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RESEARCH WITH HIGHLY PATHOGENIC AVIAN INFLUENZA H5N1

The University of Pittsburgh has developed guidelines to establish a system of education and safeguards to ensure compliance with both the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH rDNA Guidelines)¹ and the Select Agent Program for all personnel working with wild-type and recombinant strains of Highly Pathogenic Avian Influenza H5N1 (HPAI H5N1). These guidelines have been developed in consultation with the Allegheny County Health Department.

The NIH rDNA Guidelines define specific work practices and administrative controls for work with recombinant forms of certain Risk Group 3 influenza viruses, including recombinant strains of Highly Pathogenic Avian Influenza H5N1 (HPAI H5N1). The NIH rDNA Guidelines require a detailed occupational health and safety plan *in advance* of any University personnel working with recombinant HPAI H5N1.

The use of either wild-type or recombinant strains of HPAI H5N1 is also regulated by the Select Agent Program. The United States Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) has defined a list of facility enhancements that apply to work with HPAI H5N1.

These EH&S Guidelines apply to work with wild-type or recombinant strains of HPAI H5N1 only. Before work with any other Risk Group 3 influenza strains may be approved in University facilities, a strain-specific occupational health and safety plan must be developed and approved by the University.

1. SCOPE

1.1. **Agent** – Highly Pathogenic Avian Influenza H5N1 (HPAI H5N1) is an Influenza virus of the family *Orthomyxoviridae*. Wild-type HPAI H5N1 and reassortant strains of influenza expressing the hemagglutinin (HA) gene from HPAI H5N1 strains are currently regulated as Select Agents. Recombinant strains of influenza containing a majority of genes and/or segments from HPAI H5N1 influenza virus, are defined in Section III-D-7-b of the NIH rDNA Guidelines (recombinant HPAI H5N1) and are assigned to Risk Group 3¹. The NIH work practices and administrative enhancements are listed in Appendix G-II-C-5 “Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.”

1.2. **Incidence** – Outbreaks in poultry and wild birds have been reported in Asia, the Middle East, Europe, and Africa since 2003², and there have been isolated cases of HPAI H5N1 in other animals such as pigs, cats, and dogs. HPAI H5N1 infections in humans remain rare, but sporadic cases have been reported in 15 countries. Most cases have been attributed to close contact with sick or dead poultry or wild birds³.

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1.3. **Sequelae** – The clinical course of disease associated with HPAI H5N1 is more severe than that caused by seasonally-circulating influenza viruses. Rapid progression of severe respiratory disease, viral pneumonia, and multiple organ failures have occurred. The current case fatality rate is approximately 60% for cases reported since November 2003³.

1.4. **Vaccine** – No specific vaccine for HPAI H5N1 is currently available. However, University and NIH rDNA Guidelines require that all personnel be vaccinated with the annual seasonal influenza vaccine prior to working with wild-type or recombinant strains of HPAI H5N1. The seasonal influenza vaccine is composed of three influenza virus subtypes that the Federal Food and Drug Administration (FDA) has projected to be most common during an upcoming flu season. The seasonal influenza vaccine is contraindicated in individuals with an allergy to eggs, individuals who have previously had a severe reaction to an influenza vaccine, individuals currently experiencing a moderate-to-severe illness with a fever, and individuals with a history of Guillain-Barré Syndrome. Additional details are available upon consultation with Employee Health Services.

1.5. Laboratory Hazards and Communicability

1.5.1. Use of HPAI H5N1 is restricted by the Select Agent Program to Biosafety Level 3 Enhanced or Animal Biosafety Level 3 Enhanced facilities. Facility enhancements required for work with HPAI H5N1 are promulgated by USDA APHIS.

1.5.2. HPAI H5N1 may be transmitted in the laboratory via animal bite or scratch, percutaneous exposure such as a needlestick or cut, a splash to an open cut or wound, mucous membrane exposure, or inhalation of an aerosol.

1.5.3. It is currently unknown whether HPAI H5N1 may be transmitted via a person-to-person route, but the potential public health impact of this transmission route is of great concern.

