PERSPECTIVE

The Science of Security Versus the Security of Science

Nicole M. Bouvier

Department of Medicine, Division of Infectious Diseases, and Department of Microbiology, Mount Sinai School of Medicine, New York, New York

(See the perspectives by Osterholm and Relman, on pages 1636–8 and Herfst et al, on pages 1628-31, and the editorial commentary by Hirsch on pages 1621.)

A very public controversy has arisen from the creation of two influenza A viruses based all or in part on highly pathogenic avian influenza (HPAI) H5N1 strains. These viruses were genetically modified, specifically and intentionally, to enhance their ability to transmit by air between ferrets, a commonly used animal model for influenza virus transmission studies.

One virus, from the Erasmus Medical Center in the Netherlands, was mutated to include 3 amino acid polymorphisms already known to enhance the transmissibility of avian influenza virus strains among mammals. When that virus failed to transmit from ferret to ferret by air, it was then serially passaged through more ferrets until it acquired 2 further mutations, one or both of which conferred airborne transmissibility among ferrets. The resulting virus was initially described as similarly pathogenic as related H5N1 viruses, which cause severe disease in this species, and as efficiently transmissible as seasonal influenza viruses [1,2]. Subsequent data from the Erasmus group, however, suggest that the airborne virus is actually less transmissible and less virulent than original reports seemed to indicate [3].

The other virus, engineered at the University of Wisconsin–Madison, took the hemagglutinin (HA) receptor-binding proteins from several H5N1 viruses and expressed them with the remaining viral genes from a 2009 pandemic H1N1 (H1N1pdm09) influenza strain. It appears that at least one of these H5N1-H1N1 reassortant viruses was able to transmit among ferrets via airborne respiratory particles; however, like its parental H1N1pdm09 virus, it did not kill infected ferrets [4].

Both groups of researchers submitted their findings to respected scientific journals, the Erasmus group to *Science* and the Wisconsin group to *Nature*, and both manuscripts were peer-reviewed and accepted for publication. However, the National Science Advisory Board for Biosecurity (NSABB), which advises the US government on dual-use research (defined as "biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security" [5]) concluded that the "significant potential for harm in fully publishing these results … exceeded the benefits of publication" and, thus, recommended that "communication of the results in the two manuscripts … should be greatly limited in terms of the experimental details and results" [6]. As of this writing, the journals and the authors appear prepared to accept the NSABB's recommendation to publish these manuscripts in redacted form [7], striking from them key details that would allow others to replicate these experiments. This concession conflicts with a fundamental ethical principle underlying responsible conduct in research, namely, that peer-reviewed scientific manuscripts must document the methods necessary to reproduce the experiments and the data required to evaluate the legitimacy of the authors' conclusions [8–12].

I can appreciate the concerns of both sides in this debate, without necessarily agreeing with them. On one side are those who believe that the methods and data in these manuscripts are too dangerous for unfettered dissemination. How dangerous is unclear, as we have limited data from which to extrapolate a meaningful H5N1 case-fatality rate. The case-fatality rate usually reflects the total number of H5N1-attributable deaths divided by the total number of persons infected with, and thus at risk of dying from, H5N1 viruses. However, the oft-cited case-fatality rate of 55%–60% is instead calculated by dividing the number of H5N1-attributable deaths by the total number of confirmed H5N1 cases reported to the World Health Organization (WHO). By this definition, unconfirmed or unreported cases are absent from the denominator, artificially inflating the case-fatality rate; however, we lack solid data to know by how much. The true case-fatality rate is undoubtedly lower than the WHO figure,

Received 11 July 2011; accepted 29 February 2012; electronically published 27 March 2012.

Correspondence: Nicole M. Bouvier, MD, Mount Sinai School of Medicine, One Gustave Levy PL, Box 1124, New York, NY 10029 (nicole.bouvier@mssm.edu).

The Journal of Infectious Diseases 2012;205:1632–5

DOI: 10.1093/infdis/jis256

but it would have to be orders of magnitude lower to provide much comfort, should a bioterrorist or a "garage virologist" recreate and release influenza viruses as dangerous as these are purported to be. By invoking the Hippocratic imperative to "do no harm," those on this side of the debate hold that even the slightest risk of a pandemic caused by a highly transmissible, highly pathogenic H5 influenza virus outweighs any benefits that might accrue from open access to this research.

On the other side are those who see the NSABB's unprecedented recommendation—and, stemming from it, the anticipated publication of federally funded, peer-reviewed scientific manuscripts without methods and without data—as an assault on the openness and accessibility upon which the modern scientific endeavor relies. Scientists [8, 9], funders [11], and governments [10, 12] have all committed to an ethical framework that demands, in part, the free sharing of methods, data, and reagents so that experiments can be repeated and data reproduced, thereby increasing the reliability of the findings. The ethic of openness is not just an abstract ideal but also has a very practical purpose:

> Science is not an individual experience. It is shared knowledge based on a common understanding of some aspect of the physical or social world. For that reason, the social conventions of science play an important role in establishing the reliability of scientific knowledge. If these conventions are disrupted, the quality of science can suffer [9].

