# Gain-of-function studies of Concern

University of Wisconsin-Madison
Yoshihiro Kawaoka, DVM, PhD

## Regulations on H5N1 transmission studies

H5N1 transmission studies are highly regulated.

NSABB meeting, October 22, 2014

Working Paper by the NSABB Working Group on

Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

## Recommendation 1

Research proposals involving **GOF studies of concern** entail the greatest risks and should be reviewed carefully…

### Example

An experiment that is anticipated to generate **avian influenza** viruses that are **airborne transmissible** in mammals if the starting virus is **pathogenic in humans**.

## Recommendation 2

In general, oversight mechanisms for GOF studies of concern should be incorporated into **existing policy frameworks**.

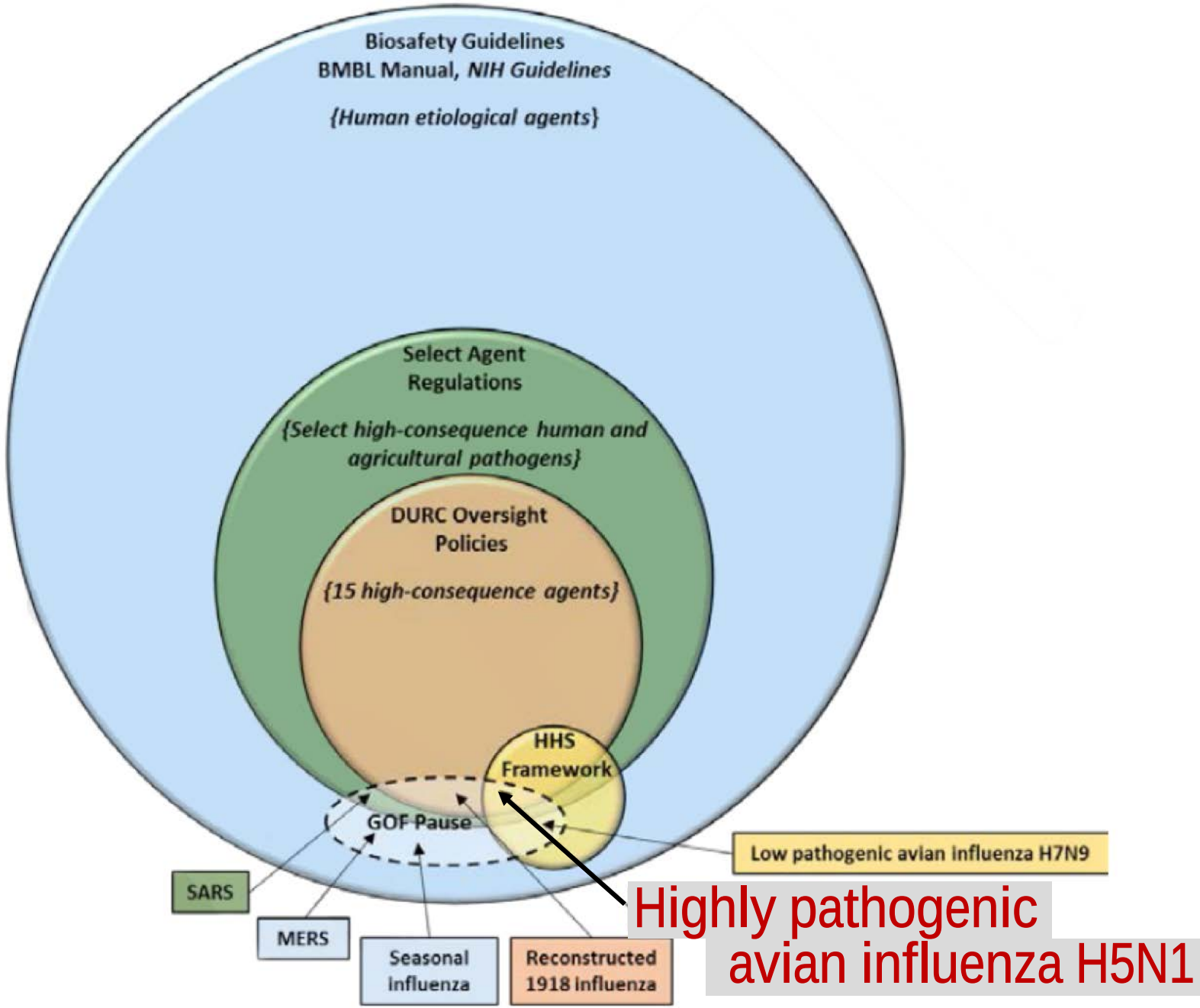
# Working Paper by the NSABB Working Group on

## Evaluating the Risks and Benefits of Gain-of-Function Studies to Formulate Policy Recommendations

### Key Finding 2.

The U.S. government has effective **policy frameworks** in place for managing the risks associated with life sciences research.

