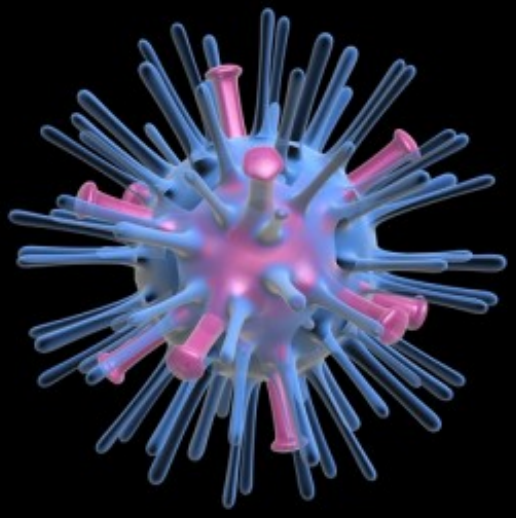
A Path Forward

A Proposed Framework for Guiding HHS Funding Decisions about Highly Pathogenic Avian Influenza H5N1 Gain-of-Function Research

November 27, 2012

Highly Pathogenic Avian Influenza (HPAI) H5N1 Virus

- Widespread among poultry in parts of Asia and the Middle East
  - Since 2003, has killed or forced the culling of more than 400 million domestic poultry
  - Caused an estimated US$20 billion in economic damage across the globe[1]
- Infection of humans is rare but causes severe respiratory illness
  - ~600 human cases reported since 2003 with ~60% mortality rate[2]
  - At present H5N1 is not well-adapted for sustained human-to-human transmission
  - Recent studies underscore the growing concern that the virus may acquire this ability



1. FAO. H5N1 Highly Pathogenic Avian Influenza - Monthly Global Overview. Issue no.31: January-March, 2012.

2. http://www.cdc.gov/flu/avianflu/h5n1-virus.htm

The Importance of Influenza Research

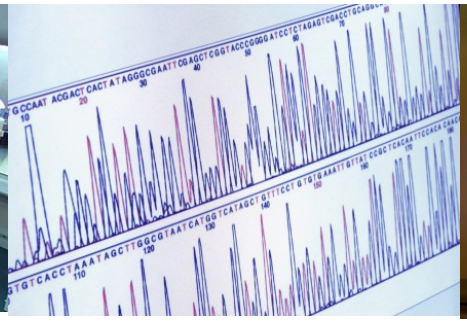
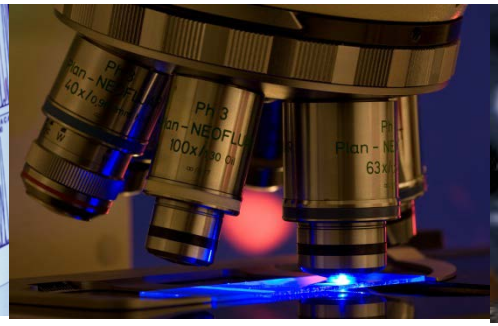
- **Research on influenza viruses is critical to public health**
- **Such research aims to better prevent, predict, and control the spread of influenza viruses by:**
  - **Identifying the genetic elements that contribute to virus transmissibility, pathogenicity, and host range specificity and thereby enabling:**
    - **Surveillance of naturally occurring strains of influenza**
    - **Development and evaluation of countermeasures such as vaccines, antivirals, and diagnostics**
    - **Enhanced preparedness and response strategies**

Influenza Research: Examples of Experimental Approaches

- **The genetic elements responsible for transmissibility, pathogenicity, and host range can be examined in various ways:**
  - **Comparative genomics**
  - **Predictive modeling**
  - **Loss-of-function experiments**
  - **Gain-of-function experiments**
    - **Generating influenza viruses with enhanced transmissibility, enhanced pathogenicity, and/or altered host range and testing these viruses *in vitro* and/or *in vivo***

Key Questions about HPAI H5N1

- ***Could the currently-circulating HPAI H5N1 viruses evolve to spread efficiently in humans?***
- ***What are the genetic determinants of pathogenicity, transmissibility, host range specificity, and viral resistance to therapeutics?***
- ***Are gain-of-function experiments necessary to address these questions?***


Issues

- ***Is there any HPAI H5N1 gain-of-function research that should not be funded by HHS?***
- ***What are the risks associated with <u>not</u> conducting such research?***
- ***What principles and risk assessment framework should guide decisions about the types of gain-of-function research that should be funded, if any?***
- ***For such research that is acceptable for HHS funding:***
  - **What review and oversight is appropriate?**
  - **What biosafety and biosecurity measures are appropriate?**
- ***Should HHS fund research that cannot be openly communicated?***

A Proposed Framework for Guiding HHS Funding Decisions about HPAI H5N1 Gain-of-Function Research

