The Journal of Infectious Diseases

EDITORIAL COMMENTARY

Infectious Diseases Society of America and Gain-of-Function Experiments With Pathogens Having Pandemic Potential

Gregory M. Frank,[1] Amesh Adalja,[3] Alan Barbour,[4,5] Arturo Casadevall,[8] Philip R. Dormitzer,[10,a] Jeff Duchin,[13,14] Frederick G. Hayden,[2] Martin S. Hirsch,[11] Noreen A. Hynes,[9] Marc Lipsitch,[12] Andrew T. Pavia,[15] and David A. Relman[6,7,b]

[1]Infectious Diseases Society of America, Arlington, and [2]University of Virginia School of Medicine, Charlottesville; [3]UPMC Center for Health Security, University of Pittsburgh Medical Center, Pennsylvania; [4]Department of Medicine, [5]Department of Microbiology and Molecular Genetics, University of California–Irvine, [6]Department of Medicine, and [7]Department of Microbiology and Immunology, Center for International Security and Cooperation at Stanford University, California; [8]Department of Molecular Microbiology and Immunology, and [9]Center for Immunization Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [10]NVS Influenza Vaccines, Cambridge, [11]Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, and [12]Department of Epidemiology, Center for Communicable Disease Dynamics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts; [13]Public Health–Seattle and King County, and [14]University of Washington, Seattle; and [15]Department of Pediatrics, Primary Children's Medical Center, University of Utah School of Medicine, Salt Lake City

(See the review article by Kilianski, Nuzzo, and Modjarrad on pages 1364–9.)

Keywords. gain-of-function; potential pandemic pathogens; influenza; science policy; health policy.

The rapid pace of technological advances in the life sciences has provided powerful tools for understanding and managing human-microbe interactions. These new capabilities can aid the development of vaccines, diagnostic tools, and therapeutic interventions. These same capabilities, especially the ability to manipulate genomes and, therefore, the properties of bacteria, viruses, and other infectious agents, could also pose important risks. Efforts to study and/or predict the natural evolution and emergence of pathogenic microbes by deliberately creating, in the laboratory, pathogens with enhanced disease-causing or transmission-promoting properties pose the greatest concern. Examples of this type of gain-of-function (GOF) research include the recent creation of highly pathogenic avian influenza viruses with altered host range, enhanced transmissibility, and/or the ability to evade certain forms of human immunity.

As Infectious Diseases Society of America (IDSA) members, most of whom are involved in direct patient care, research, and public health responses, we recognize that some of the same laboratories, technologies, and types of research that have given rise to concern are also essential to protect public health. Just as we have an ethical responsibility to first do no harm to our patients, we are also responsible for ensuring that we do no harm to the public, either through unnecessarily dangerous scientific experimentation or, conversely, by unduly burdening and delaying scientific work that serves essential clinical and public health purposes. This responsibility means we must identify those experiments whose potential benefits to scientific knowledge and public health clearly outweigh the risks they pose to the public and could not be achieved by safer means.

In fall 2014, the US government issued a pause of GOF research projects of concern and tasked the National Science Advisory Board for Biosecurity (NSABB), a federal advisory committee formed at the request of the US government to address issues related to biosecurity and dual use research of concern, to establish recommendations on how GOF research of concern should be assessed for its risk and benefit to public health. The NSABB recently developed a framework to guide its efforts and is working with a contractor to undertake a risk-benefit assessment (RBA) of the paused GOF projects. Given the robust public discussion about this topic, the NSABB plans to engage with stakeholders as it continues to develop its final recommendations [1–4].

In their review in this issue of *The Journal of Infectious Diseases*, Kilianski et al remind us of the importance of including the clinician perspective in any conversation about how best to assess the risk and benefit of GOF research [5]. Infectious diseases specialists will be among the physicians who will respond to any microbial disease outbreak and care for affected individuals, be it of natural origin or laboratory engineered through accidental or deliberate means. Infectious diseases specialists are also among those leading research efforts to counter these disease threats. Accordingly, they are especially well positioned to understand

Received 22 September 2015; accepted 23 September 2015; published online 27 September 2015.

This editorial was adapted from comments the Infectious Diseases Society of America Dual Use Research of Concern working group supplied to the National Science Advisory Board for Biosecurity on 10 August 2015. The original statement is accessible online (available at: http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Support_for_Medical_Education_and_Research/Letters/IDSA%20Comments%20to%20NSABB%20RE%20GOF%20081015.pdf).

[a]NVS Influenza Vaccines has since been acquired by the CSL Group and is presently known as Seqirus.

[b]All listed authors are members of the Infectious Diseases Society of America (IDSA) Dual Use Research of Concern (DURC) working group. This group was convened in 2014 to provide expert advice to the IDSA on issues related to DURC, as well as to gain of function experiments of concern.

Correspondence: G. M. Frank, Infectious Diseases Society of America, 1300 Wilson Blvd, Arlington, VA 22209 (gfrank@idsociety.org).