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- International treaties and agreements, and other relevant policies
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses


Biosafety Guidelines
BMBL Manual, NIH Guidelines
{Human etiological agents}
Select Agent Regulations
{Select high-consequence human and agricultural pathogens}
DURC Oversight Policies
{15 high-consequence agents}
HHS Framework
GOF Pause
Low pathogenic avian influenza H7N9
SARS
MERS
Seasonal influenza
Reconstructed 1918 influenza
Highly pathogenic avian influenza H5N1

# Example

**Grant Number:** 2R01AI069274-06A1
**Principal Investigator(s):** Yoshihiro Kawaoka
**Project Title:** Transmissibility of avian influenza viruses in mammals

Aim 1: To identify the **mechanisms** that control **H5N1 virus transmissibility** in mammals

Aim 2: To characterize the contribution of **viral genes other than HA** to H5N1 virus transmissibility

**Key Finding 2.**
The U.S. government has effective **policy frameworks** in place for managing risks associated with life sciences research.

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# Policy frameworks

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# Policy frameworks

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] Reviewed by IBC prior to grant submission

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# Oversight

## Policy frameworks

- NIH Guidelines
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the Federal and institutional oversight of DURC

### UW-Madison DURC Subcommittee:

Members have expertise in microbiology, virology, biosafety, biosecurity, infectious disease, public health, applicable regulations, and risk mitigation.

### UW-Madison Biosecurity Task Force:

Regularly reviews the research program and ongoing activities of the laboratory.

The task force comprises individuals with expertise in biosafety, facilities, compliance, security, law, communications, information security, and public health.

Written comments for NSABB meeting Jan 7-8, 2016

Marc Lipsitch, DPhil

Harvard T.H. Chan School of Public Health

Cofounder, Cambridge Working Group

*Contains original written comments submitted December 31, 2015 plus additional comments (on benefits) submitted January 3, 2016. Additional comments added to this version concern the Benefit Assessment and are in dark red font.*

Dear Chairman Stanley and Members of the NSABB:

*Comment I.6.* **The suggestion to use existing regulatory approaches for regulating GOF of concern requires that institutional oversight have the capacity to deal with this topic, making fine distinctions that have not yet been defined, much less codified in ways that can be applied at the institutional level.** There is no reason to think that Institutional Biosafety Committees have the requisite expertise to perform risk-benefit evaluations on this scale. As an example, the minutes of the University of Wisconsin IBC obtained by *Nature* for GOF work by Prof. Kawaoka (http://www.nature.com/polopoly_fs/7.18249!/file/WISC_Review.pdf) contain no numerical estimates of risk (that is to say, do not perform risk assessment, although they assert on p. 1 that it includes a risk benefit assessment) and accept uncritically all assertions

- Numerical estimates of risk are not done by the University of Wisconsin-Madison DURC Subcommittee.
- This is precisely why both institutional and federal (the HHS review group) oversite of DURC is needed.

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UW-Madison Registration

- Historically 3 years
- Rigorous inspections by the CDC and APHIS (Both planned and unannounced)
  - Facilities
  - Training
  - SOPs
  - Drills

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We ensure our research activities are in compliance with these guidelines and regulations.

# Policy frameworks

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February 21, 2013

# **Framework** for Guiding **Funding Decisions** about Research Proposals with the Potential for Generating **Highly Pathogenic Avian Influenza H5N1 Viruses** that are **Transmissible** among Mammals by Respiratory Droplets

**Grant Number:** 2R01AI069274-06A1
**Principal Investigator(s):** Yoshihiro Kawaoka
**Project Title:** Transmissibility of avian influenza viruses in mammals

After the above grant proposal was peer-reviewed, it was then reviewed by the **HHS review group**, which includes participants from 8 different **agencies** with multidisciplinary expertise, to:

- evaluate the proposed research according to the **7 criteria** outlined in the Framework
- review the funding agency's risk assessment and the risk measures in place.

