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RESEARCH WITH HIGHLY PATHOGENIC AVIAN INFLUENZA VIRUSES

The University of Pittsburgh has developed guidelines to establish a system of education and safeguards to ensure compliance with the NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines)¹, the Federal Select Agent Regulations, and other applicable biosafety guidelines and best practices for all personnel working with wild-type and recombinant strains of Highly Pathogenic Avian Influenza (HPAI). These guidelines have been developed in consultation with the Allegheny County Health Department.

The NIH 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 (HPAI). The NIH Guidelines require a detailed occupational health and safety plan *in advance* of any University personnel working with recombinant HPAI.

The use of either wild-type or recombinant strains of HPAI is also regulated by the Federal Select Agent Program. The United States Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS) has defined a list of facility and work practice enhancements that apply to work with HPAI².

These EH&S Guidelines apply to work with wild-type or recombinant strains of HPAI, and a strain-specific occupational health and safety plan must be developed and approved by the University Biohazards Committee and EH&S before work with any HPAI influenza strains may begin.

SCOPE

Agent – Highly Pathogenic Avian Influenza (HPAI) is an influenza virus of the family *Orthomyxoviridae*. Internationally recognized criteria and standardized *in vitro* and *in vivo* testing are used to classify an avian influenza virus as low or highly pathogenic based upon pathogenicity index in chickens and the amino acid sequence of the HA protein cleavage site^{2,4}. Wild-type HPAI, and reassortant strains of influenza expressing the hemagglutinin (HA) gene from HPAI strains, are currently regulated as Select Agents². 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 Guidelines (recombinant HPAI H5N1) and are assigned to Risk Group 3¹. The NIH work practices and administrative enhancements for work with HPAI H5N1 are listed in Appendix G-II-C-5 “Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses.”

Incidence – Outbreaks of HPAI in poultry and wild birds have been reported in 68 countries and territories during the period from 2013-August 2018, and there have been isolated cases of HPAI in other animals such as pigs, cats, and dogs^{2,5}. Outbreaks have occurred in the United States in 1924, 1983, 2004, 2015, and 2017, with the 2015 outbreak resulting in ~\$1.6 billion in lost birds and ~\$3.3 billion in losses across the national economy². Confirmed infections with HPAI or other novel influenza A viruses associated with severe disease in humans have been reported in

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16 countries and territories⁵. Most cases have been attributed to close contact with sick or dead poultry or wild birds.

Sequelae –Infection with HPAI, or other novel influenza A viruses associated with severe disease in humans, results in a more severe clinical course of disease than that caused by seasonally-circulating influenza viruses. Rapid progression of severe respiratory disease, viral pneumonia, and multiple organ failures have occurred^{6,7}. The current case fatality rate ranges from ~31%-53%, depending upon the specific strain of virus identified in reported cases^{5,8}

Vaccine – No specific vaccine for HPAI is currently available. However, University and NIH Guidelines require that all personnel be vaccinated with the annual seasonal influenza vaccine prior to working with wild-type or recombinant strains of HPAI. The seasonal influenza vaccine is composed of three influenza virus subtypes that the World Health Organization (WHO) and 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.

Laboratory Hazards and Communicability

Use of HPAI is restricted by the Select Agent Program to Biosafety Level 3 or Animal Biosafety Level 3 facilities with facility design and work practice enhancements as promulgated by USDA APHIS².

HPAI 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.

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

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

GUIDELINES

All Principal Investigators (PIs) using wild-type or recombinant strains of HPAI must be registered with the Biosafety Officer/EH&S. PIs may register via completion of a protocol application in the MyIBC system (<http://www.abc.pitt.edu/test-123>).

Certain recombinant strains, and all wild-type strains of HPAI are regulated by the USDA Select Agent Program. 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,

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receive an approved Security Risk Assessment from the Department of Justice, and complete specified training for the University Select Agent Program.

All PIs using recombinant strains of HPAI must be registered with the University of Pittsburgh Institutional Biosafety Committee in accordance with the NIH Guidelines¹. PIs may register via completion of a protocol application in the MyIBC system (<http://www.ibt.pitt.edu/test-123>).

Biosafety Level 3 with enhanced work practices, administrative controls, containment equipment and facilities are required for all activities involving the use or manipulation of wild-type or recombinant strains of HPAI and/or infected animals.

Work practices and administrative controls to prevent inadvertent cross contamination of HPAI with other strains of influenza A shall include:

Change of gloves and sleeve covers (at a minimum) after full decontamination of work area,

Temporal spacing (e.g. full decontamination of work area and personal protective equipment with a 20 minute wait period) between experiments performed with HPAI and experiments performed with other influenza viruses,

Shower out, full clothing, and PPE change between experiments performed with HPAI and experiments performed with other influenza viruses,

Separate reagents to be used solely for work with HPAI, and

No concurrent work with HPAI and other influenza viruses by the same laboratory worker or by two laboratory workers working simultaneously within the same work space.

In cases where non-HPAI strains of influenza viruses must be used within the same experiment or work-space, separate, dedicated stocks of non-HPAI strains must be used and shall be handled as if potentially contaminated with HPAI.

Small animals (rodents) infected with HPAI shall be housed in individually vented caging systems for primary containment.

Other animals (such as ferrets or non-human primates) infected with HPAI shall be housed in primary containment caging.

Investigators shall notify the Biosafety Officer/EH&S if work with HPAI is planned in animal species that cannot be housed in primary containment caging as additional facility, work practice, and administrative controls will be required.