- **Defines scope and applicability of the framework**
- **Outlines criteria that must be met in order to be funded**
- **Describes characteristics of such research that may warrant additional (Department-level) review**
- **Underscores the importance of assessing and managing biosafety, biosecurity, and dual use risks**

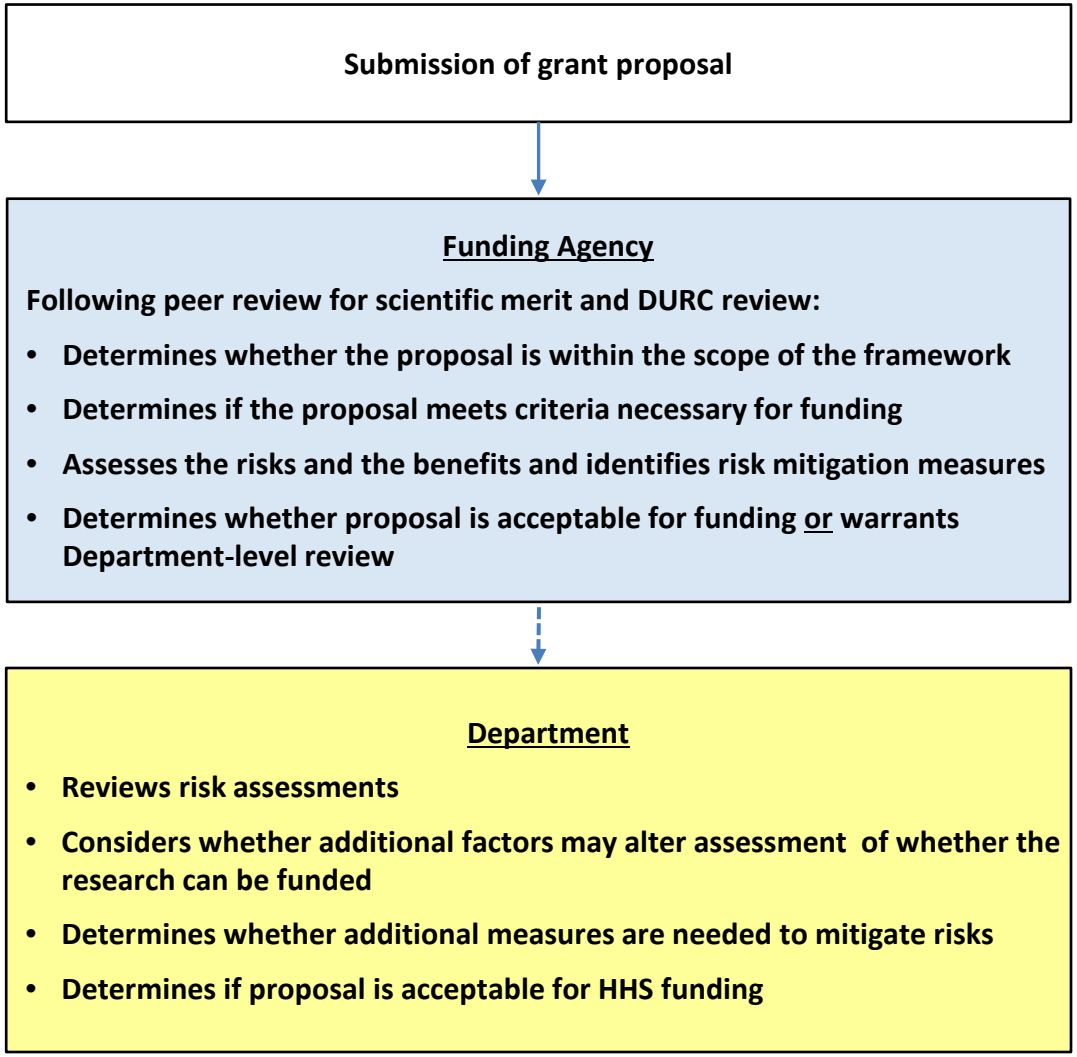
Applicability of Proposed Framework

- **Aim: To ensure additional review of proposals that can be reasonably anticipated to generate HPAI H5N1 viruses with enhanced transmissibility, enhanced pathogenicity, and/or altered host range**
- **Applies to proposals that involve:**
  - **Any experimental reassortant virus expressing the virulent HA gene from highly pathogenic H5N1; and**
  - **The manipulation of influenza viruses that will or is reasonably anticipated to produce highly pathogenic H5N1 viruses with gain-of-function attributes**