# The 7 criteria

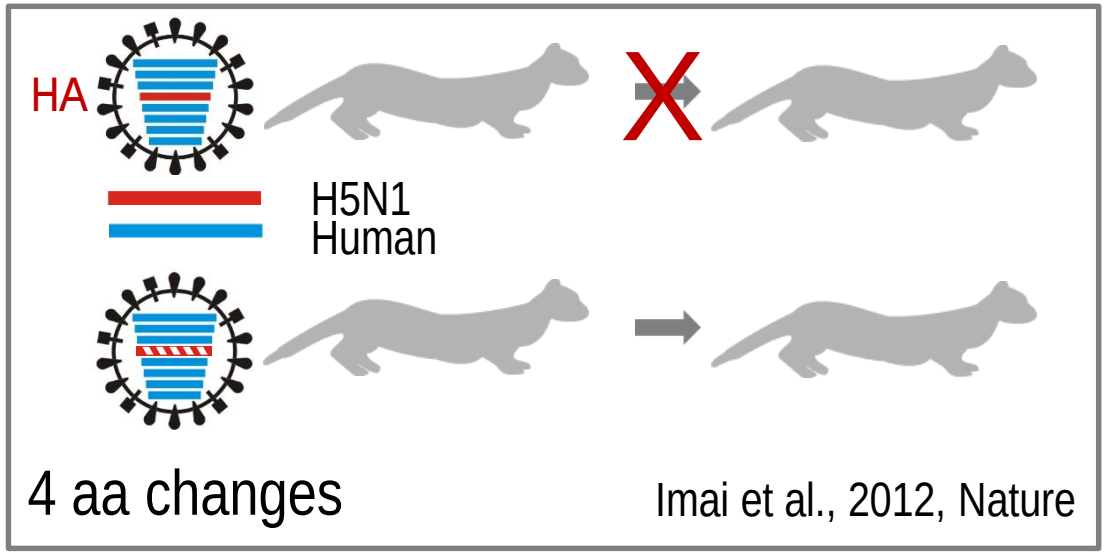
1. The virus anticipated to be generated could be produced through a natural evolutionary process
2. The research addresses a scientific question with high significance to public health
3. There are no feasible alternative methods to address the same scientific question in a manner that poses less risk 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
7. The research will be supported through funding mechanisms that facilitate appropriate oversight of the conduct and communication of the research