The Journal of Infectious Diseases® 2016;213:1359–61
 DOI: 10.1093/infdis/jiv474

the risks and benefits posed by potentially dangerous experiments involving pathogenic microbes and can be valuable advisors for those who will need to undertake the complex RBA for GOF research.

The IDSA appreciates the NSABB's efforts on the GOF debate and its willingness to engage with the public as it develops its final recommendations. We agree with Kilianski et al that this effort represents a key opportunity for clinicians to join the discussion about GOF research. To that end, we highlight below 6 key recommendations that the IDSA recently shared with the NSABB as we discuss how best to assess the benefits and risk of GOF research of concern.

FOCUS ON THE GOF EXPERIMENTS OF SPECIAL CONCERN

The IDSA remains concerned that the NSABB framework's broad definition of GOF research of concern may inadvertently capture areas of research that pose a lower risk to the public. For example, while the NSABB recognizes the benefit of research aiding the development or selection of new or more-effective vaccines, its framework still targets influenza vaccine production methods that rely on adaptation of vaccine candidate viruses for improved growth in culture as GOF research. The adaptation and manipulation of wild-type influenza virus for growth in eggs or mammalian cell lines are critical to vaccine manufacturing. This approach to producing high-growth vaccine candidates has been practiced since the 1940s [6, 7] and is essential to protect the public from both seasonal and pandemic influenza.

The IDSA strongly urges the NSABB to narrow its definition of GOF research to be considered for risk-benefit assessment (RBA), to avoid this inadvertent capture of low-risk research, which is not mentioned in the White House Office of Science and Technology Policy's original description of the types of research that should be included in the deliberative process. We recommend that the RBA process focus on research that is reasonably anticipated to result in a pathogen that combines a high risk of transmissibility with severe pathogenicity in humans, as this combination poses the greatest risk to public health. Such research may involve enhancing one of these properties in a pathogen already possessing the other or simultaneously enhancing both properties. Whereas other types of GOF research are also of concern, notably those involving increased resistance to known medical countermeasures, they are secondary to the two properties described above. The IDSA believes that this definition strikes a balance between impeding experiments with a lower public health risk that society has accepted for many years while ensuring that experiments of special concern are assessed appropriately.

ADDRESS THE UNCERTAINTY IN ESTIMATING BOTH RISK AND BENEFIT

The risk assessment process to be used by the NSABB will use estimated data in the models, as it will have to make assumptions on both risks and benefits. Although the IDSA understands that assumptions are necessary to assess risk and benefit, we urge the NSABB to hold robust discussions with experts about the uncertainty of its estimates of risk. We also recommend that the NSABB ensure that any analysis of uncertainty not only include uncertainties in the outcome of the research, such as the pathogenicity changes in a GOF organism, but also the uncertainties in the assessments of the likelihood of misuse of the science, as well as the consequences of accidents, misuse, and regulations on the conduct of the science. Whereas the NSABB will use a qualitative assessment of the benefits of GOF research, we urge that the uncertainties about the benefits of research be explicitly considered. Finally, the IDSA recommends that the NSABB consider communicating specific assumptions used in its modeling as well as error due to uncertainty to assist other policy makers in better understanding the risk/benefit estimates.

SEEK A WIDE BREADTH OF EXPERTISE TO AID IN THE RBA PROCESS

The NSABB has indicated that it will interview subject-matter experts to obtain additional input to aid its RBA efforts. The IDSA strongly supports these actions and also urges the NSABB to consider seeking additional perspectives to inform the RBA process, including those of a range of experts in vaccine development, microbial risk assessment, and public health response; physicians whose work is primarily clinical; and the public. In addition, the moral and ethical implications surrounding GOF research have not been adequately addressed in the NSABB framework [8]. Several experts in this field are actively engaged in the GOF research debate, and their unique viewpoints can be valuable to the RBA process.

Some stakeholders have expressed concern that the experts best positioned to evaluate the risk and benefits of GOF research are in some cases the ones who are actively conducting the research. The IDSA agrees that this potential conflict of interest is an issue that should be considered and strongly believes that, while this RBA evaluation needs as many expert perspectives as possible, those perspectives must be transparent, with all relevant interests disclosed.

RISK SHOULD ACCOUNT FOR THE IMPACT ON THE PUBLIC PERCEPTION OF SCIENCE

One important type of risk that is not included in the NSABB framework is the ethical, reputational, and credibility risk for science with the public. The recent laboratory mishaps at some of the nation's most prestigious laboratories have placed a strain on the public's trust for scientific research. Should a US government–funded GOF study result in an accident or a deliberate act that places the public at risk, the credibility of science as a whole may suffer. This occurrence, in turn, could lead the public to question the quality of public stewardship of biomedical funding and the reliability of scientific and medical

advice on risk. Such a loss of public trust could significantly impair science's ability to inform evidence-based policy decisions. The IDSA recommends that the NSABB consider recruiting additional perspectives, such as those from individuals with expertise in sociology and ethics, to assess this risk, as the NSABB develops its final recommendations.