Applicability of Proposed Framework

- **Does not apply to:**
  - **Routine characterization studies of naturally occurring HPAI H5N1 viruses that are neither intended to nor can be reasonably anticipated to generate gain-of-function**
    - **"Characterization studies" include sequencing and testing of antigenicity, antiviral drug susceptibility, transmissibility, and pathogenicity**
    - **"Naturally occurring" is intended to refer to mutations that arise in nature or through a natural process, and were not engineered by researchers or obtained by serial passaging of virus**
  - **Rationale: Need to ensure that the properties of H5N1 viruses that continue to circulate in birds and occasionally infect humans can be determined as quickly as possible**

Overview: Proposed Framework for Guiding HHS Funding Decisions about HPAI H5N1 Gain-of-Function Research



Criteria for Guiding HHS Funding Decisions for HPAI H5N1 Gain-of-Function Research

- **HPAI H5N1 gain-of-function research can only be considered for funding if:**
  1. **The research addresses a scientific question with high significance to public health;**
  2. **The research does not intend, nor is reasonably anticipated to yield a HPAI H5N1 experimental virus which has increased transmissibility, pathogenicity, or expanded host range, unless there is evidence that such a virus could be produced through a natural evolutionary process in the foreseeable future;**
  3. **There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach;**
  4. **Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed;**
  5. **Biosecurity risks can be sufficiently mitigated and managed;**
  6. **The research information is anticipated to be broadly shared in order to realize its potential benefits to global health; and**
  7. **The research is supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research**

Criterion 1: Explication

The research addresses a scientific question of high significance to public health.

- **Since HPAI H5N1 gain-of-function research involves 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 scientific merit but also importance in advancing public health**

Criterion 2: Explication

The research does not intend, nor is reasonably anticipated to yield an HPAI H5N1 experimental virus which has increased transmissibility, pathogenicity, or expanded host range, unless there is evidence that such a virus could emerge through a natural evolutionary process in the foreseeable future.

- **The risks associated with gain-of-function experiments may be justifiable if they advance the understanding of strains that exist or are likely to emerge in nature**
- **These risks are not justifiable for research that could generate viruses with pandemic potential that are highly unlikely to emerge in nature in the foreseeable future**

Criterion 3: Explication

There are no feasible alternative methods to address the same scientific question in a manner that poses less risk than does the proposed approach.

- **There are inherent risks involved with gain-of-function approaches that confer new properties to an already infectious agent**
- **These approaches should only be funded if alternative approaches to address the same scientific question in a less risky manner have been thoroughly explored**

Criterion 4: Explication

Biosafety risks to laboratory workers and the public can be sufficiently mitigated and managed.

- **Funding for HPAI H5N1 gain-of-function studies should only be awarded to institutions that:**
  - **Are compliant with the Select Agent Regulations**
  - **Use appropriate laboratory practices, procedures, and safety equipment;**
  - **Adhere to all training requirements for personnel;**
  - **Conduct regular reviews by an Institutional Biosafety Committee;**
  - **Enroll researchers in appropriate occupational health programs; and**
  - **Have access to the requisite research facilities and containment barriers**
- **Consideration should be given to whether some of this research may need to be conducted only in designated facilities**

Criterion 5: Explication

Biosecurity risks can be sufficiently mitigated and managed.

- **Biosecurity risks, including dual use risks, can never be eliminated entirely, but HPAI H5N1 gain-of-function research should only be funded if appropriate physical, personnel, and other security measures are in place to prevent theft or unauthorized use of research products or materials**

- **This includes:**
  - **Compliance with the Select Agent Regulations**
  - **Physical security measures, such as barriers and locks, commensurate with the risk**
  - **Personnel security measures, such as authorized access to pathogens, commensurate with the risk**
  - **Compliance with the DURC risk mitigation measures required by funding agencies[1]**

1. As stipulated by the *U.S. Government Policy for the Oversight of Life Sciences DURC*, March 29, 2012.

Criterion 6: Explication

The research information is anticipated to be broadly shared in order to realize its potential benefits to global health.

- **Preventing and managing outbreaks of HPAI H5N1 is a global challenge that requires international cooperation and sharing of information (e.g., WHO Pandemic Influenza Preparedness framework)**
- **As a general matter, HHS should only fund research that is reasonably anticipated at the proposal stage to generate information, products, and technologies that can be openly communicated**
- **It is impossible to anticipate all of the results that will be generated by a research proposal and unanticipated results will likely occur**
  - **It may be necessary to require that certain proposals employ additional risk mitigation measures (e.g., requiring regular DURC reviews or periodic reassessments) as a term and condition of funding[1]**

1. As stipulated by the *U.S. Government Policy for the Oversight of Life Sciences DURC*, March 29, 2012.

Criterion 7: Explication

The research is supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research.

