

**National Science Advisory Board for Biosecurity
Findings and Recommendations
March 29-30, 2012**

Summary

On March 29-30, 2012, the National Science Advisory Board for Biosecurity (NSABB or Board) convened to examine two revised manuscripts regarding the transmissibility of highly pathogenic avian influenza A virus H5N1 (H5N1) in ferrets. After careful deliberation, the NSABB unanimously recommended that the revised manuscript submitted by Dr. Yoshihiro Kawaoka be communicated in full. The NSABB also recommended, in a 12-to-6 decision, that the data, methods, and conclusions presented in the revised manuscript submitted by Dr. Ron Fouchier be communicated after appropriate scientific review and revision.

Background

In the Fall of 2011, the NSABB reviewed manuscripts from Dr. Ron Fouchier, Erasmus Medical Center, and Dr. Yoshihiro Kawaoka, the University of Wisconsin, reporting the transmissibility of H5N1 in mammals. The manuscripts, submitted for publication in *Science* and *Nature* respectively, described the generation of mutations in H5N1 that enable the airborne transmission of the virus between ferrets. Ferrets are commonly used as an animal model for influenza transmissibility in humans. At that time, the Board recognized the importance of the research in advancing knowledge of influenza transmission and supporting public health efforts. Specifically, the Board recognized that the experiments confirmed that H5N1 had the potential to become mammalian transmissible and thus posed a threat of a future pandemic. This information was significant because until then it had been uncertain whether this virus had the evolutionary capacity to adapt to mammalian transmissibility. The Board understood, however, that the specific findings would enable others to synthesize and express an H5N1 strain with mammal-to-mammal airborne transmissibility, and thus it had significant concerns that the information in the manuscripts could be misused to endanger public health and national security. Given these dual use concerns,¹ the Board recommended that the information in these manuscripts be published in a redacted form with the omission of certain details that could enable the direct misuse of the research by those with malevolent intent. The goal was to deliver the critical information about the H5N1 potential for pandemic spread while minimizing the possible risk that the information could be used for nefarious purposes.

In February 2012, the World Health Organization (WHO) convened a technical consultation to “clarify key facts about the studies and to address the most urgent issues concerning the management of these laboratory-modified viruses, and how access to and dissemination of any findings should be handled.”² At this meeting, additional non-public data were presented and discussed, and key clarifications were made by the authors, who subsequently revised the manuscripts. In light of this, the United States Department of Health and Human Services convened the NSABB in a closed session March 29-30, 2012, to review the newly revised manuscripts and to recommend whether and/or how the information

¹ In the *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*, the NSABB defined “dual use research” as “[r]esearch yielding new technologies or information with the potential for both benevolent and malevolent applications.”

² WHO Report on Technical Consultation on H5N1 Research Issues
http://www.who.int/influenza/human_animal_interface/mtg_report_h5n1.pdf

should be communicated. Taking into account the additional information in the revised manuscripts, new non-public epidemiological information, and security information to be presented in a classified briefing, the NSABB was charged with:

- Assessing the dual use research implications of two unpublished, revised manuscripts on the transmissibility of highly pathogenic avian influenza A virus H5N1;
- Considering the risks and benefits of communicating the research results; and
- Developing findings and recommendations regarding whether the information should be communicated, and if so, to what extent.

NSABB Approach

On March 29-30, 2012, the NSABB members read the revised copies of the manuscripts, heard presentations, and discussed the findings with the authors. The Board also engaged public health officials, influenza experts, journal editors, security experts, and individuals involved in the oversight of H5N1 research both from the United States and from the international communities. The Board's discussions were informed by the analytical frameworks³ that it previously developed for considering the risks and benefits associated with the communication of dual use research of concern.⁴

Findings

The NSABB strongly supports the unrestricted communication of research information unless that information could be directly misused to pose a significant and near-term risk to public health and safety or if the risks associated with misuse of the information are so significant that no amount of potential benefits can justify the risks. The Board concluded that the communication of the information in these revised manuscripts still presents dual use research concerns. The risks and benefits associated with communicating, or not communicating, these findings were considered in light of additional information and key clarifications. The majority of the members of the NSABB concluded that:

- ***The data are not immediately enabling.*** As currently written, the revised manuscripts do not appear to provide information that would enable the near-term misuse of the research in ways that would endanger public health or national security. The mutations described in the manuscripts do not appear to result in H5N1 viruses that are both highly pathogenic and transmissible between ferrets through the air. The Board emphasized that if additional information were included that would enable the construction of an H5N1 virus that was both highly pathogenic and transmissible between mammals through the air, then the information in the manuscripts would have more implications for misuse and would require additional consideration regarding communication.

