there are issues related to containment measures.

CLOSING REMARKS

In his final remarks Fineberg stated that he was very impressed with the thoughtfulness and respectful dialogue exhibited during the symposium in contrast to many of the other "so-called discussions" about GoF research. "I think there has been a lot of talking to rather than talking past in the course of this last day and a half . . . even more importantly, a great deal of listening to." This met one of the hopes he articulated in his opening comments, to get beyond how some of the scientists who have been involved felt: as though they were treading water, a little bit like the movie *Groundhog Day*, where every day they had to wake up and relive, rehearse, and revisit the same arguments and discussions and debates, sometimes with the same people and sometimes with a slightly wider audience. He said that one of the key lessons is that it will be incumbent to develop a schema that identifies the research that is of particular concern and that an important contribution will be one that identifies and structures the nature of the considerations that should enter the problem.

If there is any area of commonality, said Fineberg, then it is around the acceptance of the legitimacy of the concerns that have been raised on all sides of this issue. What is much less clear is how to inform, evaluate, quantify, and weigh those various elements. Where are the points of contention, and where are the pivot points—those particular elements of estimation, understanding, projection, and possibility that, when entered into the final assessment, are really the ones that will make the most difference? That is where one has to then concentrate all of the ability one can to mobilize and manage the information that will inform and develop those particular aspects. As noted before, quantifying an assessment does not mean that a decision is reached because the whole idea of risk/benefit analysis is not tantamount to a decision. It is one piece in a balance of information that can inform decision-making. What comes out of it, if well done, will identify those points that really make the most difference in the final decisions and that will enable a set of activities to go forward in a way that gives confidence to the public as well as to the policy makers.

Fineberg closed the meeting by noting that the reality is that the virology community brings a special understanding and depth of experience to these particular problems, while the larger scientific community brings a perspective of understanding what is at stake for science. However, those who are part of the security community have a perspective of understanding of what it takes to live securely, what is at stake internationally, and what it may take globally to establish a higher degree of harmony in the conduct of the global research enterprise.

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Appendix A

Key Issues for Risk/Benefit Assessment for Gain-of-Function Research

The purpose of this appendix is to compile key points from the presentations and discussions at the symposium. Each of the points is attributed to the person(s) who made it, or to the discussions from which it emerged, along with the page number(s) where it may be found. More detailed versions of these points and the rationales for them may be found in the foregoing chapters.

CHAPTER 2: ASSESSING RISKS AND BENEFITS

1. Although the major steps in risk assessment were first enunciated in a National Research Council report titled *Risk Assessment in the Federal Government: Managing the Process*, the basic steps in the process remain the same today:
   - Hazard Assessment: The determination of whether a particular chemical (or microbiological agent) is or is not causally linked to particular health effects.
   - Exposure Assessment: The determination of the extent of human exposure and the probability of occurrence of the health effects in question.
   - Dose-Response Assessment: The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
   - Risk Characterization: The description of the nature and magnitude of human risk, including attendant uncertainty.

- Risk Management: The reduction of risks and the increase of expected benefits.

2. Risk Communication and Appropriate Involvement of Stakeholders (Haas, 2014:7).The major focus of attention with regard to GoF research has been on hazard assessment, which has largely been focused on occupational health risks, but it is important to go beyond this to consider risks to the members of the public near research sites as well as global risks from pandemic organisms. Scarce attention has been paid to either exposure assessment or dose response assessment (Haas, 2014:7-8).
3. There are a number of questions to be addressed in a risk assessment such as whether the safety records of high-containment laboratories provide an appropriate basis for quantifying the risks of lab accidents that lead to worker or public exposures and how deliberate misuse of either the pathogens themselves or the information obtained through the research on these pathogens is to be incorporated into the risk assessment (Haas, 2014:8).
4. Risk assessment can *inform* decisions, but it is not determinate per se. Determining what is "acceptable" risk is a policy decision (Haas, 2014:9).
5. In addition to following the framework given above, the risk/benefit analysis for GoF research requires socially acceptable, technically sound definitions of "risk" and "benefit;" a strategic focus on design or decision, with proper disciplinary breadth and treatment of uncertainty; ongoing, scientifically sound two-way communication with stakeholders; and organization for transparency and learning (Fischhoff, 2014b:9-11, 17).
6. All analyses embody values that favor some interests above others. Thus, when transparent, the underlying assumptions can be controversial, and, therefore, an analytical and deliberative process is required to create socially acceptable definitions that acknowledge subjectivity (Fischhoff, 2014a:9).
7. Risk assessments on low-probability/high-consequence events are not new, and because the roles of uncertainty and human factors are crucial in risk assessment, acknowledging and incorporating them are an important goal (Fischhoff, 2014a:11).
8. "Human factors" research is the study of the interrelationships between humans, the tools they use, and the environment in which they live and work. Eighty percent of motor vehicle accidents, 80 percent of medical errors, and 60-80 percent of aviation accidents are estimated to be attributable to human factors. Studies have shown that physical (e.g., working in personal protective equipment) and cognitive (e.g., working under conditions

of fatigue) stresses undermine human reliability and that not only can human error not be eliminated, but it has also actually increased as a contributor to accidents in some arenas. Analyses of human reliability and errors identify the critical areas that are incompatible with human capabilities and the areas where a system is vulnerable to human error (Huntley-Fenner, 2014:11-13).

9. Key questions regarding human factors include
   - Are task demands compatible with human capabilities and characteristics?
   - Has the system been designed to cope with the inevitability of human error?
   - Does the system take advantage of unique human capabilities? (Huntley-Fenner, 2014:12).
10. Other areas of limitations in risk assessment include variability among observations, quality of the studies the analysis is based on (internal validity), whether these studies are generalizable (external validity), and how good the underlying science is ("pedigree") (Fischhoff, 2014a:13).
11. In the case of GoF research, "public" engagement may require dealing with the local public, the national public, and even the global public given that the consequences of a failure might be a global pandemic of infectious disease (Schoch-Spana, 2014:13-14).
12. There are three different kinds of public engagement: communication, consultation, and collaboration:
    - In the communication mode, an official or an agency conveys information to members of the public in a one-way fashion, often with the intent of educating and informing the public. Public feedback is not required and not necessarily sought.
    - The consultation mode is an interaction in which authorities solicit opinions through surveys, polls, and focus groups or during public comment periods. Again, this communication is one-way, but it is *from* the citizens *to the authorities*.
    - Collaboration is a two-way flow of information and influence between citizens and authorities; it is about dialogue fostering better understanding of very complex problems from all sides and perspectives and allows an opportunity for collective learning as part of honest and respectful interaction among the authorities and diverse constituents. Such iterative exchanges are necessary to approach policy concerns that are technically and ethically complex (Schoch-Spana, 2014:14-15).
13. Engaging the public improves product quality, enhances legitimacy of decisions, and builds a foundation of trust and mutual

understanding as well as practical experience with dialogue (Schoch-Spana, 2014:15-16).

14. Because the expected benefits of GoF research are potentially reduced risks, the same methodologies apply to assessing both the risks and expected benefits (Fischhoff, 2014a:9). Assessing the benefits side of the equation is more difficult and poses more interesting problems that require an investment in formalizing the benefit arguments as well as the arguments for alternative paths. Knowing which numbers are really important and whether they are even relevant to an analysis would assist with that process (Fischhoff, 2014b:17).
15. The risk/benefit assessment may also need to address the consequences of *not* doing GoF research (Haas, 2014:9).

CHAPTER 3: GAIN-OF-FUNCTION RESEARCH: BACKGROUND AND ALTERNATIVES

1. In virology, GoF research encompasses a broad range of experiments including any selection process involving an alteration of genotypes and their resulting phenotypes (Subbarao, 2014:16).
2. Research leading to the generation of viruses with properties that do not exist in nature could be categorized differently than research on strains that may be more pathogenic and/or transmissible than the wild-type viruses but are comparable to or less problematic than those existing in nature (Kawaoka, 2014:17). Routine virological methods involve experiments that aim to produce a gain of a desired function, such as higher yields for vaccine strains, but often also lead to loss of function, such as loss of the ability for a virus to replicate well, as a consequence (Subbarao, 2014:16).
3. GoF research on SARS-CoV and MERS-CoV is likely to be extremely different than influenza research because of fundamental biological differences and complexity that make these viruses very different (Baric, 2014:18). Unlike flu, there are currently no small animal models suitable for MERS or SARS transmissibility assays (Baric, 2014:30). Research on SARS-CoV infectivity has shown that adaptation of the virus to the mouse ACE2 receptor decreases its interaction fitness with the human receptor (Baric, 2014:18). Given that we are in the midst of a MERS-CoV pandemic, the "pause" on GoF research for MERS can have unintended and severe consequences. There are currently no small animal models to study MERS-CoV and, therefore, MERS-CoV restrictions should be lifted immediately (Baric, 2014:20).

4. The term GoF needs some refinement that will differentiate the type of research typically performed for basic virological research from experiments that clearly raise concerns (see "GoF Research as Defined by the U.S. Government" on pp. 25-27)
5. Research on CoV should be considered using a case-based approach and be subject to an iterative process that incorporates risk, milestones, and identifies problems along the way (Denison, 2014:25-26, 41, 45).
6. Research leading to the combination of increased transmissibility and virulence with the lack of efficient counter-measures would clearly define the line that would prompt the use of alternatives (Relman, 2014:25, 47-51).
7. Although alternative scientific approaches are not only less risky, but also more likely to generate results that can be readily translated into public health benefits (Lipsitch, 2014:42-43), alternatives to GoF research do not always provide the full answers to the key virology questions (Kawaoka, 2014:27).