A protocol-specific Biosafety Level 3 Manual is required for all research with wild-type or recombinant strains of HPAI, and must be approved by EH&S and the University Biohazards Committee prior to initiating research.

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Laboratories shall be inspected by EH&S at least annually to verify appropriate Biosafety Level 3 containment, including facility enhancements, enhanced work practices and restricted access.

Occupational Health Requirements

All personnel entering any BSL-3/ABSL-3 facility at the University of Pittsburgh where HPAI is in use must be enrolled in the University's Respiratory Protection Program, and must wear a Powered Air-Purifying Respirator (PAPR).

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.

All individuals who directly handle a) cultures or b) animals contaminated or infected with wild-type or recombinant strains of HPAI 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, or animals infected with wild-type or recombinant strains of HPAI at the University of Pittsburgh.

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 in culture or handling infected animals at the University of Pittsburgh. This requirement shall be stated in respective job descriptions for University personnel.

For persons entering research facilities using wild-type or recombinant strains of HPAI at the University of Pittsburgh, but who are not directly handling cultures or infected animals, the seasonal influenza vaccine is recommended and is available at no cost by contacting Employee Health Services.

Individuals refusing or having a medical contraindication to the seasonal influenza vaccine as determined by Employee Health Services will be prohibited from handling wild-type or recombinant strains of HPAI in culture or infected animals at the University of Pittsburgh. The determination of all prohibited tasks will be made by the employee's supervisor in consultation with EH&S.

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.

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 University Counsel and the Office of the Provost (and as necessary EH&S and

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Employee Health Services), will consider the effects of vaccine refusal or medical contraindication on employment status of the faculty member.

All individuals who work with wild-type or recombinant strains of HPAI 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.

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, sleeve covers, 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.

Response to Potential Employee Exposures

In case of a potential exposure to wild-type or recombinant strains of HPAI, personnel shall be required to follow the post-exposure response procedures outlined in this document, and the PI's incident response plan and/or biosafety manual. Risk assessment regarding the potential for the exposure to result in infection will be performed collectively by the Employee Health Services Medical Director, PI, and EH&S.

Known Exposure with High Risk for Infection

In case of a known exposure to wild-type or recombinant strains of HPAI with a high risk for infection, 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,

Self-isolate from the general public until specimens are confirmed to be negative for wild-type or recombinant strains of HPAI, and

Self monitor for development of signs/symptoms of influenza.

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.

If personnel who have had a known exposure to wild-type or recombinant strains of HPAI 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.

Employee Health Services, in consultation with the Allegheny County Health Department, will determine whether the exposed individual shall be admitted to the University of Pittsburgh

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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.

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 are used to assure that individuals handling HPAI or infected animals are:

Enrolled in the occupational health requirements of this Guideline,

Vaccinated prior to initial handling of HPAI,

Listed on any relevant IBC and/or IACUC protocol,

Approved for access to Select Agents at the University of Pittsburgh,

Provided with, and have signed, an informed consent form agreeing to meet all public health requirements in the event of a known exposure to wild-type or recombinant strains of HPAI with a high risk of infection.

REFERENCES

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3. World Organisation for Animal Health (OIE). (2017). Terrestrial Animal Health Code, Chapter 10.4, Infection with Avian Influenza Viruses. https://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_avian_influenza_viruses.htm; accessed 10/17/2019.
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5. World Organisation for Animal Health (OIE). (2018). OIE Situation Report for Highly Pathogenic Avian Influenza. <https://www.oie.int/en/animal-health-in-the-world/update-on-avian-influenza/2016/>; accessed 10/17/2019.

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7. United States Centers for Disease Control and Prevention (CDC). (2018). Asian lineage Avian influenza A(H7N9) virus. <https://www.cdc.gov/flu/avianflu/h7n9-virus.htm>; accessed 10/17/2019.

8. World Health Organization (WHO). (2019). Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2019. https://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/; accessed 10/17/2019.

INFORMED CONSENT FORMS – Continue on pages 8 and 9.

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University of Pittsburgh

**Informed Consent for Individuals Involved in Research
with Highly Pathogenic Avian Influenza (HPAI)**

Print Name

2P Number

I understand that due to my occupational exposure to Highly Pathogenic Avian Influenza (HPAI) 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 HPAI in the research environment.

I have read and understand the University of Pittsburgh Guidelines for Work with HPAI. I understand that in the event of a known exposure to HPAI 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 Employee Health Services and EH&S under the Guidelines) to HPAI in the research environment, that I am required by Federal, Allegheny County Health Department and/or University guidelines to report the symptoms immediately to Employee Health Services and my supervisor; and that isolation in a medical facility will occur until HPAI or other infection of concern is ruled out by appropriate testing.

I acknowledge and accept these conditions for working with HPAI 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 HPAI at the University of Pittsburgh.

Signature of DECLINATION

Date

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University of Pittsburgh
Consent for REQUIRED Flu Vaccination

Print Name

2P Number

I understand that due to my occupational exposure to highly pathogenic avian influenza (HPAI) viruses that I may be at risk of acquiring a serious infection. This infection could be fatal. I have read and understand the EH&S Guidelines and the infectious agent fact sheet for HPAI. 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 **REQUIRED annually** by Federal and University guidelines prior to my direct manipulation of HPAI at the University of Pittsburgh, and that the current seasonal influenza vaccine may not provide protection from infection with HPAI. 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 HPAI 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 HPAI 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 HPAI at the University of Pittsburgh.

Signature

Date