

Biosafety Guidance for Research involving Highly Pathogenic Avian Influenza (HPAI) H5N1 Viruses Transmissible between Mammals by Respiratory Droplets

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OVERVIEW

- **Biosafety framework under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)****
- **Current BL3 enhanced containment practices for research involving highly pathogenic avian influenza viruses of Goose/Guangdong/96-like H5 lineage (HPAI H5N1)**
- **RAC Biosafety Working Group (RAC BSWG) recommendations for additional enhancements for research with mammalian transmissible HPAI H5N1**

**In March the NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules will go into effect.*

Risk Groups (RG) Under the *NIH Guidelines*

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

Containment Level (Biosafety Level) may be raised or lowered depending on a comprehensive risk assessment considering recombinant agent factors and type of manipulation.

Current *NIH Guidelines*: Risk Group Classifications

Risk Group 4 Agents

Associated with serious or lethal human disease for which preventive or therapeutic interventions *are not usually* available (high individual risk and high community risk)

e.g.,

- Ebola virus
- Marburg virus
- Lassa virus

Current *NIH Guidelines*: Risk Group Classifications

Risk Group 3 Agents

Associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk and low community risk).

- 1918 H1N1
- Human H2N2 (1957-1968)
- HPAI H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1)

Containment for RG3 Influenza viruses

- In 2009, NIH revised the *NIH Guidelines* to set containment standards for RG3 influenza viruses, including HPAI H5N1, that have the potential to cause a pandemic
- These viruses - 1918 H1N1, HPAI H5N1 and H2N2 (that circulated in humans from 1957-1968) - were designated RG3 agents because of the availability of vaccines and/or antivirals.
- However, it was also recognized that these viruses have the potential to pose a risk to the community if they escaped from the lab, and Biosafety Level (BL) 3 enhanced containment was recommended

Additional Considerations HPAI H5N1

- **Influenza viruses that contain the HA gene from a HPAI avian influenza (or have the characteristics of an HPAI HA gene) are currently US Department of Agriculture (USDA) Animal and Plant Health Inspection Agency (APHIS) Select Agents and thus biosafety conditions for research with HPAI H5N1 are determined by the USDA/APHIS.**

Review of Biosafety Containment for Mammalian Transmissible Strains

- **Office of Biotechnology Activities convened the RAC Biosafety Working Group and consulted with:**
 - **The CDC Division of Select Agents and Toxins and the USDA APHIS**
 - **The following subject matter experts:**

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CDC - Centers for Disease Control and Prevention

USDA - US Department of Agriculture

BARDA - Biomedical Advanced Research Development Authority ⁸

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Overview of Biosafety Recommendations

- **Facility/Airflow enhancements**
- **Primary animal containment**
- **Waste handling**
- **Maintenance of antiviral susceptibility throughout research**
- **Laboratory worker personal protective devices and practices**
- **Occupational health measures**

Current *NIH Guidelines* : Facility Air Handling for HPAI H5N1

Laboratory Facilities (Air Handling Sections): same as BL3 - no additional enhancements currently specified for HPAI H5N1 research

BL3 Air Handling Sections:

- **Appendix G-II-C-4-i.**
 - A ducted exhaust air ventilation system.
 - Directional airflow that draws air into the laboratory through the entry area.
 - Exhaust air is not recirculated
 - Exhaust discharged to the outside away from the occupied areas and air intakes.
 - No requirement that air be filtered or treated prior to discharge

Current *NIH Guidelines*: Facility Air Handling

BL3 Air Handling Sections:

- **Appendix G-II-C-4-j.**
 - **Air exhausting from Class I or Class II biological safety cabinets is HEPA filtered prior to discharge to the outside**
 - **Exhaust air from Class I or II biological safety cabinets may be recirculated within the laboratory if the cabinet is tested and certified at least every twelve months**
 - **If the HEPA-filtered exhaust air from Class I or II biological safety cabinets is to be discharged to the outside through the building exhaust air system, it is connected to this system in a manner that avoids any interference with the air balance of the cabinets or building exhaust system**

RAC BSWG Recommendations for **Additional Enhancements for Mammalian- Transmissible HPAI H5N1**

BL3 with the following provisions:

Air Handling:

- **Mandatory HEPA filtration of laboratory exhaust air, not only air from a biosafety cabinet**
- **The exhaust system must have a sealed ductwork system from the containment barrier to the filter**
- **The air handling shall be designed such that under failure conditions the airflow will not be reversed and this shall be periodically validated**

RAC BSWG Recommendations for **Additional Enhancements for Mammalian- Transmissible HPAI H5N1**

BL3 with the following provisions:

Facility:

- **The facility shall have a back-up system for power for those critical controls and instrumentations necessary to prevent a loss of containment**

Recommendations: Facilities and Air Handling

Current NIH Guidelines (BL3 – no specific enhancement for HPAI H5N1)	Enhancements for Mammalian-Transmissible HPAI H5N1	Rationale
<p>Ducted exhaust air ventilation system. Exhaust air is discharged to outside without being filtered or treated. (Appendix G-II-C-4-i.)</p>	<p>Mandatory HEPA filtration of exhaust air with sealed ductwork system from containment barrier to filter</p>	<p>Provide further protection against loss of containment</p>
<p>Single pass of air, may not be recirculated to other parts of building.</p>	<p>Air handling should be designed such that under failure conditions the airflow will not be reversed. Periodic validation.</p>	<p>Goal is to maintain containment in the event of an exhaust system failure</p>
<p>Facility not required to have back-up power</p>	<p>Back-up power is available for critical controls and instrumentation</p>	<p>Further redundancy against loss of containment</p>

Overview of Biosafety Recommendations

- Facility/Airflow enhancements
- **Primary animal containment**
- Waste handling
- Maintenance of countermeasure susceptibility throughout research
- Laboratory worker personal protective devices and practices
- Occupational health measures

Current Appendix G-II-C-5-b: Containment for Animal Research

- **G-II-C-5-b-(1) Research with small animals shall be conducted in a class II biosafety cabinet.**
- **Small animals such as rodents (e.g. mice, hamsters, rats, guinea pigs) can be housed within a negative pressure BL3 animal suite using high-density individually vented caging (IVC) systems that independently supply high efficiency particulate air/HEPA-filtered and directional air circulation.**
- **Other animals (e.g. rabbits, ferrets) that are of a size or have growth or caging requirements that preclude the use of high-density IVC systems are to be housed in negative pressure bioisolators.**

Overview of Biosafety Recommendations

- Facility/Airflow enhancements
- Primary animal containment
- **Waste handling**
- Maintenance of countermeasure susceptibility throughout research
- Laboratory worker personal protective devices and practices
- Occupational health measures

Current NIH Guidelines: Waste Handling

BL3 Waste Handling Sections:

- **Appendix G-II-C-2-n. All waste from laboratories and animal rooms are appropriately decontaminated before disposal.**
- **Appendix G-II-C-4-h. An autoclave for decontaminating laboratory wastes is available preferably within the laboratory.**

Recommendations: Facilities Waste Handling

Current NIH Guidelines (BL3 – no specific enhancement for HPAI H5N1)	Enhancements for Mammalian-Transmissible HPAI H5N1	Rationale
<p>All waste from laboratories and animal rooms are appropriately decontaminated before disposal.</p> <p>An autoclave for decontaminating laboratory wastes is available preferably within the laboratory.</p>	<p>Liquid effluents originating from laboratories should be collected locally and chemically disinfected or heat treated, or collected and processed in a central effluent decontamination system before being released into the local sanitary system.</p> <p>Decontamination of shower and toilet effluents not required if there is appropriate practice and procedures for primary containment.</p>	<p>Additional specificity for liquid waste disposal.</p>

Summary of Differences between current *NIH Guidelines* and Recommendations: Facilities Waste Handling

<i>NIH Guidelines (cont.)</i>	Enhancements for Mammalian-Transmissible HPAI H5N1	Rationale
Appropriate decontamination of animal wastes (e.g., rodents, ferrets)	All animal tissues, carcasses, and bedding originating from the animal room must be decontaminated by an effective and validated method (e.g., use of an autoclave) preferably before leaving the containment barrier. If an autoclave is not convenient to areas where infectious materials and/or animals are housed or are manipulated, special practices should be developed for transport of infectious materials to designated alternate locations within the facility.	Additional specificity for animal waste disposal

Summary of Differences between current *NIH Guidelines* and Recommendations: Facilities Waste Handling