CHAPTER 4: POTENTIAL BENEFITS OF GAIN-OF-FUNCTION RESEARCH

1. Because it is not possible to predict what breakthroughs may occur as a result of fundamental research, including GoF, it is impossible to quantify the benefits of GoF research for risk/benefit analyses. Long-term research benefits are achievable, but it is not possible to specify what these are when the research is initiated (Atlas, 2014:29).
2. GoF research in the short term can be used to help adapt viruses to growth in culture for vaccines and to develop essential animal models for the study of emerging pathogens and escape mutations with which to understand drug resistance and viral evasion of the immune system (Atlas, 2014:29).
3. GoF research may also allow the generation of information that is not obtainable through other methods, but whether all the long term benefits envisioned for GoF research will actually be realized is still unclear (Atlas, 2014:30).
4. There is significant disagreement about whether GoF methods are essential for vaccine development; therefore evaluating its contributions to benefits could clarify this. These methods appear to have limited utility for current production methods, but there were arguments that the increasing introduction of synthetic methods of production based on genomics and other molecular

techniques could increase the contributions of GoF research (see discussion on pp. 42-45).

5. GoF research-derived information is used to develop the Influenza Risk Assessment Tool that looks at the properties of a virus, especially the molecular determinants of virulence and transmissibility that can help identify candidate vaccine viruses in a time of limited resources (Shultz-Cherry, 2014:31).
6. Genotype to phenotype prediction is one of the holy grails of influenza biology research (Russell, 2014:34). Some argue that studies of particular amino acid changes in one strain of virus may not apply to another strain and that it is not possible to calculate the level of risk from the mutational landscape (Fraser, 2014:32). Others think GoF studies must continue so that eventually this inability to predict phenotypes can be overcome (Shultz-Cherry, 2014:31).

CHAPTER 5: POTENTIAL RISKS: BIOSAFETY AND BIOSECURITY

1. There was considerable support among attendees for David Relman's proposal to focus risk assessments on GoF experiments that involve the deliberate creation of viruses with a high degree of pathogenicity and transmissibility and perhaps with properties that would make the infectious agent impervious to currently available countermeasures. Experiments that produce this combination of properties are of more concern than the experimental approach per se (Relman, 2014:47-51).
2. Assessments of potential biosafety risks will have to deal with serious issues related to availability and quality of data about the frequency and severity of accidents, exposures, and Laboratory Acquired Infections (LAIs). Experience suggests there is substantial underreporting of LAIs, if not primarily in the United States, then in other less developed countries (Johnson, 2014:52). In the United States, there are systematic data available from the Select Agent Program relating to some of the most dangerous pathogens for the period 2005-2012 (Weyant, 2014:54-55). Comparable international data do not exist and there is no central point for reporting all accident and exposure data either inside or outside the United States (see Evans comment on p. 58).
3. The continuing expansion of high containment (i.e., BSL-3 and -4) laboratories affects potential biosafety risks primarily, but certainly not exclusively, in developing countries (Johnson, 2014:54).
4. There are substantial and important differences among the models used and the results obtained in efforts to assess the risks

of accidental releases of a dangerous pathogen. Understanding the sources of the differences could inform the risk assessment (Lipsitch, 2014:57; see also discussion between Lipsitch and Fouchier on p. 58).

5. While biosafety and biosecurity are inextricably linked, they mitigate different risks. Consequently, biosafety measures, in and of themselves, cannot fully address biosecurity risks (Linden, 2014:62).
6. Because there have been relatively few bioterrorists incidents, uncertainty is endemic for most factors that would contribute to a biosecurity risk assessment (Koblentz, 2014:60). Including evaluation by both security and scientific personnel in any assessment of a bioterrorist threat risk could expose the limits of our understanding of the following factors:
   - organism/pathogen and its weaponization potential;
   - capability (including both scientific knowledge, tacit knowledge, and technological know-how) and intent of an adversary; and
   - potential consequences of intentional release or misuse and the ability of the targeted population/country to respond (see comment by Ed You, p. 59).
7. Periodic reassessments for bioterrorist threats could take into account:
   - advances in science and technical skill;
   - changes in actor and targeted country capacity and infrastructure;
   - increases in the number of laboratories undertaking research of particular concern; and
   - the changing nature of the threat environment (see Hale comment on pp. 59-60).

CHAPTER 6: POLICY IMPLICATIONS

1. It would assist the understanding of the policy trade-offs for GoF research if there was greater clarity about whether the discussion is about marginal benefits versus marginal increases in risks. For example, there was a tendency during the discussions to move unpredictably between the potential value of GoF research overall versus looking at its net benefit or its marginal increase in value when viewed as an addition to all the other types of research or public health efforts that are being done to address the same problem. This appears in the discussions around whether GoF research would help make new vaccines versus GoF research as

helpful—in addition to everything done in terms of monitoring—in making more precise predictions of which influenza strain should be worked on next year. (Charo, 2014:66)

2. The choice among policy options will be heavily influenced by the presumptions one brings to the problem. Given that many of the issues will inevitably fall into a "grey zone," where there can be disagreements about whether their potential benefits outweigh their potential risks, the chosen default position will determine whether they go forward. If the presumption is that one must prove that an experiment is needed, then anything in the grey zone is going to be prohibited. If the presumption is that research is free to proceed until the government, or some other authoritative body, has determined that it is unacceptable for some reason, then everything in the grey zone will proceed because the burden of proof will be on the government. Whoever has the burden of proof of making the case will have the more difficult time, and that is a fundamental issue for any policy (Charo, 2014:66-67).
3. The discussions in the symposium brought out three possible approaches for how a policy for GoF research might operate. One possibility would be to create a threshold beyond which experiments are either prohibited or given special attention. Another would be a purely case-by-case approach, probably at the funding stage, reviewing each of the factors considered important to making the choice whether to allow the experiment to proceed independently and then assessing the overall project holistically. The third would be "risk-based" regulation that reflects experience with a particular type of research, agent, or setting (Charo, 2014:67).
4. Although the symposium focused on a U.S. deliberative process, there will be special challenges for policy because of the global nature of GoF research. For example, one issue for the safety and security risk assessment cited by several participants would be the extent and impact of the diffusion of research capacity on the efficacy of policy options affecting U.S.-funded international research collaborations. The global nature of GoF research poses a series of special challenges:
    a. National cultures—To what extent is there agreement about the general balance between risk avoidance and support for innovation and research?
    b. Governmental powers—Which powers are traditionally used to regulate or prohibit research: conditions on receipt of funds, direct regulation of personal activity, licensing of

institutions, etc.? Does this work primarily through rules with force of law or by advice and voluntary actions?

c. Relative resources—Given that protective measures can be resource intensive (both equipment and personnel) and countries vary in their capacity, how much should be spent to achieve a minimum level of safety? Or an optimal level of safety?
d. International governance—How to manage regulation or prohibition in cases of research collaborations that cross borders? (Charo, 2014:68).

Appendix B

Committee Biographies

Harvey V. Fineberg, MD, PhD (*Committee Chair*) is Visiting Professor and Presidential Chair at the University of California, San Francisco, and he served two consecutive terms as President of the Institute of Medicine (2002-2014). He served as Provost of Harvard University from 1997 to 2001, following 13 years as Dean of the Harvard School of Public Health. He has devoted most of his academic career to the fields of health policy and medical decision-making. His past research has focused on the process of policy development and implementation, assessment of medical technology, evaluation and use of vaccines, and dissemination of medical innovations. Dr. Fineberg helped found and served as President of the Society for Medical Decision Making and has been a consultant to the World Health Organization. At the Institute of Medicine, he chaired and served on a number of panels dealing with health policy issues, ranging from AIDS to new medical technology. He also served as a member of the Public Health Council of Massachusetts (1976-1979), as Chairman of the Health Care Technology Study Section of the National Center for Health Services Research (1982-1985), and as President of the Association of Schools of Public Health (1995-1996). Dr. Fineberg is co-author of the books *Clinical Decision Analysis, Innovators in Physician Education*, and *The Epidemic That Never Was*, an analysis of the controversial federal immunization program against swine flu in 1976. He has co-edited several books on such diverse topics as AIDS prevention, vaccine safety, and understanding risk in society. He has also authored numerous articles published in professional journals. Dr. Fineberg is the recipient of several honorary

degrees and the Stephen Smith Medal for Distinguished Contributions in Public Health from the New York Academy of Medicine. He earned his bachelor's and doctoral degrees from Harvard University.

Ronald M. Atlas, PhD is Professor of Biology at the University of Louisville. After receiving his master's and PhD degrees from Rutgers University, he became a postdoctoral fellow at the Jet Propulsion Laboratory where he worked on Mars life detection. He has served as Chair of NASA's Planetary Protection Subcommittee, Co-Chair of the American Society for Microbiology (ASM) Task Force on Biodefense, and a member of the FBI Scientific Working Group on Microbial Genetics and Forensics. He also served as President of ASM and was a member of the NIH Recombinant Advisory Committee. He currently chairs the Public and Scientific Affairs Board of the ASM. His research has included development of detection methods for pathogens in the environment. Dr. Atlas is the author of nearly 300 manuscripts and 20 books, and he regularly advises the U.S. government on policy issues related to the deterrence of bioterrorism.

Ralph Baric, PhD received his BS from North Carolina State University in 1977. He obtained his PhD from the Department of Microbiology of North Carolina State University in 1982, studying alphavirus host interaction and pathogenesis under the direction of Robert E. Johnston. He continued his postdoctoral training on coronavirus replication and pathogenesis under the direction of Michael M. C. Lai at the University of Southern California. In 1986, Dr. Baric was hired as an assistant professor in the Department of Parasitology and Laboratory Practice, and he is currently a professor in the Department of Epidemiology and the Department of Microbiology and Immunology of the University of North Carolina at Chapel Hill. During his early training, Dr. Baric was a Harvey Weaver Scholar of the National Multiple Sclerosis Society and an established investigator for the American Heart Association in association with his studies of coronavirus replication, cross-species transmission, persistence, evolution, and pathogenesis. He is a member of the Editorial Board of the *Journal of Virology* and a senior editor for *PLoS Pathogens*. Dr. Baric is a permanent member of a National Institutes of Health (NIH) study section (VirB); has been a consultant for the World Health Organization, the Centers for Disease Control and Prevention, and NIH; and has served on various institutional recombinant-DNA review committees. He has published more than 130 peer-reviewed manuscripts, including several in *Science*, *Proceedings of the National Academy of Sciences of the United States of America*, and *Nature Medicine*, and his research efforts are supported by several NIH research grants. Dr. Baric's expertise is primarily in norovirus

molecular evolution and susceptibility and in coronavirus reverse genetics, synthetic genome reconstruction, pathogenesis, vaccine design, and cross-species transmission of viruses, often using the Severe Acute Respiratory Syndrome (SARS) coronavirus or noroviruses as models.