- **Conditions may arise where certain awards require the implementation of additional risk mitigation measures as the project progresses**
- **HPAI H5N1 should only be funded through funding mechanisms (e.g., grant, contract) that provide the ability to require additional risk mitigation measures as necessary**

Assessing the Range of Risks

- **In applying the framework, HHS funding agencies should assess:**
  - **The risks associated with the intrinsic nature of the agent(s) used in the proposal**
    - **i.e., starting viral strain transmissibility, pathogenicity, and host range**
  - **The risks associated with the experimental manipulations in the proposal**
    - **i.e., the likelihood that the virus will become more transmissible, pathogenic, and/or have an expanded host range**
  - **Whether an experiment described in a proposal possesses or can be anticipated to generate the characteristics warranting Department-level review**

HPAI H5N1 research should undergo an HHS Department-level review if the studies intend or are reasonably anticipated to:

- **Increase pathogenicity, virulence, and/or transmissibility of a virus in mammals; or**
- **Confer mammalian-transmissibility to a highly pathogenic strain; or**
- **Increase pathogenicity or virulence in mammals of a mammalian-transmissible strain; or**
- **Disrupt the induction of a host's innate immunity; or**
- **Interfere with the effectiveness of an available vaccine; or**
- **Confer to the agent resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that agent; or**
- **Facilitate the virus' ability to evade detection methodologies**

Department-level HHS Review

- Reviews funding agency's assessments
- Brings additional and multi-disciplinary expertise to consider whether additional factors may alter assessment of whether the research can be funded
  - For example, expertise in security, intelligence, preparedness and response capabilities (e.g., countermeasures)
- Determines whether additional measures are needed to mitigate risks
- Takes into account the overall HHS portfolio of HPAI H5N1 gain-of-function research
- Determines whether a proposal is acceptable for HHS funding

Possible Outcomes of HHS Review

- **HHS may determine that the HPAI H5N1 gain-of-function research proposal:**
  - **Is acceptable for HHS funding with the usual terms and conditions for HHS-funded awards**
  - **Is acceptable for HHS funding with additional terms and conditions concerning reporting and conduct of research**
  - **Is not acceptable for HHS funding but will be referred to another Federal agency that funds classified research**
  - **Is not acceptable for HHS funding**

Broad Consultations and International Engagement

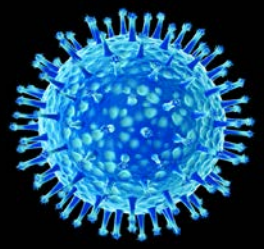
- **Global health implications of this research call for broad input on the proposed framework**
- **At HHS' request:**
  - **National Science Advisory Board for Biosecurity will discuss the framework**
  - **Recombinant DNA Advisory Committee will provide recommendations on biosafety issues**

Broad Consultations and International Engagement

- **HHS is sponsoring an international workshop (December 17-18, 2012) to gather broad stakeholder input on the benefits and risks of HPAI H5N1 gain-of-function research and the appropriate path forward**

  Questions to be discussed include:

  - **Are there any gain-of-function experiments that should be done, and why or why not?**
  - **IF any of this research should go forward, under what conditions would it be conducted?**
  - **What is the conceptual framework that should guide our thinking on this issue?**



Gain-of-Function Research on Highly Pathogenic Avian Influenza H5N1 Viruses

An International Consultative Workshop

December 17-18, 2012 | Natcher Conference Center | National Institutes of Health | Bethesda, Maryland

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agenda Overview

Day 1

- **Panel I: HPAI H5N1 GOF Research and Its Implications for Global Public Health**
  - This session will explore the state of the field of HPAI H5N1 research, including the rationale, experimental aims and designs of studies that increase transmissibility, increase pathogenicity, and/or alter host range; the public health context of this research, the current trajectory of the research, and any anticipated benefits associated with the research.

- **Panel II: Risks and Concerns Associated with HPAI H5N1 GOF Research**
  - This session will explore specific concerns that have been raised over HPAI H5N1 GOF, including biosafety risks, biosecurity risks, and the implications for national and global health and security.

- **Panel III: Perspectives on the Proposed HHS Framework for Funding Decisions about HPAI H5N1 GOF Research**
  - This session will discuss the proposed HHS framework for guiding funding decisions about HPAI H5N1 GOF research.

- **Panel IV: Discussion of HPAI H5N1 Gain-of-Function Research Case Studies**
  - This session will apply the proposed HHS framework to examples of research that illustrate a range of gain-of- function experiments.

Day 2

- **Panel V: Identifying Conditions, if any, under which HPAI H5N1 GOF Research Should be Conducted**
  - This session will discuss the conditions, if any, under which HPAI H5N1 GOF research should be supported or conducted, identifying specific standards for future research in this area

- **Panel VI: Overview and Discussion of Main Points**

Questions for Discussion

- **Is the scope of the HHS framework appropriate? Does it capture the types of experiments that are concerning?**
- **Are the criteria for guiding HHS decisions appropriate?**
- **Other comments?**