1.6. **Employees at Risk-** Handling of wild-type or recombinant strains of HPAI H5N1 or animals infected with wild-type or recombinant strains of HPAI H5N1 poses a risk of exposure to personnel.

2. GUIDELINES

2.1. All Principal Investigators (PIs) using wild-type or recombinant strains of HPAI H5N1 must be registered with the Biosafety Officer/EH&S. A registration document may be obtained from the web site www.ehs.pitt.edu.

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- 2.2. Certain recombinant and all wild-type strains of HPAI H5N1 are regulated by the USDA Select Agent Program and individuals in possession of or having access to the agent or infected animals must be registered with the Responsible Official (RO) for the University Select Agent Program, receive an approved Security Risk Assessment from the Department of Justice, and complete specified training for the Select Agent Program.
- 2.3. All PIs using recombinant strains of HPAI H5N1 must be registered with the University of Pittsburgh Institutional Biosafety Committee in accordance with the NIH rDNA Guidelines¹.
- 2.4. Biosafety Level 3 Enhanced work practices, administrative controls, containment equipment and EH&S-approved BSL3/ABSL3 Enhanced facilities are required for all activities involving the use or manipulation of wild-type or recombinant strains of HPAI H5N1 and/or infected animals.
- 2.4.1. Work practices and administrative controls to prevent inadvertent cross contamination of recombinant HPAI H5N1 with other strains of influenza A shall include: 1) temporal spacing (i.e. full decontamination of work area and personal protective equipment with a 30 minute wait period) between experiments performed with recombinant HPAI H5N1 and experiments performed with other influenza viruses; 2) separate reagents to be used solely for work with recombinant HPAI H5N1; and 3) no concurrent work with recombinant HPAI H5N1 and other influenza viruses by the same laboratory worker or by two laboratory workers working simultaneously within the same work space.
- 2.4.2. Small animals (rodents) infected with recombinant HPAI H5N1 shall be housed in individually vented caging systems for primary containment.
- 2.4.3. Other animals (such as ferrets) infected with recombinant HPAI H5N1 shall be housed in primary containment caging.
- 2.4.4. Investigators shall notify the Biosafety Officer/EH&S if work with recombinant HPAI H5N1 is planned in animal species that cannot be housed in primary containment caging as additional facility, work practice and administrative controls will be required.
- 2.5. A protocol-specific Biosafety Level 3 Manual is required for all research with wild-type or recombinant strains of HPAI H5N1, and must be approved by EH&S and the University Biohazards Committee prior to initiating research with wild-type or recombinant strains of HPAI H5N1.
- 2.6. Laboratories shall be inspected by EH&S at least annually to verify appropriate Biosafety Level 3 Enhanced containment, practices and restricted access.

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- 2.7. All individuals who directly handle a) cultures or b) animals contaminated or infected with wild-type or recombinant strains of HPAI H5N1 must be medically screened by Employee Health Services for contraindications to the seasonal influenza vaccine. Vaccination is required annually for individuals seeking to handle wild-type or recombinant strains of HPAI H5N1 or animals infected with wild-type or recombinant strains of HPAI H5N1 at the University of Pittsburgh.
- 2.8. All individuals who work with wild-type or recombinant strains of HPAI H5N1 shall be provided with medical alert cards which include the following information: characterization of the influenza virus to which they have been potentially exposed, and 24-hour contact numbers for the PI and Employee Health Services.
- 2.9. Occupational Health Requirements
- 2.9.1. All personnel entering any BSL-3/ABSL-3 facility at the University of Pittsburgh where HPAI H5N1 is in use must be enrolled in the University's Respiratory Protection Program, and must wear a Powered Air-Purifying Respirator (PAPR).
- 2.9.2. All personnel entering BSL-3/ABSL-3 facilities must have undergone a BSL-3 Worker Health Screening from Employee Health Services in the previous twelve months.
- 2.9.3. Evidence of vaccination for seasonal influenza within the prior 12 months is required for all individuals before handling wild-type or recombinant strains of HPAI H5N1 in culture or handling animals infected with wild-type or recombinant strains of HPAI H5N1 at the University of Pittsburgh. This requirement shall be stated in respective job descriptions for University personnel.
- 2.9.4. For persons entering research facilities using wild-type or recombinant strains of HPAI H5N1 at the University of Pittsburgh, but who are not directly handling wild-type or recombinant strains of HPAI H5N1 or infected animals, the seasonal influenza vaccine is available at no cost by contacting Employee Health Services.
- 2.10. Individuals refusing or having a medical contraindication to the seasonal influenza vaccine as determined by the Employee Health Services will be prohibited from handling wild-type or recombinant strains of HPAI H5N1 in culture or animals infected with wild-type or recombinant strains of HPAI H5N1 at the University of Pittsburgh. The determination of all prohibited tasks will be made by the employee's supervisor in consultation with EH&S.