Ruth L. Berkelman, MD is the Rollins Chair and Director of the Center for Public Health Preparedness and Research, at the Rollins School of Public Health at Emory University. She holds appointments in the departments of Epidemiology, Global Health, and Medicine, and serves as a senior associate faculty member in Emory's Center for Ethics. She previously served as an Assistant Surgeon General in the U.S. Public Health Service at the U.S. Centers for Disease Control and Prevention (CDC). Elected to the Institute of Medicine (IOM) in 2004, she has served on various committees, the IOM's Forum on Emerging Infectious Diseases and the National Research Council's (NRC's) Board on Life Sciences. She has been a member of the National Biodefense Science Board and the Board of Trustees at Princeton University. She was previously Chair of the Public and Scientific Affairs Board of the American Society of Microbiology. She currently chairs the Board of Scientific Counselors for infectious diseases at CDC.

Donald S. Burke, **MD** is the Dean of the Graduate School of Public Health, Director of the Center for Vaccine Research, and Associate Vice Chancellor for Global Health at the University of Pittsburgh. He is also the first occupant of the UPMC-Jonas Salk Chair in Global Health and a Distinguished University Professor of Health Science and Policy. He was an intern and resident in medicine at Boston City and Massachusetts General Hospitals and trained as a research fellow in infectious diseases at the Walter Reed Army Medical Center. Dr. Burke has expertise in the prevention and control of infectious diseases of global concern, including HIV/AIDS, influenza, dengue, and emerging infectious diseases. He is an IOM member and has served on previous NRC and IOM committees including the Committee on the Special Immunizations Program for Laboratory Personnel Engaged in Research on Countermeasures for Select Agents and the Committee on Assessment of Future Scientific Needs for Live Variola Virus. Dr. Burke received his BA from Western Reserve University and his MD from Harvard Medical School.

R. Alta Charo, JD is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin (UW)-Madison, where she is on the faculty of the Law School and the Department of Medical History and Bioethics at the medical school. She has also served on the faculty of the UW Masters in Biotechnology Studies program and lectured in the MPH

program of the Department of Population Health Sciences. Alta Charo (BA biology, Harvard University, 1979; JD Columbia University, 1982) is an elected member of the World Technology Network (2004), the Wisconsin Academy of Sciences, Arts and Letters (2005), and the IOM (2006). In 2013 she was awarded the Adam Yarmolinsky Medal for her service to the IOM, and she currently serves on the IOM Council. Professor Charo served on President Obama's transition team, where she was a member of the U.S. Department of Health and Human Services (HHS) review team, focusing her attention particularly on transition issues related to NIH, Food and Drug Administration (FDA), bioethics, stem cell policy, and women's reproductive health. She was on leave from 2009-2011 to serve as a senior policy advisor on emerging technology issues in the Office of the Commissioner at the FDA.

Philip Dormitzer, MD, PhD is Head of U.S. Research, Global Head of Virology, and Vice President at Novartis Vaccines in Cambridge, Massachusetts. He is a practicing physician, who is board certified in internal medicine. After studying anthropology at Harvard College and carrying out a field study of the Efe Pygmies in the Ituri Forest of Zaire, he completed his MD and PhD in cancer biology at Stanford University. Dr. Dormitzer completed house-staff training in internal medicine at Massachusetts General Hospital and a fellowship in the Harvard Combined Infectious Diseases Training Program. He conducted his fellowship research in the Laboratory of Molecular Medicine, led by Dr. Stephen Harrison. As an Assistant Professor of Pediatrics at Harvard Medical School, Dr. Dormitzer led a structural virology laboratory. The Dormitzer group and its collaborators determined the structures of the rotavirus neutralization antigens by nuclear magnetic resonance (NMR) spectroscopy, X-ray crystallography, and near atomic resolution electron cryomicroscopy. At Novartis, as Senior Project Leader for Viral Vaccine Research, he led global vaccine research projects. In 2009, these projects included the research component of the Novartis response to the H1N1v influenza pandemic, supporting the development and licensure of three pandemic influenza vaccines in the most rapid vaccine response in history. As Head of the Viral Advanced Programs Global Team, he coordinated scientific and industrial functions to advance novel vaccine projects toward licensure, with a primary focus on an engineered RSV F subunit vaccine candidate, intended for maternal immunization. As Head of U.S. Vaccines Research, he now leads approximately 70 scientists based at the Novartis Vaccines Cambridge Research Center in their mission to discover new vaccines, support vaccine development, and sustain licensed vaccines. The team's technology platforms include structurally engineered antigens, adjuvants that target toll-like receptors, and self-replicating messenger RNA vaccines. In a Biomedical Advanced Research

Development Authority (BARDA)-funded collaboration with the J. Craig Venter Institute and Synthetic Genomics Vaccines, Inc., the team developed a process to synthesize influenza vaccine seed viruses and deployed the technology in response to the H7N9 influenza outbreak in China.

Baruch Fischhoff, PhD is the Howard Heinz University Professor in the departments of Social and Decision Sciences and of Engineering and Public Policy at Carnegie Mellon University, where he heads the Decision Sciences major. A graduate of the Detroit Public Schools, he holds a BS in mathematics and psychology from Wayne State University and an MA and PhD in psychology from the Hebrew University of Jerusalem. He is a member of the IOM and is past President of the Society for Judgment and Decision Making and of the Society for Risk Analysis, and recipient of its Distinguished Achievement Award. He was founding Chair of the FDA Risk Communication Advisory Committee, recently chaired the NRC Committee on Behavioral and Social Science Research to Improve Intelligence Analysis for National Security, and currently co-chairs the NRC Committee on Future Research Goals and Directions for Foundational Science in Cybersecurity and the National Academy of Sciences Sackler Colloquium on "The Science of Science Communication." He is a former member of the Eugene, Oregon Commission on the Rights of Women, Department of Homeland Security's Science and Technology Advisory Committee, World Federation of Scientists Permanent Monitoring Panel on Terrorism, and Environmental Protection Agency Science Advisory Board, where he chaired the Homeland Security Advisory Committee. He is a fellow of the American Psychological Association, Association for Psychological Science (previously the American Psychological Association), Society of Experimental Psychologists, and Society for Risk Analysis. He has co-authored or edited 11 books: *Acceptable Risk* (1981); *A Two-State Solution in the Middle East: Prospects and Possibilities* (1993); *Elicitation of Preferences* (2000); *Risk Communication: A Mental Models Approach* (2002); *Intelligence Analysis: Behavioral and Social Science Foundations* (2011); *Risk: A Very Short Introduction* (2011); *Communicating Risks and Benefits: An Evidence-Based Guide* (2011); *Judgment and Decision Making* (2011); *Risk Analysis and Human Behavior* (2011); *The Science of Science Communication* (2013); and *Counting Civilian Casualties* (2013).

Charles N. Haas, PhD is the L.D. Betz Professor of Environmental Engineering and head of the Department of Civil, Architectural and Environmental Engineering at Drexel University, where he has been since 1991. He also has courtesy appointments in the Department of Emergency Medicine of the Drexel University College of Medicine and in the School of Public Health. He received his BS (biology) and MS (environmental

engineering) from the Illinois Institute of Technology and his PhD in environmental engineering from the University of Illinois at Urbana-Champaign. He served on the faculties of Rensselaer Polytechnic Institute and the Illinois Institute of Technology prior to joining Drexel. He co-directed the U.S. Environmental Protection Agency (EPA)/Department of Homeland Security (DHS) University Cooperative Center of Excellence—Center for Advancing Microbial Risk Assessment (CAMRA). He is a fellow of the American Academy for the Advancement of Science, Society for Risk Analysis, American Society of Civil Engineers, and American Academy of Microbiology. He is a board-certified environmental engineering member by eminence of the American Academy of Environmental Engineers. For more than 35 years, Professor Haas has specialized in the assessment of risk from and control of human exposure to pathogenic microorganisms, and in particular the treatment of water and wastewater to minimize microbial risk to human health. Professor Haas has served on numerous NRC panels. He is a past member of the Water Science and Technology Board of the National Academies, and the EPA Board of Scientific Counselors.

Stephen C. Harrison, PhD is Giovanni Armenise-Harvard Professor of Basic Medical Sciences, Harvard Medical School and Boston Children's Hospital, and Investigator in the Howard Hughes Medical Institute. He obtained his BA from Harvard University in 1963 and his PhD in biophysics from Harvard University in 1968. He has served on the Harvard University faculty since 1971. Between 1972 and 1996, he was Chair of the Board of Tutors in Biochemical Sciences, Harvard's undergraduate program in biochemistry. He was Chair of the Department of Biochemistry and Molecular Biology (Faculty of Arts and Sciences) from 1988 to 1992 and Acting Chair of the Department of Biological Chemistry and Molecular Pharmacology (Harvard Medical School) from 2009 to 2012. He is also head of the Laboratory of Molecular Medicine, Boston Children's Hospital. For many years, his research laboratory was linked closely with that of the late Don C. Wiley. Dr. Harrison has made important contributions to structural biology, most notably by determining and analyzing the structures of viruses and viral proteins, by crystallographic analysis of protein/DNA complexes, and by structural studies of protein-kinase switching mechanisms. The initiator of high-resolution virus crystallography, he has moved from his early work on tomato bushy stunt virus (1978) to the study of more complex human pathogens, including the capsid of human papillomavirus, the envelope of dengue virus, rotavirus particles, and several components of HIV. He has also turned some of his research attention to even more complex subcellular assemblies, such as clathrin coated vesicles and kinetochores. Dr. Harrison is a member of the National Academy of Sciences, a fellow of the American Academy of

Arts and Sciences, a member of the American Philosophical Society, and a foreign member of EMBO and the Royal Society. He received the Louisa Gross Horwitz Prize (with Don Wiley and Michael Rossmann) in 1990, the ICN International Prize in Virology in 1998, and the Paul Ehrlich and Ludwig Darmstaedter Prize (with Michael Rossmann) in 2001.

