Published in final edited form as:
Science. 2013 March 1; 339(6123): 1036–1037. doi:10.1126/science.1236194.

A Framework for Decisions About Research with HPAI H5N1 Viruses

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Abstract

The U.S. Department of Health and Human Services unveils a Framework for funding decisions about highly pathogenic avian influenza H5N1 research.

Since it appeared in Hong Kong in 1997, the highly pathogenic avian influenza (HPAI) H5N1 virus has presented a persistent threat to public health and agriculture. Worldwide, hundreds of millions of birds have died as a result of infections or culling to prevent further spread of outbreaks among domestic flocks (1). HPAI H5N1 has caused severe respiratory illness and death in a relatively small number of humans—primarily those who have worked in direct contact with infected poultry (2). Of the ~600 laboratory-confirmed human cases from 2003 to the present, nearly 60% were fatal. At present, the virus does not appear well-adapted for sustained transmission among mammals by respiratory droplets. However, if the viruses occurring in nature were to become readily transmissible among mammals, they could pose the risk of a pandemic.

Research aimed at understanding the host adaptability and transmission of HPAI H5N1 virus is a public health imperative. Internationally, scientists are seeking insights that will enable more effective surveillance capabilities, vaccines, and therapies, as well as a foundation for innovative public health solutions in the future.

In 2011, two studies funded by the National Institutes of Health (NIH), which examined mammalian transmissibility of HPAI H5N1, generated controversy (3, 4). Using a “gain-of-function” approach, researchers engineered HPAI H5N1 viruses to render them transmissible by respiratory droplets among ferrets, an animal commonly used to model human influenza infection. These studies provided critical information to scientists and public health officials by demonstrating that HPAI H5N1 viruses can mutate to enable them to spread efficiently among certain mammals and, therefore, perhaps among humans. However, the generation of these strains raised safety and security concerns centered on whether the engineered strains could be released accidentally or used nefariously to threaten public health or national security. They triggered a global discussion regarding the benefits and risks of funding, conducting, and publishing these types of gain-of-function studies.

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As a result, members of the influenza research community initiated a voluntary moratorium on gain-of-function studies involving HPAI H5N1 mammalian transmissibility (5, 6). This pause allowed for intense discussions of the risks and benefits associated with the research and provided governments and other funding organizations an opportunity to develop appropriate oversight policies. The moratorium was initially intended to last 60 days but was extended for 1 year. Recently, the signatories have announced an end to the moratorium for scientists with appropriate facilities and national oversight (7). They urged scientists to continue the research pause if they are working in countries that had not yet finalized the appropriate conditions for conducting HPAI H5N1 transmission research.

The U.S. Department of Health and Human Services (HHS) has grappled with the challenge of how best and, indeed, whether to support certain types of HPAI H5N1 gain-of-function research (8). Toward this end, HHS has developed a Framework (www.phe.gov/S3/dualuse) for guiding funding decisions on individual proposals involving HPAI H5N1 research with specific attributes. The Framework aims to ensure a robust review of research proposals—before making a funding decision—that considers the scientific and public health benefits of the proposal, the bio-safety and biosecurity risks associated with the proposal, and the appropriate risk mitigation measures required for such research. In November 2012, a draft version of this Framework was presented to the National Science Advisory Board for Biosecurity (NSABB) for its consideration and subsequently posted for public comment.

HHS also sought international and multidisciplinary perspectives at a workshop held in Maryland on 17 and 18 December 2012 (9). Participants discussed the risks and benefits of HPAI H5N1 gain-of-function research, the biosafety conditions that should be in place for conducting such research, and the importance of international cooperation in preventing future pandemics. Some expressed concerns that the information generated by this research could enable others to replicate the studies under less-than-ideal biosafety conditions or for malevolent purposes. Although it was generally noted that gain-of-function studies will provide important scientific insights, there was debate over how readily and directly this information can be applied to vaccine development or surveillance efforts, at least in the near term.

Commenters noted that while gain-of-function experiments that enhance virulence or alter host range of HPAI H5N1 are concerning, it is conferring the ability to efficiently spread among mammals by respiratory droplets that raises the most concern and warrants special consideration prior to funding. This and other input was instrumental in finalizing the HHS Framework. In developing the Framework, HHS has considered several key questions: Is this subset of gain-of-function experiments necessary to address the public health threat posed by HPAI H5N1 viruses? Would discontinuing this type of research introduce new risks by compromising our ability to prepare for and respond to influenza outbreaks? Should such research be supported by HHS and its funding agencies? If so, under what biosafety conditions should this research be conducted? In considering these questions, a number of important principles have emerged.