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- 2.10.1. Staff members refusing or having a medical contraindication to the seasonal influenza vaccine shall be referred to their supervisor. The supervisor in consultation with the Office of Human Resources (and if necessary EH&S and Employee Health) will consider the effects of vaccine refusal or medical contraindication on employment status of the employee.
- 2.10.2. Faculty members refusing or having a medical contraindication to the seasonal influenza vaccine shall be referred to the respective department chair or dean. The supervisor in consultation with the Office of General Counsel and the Office of the Provost (and as necessary EH&S and Employee Health Services) will consider the effects of vaccine refusal or medical contraindication on employment status of the faculty member.
- 2.11 Laboratory personnel must wear personal protective equipment when handling these agents to include at a minimum a full clothing change, facility dedicated scrubs, liquid-barrier coverall suit, a powered air-purifying respirator (PAPR), double gloves, and shoe covers over facility dedicated shoes or liquid impervious boots. All personnel entering BSL-3 containment facilities must abide by the garbing requirements for the specific facility as established by EH&S. Refer to the University of Pittsburgh Safety Manual Section V, Guidelines 05-003 and 05-023 for more details on Biosafety Level 3 requirements. In case of a potential exposure to wild-type or recombinant strains of HPAI H5N1, personnel shall be required to follow the post-exposure response procedures outlined in the PI's incident response plan and/or biosafety manual. Risk assessment regarding the exposure will be performed collectively by the Employee Health Services Medical Director, PI, and EH&S. In case of a known exposure to wild-type or recombinant strains of HPAI H5N1 with a high risk for infection by HPAI H5N1, the exposed individual shall be required to: Submit specimens via Employee Health Services for testing to rule out infection by wild-type or recombinant strains of HPAI H5N1,
- 2.13.2 Self-isolate from the general public until specimens are confirmed to be negative for wild-type or recombinant strains of HPAI H5N1, and
- 2.13.3 Self monitor for development of signs/symptoms of influenza.
- 2.13.3.1 During this period of self-isolation, absent any signs or symptoms of influenza infection, the employee will be given a paid, approved leave of absence by his or her supervisor.
- 2.13.4 If personnel who have had a known exposure to wild-type or recombinant strains of HPAI H5N1 begin to develop signs and/or symptoms of influenza infection (fever, chills, headache, cough, muscle aches) within 10 days of the exposure they shall immediately inform Employee Health Services.

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2.13.5 Employee Health Services will perform a clinical assessment in coordination with the Allegheny County Health Department at the exposed individual's site of self-isolation. In consultation with public health authorities the exposed individual can be ordered to be transported to the University of Pittsburgh Medical Center Presbyterian Hospital for respiratory isolation, treatment, and testing to determine whether the symptoms are due to an infection with wild-type or recombinant strains of HPAI H5N1.

2.14 It shall be the responsibility of the Principal Investigator and/or individuals responsible for control of access to a facility where wild-type or recombinant strains of HPAI H5N1 are used to assure that individuals handling HPAI H5N1 or animals infected with HPAI H5N1 are enrolled in the occupational health requirements of this Guideline; are vaccinated prior to initial handling of HPAI H5N1; are listed on any relevant IBC and/or IACUC protocol; are approved for access to Select Agents at the University of Pittsburgh (provided that the strain is regulated as a Select Agent); and have signed an informed consent form agreeing to meet the public health requirements in the event of a known exposure to wild-type or recombinant strains of HPAI H5N1 with a high risk of infection.

