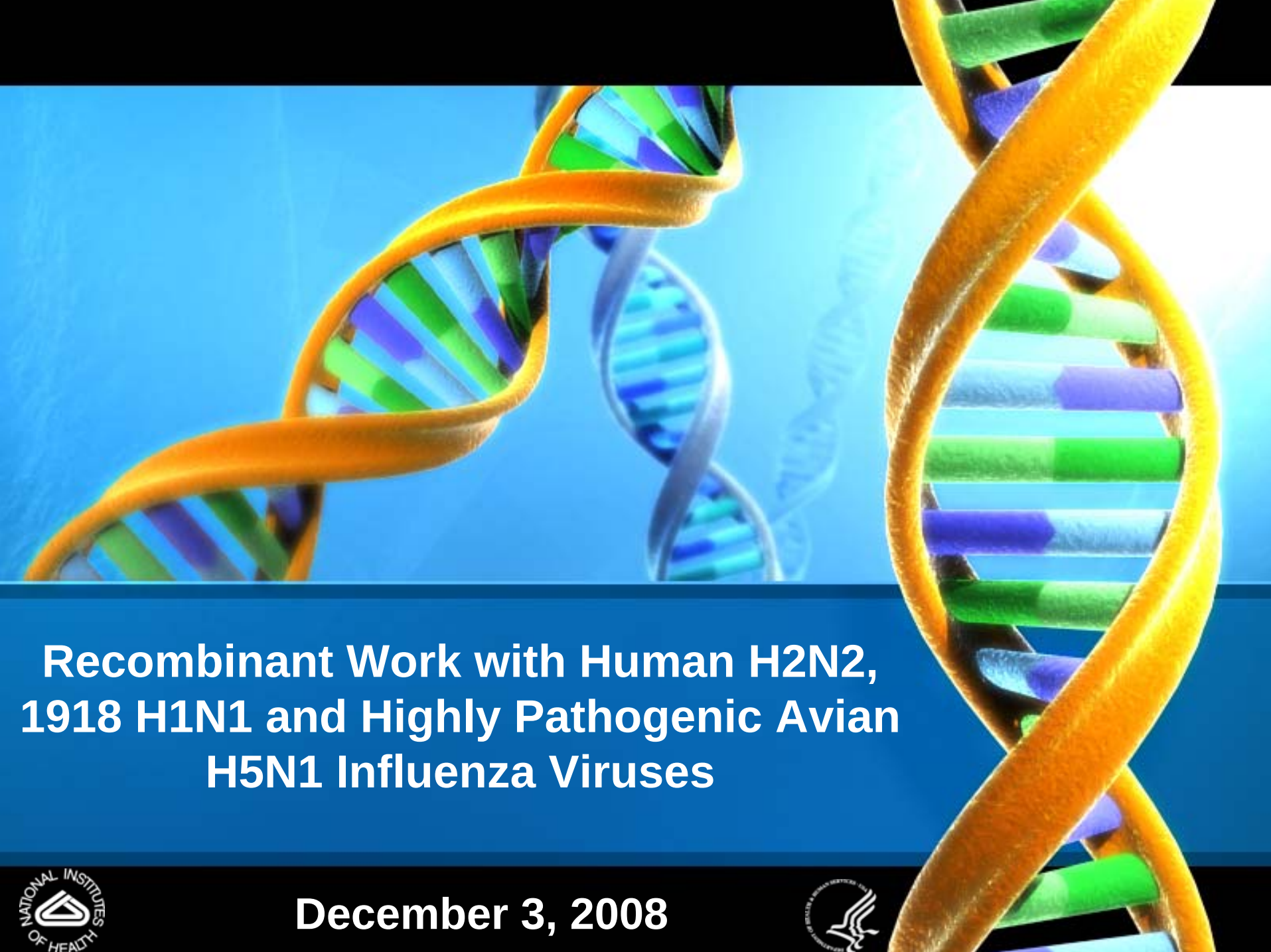

Recombinant Work with Human H2N2, 1918 H1N1 and Highly Pathogenic Avian H5N1 Influenza Viruses

December 3, 2008

Tasks for the RAC Biosafety Working Group

- **Determine the Risk Group classifications for the potentially pandemic influenza strains, human H2N2, reconstructed 1918 H1N1, and Highly Pathogenic H5N1**
- **Determine what additional biosafety guidance should be provided in the *NIH Guidelines* for research involving recombinant viruses containing sequences from these influenza strains**
  - **Consider current guidance provided by the CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) and USDA Animal and Health Inspection Service (APHIS)**
  - **Review additional scientific data**

Risk Groups Under the *NIH Guidelines*

- **Risk Groups**

RG1	**Agents are not associated with disease in healthy adult humans.**
RG2	**Agents are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available.**
RG3	**Agents are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk and low community risk).**
RG4	**Agents are likely to cause serious or lethal human disease for which preventive or therapeutic interventions *are not usually* available (high individual risk and high community risk).**

- **Containment levels (BL, BSL)**
  - **Containment level may be raised or lowered depending on a comprehensive risk assessment.**

RAC Biosafety Working Group

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RAC Biosafety Working Group Activities to Date

- **June 24, 2008: Conference on Risk Group *Classification and Risk Assessment for Human H2N2, 1918 Influenza Virus and Highly Pathogenic Avian Influenza Virus H5N1***
- **Teleconferences and consultations with outside experts**
- **Initial Proposal: September 10, 2008 RAC meeting**
- **December 2, 2008: Safety Symposium *Public Health and Biosafety Practices for Work with 1918 H1N1 Influenza Virus***

