Creating a Mammalian-Transmissible A/H5N1 Influenza Virus: Social Contracts, Prudence, and Alternative Perspectives

Michael T. Osterholm and David A. Relman

1Center for Infectious Disease Research and Policy, 2Division of Environmental Health Sciences, School of Public Health, and 3School of Medicine, University of Minnesota, Minneapolis; 4Division of Infectious Diseases, Department of Medicine, and 5Department of Microbiology and Immunology, Stanford University School of Medicine, Palo Alto, California

(See the editorial commentary by Hirsch, on pages 1621, the perspectives by Herfst, on pages 1628–31 and Bouvier, on pages 1632–5.)

Much has been written about 2 unpublished manuscripts submitted to Science and Nature that describe research studies in which mutant derivative strains of highly-pathogenic influenza A/H5N1 virus were created that can be transmitted by respiratory droplets or aerosols between mammals (specifically, ferrets) [1–23]. These manuscripts were referred by the US government to the National Science Advisory Board for Biosecurity (NSABB) for assessment of the dual-use research implications of this work and to make recommendations regarding the responsible communication of the work. The results of the NSABB risk-benefit review process and the subsequent recommendation that neither manuscript be fully communicated in an open forum are well-known to the international life sciences community.

We propose to address this critical issue from both a historical perspective, the view through the rearview mirror, and from a future perspective, the view forward through the windshield. From the rearview mirror perspective, we review critical guidance from the life sciences community that predates the formation of the NSABB but clearly provides a relevant framework for our deliberations regarding the recent A/H5N1 virus research. We also consider existing work that the NSABB had completed prior to this recent research. From the windshield perspective, we consider 3 issues involving social and ethical principles that these 2 studies and any other future research efforts must address. We do not cover issues related to the A/H5N1 case-fatality rates or the potential benefits in sharing the entire research record of these studies for purposes of improving A/H5N1 infection surveillance or countermeasure production. We posit that the case-fatality rates associated with A/H5N1 virus infection are worrisome and that the potential benefits at present are limited, but we suggest that other important matters deserve treatment here.

The concept of dual-use research of concern (DURC) is not a new issue in science. It was recognized in the early days of atomic physics that scientific research can be used to bring both benefit and harm to society (originally framed as research with both civilian and military applications) [24]. While the post–World War II threat of biowarfare was a serious concern, it rarely involved international life sciences research communities in the academic or private sectors. Much of the work in this area was classified and was conducted in government research laboratories, where public dissemination of the methods or results of the studies was never intended. And then the events of 9/11 and the subsequent anthrax attacks in the United States changed the worldview about the willingness of individuals to sacrifice themselves in order to harm many others and about the methods that they might be willing to use to do so. Meanwhile, the revolution in the life sciences continued to unfold [25, 26].

In 2004, the National Research Council (NRC) published a seminal report, commonly known as the Fink Report, after Gerald Fink, the chairman of the committee that composed the report [27]. The charge to the committee was to consider ways of minimizing threats from biological warfare and bioterrorism without hindering the progress of biotechnology, the latter of which is essential for improving global health. The report summarized the work of experts mostly from the academic community and, thus, reflected the response of the life sciences community to increased concerns about bioterrorism. It concluded that DURC should not
necessarily be prohibited but should be scrutinized carefully and that, if undertaken, should be performed with awareness of the potential threat of misuse.

The Fink Report also made 7 overarching recommendations, including one asserting “that the Department of Health and Human Services augment the already established system for review of experiments involving recombinant DNA conducted by the National Institutes of Health to create a review system for seven classes of experiments (the Experiments of Concern) involving microbial agents that raise concerns about their potential for misuse” [27]. These experiments “illustrate the types of endeavors or discoveries that will require review and discussion by informed members of the scientific and medical community before they are undertaken or, if carried out, before they are published in full detail.” The report called for the creation of a board, the NSABB, that would provide advice, guidance, and leadership for this system of review. Two of the experiments of concern identified in the report included altering the host range of a pathogen and increasing the transmissibility of a pathogen.