<i>NIH Guidelines (cont.)</i>	Enhancements for Mammalian- Transmissible HPAI H5N1	Rationale
When an animal covered by Appendix Q (large animals) containing recombinant DNA or a recombinant DNA-derived organism is euthanized or dies, the carcass shall be disposed of to avoid its use as food for human beings or animals, (i.e. incineration or alkaline hydrolysis/heat).	No enhancements recommended	Incineration is usually done for large animals

Overview of Biosafety Recommendations

- Facility/Airflow enhancements
- Primary Animal Containment
- Waste disposal
- Maintenance of antiviral susceptibility throughout research
- Laboratory worker personal protective devices and practices
- Occupational Health Measures

Current Section III-D-7-d: Antiviral Susceptibility and Containment

- **Current *NIH Guidelines* states that continued antiviral susceptibility is an important safeguard for experiments with 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968).**
- **If an influenza virus containing genes from one of these viruses is resistant to both classes of current antiviral agents, adamantanes and neuraminidase inhibitors, higher containment may be required based on the risk assessment considering transmissibility to humans, virulence, pandemic potential, and alternative antiviral agents if available.**

Current III-D-7-d: Antiviral Susceptibility

- Experiments designed to create resistance to neuraminidase inhibitors or other effective antiviral agents (including investigational antiviral agents being developed for influenza) would be subject to Section III-A-1 (Major Actions) and require RAC review and NIH Director approval unless such experiments require regulatory approval by another Federal agency, such as USDA
- In the latter case, NIH will defer to the Federal agency with regulatory authority

Section III-A-Experiments (Major Actions)

- **Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will be reviewed by the RAC and approved by the NIH Director.**

Generation of Antiviral Resistant Mammalian-Transmissible HPAI H5N1

- There are reports of circulating strains of non-mammalian-transmissible HPAI H5N1 that are resistant to oseltamivir
- However, generation of a mammalian-transmissible HPAI H5N1 that is resistant to neuraminidase inhibitors or effective antivirals will be considered a Major Action under the *NIH Guidelines* and require RAC review and NIH Director approval, unless the experiment is approved by a Federal agency having regulatory authority, e.g. USDA

Current Appendix G-II-C-5-a-(5)

Maintenance of Antiviral Susceptibility

- Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968) to antiviral agents shall be established by sequence analysis or suitable biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed.**

RAC BSWG Recommendations for **Additional Enhancements** for Mammalian- Transmissible HPAI H5N1

- **If it is discovered that as a result of genetic modification or serial passaging of a mammalian-transmissible HPAI H5N1 susceptibility to neuraminidase inhibitors or other effective antiviral agents is lost, then any research on this antiviral resistant virus should be stopped and research on that strain should only proceed after review by NIH or the appropriate Federal regulatory agency and under the conditions specified by that review.**

Overview of Biosafety Recommendations

- Facility/Airflow enhancements
- Primary animal containment
- Waste disposal
- Maintenance of countermeasure susceptibility throughout research
- Laboratory worker personal protective devices and practices
- Occupational health measures

Current Appendix G-II-5-a-(1) Enhanced Practices for Research with wild-type HPAI H5N1

- **Personal Protective Equipment (PPE) and Practices**
 - **Powered Air-purifying Respirator (PAPR)**
 - **Protective suit**
 - **Wrap-back disposable gown**
 - **Double gloving**
 - **Appropriate shoe coverings**
 - **Showers prior to exiting laboratory should be considered depending upon risk assessment of research activities. (Shower out capability may be required by USDA/APHIS for certain experiments with HPAI H5N1)**

RAC BSWG Recommendations for **Additional Enhancements** for Mammalian-Transmissible HPAI H5N1

- Use of protective sleeves over gown when working in a biosafety cabinet.
- Spray or wipe down of PPE with disinfectant that has activity against influenza virus prior to leaving containment
- Shower required prior to exiting the laboratory
- In order to promote adherence to proper practices, including proper removal of PPE, and reporting of any loss of containment or exposures, at least two individuals should be in the lab at all times when research is ongoing and during removal of PPE

RAC BSWG Recommendations for **Additional Enhancements for Mammalian-Transmissible HPAI H5N1**

- **Laboratory workers shall not have contact with susceptible avian species for a minimum of 5 days after last engaging in work with the virus**
 - **Susceptible species includes avian wildlife, pet birds, backyard poultry, fair birds, commercial poultry operations, and zoos.**