³ www.biosecurityboard.gov, see the *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information* in the NSABB Documents link.

⁴ In the *Proposed Framework for the Oversight of Dual Use Life Sciences Research: Strategies for Minimizing the Potential Misuse of Research Information*, the NSABB defined “dual use research of concern” 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.”

- ***These data may benefit public health and surveillance efforts.*** New information regarding epidemiology and the natural evolution of the virus in the field has emerged that underscores the fact that understanding specific mutations and the biologic properties associated with these mutations may improve international surveillance and public health efforts. While more research needs to be conducted to validate these ideas, potential public health benefits may include enhanced surveillance of viruses in birds and humans and other mammals (e.g., possible reassortment viruses in pigs) and improved risk assessment of circulating strains. The information in the manuscripts also may help inform public health decisions regarding pandemic preparedness (e.g., maintenance or strengthening of vaccine stockpiles and strain selection for vaccine development). The revised manuscripts provided a greater appreciation of the direct applicability of the information to ongoing and future influenza surveillance efforts.
- ***Global cooperation is essential for pandemic influenza preparedness.*** The Board recognizes that international cooperation is critical to ensuring public health and safety on a global scale and that such cooperation is predicated upon the free exchange of information. The Board's discussions underscored the risks associated with not sharing the information, which could jeopardize pandemic influenza preparedness efforts. Specifically, there was concern that the United States would be perceived as redacting information with potential public health benefits and that this could undermine valuable international collaborations. The information in these manuscripts will help public health officials prepare for influenza outbreaks in parts of the world where the virus is endemic.
- ***The research was conducted under appropriate conditions.*** The NSABB noted during its review of the initial and revised manuscripts that both studies were conducted under rigorous biosafety conditions, including appropriate biosafety containment, practices, training, and occupational-health programs. Because the research involved the use of a select agent, the research also was conducted under the oversight of the Select Agent Program, including periodic inspection of the facilities and biosecurity review by the United States Centers for Disease Control and Prevention (CDC) and/or the United States Department of Agriculture (USDA).

However, the Board recognized that biosafety requirements might be different if the engineered viruses had greatly altered properties. A review of the biosafety regulations would be prudent, should be performed by qualified professionals, and should be based upon a risk assessment of the work environment and the altered viruses.

- ***There is an urgent need for effective United States and international policies for the oversight and communication of dual use research of concern.*** The NSABB has noted previously that it is important that dual use research issues are identified and managed early in the research process rather than after the research has been conducted, let alone when a manuscript is ready for publication. The newly released *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern*⁵ was based upon this principle and the urgency of the recent deliberations. This policy applies to life sciences research funded by the United States and will ensure that dual use concerns are addressed during the evaluation of ongoing and

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http://oba.od.nih.gov/oba/biosecurity/PDF/United_States_Government_Policy_for_Oversight_of_DURC_FINAL_version_032812.pdf

future federally funded research on H5N1 influenza virus. The Board's discussion was informed by this new policy initiative.

The Board also noted the need for guidelines to aid in the determination of how/whether certain types of "gain-of-function" experiments with influenza should be conducted or communicated. These two H5N1 studies both used well-known techniques to change the mode of transmission of H5N1 avian influenza virus from fecal-oral to respiratory and from avian-avian transmission to mammal-mammal transmission. Further gain-of-function experiments of this type are likely to be contemplated by these and other laboratories around the world. Experiments that change the mode of transmission or host range of a zoonotic agent are of particular concern and require detailed analyses of risks and benefits before they are conducted or communicated. At the present time, no specific guidelines exist to aid in these analyses for future studies of influenza virus.

Since scientific research and protecting public health are global endeavors, the Board urges the U.S. Government to closely engage the international community during the policy-development process so that scientific information can be shared between and among appropriate global partners. To this end, the Board will soon consider the findings and recommendations of its Working Group on Global Engagement, which has been charged with addressing the communication and other challenges presented by H5N1 dual use research of concern, challenges that are inherently international in scope.

- ***There is a critical need for a mechanism for disseminating sensitive scientific information.*** There remains a pressing need for an effective and feasible mechanism to provide controlled access to scientific information that has potential public health benefits but poses a significant risk for misuse if broadly disseminated. There are complex questions involved in developing such a mechanism, many of them legal issues. Nonetheless, a feasible, secure mechanism for sharing sensitive scientific information with individuals who have a legitimate need to know in order to support public health, safety, and security efforts is essential.