In previous work, the NSABB has elaborated on the conclusions of the Fink Report, as well as on those of the 2006 follow-up report by the NRC [28]. The NSABB has defined DURC 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 health….” Reverse engineering and synthesizing a mutant A/H5N1 virus strain will be easier for many scientists if they have access to the complete methods and results of the 2 research efforts and do not need to surmise the steps of the investigators. The intentional or unintentional release of A/H5N1 virus that can be transmitted between mammals, even if the virulence of the virus in humans is similar to that of the current wild-type A/H5N1 viruses, could lead to a substantial increase in human cases or to ongoing reassortment with other mammal-associated influenza viruses. The determination by the NSABB that this work not be fully communicated in an open forum flows from this conclusion and a subsequent risk assessment.

As we view DURC through our windshield, we must consider 3 issues involving social and ethical principles that these 2 studies and any other future research efforts must address. First, there has been limited discussion since this controversy emerged as to who should be involved in deciding when, how, where, and whether such research should be conducted. This idea goes far beyond the authority of and charge to the NSABB. We believe that when considering life sciences research that carries the possibility of substantial risk to the public, a decision about whether to proceed should not to be made by life scientists alone. An international group of individuals who have relevant scientific expertise and are free of conflicts of interest, including biosecurity experts who are not considered a part of the life sciences community, must be actively involved in decisions about the risks and benefits of the research. Furthermore, the public has a right to be involved in this decision process as part of the social contract that balances the privilege of doing scientific research in our communities with the principle of not putting the public in potential harm’s way as a result of that research. This does not mean that the general public requires access to sensitive aspects of planned research; rather, it means that the public should receive a general overview of the risk-benefit aspects of the work. We believe that, on a global basis, it is critical to include more discussions about ethics in debates about the governance of DURC.

Second, the idea of censorship of scientific research generally has been rejected by the NSABB as an effective way to address DURC. The NSABB has articulated a body of work that spells out the benefits of free and unfettered scientific exchange as a primary means of addressing many of the problems involving life sciences research of the day. However, in this situation, when we realize that the detailed research methods and results are known to some in the influenza research community, further dissemination must be on a need-to-know basis because of the risks noted above. We believe that the argument by some that the recommendation of the NSABB represents a slippery slope toward a new normal for future information sharing is without merit. In a sense, we were presented with the results of these studies at the last moment before publication. The “we” includes the NSABB, the journal editors, and even the life sciences and biosecurity communities—not to mention the general public! Future DURC research that results
in a benefit to society that is substantial and outweighs the risk will still need a responsible and effective plan for sharing study methods and results. In no way should this last-minute NSABB recommendation with regard to these studies be considered a future plan for information control. We must do better.

The third windshield issue involves the use of the precautionary principle when approaching the issue of DURC. Why should scientists take chances with a potential intentional or unintentional release of an infectious agent that could result directly or indirectly in a global pandemic (eg, transmission of a low virulence influenza virus with subsequent reassortment that results in a highly virulent virus)? In this situation, the benefit of this work to public health is unclear, other than its role as an example of one possible evolutionary path (guided by laboratory manipulation) by which a strain of influenza virus can acquire pandemic potential or as a stark reminder to the world that an A/H5N1 virus may be able one day to cause a catastrophic human pandemic. It now appears that these benefits have already been realized without the wide dissemination of the studies’ methods or results. As noted above, we believe that wide dissemination of the details of these studies will not directly enhance disease surveillance or countermeasure availability in the near future. For these reasons, the precautionary principle demands that we err on the side of “do no harm.”

In conclusion, we find ourselves at a seminal moment in the conduct of the life sciences [31]. It seems as if each day brings a new twist to the story. We are tempted to react as if this is a daily news story. But it is much more: it represents a moment that will help to define our future in the life sciences for many years to come. We believe it is time to take our eyes off the dashboard and to, instead, take a meaningful gaze through the windshield and in the rearview mirror. These latter 2 perspectives will be critical in moving life sciences forward in such a way that we bring real benefit to society while minimizing the risk of events that have potentially catastrophic consequences.

Notes

Disclaimer. Drs Osterholm and Relman are members of the NSABB. Their views expressed here do not represent the official policy or scientific conclusions of the NSABB.

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