Current G-II-C-5-a-(4)

Avoiding Inadvertent Cross Contamination

No changes proposed

To avoid inadvertent cross contamination of 1918 H1N1, HPAI H5N1 or human H2N2 (1957-1968):

- **Containment facilities and practices appropriate for highest risk group virus shall be used at all times with lower risk group viruses, when studied in the same laboratory room.**
- **Tissue cultures with these viruses shall be conducted at separate times (temporal spacing) in the same room.**
- **Separate reagents shall be used to minimize risk of cross contamination.**
- **A laboratory worker shall not perform concurrent influenza virus experiments that carry the risk of unintended reassortment among 1918 H1N1, human H2N2 (1957-1968), HPAI H5N1 and other human influenza viruses.**

Current G-II-C-5-a-(4)

Avoiding Inadvertent Cross Contamination

No changes proposed

- Two or more laboratory workers shall not perform within the same work area simultaneous influenza virus experiments that carry the risk of unintended segment reassortment between 1918 H1N1, or HPAI H5N1, or human H2N2 (1957-1968) and other human influenza viruses.
- Between experiments good biosafety decontamination practices (e.g., surface and biosafety cabinet surface decontamination according to standard BL3 procedures) shall be used and there shall be a thirty minute wait period after decontamination before equipment is used for experiments with any other influenza A viruses.
- Between experiments, in addition to decontamination of the work area, clothing changes and PAPR disinfection shall be performed prior to handling a different influenza virus in the same work area. (Shower-out capability may be required by USDA/APHIS for certain experiments with HPAI H5N1).

Current G-II-C-5-a-(2): Training of Laboratory Workers

- **As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially in the proper use of respiratory equipment, such as PAPRs, and clothing changes is required.**

RAC BSWG Recommendations **for Additional Enhancements for Mammalian-** **Transmissible HPAI H5N1**

- **A document shall be developed by the Institution to be signed by laboratory workers**
- **This document shall include:**
 - **a statement that the laboratory worker understands and agrees to adhere to biosafety, biosecurity, and occupational health requirements**
 - **a statement that the laboratory worker will report any exposures or accidents, including those observed by the worker**

Overview of Biosafety Recommendations

- **Facility/Airflow enhancements**
- **Primary animal containment**
- **Waste handling**
- **Maintenance of countermeasure susceptibility throughout research**
- **Laboratory worker personal protective devices and practices**
- **Occupational health measures**

Current G-II-C-5-c: Occupational Health Plan

G-II-C-5-c: A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (e.g. local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan should include an incident reporting system and laboratory workers shall report all incidents.

Other language in *NIH Guidelines* regarding incident reporting:

G-II-C-5-a-(3): Reporting of all spills and accidents, even if relatively minor, is required as described in Appendix G-II-C-2-q

G-II-C-2-q: Spills and accidents which result in overt or potential exposures to [RG3] organisms containing recombinant DNA molecules are immediately reported to the Biological Safety Officer, Institutional Biosafety Committee, and NIH/OBA...Appropriate medical evaluation, surveillance, and treatment are provided and written records are maintained.

RAC BSWG Recommended Clarification

Revise G-II-C-5-c to clarify incident and add a time frame.

G-II-C-5-c: A detailed occupational health plan shall be developed in advance of working with these agents in consultation, as needed, with individuals with the appropriate clinical expertise. In addition, the appropriate public health authority shall be consulted (e.g. local public health officials) on the plan and a mock drill of this plan shall be undertaken periodically. The plan shall include a description of the incident reporting system in place for incidents, which includes any loss of containment, spills, accidents, or potential exposures. The plan must specify that all incidents must be reported immediately to the appropriate institutional authorities, and no later than 24 hours to the appropriate public health authorities (e.g., USDA, CDC, NIH, local and state health authorities).

Current G-II-C-5-c: Occupational Health Medical Cards

- **Appendix G-II-C-5-c-(1). Laboratory workers shall be provided with medical cards which include, at a minimum, the following information:**
 - **characterization of the influenza virus to which they have been potentially exposed**
 - **24-hour contact numbers for the principal investigator and institution's occupational health care provider(s).**

Current G-II-C-5-c: Occupational Health Vaccination

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall include:

(1) Unless there is a medical contraindication to vaccination (e.g. severe egg allergy) annual seasonal influenza vaccination as a prerequisite for research to reduce risk of influenza like illness requiring isolation and tests to rule out infection with experimental virus and possible co-infection with circulating influenza strains.