In contrast, a minority of members of NSABB concluded that:

- ***The data in the newly-revised Fouchier manuscript are immediately and directly enabling.*** As currently written, the revised Fouchier manuscript provides information that would enable the near-term misuse of the research in ways that would endanger public health or national security. The mutations described in this manuscript appear to result in modified H5N1 viruses that are transmissible between ferrets by respiratory route, as claimed by the authors, and in modified viruses that appear to be as pathogenic as the parental H5N1 strain, which in nature is known to be highly pathogenic in humans. The data in the Kawaoka paper, however, are less immediately and directly enabling because the approach involved the use of less virulent viral strains.
- ***While the data in the two manuscripts may benefit public health and surveillance efforts, these data may not be directly relevant or immediately helpful to the current public health or surveillance infrastructure.*** The evolutionary paths taken by naturally occurring H5N1 viruses may not be similar to those selected under these laboratory conditions. The relevance of the laboratory-derived mutations and their meaning for the evolution of H5N1 viruses in natural environments are unclear. Excessive attention to these mutations may in fact distract

surveillance efforts from what might be the naturally occurring mutations of greater interest. Furthermore, the current surveillance infrastructure is ill-equipped to detect the emergence of highly transmissible influenza viruses in real-time prior to their dissemination in nature. While there may be benefits to the dissemination of the mutation data in the Fouchier manuscript and global cooperation is essential for pandemic influenza preparedness, it is unlikely that the benefits will be fully realized in the near-term.

These Board members agreed with the rest of the Board about the general importance of global cooperation, the urgent need for effective policies for the oversight and communication of dual use research of concern, and the critical need for a mechanism for disseminating sensitive scientific information.

Recommendations

The Board considered the manuscripts separately and after careful deliberation made the following recommendations:

- ***The revised Kawaoka manuscript should be communicated in full.*** The NSABB unanimously recommended the full communication of this revised manuscript.
- ***The data, methods, and conclusions presented in the revised Fouchier manuscript should be communicated, but not as currently written.*** In a 12-to-6 decision, the NSABB recommended communicating the data, methods, and conclusions presented in this revised manuscript. However, the Board identified a number of scientific clarifications that should be made prior to publication of the manuscript. Importantly, the Board also noted that additional information that would enable the construction of an H5N1 virus that is both highly pathogenic and transmissible between mammals through the air should not be included in the manuscript. Such information could conceivably be directly misused to threaten public health or national security and additional considerations regarding communication would be necessary. Six of the 18 voting members felt that the data, methods, and conclusions presented in the revised Fouchier manuscript should not be communicated.
- ***The U.S. Government should continue to develop national, and participate in the development of international, policies for the oversight and communication of dual use research of concern.*** The newly released *United States Government Policy for Oversight of Life Sciences Dual Use Research of Concern* is an important first step in ensuring that dual use concerns associated with federally funded life sciences research will be addressed and managed early in and continuously during the research process. This policy will apply to H5N1 research as well as other agents and toxins that pose the greatest risk of misuse. In implementing this policy, the U.S. Government should monitor how effectively it facilitates the identification and timely management of dual use research of concern. However, it is essential that such oversight does not unduly burden or slow the progress of life sciences research. The oversight process should be periodically and robustly reviewed and modified as necessary to address these issues.

The U.S. Government should also provide guidance on how to deal with “gain-of-function” studies that increase pathogenesis of zoonotic agents, particularly avian influenza viruses. Experiments that change the mode of transmission or host range of a zoonotic agent are of

particular concern and require a detailed analysis of risks and benefits before they are conducted or communicated.

Scientific research and protecting public health and safety are global endeavors. It is therefore critical that the U.S. Government continue to work with its international partners to develop, enforce and continually review consistent policies for the oversight of dual use research that enable the effective management and sharing of sensitive research information.

- ***The U.S. Government should expeditiously develop a mechanism to provide controlled access to sensitive scientific information.*** The majority of the NSABB recommends that the information contained in these revised H5N1 manuscripts should be communicated in full, but the Board also recognizes that research findings will likely emerge in the very near future that should not be widely disseminated because of a high risk of misuse but that nevertheless should be made available to certain researchers and public health officials around the world who have a legitimate need to know. The need for an effective, practical, and feasible mechanism for selectively sharing sensitive scientific information has never been more apparent. In order to manage the risks posed by communicating future cases of dual use research of concern, the Board strongly urges the U.S. Government to develop in an expeditious manner a practical and secure mechanism for sharing sensitive scientific information in order to support public health, safety, and security efforts.