RISK SHOULD ACCOUNT FOR THE IMPACT OF ANY NEW GOF FRAMEWORK ON THE COURSE OF SCIENCE

The ability of humanity to protect itself against pathogens with pandemic potential rests on a vigorous and healthy scientific enterprise. Some, including IDSA members, have raised the concern that as controversy swirls around GOF experiments, investigators might abandon certain types of scientific approaches that are powerful tools of scientific inquiry [9]. Furthermore, the concern has been raised that the best and brightest researchers will avoid these areas of inquiry simply because of the weight of regulation, the uncertainty in planning careers in areas subject to moratoriums and increased scrutiny, and the controversial nature of the work [10]. If this happens, humanity will be more vulnerable to future threats. The IDSA recommends that the possible risk of regulation to the scientific enterprise and, in particular, to certain fields of inquiry be factored in the overall RBA.

CONSIDER RECOMMENDATIONS ON HOW TO MAKE GOF RESEARCH SAFER

In the NSABB's assessment approach for GOF research benefit, it states that it will evaluate "other GOF experiment types" in addition to alternative approaches. The IDSA believes these efforts will yield valuable information that may be useful in developing constructive recommendations on how GOF research may be conducted more safely. For example, during the December 2014 National Academies of Science discussion on the pause in GOF research, one researcher presented data on how to engineer high-risk influenza virus strains to only generate productive infection in experimental animals, posing minimal risk to public health [11]. This search for pragmatic solutions that lower the risk of GOF has not been widely discussed, and the IDSA urges that such solutions be a more prominent component in the NSABB's final recommendations.

The IDSA is committed to ensuring that the broader scientific and science policy community participates in efforts to guide GOF research appropriately. To complement the NSABB's efforts, the IDSA calls for a continued series of transparent, broad discussions on GOF research and dual use research of concern among stakeholders, including scientists, healthcare workers, policy makers, ethicists, and representatives from the public. These discussions should include a consideration of RBA methods, governance models, classified research, and social responsibilities of scientists and journal editors; increased vigilance of biosafety and security concerns; and societal values. The discussions should also solicit international input. We look forward to working with the public, as well as with the US government, to ensure that GOF research of concern is conducted appropriately and only when the risk is outweighed by the benefit to public health.

Note

Potential conflicts of interest. P. R. D. was an employee and shareholder in Novartis Influenza Vaccines during the drafting of this manuscript, is a Pfizer employee and shareholder, and is listed as an inventor on multiple influenza and vaccine-related patent applications and patents. M. L. has received grants from Pfizer and Path Vaccine Solutions on vaccine modelling. A. T. P. has received royalties from Antimicrobial Therapy, honoraria from WebMD for CME materials preparation, and compensation from Biofire Diagnostics for advisory board participation. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Casadevall A, Imperiale MJ. Risks and benefits of gain-of-function experiments with pathogens of pandemic potential, such as influenza virus: a call for a science-based discussion. MBio **2014**; 5: e01730–14.
2. Duprex WP, Fouchier RA, Imperiale MJ, Lipsitch MRelman DA. Gain-of-function experiments: time for a real debate. Nat Rev Microbiol **2015**; 13:58–64.
3. Lipsitch M, Inglesby TV. Moratorium on research intended to create novel potential pandemic pathogens. MBio **2014**; 5:e02366-14.
4. Wain-Hobson S. The irrationality of GOF avian influenza virus research. Front Public Health **2014**; 2:77.
5. Kilianski A, Nuzzo JB, Modjarrad K. Gain-of-function research and the relevance to clinical practice. J Infect Dis **2016**; 213:1364–9.
6. Burnet FM. Growth of influenza virus in the allantoic cavity of the chick embryo. Aust J Exp Biol Med Sci **1941**; 19:291–5.
7. Members of the Commission on Influenza, Board for The Investigation and Control of Influenza and Other Empiric Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army. A clinical evaluation of vaccination against influenza: Preliminary report. JAMA **1944**; 124:982–5.
8. Relman DA. The increasingly compelling moral responsibilities of life scientists. Hastings Cent Rep **2013**; 43:34–5.
9. Casadevall A, Howard D, Imperiale MJ. An epistemological perspective on the value of gain-of-function experiments involving pathogens with pandemic potential. MBio **2014**; 5:e01875-14.
10. Pfeiffer JK. Is the debate and "pause" on experiments that alter pathogens with pandemic potential influencing future plans of graduate students and postdoctoral fellows? MBio **2015**; 6: e02525-14.
11. Langlois RA, Albrecht RA, Kimble B, et al. MicroRNA-based strategy to mitigate the risk of gain-of-function influenza studies. Nat Biotechnol **2013**; 31:844–7.