The unrestricted availability of data and methods increases the pool of researchers who can contribute to minimizing the risk of a highly transmissible H5N1 virus by maximizing the benefits that ensue from the research, such as improved therapeutics, vaccines, surveillance, and public health initiatives. Those on this side of the debate view the risk of a highly lethal manmade H5 pandemic as far too low to justify sacrificing either core ethical principles or the scientific advances that might be built upon this research.

Unfortunately, there may be no satisfying resolution to this particular controversy. We need to acknowledge that although both sides may have legitimate concerns, we simply do not have a research structure that is currently capable of accommodating them both. Until that changes, we will continue to be confounded by the implications of research into agents that are potentially highly pathogenic and highly transmissible.

The threat to human health is magnified when extraordinary pathogenicity and efficient transmissibility combine in the same influenza virus strain, as in the 1918 influenza pandemic. Unlike other highly pathogenic but slowly spreading viruses such as variola virus, which was ultimately stifled by the strategy of ring containment, an emergent influenza virus can be halfway around the world by the time it is recognized, as was recently demonstrated by the 2009 H1N1 influenza pandemic. The risk to human health, should a highly pathogenic and highly transmissible infectious agent escape from containment or be deliberately released, could be considerable. However, the development of therapeutics for, and vaccinations against, highly pathogenic and highly transmissible agents is without question an essential and desired benefit of dual-use research. Where to draw the line between acceptable and unacceptable risk is a subjective assessment, made by individuals with vastly different opinions, values, backgrounds, and beliefs. We simply have no objective measure by which to assess the likelihood that either risk or benefit (or both, or neither) might eventually come to pass.

As we struggle to define the problem or even to agree whether there is one, contemporary science is ill equipped to manage these uncertainties. Although the ethical arguments for and against openness in science are meaningful, so too are the realities of nongovernmental research in universities and academic medical centers. To keep their laboratories functioning, academic scientists must compete successfully for grants and faculty positions, and the only way to achieve these benchmarks of success is to conduct well-planned experiments yielding novel results that are published after peer review. The publication of redacted papers in peer-reviewed journals sets an ethically questionable precedent for all, while benefiting few. To avoid making the extraordinary concessions requested by the NSABB, these authors could withdraw their manuscripts and instead make them privately available, in full, to other legitimate researchers, rather than allow *Science* and *Nature* to go forward with the publication of redacted papers. I suspect that few practicing scientists would expect this action or be prepared to take it themselves; it would require the authors to be incredibly principled or incredibly foolish. Careers are made by publishing often and publishing well, and I doubt anyone would be surprised to see the idea of *Science* trump the ideals of science. Unfortunately, the goals of the biosecurity apparatus—containment of and control over dual-use research of concern—are not necessarily congruent with the goals of academic scientists, for whom high-impact publications are a critical factor in maintaining viable research programs.

Along with openness, though, ethical conduct in research mandates the responsible reporting of results. When the implications of dual-use research of concern are presented in inflammatory or sensationalist terms, the public is misinformed. Scientists and nonscientists alike know that animal models are not mere human replicas; otherwise, why would drug-safety regulators like the Food and Drug Administration require phased testing in humans prior to drug approval? Yet in the H5N1 furor, we have lost touch with our common sense, in part because these particular findings were presented in a sensationalist manner that failed to contextualize their significance. The ferret is frequently described as the "best model" for influenza virus transmission because, for >70 years, it was the *only* animal model known to consistently support efficient transmission of influenza A viruses. The manifestations of influenza in ferrets and in humans have been found to be very similar in some respects but rather different in others; that is why ferret research is both somewhat relevant to and yet not quite predictive of the behavior of influenza viruses in humans. Had the findings been presented with less sensationalism in the first place, much of the clamor and confusion over the meaning of this research might have been avoided.

We may never know how precisely the transmissibility of highly pathogenic avian influenza (HPAI) H5N1 viruses in ferrets augurs their transmissibility in humans, simply because we could never ethically test these viruses in humans as we do in ferrets. Still, other experiments could, and perhaps should, have been done prior to publicizing the results of the H5N1 studies. Multiple HPAI H5N1 viruses or H5 hemagglutinins could have been passaged through ferrets to evaluate whether transmission adaptations arise predictably and whether all similarly adapted viruses retain significant pathogenicity. Air-adapted viruses could also have been tested for pathogenicity and transmissibility in many other animal models—mice, cotton rats, Syrian hamsters, guinea pigs, domestic cats, domestic pigs, and nonhuman primates, to name a few—to assess more rigorously whether the mutations represent adaptation to mammals broadly or are specific to ferrets. Despite the limitations inherent in extrapolating data from animal models to human disease, additional experiments might have provided a more comprehensive and perhaps less frightening picture of these viruses. Because the primary manuscripts are under embargo, we do not know whether further experiments have been performed. Hopefully they were, but maybe they were not. In academic science, being the first to publish is often more highly regarded than being the most thorough, and this value system is not entirely compatible with the need for caution and diligence in conducting dual-use research of concern.