3. REFERENCES

- 3.1. National Institutes of Health Office of Biotechnology Activities. NIH Guidelines for Research Involving Recombinant DNA Molecules. Most current version available at http://oba.od.nih.gov/rdna/nih_guidelines_oba.html; accessed 01/31/2012.
- 3.2. CDC Highly Pathogenic Avian Influenza A (H5N1) in Birds and Other Animals, www.cdc.gov/flu/avianflu/h5n1-animals.htm; accessed 01/31/2012.
- 3.3. CDC Highly Pathogenic Avian Influenza A (H5N1) in People, www.cdc.gov/flu/avianflu/h5n1-people.htm; accessed 01/31/2012.
- 3.4. CDC Key Facts About Seasonal Flu Vaccine, www.cdc.gov/flu/protect/keyfacts.htm; accessed 01/31/2012.

4. INFORMED CONSENT FORMS

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**Informed Consent for Individuals Involved in Research
with Highly Pathogenic Avian Influenza H5N1**

Print Name

2P Number

I understand that due to my occupational exposure to H5N1 influenza virus that I may be at risk of acquiring a serious infection. This infection could be fatal and/or have potential public health consequences. Due to the potential consequences associated with infection, specific control measures are required by Federal, Allegheny County Health Department and/or University guidelines in the event that I have a known exposure to H5N1 influenza in the research environment.

I have read and understand the University of Pittsburgh Standard Operating Procedures for H5N1 influenza. I understand that in the event of a known exposure to H5N1 influenza in the research environment that I may be required by Federal, Allegheny Health Department and/or University guidelines to self-isolate from the general public until infection has been ruled out.

I further understand that if flu-like symptoms develop within 10 days of a known exposure (as determined by University EH&S under the Standard Operating Procedures) to H5N1 influenza in the research environment that I am required by Federal, Allegheny County Health Department and/or University guidelines to report the symptoms immediately to my supervisor and Employee Health Services; and that isolation in a medical facility will occur until H5N1 or other infection of concern is ruled out by appropriate testing.

I acknowledge and accept these conditions for working with H5N1 influenza virus at the University of Pittsburgh.

Signature to ACCEPT

Date

OR, I cannot accept the conditions as described above. I understand that by declining to accept these conditions, my supervisor and/or investigator will be notified of my restriction from handling H5N1 influenza at the University of Pittsburgh.

Signature of DECLINATION

Date

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Consent for REQUIRED Flu Vaccination

Print Name

2P Number

I understand that due to my occupational exposure to H5N1 influenza viruses that I may be at risk of acquiring a serious infection. This infection could be fatal. I have read and understand the Standard Operating Procedures and the infectious agent fact sheet for H5N1 influenza. There is no vaccination for this influenza strain, but I have read and understand the Vaccination Information Sheet for the current seasonal influenza vaccine. I understand that the current seasonal influenza vaccination is annually REQUIRED by Federal and University guidelines prior to my direct manipulation of H5N1 influenza at the University of Pittsburgh, and that the current seasonal influenza vaccine may not provide protection from infection with H5N1 influenza. I consent to receive the currently licensed seasonal influenza vaccine.

Signature of CONSENT

Date

OR, I decline the seasonal influenza vaccination at this time. I understand that this licensed vaccination is available at no cost to me and is a requirement for my direct manipulation of H5N1 influenza or animals infected with this agent. I understand that by declining this vaccination, my supervisor and/or investigator will be notified of my restriction from handling H5N1 influenza at the University of Pittsburgh.

Signature of DECLINATION

Date

OR, I attest that I have been previously vaccinated for seasonal influenza within the prior twelve months. Documentation must be provided to the University prior to direct manipulation of H5N1 influenza at the University of Pittsburgh.

Signature

Date