Comments on September 2008 RAC Meeting Proposal

1. **Reconsider recommendation for pre-exposure antiviral prophylaxis for research involving 1918 H1N1**
   - **Similar issue being considered by Intragovernmental Select Agent and Toxin Technical Advisory Committee (ISATTAC)**
   - **Joint safety symposium co-sponsored by NIH and CDC to consider the medical, public health and ethical issues**
2. **Specifically identify the viruses (e.g., human H2N2)**

Comments on September 2008 RAC Meeting Proposal

3. **Clarify recommendations for procedures to decrease risk of cross-contamination when working with multiple strains of influenza viruses**
4. **Clarify statement on determining susceptibility to antivirals in research strains**
5. **Clarify that specific guidance on BSL for recombinants only applies to recombinant *influenza viruses* containing segments from these viruses.**
   - Does not include insertion of influenza segment into other viruses (e.g. NDV) or plasmids

Recommendations for Human H2N2

Human H2N2 (1957-1968)

- The entire virus to be classified as a **Risk Group 3 agent**
- Containment guidance for research with recombinant human influenza viruses containing **the human H2N2 specific HA (1957-1968)**
  - **BL3 enhanced** or **BL3-N**
- .

Recommendations for Human H2N2

- Risk Group two recombinant influenza viruses containing H2N2 genes other than the HA gene can be conducted at **BL2** after an appropriate risk assessment.

- Work with the H2N2 HA gene in a cold-adapted, live attenuated vaccine strains may be done at **BL2** provided the genes responsible for conferring this phenotype are not altered.

Additional Guidance for H2N2 Containment

BL3 enhanced containment for research with recombinant human influenza viruses containing the *HA gene* from human H2N2 that circulated between 1957-1968:

- BL3 and BL3-N practices, procedures and facilities (see Appendix G of the *NIH Guidelines* and the NIH/CDC BMBL)
- **Enhancements**
  - Rigorous adherence to additional respiratory protection and clothing change protocols including double layering of gowns, gloves and shoe covers
  - Negative pressure, HEPA-filtered respirators or PAPRs are recommended
  - Laboratory exhaust HEPA-filtration may be considered
  - A shower out policy might be considered

Occupational Health Guidance Influenza Viruses containing the Human H2N2 HA

- **Susceptibility of the recombinant influenza viruses containing Human H2N2 HA genes to antivirals should be established:**
  - **By sequence analysis to confirm susceptibility, or**
  - **By suitable biological assays**

- **After genetic manipulations of genes that influence sensitivity to antivirals, susceptibility to these agents should be reconfirmed.**

Occupational Health Guidance Influenza Viruses containing the Human H2N2 HA

- **A detailed occupational health plan should be developed**
  - Strongly recommend seasonal vaccine as prerequisite for research
  - Mandatory reporting of respiratory symptoms and/or fever with a detailed occupational health plan that provides 24 hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and able to promptly provide appropriate anti-virals
  - Medical cards for laboratory workers (information to include):
    - **Strain of Influenza**
    - **24 hour contact numbers of principal investigator and institutions occupational health physician**

Avoiding Inadvertent Cross Contamination of Influenza Strains

- **To avoid inadvertent recombination between HPAI H5N1 viruses, Human H2N2HA and 1918 influenza virus, recombinant work involving genes from any of these agents together with other human influenza viruses should not be performed <u>simultaneously</u> within the same work area.**

Avoiding Inadvertent Cross Contamination of Influenza Strains

- **Between experiments adherence to:**
  - **Good biosafety practices, e.g., surface and BSC decontamination according to standard BL3 enhanced procedures, separate reagents to minimize risk of cross-contamination**
  - **30 minute wait period between experiments**
  - **Maintenance of containment facilities and practices appropriate for highest RG virus should be used at all times even with lower RG viruses when in the same lab**
  - **Tissue cultures with these viruses should be conducted at separate times (with temporal spacing)**

Additional Guidance for H5N1 Containment in *NIH Guidelines*

- **Laboratory workers should not perform concurrent influenza experiments that carry the risk of unintended recombination among HPAI H5N1 viruses, 1918 H1N1, Human H2N2 HA (1957-1968) and other human influenza viruses.**
- **Between experiments decontamination of work area, clothing changes, and PAPR disinfection should be performed prior to handling a different virus in the same work area**
- **Personnel showers should be considered for research involving animal studies in which animal to animal or animal to human transmission may occur**

High Risk Research

- **The availability of antiviral drugs as preventive and therapeutic measures is an important safeguard for research with H5N1, 1918 H1N1 and Human H2N2**
- **Experiments in which resistance to neuraminidase inhibitors or other effective antivirals (including investigational antivirals being developed for influenza) is deliberately transferred into these HPAI H5N1, Human H2N2 or 1918 H1N1 viruses would fall under Section III-A-1 (Major Actions) of the *NIH Guidelines* and require RAC review and NIH Director approval**
- **If regulated as a Select Agents, the NIH would defer to the regulatory body**

Next Steps

- **Develop Biosafety Guidance for 1918 H1N1 and HPAI H5N1**
  - **Take into consideration discussion from Safety Symposium from December 2, 2008 for 1918 H1N1**

- **Develop Points to Consider for IBCs on Risk Assessment for recombinant influenza viruses**

Questions?