Sir John Skehel, PhD is a graduate of the University College of Wales, Aberystwyth (1962) and gained his PhD from the University of Manchester in 1966. He did research at the University of Aberdeen (1965-1968) and was a Helen Hay Whitney Foundation fellow at Duke University and at the Medical Research Council (MRC) National Institute for Medical Research (NIMR) Mill Hill (1968-1971). He was MRC staff scientist at NIMR from 1971 to 2006, Director of the WHO World Influenza Centre from 1975 to 1993, Head of Infections and Immunity from 1985 to 2006, and Director of the NIMR from 1987 to 2006. He is a visiting scientist in the Division of Virology at NIMR. His research is on the influenza virus haemagglutinin and neuraminidase membrane glycoproteins and the mechanisms of their receptor binding, membrane fusion, and enzymic activities. He is a member of the Council of Aberystwyth University and a Trustee of the Animal Health Trust. He was elected member of the European Molecular Biology Organization in 1983, fellow of the Royal Society in 1984, member of the Academia Europaea in 1992, fellow of the Academy of Medical Sciences in 1998 (Vice President from 2001 to 2006) and a foreign associate of the U.S. National Academy of Sciences in 2014. He was knighted in 1996. He was Honorary Professor of Virology at Glasgow University, Liverpool John Moores University, and University College London and was awarded an honorary DSc from The Council for National Academic Awards in 1990, University College London in 2004, Liverpool John Moores University in 2007, and University of Padua (medicine and surgery) in 2010. He is a fellow of the University of Wales and an honorary member of the Society for General Microbiology.

Robert G. Webster, PhD is Professor and Rose Marie Thomas Chair, Division of Virology, in the Department of Infectious Diseases at St. Jude Children's Research Hospital. Dr. Webster received his PhD in microbiology from the Australian National University and his MSc and BSc at Otago University in New Zealand. Dr. Webster is a virologist who has defined the nature and origins of human pandemic influenza strains—the viruses that cause the flu. His work on the molecular and genetic basis of antigenic shift and of antigenic drift has been of enormous significance in shaping strategies for preventing future human flu pandemics. He has been involved recently in elucidating the origin of the avian H5N1 influenza viruses that transmitted directly to humans in Hong Kong and killed 6 of the 18 humans infected.

Appendix C

Agenda

Potential Risks and Benefits of Gain-of-Function Research
Symposium Agenda
National Academy of Sciences Building
2101 Constitution Avenue NW
Washington, DC 20036
December 15–16, 2014

Monday, December 15

7:30 am **Registration**
(coffee and tea will be served)

8:00 **Welcome**
Harvey Fineberg, Chair of Symposium Planning Committee, Moderator
Ralph Cicerone, President, National Academy of Sciences and Chairman, National Research Council
Victor Dzau, President, Institute of Medicine

8:15 **Session 1: Opening Remarks**
Moderator: Harvey Fineberg

Goals of the Symposium: Discussion of Potential Benefits and Risks of Gain-of-Function (GoF) Research and Identification of Key Principles and Considerations for Risk/Benefit Assessment (10 minutes)
Harvey Fineberg

Summary of Recent European Meetings on GoF Research (5 minutes)
Harvey Fineberg

Current U.S. Government Policy on GoF Research Proposals and Charge to the Academies (15 minutes)
Andrew Hebbeler, Assistant Director for Biological and Chemical Threats, Office of Science and Technology Policy, The White House
Mary Groesch, Senior Policy Advisor, National Institutes of Health (NIH)

Summary of and Response to October 22, 2014, National Science Advisory Board for Biosecurity (NSABB) Meeting (15 minutes)
Samuel Stanley, Chair of the NSABB

Moderated Discussion (15 minutes)
To clarify or expand on key issues that emerge from the presentations

9:15 **Session 2: Overview**
Moderator: Harvey Fineberg

Purpose: To provide a brief introduction to the current scientific and technical approaches to virology research and the study of pandemic avian influenza, Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS).

Speaker: Kanta Subbarao, National Institute of Allergy and Infectious Diseases (NIAID)/NIH (20 minutes)

Virology: What impact does virological research typically have on the viruses being studied? Where does virology cross the line into GoF research as defined by the U.S. government? Explanation of types of GoF research.

What do we know or not know about flu, SARS, and MERS and can GoF research help fill the gaps?

Moderated panel discussion (20 minutes)
To clarify or expand on key issues that emerge from the presentations

Panelists
- Thomas Briese, Columbia University
- Michael Imperiale, University of Michigan

Q&A Discussion (20 minutes)

10:15 **Session 3: What Are the Main Points of the Debate on the Potential Risks and Benefits of GoF Research?**
Moderator: Harvey Fineberg

Two Views (15 minutes each)
What are the key issues on benefits that need to be addressed in the assessments that the NIH will undertake?
Yoshihiro Kawaoka, University of Wisconsin-Madison

What are the key issues on risks that need to be addressed in the assessments that the NIH will undertake?
David Relman, Stanford University

Respondent: Robert Webster, member of Symposium Planning Committee (15 minutes)
To probe and explore the evidence for the statements made by speakers above.

Q&A Discussion (30 minutes)

11:30 Break

12:00 pm **Session 4: Potential Benefits of GoF Research I: Surveillance, Detection, and Prediction**
Moderator: Philip Dormitzer, member of Symposium Planning Committee

Focus: Potential for contributions to public health and biosecurity (early detection and identification of dangerous strains) as well as design and operation of disease surveillance or pandemic modeling systems.

Surveillance of emerging zoonotic diseases (10 minutes)
Stacey Schultz-Cherry, St. Jude Children's Research Hospital

Modeling of potential pandemics (10 minutes)
Christophe Fraser, Imperial College, London

Respondent: Colin Russell, University of Cambridge

Q&A Discussion (30 minutes)

1:00 **Lunch**
(boxed lunches will be provided)

2:00 **Session 5: Potential Benefits of GoF Research II: Treatment and Response**
Moderator: Baruch Fischhoff, member of Symposium Planning Committee

Focus: Potential for GoF research to accelerate vaccine and antiviral development and potential impact of GoF regulations on vaccine and antiviral development.

Panel of Academic, Government, and Industry Representatives (5 minutes each)
Philip Dormitzer, Novartis Vaccines—synthetic influenza vaccine viruses
Ralph Baric, University of North Carolina—vaccines targeting coronaviruses
George Kemble, 3-V Biosciences (formerly Medimmune)—GoF and live attenuated influenza viruses
Jerry Weir, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration—regulatory perspective on viral manipulation for biologics
Mark Denison, Vanderbilt University—GoF research and countermeasures against SARS and MERS

Moderated Discussion (15 minutes)
To clarify or expand on key issues that emerge from the presentations

Q&A Discussion (30 minutes)

3:15 **Session 6: Potential Risks of GoF Research I: Biosafety**
Moderator: Alta Charo, member of Symposium Planning Committee

Focus: Potential for inadvertent releases, laboratory acquired infections, environmental health issues, and risk mitigation for pathogen research in general and as related to GOF research.

Panel Discussion (10 minutes each)
Barbara Johnson, Biosafety Biosecurity International
Rob Weyant, Division of Select Agents and Toxins, U.S. Centers for Disease Control and Prevention
Rebecca Moritz, Biosecurity Task Force, University of Wisconsin-Madison
Marc Lipsitch, Harvard University

Q&A Discussion (30 minutes)

4:30 **Session 7: Potential Risks of GOF Research II: Biosecurity**
Moderator: Ronald Atlas, member of Symposium Planning Committee

Focus: Potential for misuse of research for biocrimes or bioterrorism or to develop new biological weapons, as well as the potential for deliberate release or sabotage.

Speakers (10 minutes each)
Gregory Koblentz, George Mason University
Carol Linden, Biomedical Advanced Research and Development Authority
Gigi Kwik Gronvall, University of Pittsburgh Medical Center (UPMC) Center for Health Security

Q&A Discussion (30 minutes)

5:30 **Adjourn for the day**

Tuesday, December 16

7:45 am Welcome
(continental breakfast will be provided)

8:00 **Session 8: Models for Risk/Benefit Assessment, Risk Mitigation, and Engaging the Public**
Moderator: Charles Haas, member of the Symposium Planning Committee

What can risk/benefit assessment do and what can it not do? What have we learned from the past about strategies, pitfalls, and limitations of risk and benefit assessments? (15 minutes)
Baruch Fischhoff, member of the Symposium Planning Committee

The role of human factors (15 minutes)
Gavin Huntley-Fenner, Huntley-Fenner Advisors

Ensuring public engagement (15 minutes)
Monica Schoch-Spana, UPMC Center for Health Security

What, if any, special considerations about GoF research need to be taken into account in the risk/benefit assessment? (30 minutes)
Ralph Baric, member of the Symposium Planning Committee
Robert Lamb, Northwestern University

- Reversibility/mitigation?
- Special considerations about alternative research methods with less risk?
- Differences among organisms?
- Exactly what functionality is being gained or lost?
- Are transmissibility, virulence, growth, and functionality (necessary for vaccine production) all similar in terms of GOF objectives?