First, open communication of research methodologies and results is a hallmark of the life sciences and of the research that HHS and its agencies support. Widespread dissemination of

research results allows rapid and sustained scientific progress and facilitates full realization of the associated public health benefits. As hypotheses and conclusions are validated or repudiated, our knowledge base is expanded, laying the foundation for new therapeutics and other applications. Therefore, HHS will only fund research that is reasonably anticipated, at the proposal stage, to generate information that can be broadly shared and openly communicated.

Second, HPAI H5N1 research involving transmission among mammals by respiratory droplets must address a scientific question with high significance to public health. HHS is a strong supporter of fundamental research, which may add to our understanding of basic biological processes and often contributes to new innovations and technologies. However, because HPAI H5N1 gain-of-function research of this type may involve a higher level of risk than other areas of study, it is important that the fundamental questions to be addressed by the research not only have high scientific merit but can be reasonably anticipated to generate information that will ultimately advance public health. Before committing to a gain-of-function approach that brings with it certain risks, researchers should explore alternative methods for addressing the same scientific question in a manner with the fewest attendant risks.

Third, the biosafety and biosecurity risks associated with a research project must be manageable. With its principal mission to protect and promote public health, HHS must, out of necessity, support some scientific research that involves a certain level of inherent risk but that is nevertheless essential for our health and well-being. Furthermore, HHS should only support proposals through funding mechanisms that allow implementation of additional risk mitigation measures as appropriate.

Like all proposals submitted to HHS funding agencies, HPAI H5N1 gain-of-function proposals are subjected to peer review to assess scientific merit. In addition, this research falls within the scope of the *U.S. Government Policy for the Oversight of Life Sciences Dual Use Research of Concern* and thus undergoes an initial and periodic review for dual use potential (10). The new HHS Framework requires additional funding agency and department-level review for research proposals that are anticipated to generate HPAI H5N1 viruses transmissible among mammals by respiratory droplets.

The Framework lists seven criteria (see the table), all of which must be met for such research proposals to be acceptable for HHS funding. The funding agency will assess whether proposed research meets these criteria and, if so, will submit the proposal for additional HHS-level review. The department-level review will bring to bear multidisciplinary expertise—including public health, scientific, security, intelligence, and countermeasures—in assessing the risks and benefits of the proposal and will also consider the proposal within the context of the broader HHS influenza research portfolio. Other federal departments and agencies; external advisory bodies—such as the NSABB, the NIH Recombinant DNA Advisory Committee (RAC), and the National Biodefense Science Board; and nongovernmental experts—may be consulted. The department-level review will determine the appropriate risk mitigation measures and whether a given proposal is acceptable for HHS funding. Research proposals that do not meet the seven criteria or

involve risks that cannot be adequately mitigated will not receive HHS funding. Characterization studies of naturally occurring H5N1 viruses are not subject to this review Framework.

HPAI H5N1 research, in common with other life-sciences research, is subject to guidelines, policies, laws, and international agreements that govern biosafety, physical security, personnel reliability, informational risks, and nonproliferation (11). Such oversight is aimed at managing risks throughout the course of the research. Risks associated with infectious disease research cannot be eliminated entirely. However, they can be managed, and as the risk-benefit landscape changes, our policy response must also change as necessary. In this regard, the Centers for Disease Control and Prevention has sought public comment regarding whether certain HPAI H5N1 viruses should be regulated as an HHS Select Agent, as well as whether any special precautionary measures (i.e., biosafety containment and practices) are necessary (12).

The NIH RAC has also recently recommended additional enhancements to bio-safety level 3 containment and practices for work with HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets (13). The *NIH Guidelines for Research Involving Recombinant DNA Molecules* (14) have been amended to include these measures.

Science is unpredictable, and not all research results can be anticipated. The HHS Framework aims to ensure consideration, at the outset, of gain-of-function research proposals that may generate HPAI H5N1 viruses that are transmissible among mammals by respiratory droplets and to make the most-informed decisions possible about whether and how to support and conduct this research. The HHS Framework will be evaluated over time and adapted to ensure that critical research needs are being met and that risks are managed appropriately. HHS will continue to engage in the collective global effort to identify the best path forward so that important research addressing this critical public health concern can continue in the most responsible manner possible.

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Table

Criteria for guiding HHS funding decisions for certain H5N1 gain-of-function research proposals

• Such a virus could be produced through a natural evolutionary process.
• The research addresses a scientific question with high significance to public health.
• There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.
• Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed.
• Biosecurity risks can be sufficiently mitigated and managed.
• The research information is anticipated to be broadly shared in order to realize its potential benefits to global health.
• The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research.