(2) Virus specific vaccination, if available, should be offered.

RAC BSWG Recommendations **for *Additional Enhancements* for Mammalian- Transmissible HPAI H5N1**

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall also include:

- **Collection of baseline serum samples;**
- **For research with HPAI H5N1 that is mammalian-transmissible by respiratory droplet, if a licensed virus-specific vaccine is available and there are no medical contraindications, it should be given to all laboratory workers, and if given, a post vaccination serum sample should be collected, assessed for immune response and stored.**

Current G-II-C-5-c: Occupational Health Plan – Potential Exposures

Appendix G-II-C-5-c-(2). A detailed occupational health plan shall include:

- (3) Reporting of all respiratory symptoms and/or fever (i.e. influenza-like illnesses).**
- (4) 24-hour access to a medical facility that is prepared to implement appropriate respiratory isolation to prevent transmission and is able to provide appropriate antiviral agents. Real-time reverse transcription-polymerase chain reaction (RT-PCR) procedures should be used to discriminate these viruses from currently circulating human influenza viruses.**

Current G-II-C-5-c: Occupational Health Plan – Potential Exposures

Appendix G-II-C-5-c-(3). In preparing to perform research with 1918 H1N1, human H2N2 (1957-1968), or HPAI H5N1, principal investigators should develop a clear plan specifying:

- who will be contacted in the event of a potential exposure (during and after work hours) to conduct a risk assessment and make decisions as to the required response, including the need for and extent of isolation of the exposed worker.**
- After any kind of potential exposure, a rapid risk assessment shall be performed by the principal investigator, health and biosafety officials and subsequent actions should depend on the appraised level of risk of respiratory infection for the individual and potential for transmission to others.**

Current G-II-C-5-c: Occupational Health Plan – Potential Exposures

- **Appendix G-II-C-5-c-(3). Laboratory workers shall be informed in advance that in the case of a known laboratory exposure to highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage with high risk for infection, they should be prepared to self isolate (for example at home) until infection can be ruled out by testing (e.g., negative RT-PCR for HPAI H5N1) of appropriately timed specimens. The action taken for other types of exposures should be based on the risk assessment. In addition, based on the risk assessment: (1) treatment with appropriate antiviral agents shall be initiated, and (2) the appropriate public health authorities shall be notified.**

RAC BSWG Recommendations for **Additional Enhancements** for Mammalian- Transmissible HPAI H5N1

- For research with HPAI H5N1 virus that is mammalian-transmissible by respiratory droplet, isolation required in a predetermined facility as for 1918 H1N1 research:
 - A laboratory worker performing research with mammalian-transmissible by respiratory droplet HPAI H5N1 shall be informed in advance that, in the case of a known laboratory exposure with a high risk for infection, e.g., involving the upper or lower respiratory tract or mucous membranes, the **laboratory worker will need to be isolated in a predetermined facility, rather than home isolation**, until infection can be ruled out by appropriate testing (e.g. negative RT-PCR for HPAI H5N1) of appropriately times specimens.

Current G-II-C-5-c:Occupational Health Influenza-like illness

Appendix G-II-C-5-c-(4). Influenza-like illness.

- If a laboratory worker, who has recent exposure (in the previous ten days) to influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or with animals exposed to such viruses, demonstrates symptoms and/or signs of influenza infection (e.g., fever/chills, cough, myalgias, headache), then the lab worker shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan.**
- The laboratory worker shall be transported to a healthcare facility that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus.**
- The appropriate public health authorities shall be informed whenever a suspected case is isolated.**

RAC BSWG Recommended Clarification

Appendix G-II-C-5-c-(4). Influenza-like illness.

- If a laboratory worker **has entered** (in the previous ten days) a laboratory conducting research with influenza viruses containing the human H2N2 HA gene, or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or housing animals exposed to such viruses, and the laboratory worker demonstrates symptoms and/or signs of influenza infection (e.g., fever/chills, cough, myalgias, headache), then the lab worker shall report by phone to the supervisor/principal investigator and other individuals identified in the occupational health plan.
- The laboratory worker shall be transported to a healthcare facility that can provide adequate respiratory isolation, appropriate medical therapy, and testing to determine whether the infection is due to a recombinant influenza virus.
- The appropriate public health authorities shall be informed whenever a suspected case is isolated.