Q&A Discussion (45 minutes)

10:00 **Session 9: Summary Discussions**
Moderator: Harvey Fineberg

The rapporteurs will report on the main ideas collected on each of the following topics:

- Potential risks
- Potential benefits
- Considerations/challenges for analysis of potential risks and benefits to Inform broader assessments
- Policy implications

11:00 **Break** (substantial snacks will be served, because there will be no lunch break)

11:30 **Session 10: Finding Common Ground**
Moderator: Harvey Fineberg

- What are the major areas of agreement on risks and benefits?
- What are the major areas of disagreement on risks and benefits?
- How should the risks be weighed against the benefits?
- What approaches may be available to diminish risks and achieve benefits simultaneously?
- What are the key principles and issues that the NIH's risk and benefit assessments need to include?

Moderated Discussion (approximately 2 hours)

1:30 **Session 11: Chairman's Summary of Meeting Highlights**

2:00 **Adjourn**

Appendix D

Speaker Biographies

Ronald M. Atlas—please see committee biographies

Ralph Baric—please see committee biographies

Thomas Briese is Associate Professor of Clinical Epidemiology at the Mailman School of Public Health at Columbia University. He obtained his scientific education at the Freie University in Berlin, the Max Planck Institute for Molecular Genetics, and the University of California at Irvine. He pioneered state-of-the-art methods in molecular biology to study the involvement of infectious agents in chronic and neuropsychiatric diseases, as well as in acute diseases. Dr. Briese's research interests include the molecular epidemiology of emerging viral diseases, virus-host cell interactions, and innovative approaches to pathogen diagnosis and discovery. Dr. Briese was responsible for cloning the genome of Borna disease virus, a novel infectious agent potentially linked to some mental disorders. His achievements have been recognized by receipt of an Albertson Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression. Another successful application of these powerful molecular techniques was the identification of the flavivirus responsible for the New York City encephalitis epidemic in 1999. In 2003, Dr. Briese participated in the investigation of the Severe Acute Respiratory Syndrom (SARS) epidemic, during which he visited and collaborated with Beijing research institutions by invitation of the Chinese Ministry of Science and Technology. He also served as an adviser to World Health Organization.

Current research efforts include the advancement of molecular detection tools for the rapid identification of potential bio-threat agents. In addition, Dr. Briese is involved in multi-center and birth cohort studies using molecular methods to assess the potential role of infection in disorders such as autism and schizophrenia.

R. Alta Charo—please see committee biographies

Ralph J. Cicerone is President of the National Academy of Sciences and Chair of the National Research Council. His research in atmospheric chemistry, climate change, and energy has involved him in shaping science and environmental policy at the highest levels nationally and internationally.

Mark Denison is the Craig-Weaver Professor of Pediatrics, and Professor of Pathology, Microbiology, and Immunology at Vanderbilt University School of Medicine in Nashville, Tennessee. Dr. Denison is a pediatric infectious disease specialist and has directed more than 25 years of National Institutes of Health-funded research on the replication, pathogenesis and evolution of coronaviruses (CoV), including SARS-CoV and Middle East Respiratory Syndrom-CoV. Dr. Denison's lab team uses targeted reverse genetic mutagenesis and adaptive experimental evolution to define key determinants of coronavirus replication fidelity and its impact on pathogenesis, adaptation, and inhibition. Notably, his lab discovered that coronaviruses encode and utilize a proofreading exonuclease (ExoN) to maintain replication fidelity, a function unprecedented in RNA virus biology. His group determined that genetic inactivation of CoV-ExoN results in a profound mutator virus phenotype (ExoN-) that increases sensitivity of CoVs to mutagens; together with the Baric lab he showed that the SARS-CoV ExoN-mutator phenotype is stable in vivo, and is attenuating and immunogenic in a SARS-CoV lethal infection mouse model. Dr. Denison also collaborated in the first demonstration of the rescue non-cultivatable Bat-CoV using synthetic genomics alone. Dr. Denison served on the steering committee for the Southeast Regional Center of Excellence in Emerging Infections and Biodefense from 2004 to 2014 where he developed teaching modules for dual-use research of concern (DURC). He has served as Chair of the Vanderbilt Institutional Biosafety Committee (IBC), and on multiple U.S. government, international panels, and journal editorial boards involved in review or consideration of biodefense, biosecurity, synthetic biology, and DURC. Dr. Denison is an elected fellow of the American Academy of Microbiology and the American Association for the Advancement of Sciences, as well as a member of the American Society for Virology.

Philip Dormitzer—please see committee biographies

Victor J. Dzau is President of the Institute of Medicine. He served nearly 10 years as Chancellor for Health Affairs at Duke University and President and CEO for Duke University Health System. Before that, Dzau held influential posts with Harvard Medical School, Brigham and Women's Hospital, and Stanford University. He is an internationally recognized trailblazer in translational research, health innovation, and global health care strategy and delivery.

Harvey V. Fineberg—please see committee biographies

Baruch Fischhoff—please see committee biographies

Christophe Fraser is currently Chair of Theoretical Epidemiology and Royal Society University Research Fellow at Imperial College London. He trained in theoretical particle physics, obtaining his PhD in 1997, and shifted areas to infectious disease epidemiology in 1998, training under Roy Anderson. He has been based at Imperial College since 2000. Professor Fraser leads the evolutionary epidemiology group, which works on developing theory, integrating data, and developing applications for public health. The evolutionary epidemiology group takes a unified view of the epidemiology and evolution of pathogens, driven by complex underlying patterns of host-host, host-pathogen, and pathogen-pathogen interactions that require careful disentangling. They use a spectrum of tools ranging from simple mathematical models to complex computer simulations, usually interacting with microbiologists, basic medical scientists, and public health professionals. They are affiliated with the Medical Research College Centre for Outbreak Analysis, and in that context work on applied epidemic modelling. Current topics of interest for the research group include HIV virulence and epidemiology, bacterial phylodynamics, influenza epidemiology, and outbreak analysis.

Charles N. Haas—please see committee biographies

Andrew Hebbeler is a former biological research scientist with foreign affairs, national security, science and technology, and nonproliferation program and policy experience. Currently, he is Assistant Director for Biological and Chemical Threats in the National Security and International Affairs division of the White House Office of Science and Technology Policy. Prior to his position at the White House, Dr. Hebbeler managed and oversaw the State Department's Biosecurity Engagement Program (BEP), which is an important component of the broader U.S. Coopera-

tive Threat Reduction effort and reduces the threat of bioterrorism by preventing terrorist access to potentially dangerous biological materials, dual-use infrastructure, and expertise, while supporting efforts to combat infectious disease and enhance public and animal health worldwide. Dr. Hebbeler was born in Cincinnati, Ohio, and received his bachelor's degree in biology and philosophy from Thomas More College in Crestview Hills, Kentucky. He completed his doctoral work in the laboratory of C. David Pauza at the University of Maryland, Baltimore, where he focused on understanding an unconventional lymphocyte population that is important during immune responses to infectious disease and cancer. Before joining the State Department, Dr. Hebbeler was a postdoctoral fellow in the laboratory of Warner C. Greene at The J. David Gladstone Institutes in San Francisco, California.

Gavin Huntley-Fenner is a human factors and safety consultant with a unique problem-solving skill set and communication style developed over more than 15 years as a researcher, author, educator, and business consultant. He regularly provides consumer product hazard analyses and has served as an expert witness for matters relating to risk perception, instruction manuals, warnings, labeling, safety and human development, human reaction time, and decision-making. Dr. Huntley-Fenner is an educator and certified Continuing Legal Education (CLE) provider, as well as a published author.

Michael Imperiale is a Professor in the Department of Microbiology and Immunology at the University of Michigan Medical School. He joined the department in 1984 as the Arthur F. Thurnau Assistant Professor of Microbiology and Immunology and was subsequently promoted to Associate Professor in 1990 and Professor in 1996. He is currently the Arthur F. Thurnau Professor and Associate Chair of Microbiology and Immunology. In 2010 Dr. Imperiale was elected as a fellow of the American Academy of Microbiology and in 2011 he was elected as a fellow of the American Association for the Advancement of Science. Before joining the University of Michigan, Dr. Imperiale carried out research training as a postdoctoral fellow at The Rockefeller University, where he first became interested in DNA tumor viruses, studying gene regulation in the human pathogen, adenovirus. He received his undergraduate and graduate training at Columbia University, receiving a BA in 1976, MA in 1978, and PhD in 1981, all in biological sciences. Currently, Dr. Imperiale's research interests focus on the study of how DNA tumor viruses interact with the host cell. Dr. Imperiale is a member of the National Science Advisory Board for Biosecurity, a position he has held since 2005. He also serves as an editor of the *Journal of Virology*, *PLos Pathogens*, and *mBio*.

Barbara Johnson is registered biosafety professional and has held positions in U.S. government and in private industry as a biosafety professional and senior scientist for more than 25 years. Currently, she develops site-specific risk assessments and mitigation strategies, assists in developing frameworks internationally to establish Institutional Biosafety Committees and support programs, reviews and develops designs for biocontainment facilities (A/BSL-2 through A/BSL-4 and BSL-3 Ag), certifies and validates containment laboratories, develops and provides biosafety and biosecurity training, and provides strategic and technical assistance in developing national-level and international biosafety, biosecurity, and biorisk management programs for conducting work with high-risk pathogens. Her company, Biosafety Biosecurity International provides technical and policy consultation in the United States and to international organizations (Department of Health and Human Services, Department of Homeland Security, Department of Justice, Department of Defense, Department of State, U.S. Department of Agriculture, United Nations, World Health Organization, and the Food and Agriculture Oranization of the United Nations), industry and universities, as well as international Ministries of Health. Approximately 30 percent of her time is spent consulting with overseas biocontainment entities and ministries. She has served on several committees for the National Academy of Sciences, developed parts of the National Biosecurity Training Program for the USDA and CDC and served as a member of the ANSI/AIHA Z9.14 Committee that developed the U.S. "Standard for Verification of BSL-3 Laboratories." Dr. Johnson is the Chief Co-Editor of the American Biological Safety Association journal *Applied Biosafety*, an approved BSL-3 Facility Certifier and Trainer by the Singapore Ministry of Health, and a past President of the American Biological Safety Association.