The greatest shame in this unfortunate episode is that it may set a regrettable precedent without appreciably improving our security. The NSABB has an admirable goal in trying to hinder irresponsible or nefarious persons from creating dangerous pathogens; however, in this particular case, the means for achieving that end are not justifiable, given the extent to which the methods and data have already been circulated. Hundreds of people already possess essential information regarding the structure and creation of these viruses, myself included. It is inconceivable that so many people could have this information without it becoming even more public eventually. In the meantime, as we wait for the inevitable leaks, we expect that two of the most respected scientific journals in the world will publish peer-reviewed articles without significant methods and data. This is a devastating precedent and a pivotal moment for modern science.

However, just because it is too late to fix this catastrophe does not mean that we should throw up our hands and retreat to our benches until the next crisis erupts. As scientists, we must acknowledge that we will never be rid of the risk-benefit tension inherent in exposing the secrets of highly pathogenic, highly transmissible infectious agents, no matter how much we believe in openness and accessibility as incontrovertible principles of scientific research. We must stand up for our ideals, but we must also concede that dual-use research of concern demands of us a high level of responsibility and circumspection, and we may need to consider conducting ourselves and our research in unfamiliar ways.

The responsibility, though, is not ours alone. Our governments and our funding agencies need also recognize that research into highly pathogenic, highly transmissible infectious agents is critically necessary, potentially risky, and not particularly compatible with the status quo of academic science. Principles and practices must be developed so that the best researchers can perform this work without violating essential ethical principles or compromising the development of their careers. Only by having all stakeholders in the debate come together, civilly and with open minds, in a joint effort to reconcile these seemingly irreconcilable contradictions might we hope to avoid a similar predicament in the future.

Notes

Acknowledgments. I thank Taia T. Wang, PhD, and Natalie Pica for thoughtful readings, constructive criticism, and editorial suggestions.

Financial support. This work was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (career development grant K08 AI089940-02).

Potential conflict of interest. Author certifies no potential conflicts of interest.

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. Fouchier R. Keynote Lecture. Presented at: Plenary session 01. The Fourth ESWI Influenza Conference; **2011** Sep 11–14; St. Julian's, Malta. Details are abstracted from the author's personal notes.
2. Herfst, S. Why is HPAI H5N1 virus not transmissible via aerosol? An extensive mutational and phenotypic analysis of mutant and reassortant H5N1 viruses. Presented at: Virus Host Interaction/Pathogenesis/Transmission (2). The Fourth ESWI Influenza Conference; **2011** Sep 11–14; St. Julian's, Malta. Details are abstracted from the author's personal notes.
3. Cohen J. Avian influenza: surprising twist in debate over lab-made H5N1. Science **2012**; 335:1155–6.
4. Kawaoka Y. H5N1: Flu transmission work is urgent. Nature **2012**; 482:155.
5. National Institutes of Health. Office of Biotechnology Activities. About NSABB. http://oba.od.nih.gov/biosecurity/about_nsabb.html. Accessed 5 February 2012.
6. Berns KI, Casadevall A, Cohen ML, et al. Adaptations of avian flu virus are a cause for concern. Science **2012**; 335:660–1.
7. Maher B. Emotion runs high at H5N1 debate. Nature News Blog. Posted 3 February

2012. http://blogs.nature.com/news/2012/02/emotion-runs-high-at-h5n1-debate.html Accessed 5 February 2012.

8. Ball CA, Sherlock G, Parkinson H, et al. The underlying principles of scientific publication. Bioinformatics **2002**; 18:1409.
9. National Academy of Sciences, National Academy of Engineering, and Institute of Medicine, Committee on Science, Engineering, and Public Policy. On being a scientist: Responsible conduct in research. 2nd ed. Washington, DC: National Academies Press, **1995**. [Section] Publication and openness, p. 9–12.
10. Science and Technology Committee. House of Commons and Parliament of the United Kingdom. Peer review in scientific publications: Eighth Report of Session 2010–12 (HC 856). London: The Stationery Office Limited, **2011**:58–9.
11. National Institutes of Health, Department of Health and Human Services. Revised policy on enhancing public access to archived publications resulting from NIH-funded research. Notice Number NOT-OD-08–033, 11 January 2008. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-033.html. Accessed 5 February 2012.
12. Organization for Economic Cooperation and Development (OECD). OECD principles and guidelines for access to research data from public funding. Paris: OECD Publications, **2007**.