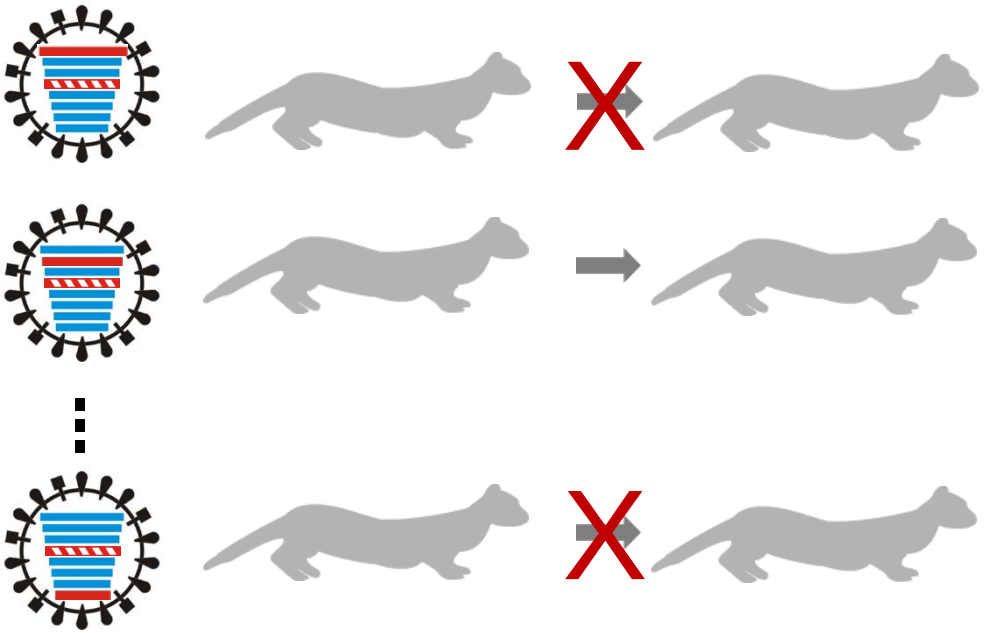
# The HHS review group

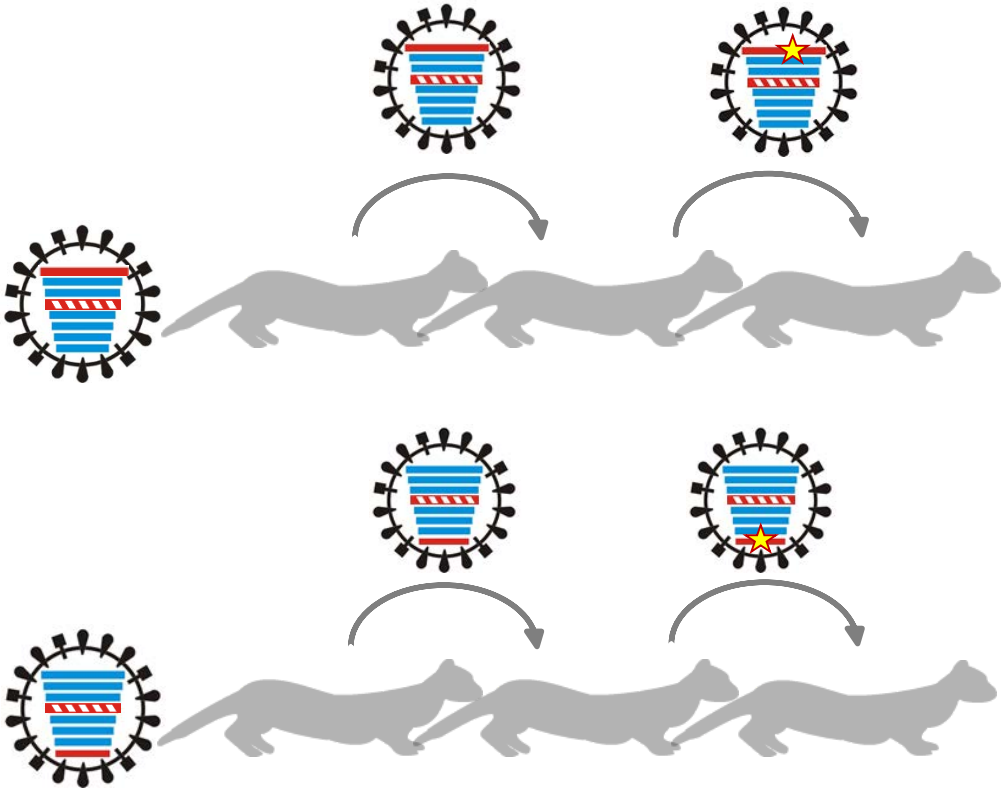
"determined that the proposed research is acceptable for funding with the exception of a set of experiments within Aim 2."

"Specifically, reassortant viruses which lose the ability to transmit among mammals would be serially passaged in the ferret model to select variants that regain transmissibility and these variants would be assessed for genetic changes."

# Experimental design





# The HHS review group

"The HHS review group felt that the viruses generated in these experiments were unlikely to be produced through a natural evolutionary process (Framework criterion one), and alternative methods with less risk could be used to address the same scientific question (Framework criterion three)."

## 7 criteria

1. The virus anticipated to be generated could be produced through a natural evolutionary process
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# The HHS review group

"The HHS review group felt that the viruses generated in these experiments were unlikely to be produced through a natural evolutionary process (Framework criterion one), and alternative methods with less risk could be used to address the same scientific question (Framework criterion three)."

"NIAID funding **may not be used** to perform these **serial passaging** experiments."

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- evaluate the proposed research according to the 7 **criteria** outlined in the Framework
- **review the funding agency's risk assessment and the risk measures in place.**

# In addition, the HHS review group asked about:

- Exposure Protocol
- Quarantine and Isolation Policy
- Animal protocols
- Risk assessments
- Communication strategies

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Recommendation 2

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**Key Finding 2.**

The U.S. government has effective **policy frameworks** in place for managing risks associated with life sciences research.

- HHS guidance
- BMBL (Biosafety in Microbiological and Biomedical Laboratories)
- Policies for the federal and institutional oversight of DURC
- Select Agent Regulations
- Export control regulations
- Various other laws and regulations
- Framework for guiding funding decisions for certain GOF studies involving H5N1 and H7N9 influenza viruses

- The US government already has effective policy frameworks in place for managing the risks associated with GOF studies of concern.
- However, GOF experiments have not been performed since the funding pause announcement in October of 2014.