Yoshihiro Kawaoka was educated in Japan, receiving his DVM in 1978 from the Ministry of Agriculture and Fishery and his PhD in 1983 from Hokkaido University. He then moved from Japan to Memphis, Tennessee, where he began a postdoctoral fellowship in influenza virology under the tutelage of Dr. Robert Webster at St. Jude Children's Research Hospital. While at St. Jude, Dr. Kawaoka established an independent program to address such fundamental questions in influenza virology as how do influenza viruses cause disease; why are certain types of influenza viruses found in humans while other types are found only in birds; and how do influenza viruses change over time. These studies led Dr. Kawaoka to identify a difference between viruses that kill birds and those that do not. He then demonstrated the significance of this difference by converting deadly bird flu viruses to milder, non-lethal forms. This information is now used by the USDA and Organisation Mondiale de la Santé Animale

(World Organisation for Animal Health) as a criterion for rapidly identifying lethal and nonlethal bird flu viruses and to produce vaccine strains for H5N1 viruses. During his tenure at St. Jude, Dr. Kawaoka ultimately achieved the status of Full Member (professor). He later assumed a professorship at the University of Wisconsin (UW)-Madison. At UW, Dr. Kawaoka continued to study fundamental concepts in influenza virology. He established reverse genetics, which allows the generation of "designer" influenza viruses. This technology—coupled with knowledge established by Dr. Kawaoka regarding the attenuation of deadly influenza viruses—was exploited in the development of candidate H5N1 influenza virus vaccines, which were proven efficacious in clinical trials. Dr. Kawaoka has also employed reverse genetics in basic research. Using this technology, he identified a change in a single gene that is critical for bird flu viruses to cause severe disease in mammals. Dr. Kawaoka has also undertaken the study of the 1918 Spanish flu virus, which killed more than 40 million people around the close of World War I. Information uncovered by Dr. Kawaoka is used globally by public health agencies as they undertake the enormous task of influenza pandemic planning. In addition to his work with influenza virus, Dr. Kawaoka also studies Ebola virus. Because of its extreme virulence, laboratories designated as biosafety level 4 (BSL-4), the highest containment environment possible, were required to carry out experiments with Ebola virus. This requirement severely hampered the progress of research with this virus, as few such facilities exist worldwide. Dr. Kawaoka therefore established several systems that allowed the analyses of Ebola virus under non-BSL-4 conditions. These systems are now widely used in many laboratories, contributing to the recent advances in Ebola virus research. Dr. Kawaoka has made significant scientific contribution to the understanding of two highly lethal pathogens, influenza and Ebola viruses. In recognition of his work, in 2006, Dr. Kawaoka was awarded the prestigious Robert Koch Award for his innovative research in the field of influenza virology.

George Kemble joined 3-V Biosciences in August 2011 as its Chief Scientific Officer. Prior to joining 3-V, Dr. Kemble was with MedImmune, Inc., a subsidiary of Astra-Zeneca PLC, where he served as Senior Vice President of R&D and Head of Research. During his tenure, Dr. Kemble was responsible for the research and development of multiple products, including the successful launch of FluMist®, the first innovation in influenza vaccines in more than 60 years. The research organization for which he was responsible included more than 700 scientists in Maryland, California, and Cambridge, England, with expertise in research biology, lead generation and translational science in the areas of infectious diseases, oncology, inflammatory, respiratory, autoimmune diseases, neuroscience,

cardiovascular, and gastrointestinal indications. Dr. Kemble began his research career as a staff scientist at Aviron, which was later acquired by MedImmune. Dr. Kemble received a BS from the University of Santa Clara and a PhD from Stanford University and did his postdoctoral training at the University of California, San Francisco, where he worked on a number of different human viruses.

Gregory Koblentz is an Associate Professor in the School of Policy, Government, and International Affairs and Deputy Director of the Biodefense Graduate Program at George Mason University. He is also a Research Affiliate with the Security Studies Program at the Massachusetts Institute of Technology, Associate Faculty at the Center for Global Studies at George Mason, and a member of the Scientist Working Group on Chemical and Biological Weapons at the Center for Arms Control and Non-Proliferation in Washington, DC. During 2012-2013, he was a Stanton Nuclear Security Fellow at the Council on Foreign Relations where he conducted research on nuclear proliferation. Prior to arriving at George Mason, Dr. Koblentz was a Visiting Assistant Professor in the School of Foreign Service and Department of Government at Georgetown University. He has also worked for the Executive Session on Domestic Preparedness at the John F. Kennedy School of Government at Harvard University and the Nuclear Non-Proliferation Project at the Carnegie Endowment for International Peace. Dr. Koblentz is the author of *Strategic Stability in the Second Nuclear Age* (Council on Foreign Relations, 2014) and *Living Weapons: Biological Warfare and International Security* (Cornell University Press, 2009) and co-author of *Tracking Nuclear Proliferation: A Guide in Maps and Charts* (Carnegie Endowment for International Peace, 1998). His research and teaching focus on international security and weapons of mass destruction. He received a PhD in political science from the Massachusetts Institute of Technology and an MPP from the John F. Kennedy School of Government at Harvard University.

Gigi Kwik Gronvall is a Senior Associate at the Center for Biosecurity of University of Pittsburgh Medical Center (UPMC) and Assistant Professor of Medicine at the University of Pittsburgh. An immunologist by training, Dr. Gronvall's work addresses how scientists can diminish the threat of biological weapons and how they can contribute to an effective response against a biological weapon or a natural epidemic. She is a term member of the Council on Foreign Relations and also serves on the American Association for the Advancement of Science (AAAS) Committee on Scientific Freedom and Responsibility. Dr. Gronvall is a founding member of the Center for Biosecurity of UPMC and, prior to joining the faculty in 2003, she worked at the Johns Hopkins University Center for Civilian

Biodefense Strategies. From 2000 to 2001 she was a National Research Council Postdoctoral Associate at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland. Dr. Gronvall earned a PhD from Johns Hopkins University for her work on T-cell receptor/MHC I interactions.

Robert Lamb is John Evans Professor of Molecular and Cellular Biology in the Department of Molecular Biosciences at Northwestern University, Professor of Microbiology-Immunology at Northwestern University Medical School, and an Investigator of the Howard Hughes Medical Institute. He received his undergraduate degree reading biochemistry at the University of Birmingham, England, and his PhD and ScD degrees from the University of Cambridge. He came to the United States to do postdoctoral work with Purnell Choppin at the Rockefeller University, where he later became a faculty member before joining the faculty of Northwestern University. His honors include consecutive NIH MERIT awards. He is past President of the American Society for Virology. Dr. Lamb is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences.

Carol Linden currently serves as the Principal Deputy Director of the Office of the Biomedical Advanced Research and Development Authority (BARDA) in the Office of the Assistant Secretary for Preparedness and Response, Department of Health and Human Services. Her duties include oversight of advanced development and acquisition programs for Project BioShield medical countermeasures for chemical, biological, radiological, and nuclear (CBRN) threats as well as pandemic influenza vaccines, drugs, diagnostics, and infrastructure. From October 2006 through April 2008 she also served as the Acting Director of BARDA, responsible for a doubling in the size of the office and implementation of the legislation that established the office. Dr. Linden previously served as the Senior Scientist for the Office of Research and Development in the Science and Technology Directorate of the Department of Homeland Security, overseeing treaty and regulatory compliance as well as international collaborations. Immediately prior to this position, she served as Deputy Director of the Office of Research Programs. Prior to joining the Department of Homeland Security, Dr. Linden was the Scientific Director for the Defense Threat Reduction Agency (DTRA) Chemical and Biological Defense Directorate from mid-2003 until spring of 2004. Before her detail to DTRA, she served as the Director for the Department of Defense Medical Chemical and Biological Defense Research Programs for more than 3 years, managing all aspects of the joint services medical Chemical and Biological Defense Program. Dr. Linden served a critical function in coordinating the work-

ing relationship between the technology base and advanced development, facilitating the transition of candidate vaccines, diagnostic technologies, and therapies to the developer. Dr. Linden obtained her bachelor's degree in biology from Bryn Mawr College and a PhD from the University of California, Los Angeles in molecular biology. She conducted postdoctoral research at the California Institute of Technology and University of Maryland prior to joining the research staff at the U.S. Army Medical Research Institute of Infectious Diseases, where she subsequently served as the Chief, Research Plans and Programs.

Marc Lipsitch is Professor of Epidemiology at the Harvard School of Public Health and Director of the Center for Communicable Disease Dynamics (CCDD), an NIH/National Insttute of General Medical Sciences MIDAS Center of Excellence. He is an author of more than 200 peer-reviewed publications on the impact of medical and public health interventions on the spread and evolution of infectious disease agents, and the consequences of these changes for human health. His group produced one of the earliest estimates of transmissibility of the SARS virus in real time in 2003 and provided a key estimate of the transmissibility of 1918 pandemic influenza, which helped to support the possibility of the use of pharmaceutical and nonpharmaceutical interventions to control the spread of future pandemics. His team at CCDD played a leading role in the analysis and response to the 2009 influenza A/H1N1 pandemic, working closely with local, state, national, and international public health agencies. In addition to ongoing studies of pandemic and seasonal influenza burden, preparedness, and response, current research includes the application of population genomics to understand the spread of infections and the changes produced in bacterial population by human immunity, and modeling the effects of pneumococcal vaccination. Experimentally, his laboratory studies the immune response to and antigenic diversity of Streptococcus pneumoniae, combining molecular biology and animal studies with population genomics, epidemiology, and mathematical modeling. Dr. Lipsitch has received several outstanding young investigator awards and has served on the editorial advisory boards/associate editor of *PLoS Medicine*, *Journal of Infectious Diseases*, *American Journal of Epidemiology*, *Epidemiology*, and *Epidemics*. He has served on the President's Council of Advisors on Science and Technology Working Group on H1N1 Influenza, as well as CDC's Team B for the 2009 H1N1 pandemic. He has provided advice on antimicrobial resistance, SARS, or influenza to the Food and Drug Administration, WHO, CDC, Congressional Budget Office, Defense Science Board, and the governments of Canada and Mexico. He was a member of the winning team in the 2013 CDC "Predict the Flu" Challenge. Dr. Lipsitch received his BA in philosophy from Yale

University, completed his doctoral work in zoology at Oxford University as a Rhodes Scholar, and did postdoctoral work at Emory University and at the CDC from 1995 to 1999. He joined the faculty of Harvard School of Public Health in 1999.

Rebecca Moritz is a biosafety and biosecurity expert with a BS in bacteriology and an MS in medical microbiology and immunology from the University of Wisconsin (UW)-Madison. She serves as the Select Agent Program Manager and Alternate Responsible Official for the UW-Madison Select Agent Program. Ms. Moritz is chair of UW-Madison's Dual Use Research of Concern Subcommittee and an appointed consultant to the UW-Madison Institutional Biosafety Committee. She is also a lead member of the UW-Madison Biosecurity Task Force, consisting of a diverse body of experts from across campus and responsible for regularly reviewing the research programs and practices of its Select Agent researchers. She is a certified biosafety professional with the American Biological Safety Association (ABSA) and member of several ABSA committees, including the Legislative Committee. Additionally, she is a specialist microbiologist with the National Registry of Certified Microbiologists. Ms. Moritz has conducted research in both private-sector and academic laboratories, including in high-containment laboratories.

Amy Patterson is the Associate Director for Biosecurity and Biosafety Policy at the NIH in the Department of Health and Human Services (HHS). In this position, she advises the NIH Director and the 27 NIH Institute and Center Directors on a wide spectrum of issues related to the federal framework for biosafety oversight, as well as biosecurity measures to preclude the misuse of the products of life science research. Specifically, she works on such matters as the science, safety, and ethics of recombinant DNA research; mitigating the risks of dual use research of concern; the biosafety and biosecurity dimensions of emerging technologies; and federal policy regarding the funding of gain-of-function research. In addition, she provides leadership in federal efforts to address the global problem of antibiotic resistance bacteria. Dr. Patterson is also a member of the HHS senior leadership team coordinating the Department's response to the Ebola crisis. In all of these efforts, Dr. Patterson works with senior leadership of other federal agencies and the White House. She also manages and staffs key federal advisory committees, including the National Science Advisory Board for Biosecurity.

David Relman is the Thomas C. and Joan M. Merigan Professor in the departments of Medicine and of Microbiology and Immunology at Stanford University, and Chief of Infectious Diseases at the Veterans

Affairs Palo Alto Health Care System in Palo Alto, California. He is also Co-Director of the Center for International Security and Cooperation and Senior Fellow at the Freeman Spogli Institute for International Studies at Stanford University. Dr. Relman's research focus is the human indigenous microbiota, and in particular, the nature and mechanisms of variation in patterns of microbial diversity and function, key features of microbial community assembly, and the basis for community stability and resilience. During the past few decades, he has also spearheaded the development of new strategies for identifying previously unrecognized microbial agents of disease. These efforts have revealed novel pathogens and commensals. Dr. Relman has served as an advisor to a number of agencies and departments within the U.S. government on matters pertaining to emerging infectious diseases, human-microbe interactions, biotechnology, and biosecurity. He currently serves as Chair of the Forum on Microbial Threats at the Institute of Medicine and is Immediate Past-President of the Infectious Diseases Society of America. Dr. Relman received a BS (biology) from MIT and MD from Harvard Medical School, completed his clinical and research postdoctoral training at Massachusetts General Hospital and at Stanford University, and joined the faculty at Stanford in 1994. He received an NIH Pioneer Award in 2006 and an NIH Transformative Research Award in 2011, and he was elected a member of the Institute of Medicine in 2011.

Colin Russell is currently a Royal Society University Research Fellow in the Department of Veterinary Medicine at the University of Cambridge and one of the chief scientists of the Cambridge World Health Organization Collaborating Center for Modelling, Evolution and Control of Emerging Infectious Diseases. He received a BS in biology from Emory University and did his doctoral work at the University of Cambridge as a Gates Scholar. He has been based at the University of Cambridge since 2002. Dr. Russell's research focuses broadly on the evolution and epidemiology of influenza viruses, and he has published papers on topics ranging from the within-host evolution of avian influenza viruses to the global circulation of seasonal influenza viruses.

Monica Schoch-Spana, a medical anthropologist, is a senior associate with the UPMC Center for Health Security, an Associate Professor of Anthropology at the Texas State University, and a former Associate Professor of Medicine at the University of Pittsburgh. Her research and policy interests include disaster resilience, community engagement, public health emergency preparedness, and nuclear incident preparedness, response, and recovery. Starting in 1998, Dr. Schoch-Spana has briefed federal, state, and local officials, as well as medical, public health, and public safety profes-

sionals on critical issues in biosecurity and public health, emergency preparedness. National advisory roles include serving on the Steering Committee of the Disaster Roundtable of the National Research Council (NRC), the Institute of Medicine Standing Committee on Health Threats Resilience, and the NRC Committee on Increasing National Resilience to Hazards and Disasters. Dr. Schoch-Spana has led research, education, and advocacy efforts to encourage authorities to enlist the public's contributions in managing epidemics, biological attacks, and other health emergencies. She has chaired national working groups to produce peer-reviewed, evidence-based consensus guidance for authorities on how to lead with the public's trust and help during bioterrorism response (2004), how to engage community partners in preparing for a health emergency such as pandemic flu (2007), and how to design a community-based approach for nuclear incident preparedness (2011). She has organized three national conferences on community resilience and public participation in emergency planning. In 2003, Dr. Schoch-Spana helped establish the Center for Health Security; prior to that she had worked at the Johns Hopkins University Center for Civilian Biodefense Strategies since 1998. She received a PhD in cultural anthropology from Johns Hopkins University (1998) and a BA from Bryn Mawr College (1986).

Stacey Schultz-Cherry's introduction to influenza pathogenesis began as a postdoctoral fellow with Dr. Virginia Hinshaw at the University of Wisconsin. Given her PhD training as a cellular biochemist with an emphasis on wound healing and extracellular matrix-growth factor interactions in the Department of Pathology at the University of Alabama-Birmingham, her postdoctoral studies focused on understanding the viral and cellular factors involved in influenza virus-induced apoptosis. She was specifically interested in how highly pathogenic avian influenza (HPAI) viruses induced extensive damage. These studies led to a faculty position at the Southeast Poultry Research Lab (USDA-ARS) studying HPAI. The timing of the move corresponded to the 1997 HPAI outbreak in humans in Hong Kong. During her 5 years at the USDA, she was intimately involved in the H5N1 outbreak in terms of diagnostics, epidemiology, surveillance, and pathogenesis and worked closely with the CDC. They were also one of the first laboratories to begin working with turkey pneumovirus, which is closely related to human metapneumovirus. In 2002, she accepted a tenure-track faculty position at the University of Wisconsin School of Medicine and Public Health, where her laboratory continued to focus on pathogenesis. She also identified and characterized a novel antiviral peptide that blocks influenza attachment. The laboratory's patent was recently licensed by a small influenza company. After receiving tenure at UW, St. Jude offered her a faculty position that she could not refuse. At

St. Jude, her laboratory is part of the Center for Excellence in Influenza Research and Surveillance and the World Health Organization Collaborating Center. The Centers are continuing with basic research studies but have also initiated surveillance efforts throughout Latin America.

Samuel L. Stanley, Jr. was appointed as the fifth President of Stony Brook University in May 2009. Since that time he has presided over a tremendous growth of the university, through the implementation of a faculty hiring program that has brought 200 net new faculty to Stony Brook, a five-fold increase in endowed professorships, the largest number of applicants and most accomplished classes in the school's history, and record fundraising totals, including one of the largest gifts ever to a public university. Before becoming President of Stony Brook University, Dr. Stanley served as Vice Chancellor for Research at Washington University in St. Louis, where he had a distinguished career as a biomedical researcher with a focus on host defense against emerging pathogens. Dr. Stanley currently serves as the Chair of the National Science Advisory Board for Biosecurity (NSABB), is a member of the National Security Higher Education Advisory Board (NSHEAB), is the Chair of Brookhaven Science Associates (BSA), which manages Brookhaven National Laboratory, is a member of the Board of Directors of Cold Spring Harbor Laboratory, and is a member of the Board of Directors of the Research Foundation, State University of New York.

Kanta Subbarao received her MBBS in 1982 from the Christian Medical College, Vellore, University of Madras, India, and completed a residency in pediatrics at Cardinal Glennon Memorial Hospital for Children at St. Louis University. She completed a fellowship in pediatric infectious diseases and earned her MPH in epidemiology from the University of Oklahoma Health Sciences Center. After postdoctoral training in the Laboratory of Infectious Diseases (LID) at the National Institutes of Health, she served on the faculty at McGill University, Montreal, Canada, and subsequently served as Chief of the Molecular Genetics Section of the Influenza Branch at the Centers for Disease Control and Prevention. Dr. Subbarao joined LID as a senior investigator in 2002.

Robert G. Webster—please see committee biographies

Jerry Weir is the Director of the Division of Viral Products (DVP), Office of Vaccines Research and Review with the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). He received his PhD in biochemistry from Vanderbilt University and did postdoctoral research in virology at the National Institutes of Health. He joined the Food and Drug Administration in 1994. In his position as Director of DVP,

Dr. Weir manages the regulatory activities and research programs of the Division. As a Senior Investigator at CBER, he directs a research program pertaining to diverse viruses, including influenza, herpesviruses, and poxviruses. Dr. Weir frequently serves as an advisor to the World Health Organization on issues relating to influenza virus vaccines activities and vaccine standards.

Rob Weyant currently serves as the Director of the Division of Select Agents and Toxins, Office of Public Health Preparedness and Emergency Response, CDC (DSAT). He holds bachelor's and master's degrees from the University of Pittsburgh and a PhD from Emory University. Prior to joining DSAT in 2006 Dr. Weyant had served as Chief of the CDC Special Bacteriology Reference Laboratory (1991-2002) and then as the CDC Biological Safety Officer (2002-2006). Dr. Weyant has authored or coauthored more than 150 scientific publications, and he served on the Steering Committee for the fifth edition of the CDC/NIH Biosafety in Microbiological and Biomedical Laboratories manual. In October of 2012 Dr. Weyant published a major update of the HHS Select Agent Regulations, defining the agents of highest risk for misuse and establishing new regulatory requirements for their safe and secure possession.

Appendix E

List of Attendees

Paul Ahlquist
Howard Hughes Medical Center
University of Wisconsin-Madison

Thomas Armel
Quantitative Scientific Solutions

Kimberly Armstrong
U.S. Food and Drug Administration

Ronald Atlas
University of Louisville

Ralph Baric
University of North Carolina

Kavita Berger
American Association for the Advancement of Science

Ken Berns
University of Florida

David Blazes
Uniformed Services University of the Health Sciences

Thomas Briese
Columbia University

Andy Burnham
Gryphon Scientific

David Carr
Wellcome Trust

Alta Charo
University of Wisconsin-Madison

May Chu
Office of Science, Technology, and Policy—The White House

Anita Cicero
UPMC Center for Health Security

Gwen Coat
CRDF Global

Michael Costa
Abt Associates, Inc.

Douglas Cyr
University of North Carolina, Chapel Hill

Genya V. Dana
U.S. State Department

Mark R. Denison
Vanderbilt University School of Medicine

Dennis M. Dixon
NIH/NIAID

Ruben Donis
U.S. Centers for Disease Control and Prevention

Philip Dormitzer
Novartis Vaccines

W. Paul Duprex
Boston University

Gerald Epstein
U.S. Department of Homeland Security

Stephen Eubank
Virginia Tech

Nicholas Greig Evans
University of Pennsylvania

Robin Fears
European Academies Science Advisory Council

Robert Feinberg
Genetic Expert News Service

Harvey Fineberg
University of California, San Francisco

Andi Fischhoff

Baruch Fischhoff
Carnegie Mellon University

Meg Flanagan
U.S. State Department

Ron Fouchier
Erasmus MC

Greg Frank
IDSA

Christophe Fraser
Imperial College London

Matthew Frieman
University of Maryland

Adolfo Garcia-Sastre
Icahn School of Medicine at Mount Sinai

John S. Gardenier
NCHS

Turkan K. Gardenier
Pro-File Computer Institute
Laurie Garrett
Council on Foreign Relations

Carolyn Garvey
U.S. Government Accountability Office

Elizabeth Geltman
Hunter College

Dylan George
BARDA

Brett Goode
U.S. State Department

Christine Grant
InfecDetect Rapid Diagnostic Tests, LLC

Ashley Grant
U.S. Department of Defense

Nell Greenfieldboyce
National Public Radio

Steven Greidinger
Predictive Health

Mary Groesch
National Institutes of Health

Gigi Kwik Gronvall
UPMC Center for Health Security

Jack Gruber
USA Today

Charles Haas
Drexel University

Peter Hale
The Foundation for Vaccine Research

Wendy Hall
DHS HQ Office of Policy

Marie-Louise Hammarskjold
University of Virginia School of Medicine

Christopher Hanson
NIAID/NIH

Teresa Hauguel
NIAID/NIH

Andrew Hebbeler
Office of Science and Technology Policy—The White House

Kelly Hills
Virtually Speaking Science

Rona Hirschberg
Consultant

India Hook-Barnard
Institute of Medicine

Gavin Huntley-Fenner
Huntley-Fenner Advisors, Inc.

Jean Hu-Primmer
BARDA

Jo L. Husbands
National Research Council

Michael Imperiale
University of Michigan

Tom Inglesby
UPMC Center for Health Security

Harold W. Jaffe
U.S. Centers for Disease Control and Prevention

Peter Jahrling
National Institutes of Health

Barbara Johnson
Biosafety Biosecurity International

Jocelyn Kaiser
Science Magazine

Dmitry Kaledin
Russian Embassy

Joe Kanabrocki
University of Chicago

Yoshihiro Kawaoka
University of Wisconsin-Madison

Stephen Kendall
National Research Council

Andy Kilianski
Edgewood Chemical Biological Center

Gregory Koblentz
George Mason University

Angela Kolesnikova
National Research Council

Karolina Konarzewska
National Research Council

Dan Lackner

Robert A. Lamb
Northwestern University

Gardiner Lapham
Citizens United for Research in Epilepsy (CURE)

Jason Lee
U.S. Department of Justice

Betty Lee
Department of Commerce

Howie Lempel
Open Philanthropy Project

Rachel Levinson
Arizona State University

Carol Linden
U.S. Department of Health and Human Services

Marc Lipsitch
Harvard School of Public Health

Amjad Mahasneh
PHBC—Jordan University of Science and Technology

Anne-Marie Mazza
National Research Council

Piers Millett
Biosecure Ltd.

Susan Coller Monarez
Executive Office of the President

Jonathan Moreno
University of Pennsylvania

Rebecca Moritz
University of Wisconsin-Madison

Stephen S. Morse
Columbia University

Dee Mukherjee
Attorney at Law

Jenna Ogilvie
National Research Council

Giorgio Palu
University of Padova, Italy

Christopher Park
U.S. State Department

Rebecca T. Parkin
The George Washington University Medical Center

Andrew Pekosz
Johns Hopkins University

Diane Post
NIAID/NIH

Kevin Ramkissoon
National Institutes of Health

Johannes Rath
University of Vienna

David Relman
Stanford University

Kalpana Rengarajan
Emory University

I. Gary Resnick
IGR Consulting
Los Alamos National Laboratory

Sarah Rhodes
National Institutes of Health

Richard J. Roberts
New England Biolabs, Inc.

Lauren Rugani
National Research Council

Colin Russell
University of Cambridge

Charles J. Russell
St. Jude Children's Research Hospital

Eugene Schenecker

Monica Schoch-Spana
UPMC Center for Health Security

Stacey Schultz-Cherry
St. Jude Children's Research Hospital

Fran Sharples
National Research Council

Michael W. Shaw
U.S. Centers for Disease Control and Prevention

Dana Shea
Congressional Research Service

Katherine Sixt
Institute for Defense Analyses

Monica Smith
IDA

Amy Smithson
Center for Nonproliferation Studies

Lauren Soni
National Research Council

Alberto Armando Solis Verugo
Polytechnic University of Chiapos Mexico

Samuel L. Stanley, Jr.
Stony Brook University

Erik Stemmy
NIAID/NIH

Kanta Subbarao
NIAID/NIH

Anne Tatem
National Institutes of Health

Christine Tomlinson
Schafer Corporation

Koos van der Bruggen
Royal Netherlands Academy of Arts and Sciences

Christopher Viggiani
National Institutes of Health

Simon Wain-Hobson
Institut Pasteur

Jennifer Walsh
National Research Council

Richard Webby
St. Jude Children's Research Hospital

Robert Webster
St. Jude Children's Research Hospital

Jerry P. Weir
U.S. Food and Drug Administration Center for Biologics

Jim Welch
Elizabeth R. Griffin Foundation

Annalyn Welp
Institute of Medicine

Rob Weyant
U.S. CDC Office of Public Health Preparedness and Response

Susan M. Wolf
University of Minnesota

Carrie Wolinetz
Association of American Universities

Edward You
U.S. Federal Bureau of Investigation

Alison Young
USA Today

In addition to those listed above who attended the symposium in person, approximately 300 people viewed the symposium via webcast.

Appendix F

Acronym List

ABSL	animal biosafety level
ACE-2 receptor	Angiotensin-converting enzyme 2
APHIS	Animal and Plant Health Inspection Service
BARDA	Biomedical Advanced Research and Development Authority
BMBL	*Biosafety in Microbiological and Biomedical Laboratories*
BSAT	Biological Select Agents and Toxins
BSL	biosafety level
CDC	U.S. Centers for Disease Control and Prevention
cDNA	complementary deoxyribonucleic acid
CoV	coronavirus
CRISPR	clustered regularly interspaced short palindromic repeats
DNA	deoxyribonucleic acid
DURC	dual use research of concern
EID	*Emerging Infectious Diseases*
FBI	Federal Bureau of Investigation

GAO	Government Accountability Office
GOF	gain-of-function
HA	hemagglutinins
HAE	human airway epithelial
HEPA	high-efficiency particulate arrestance
HPAIV	highly pathogenic avian influenza viruses
IACUC	Institutional Animal Care and Use Committees
IBC	Institutional Biosafety Committee
IOM	Institute of Medicine
IRI	Influenza Research Institute (at the University of Wisconsin-Madison)
JCVI	J. Craig Venter Institute
LAI	Laboratory Acquired Infection
mAb	monoclonal antibody
MERS	Middle East respiratory syndrome
NA	neuraminidase
NAS	National Academy of Sciences
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NSABB	National Science Advisory Board for Biosecurity
NRC	National Research Council
PLoS	Public Library of Science
PPE	personal protective equipment
PPP	potential pandemic pathogens
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome
SGVI	Synthetic Genomics Vaccines
SL-CoV	SARS-like CoV
S&T	science and technology
UPMC	University of Pittsburgh Medical Center
USDA	U.S. Department of Agriculture
USG	U.S. Government
USNRC	U.S. Nuclear Regulatory Commission

UW	University of Wisconsin-Madison
WHO	World Health Organization