Availability of Antiviral Medications

- **Appendix G-II-C-5-c-(6). Antiviral agents for post-exposure prophylaxis shall be provided only after medical evaluation. Home supplies shall not be provided in advance for research with 1918 H1N1 or influenza viruses containing the HA gene from human H2N2.**
- **Home supplies of antivirals shall not be provided for research with mammalian transmissible HPAI H5N1**

Summary of Additions to Biosafety Level Enhanced for Mammalian Transmissible HPAI H5N1

Current <i>NIH Guidelines</i> (BL3 – no specific enhancement for HPAI H5N1)	Additional Enhancements for Mammalian- Transmissible HPAI H5N1
FACILITIES AND AIR HANDLING	
Ducted exhaust air ventilation system. Exhaust air is discharged to outside without being filtered or treated. (Appendix G-II-C-4-i.)	Mandatory HEPA filtration of exhaust air with sealed ductwork system from containment barrier to filter
Single pass of air, may not be recirculated to other parts of building.	Air handling shall be designed such that under failure conditions the airflow will not be reversed. Periodic validation shall be performed.
Back up power not required	Back-up power shall be available for critical controls and instrumentation necessary to maintain containment

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1 (2)

Current *NIH Guidelines* (BL3 – no specific enhancement for HPAI H5N1)

Additional Enhancements for Mammalian -Transmissible HPAI H5N1

Waste Disposal

All waste from laboratories and animal rooms are appropriately decontaminated before disposal. An autoclave for decontaminating laboratory wastes is available preferably within the laboratory.

Liquid effluents should be chemically disinfected or heat treated, or collected and processed in a central effluent decontamination system. Decontamination of shower and toilet effluents is not a requirement, provided appropriate practices and procedures are in place for primary containment.

Animal tissues, carcasses, and bedding originating from the animal room must be decontaminated by an effective and validated method (e.g., use of an autoclave) preferably before leaving the containment barrier

If waste must be transported, special practices should be developed for transport of infectious materials to designated alternate location/s within the facility

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1 (3)

Current *NIH Guidelines*

Additional Enhancements for Mammalian- Transmissible HPAI H5N1

Antiviral Susceptibility

If an influenza virus containing genes from one of these viruses is resistant to both classes of current antiviral agents, adamantanes and neuraminidase inhibitors, higher containment may be required based on the risk assessment considering transmissibility to humans, virulence, pandemic potential, alternative antiviral agents if available.

Experiments designed to create resistance to neuraminidase inhibitors or other effective antiviral agents (including investigational antiviral agents being developed for influenza) would be subject to Section III-A-1 (Major Actions) and require RAC review and NIH Director approval unless such experiments are approved by Federal agency with regulatory authority, such as USDA

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1 (4)

Current <i>NIH Guidelines</i>	Additional Enhancements for Mammalian- Transmissible HPAI H5N1
Antiviral Susceptibility and maintenance of antigenicity	
<p>Continued susceptibility of the reassortant influenza viruses containing genes and/or segments from 1918 H1N1, HPAI H5N1, and human H2N2 (1957-1968) to antiviral agents shall be established by sequence analysis or suitable biological assays. After manipulation of genes that influence sensitivity to antiviral agents, susceptibility to these agents shall be reconfirmed.</p>	<p>If it is discovered that as a result of genetic modification or serial passaging of a mammalian transmissible HPAI H5N1 susceptibility to neuraminidase inhibitors or other effective antiviral agents is lost, then any research on this antiviral resistant virus should be stopped and research on that strain should only proceed after review by NIH or the appropriate Federal regulatory agency and under the conditions specified by that review.</p>

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1(5)

Current <i>NIH Guidelines</i>	Additional Enhancements for Mammalian -Transmissible HPAI H5N1
Laboratory worker personal protective devices and practices	
<ul style="list-style-type: none">•Powered Air-purifying Respirator (PAPR)•Protective suit•Wrap-back disposable gown•Double gloving•Appropriate shoe coverings•Showers prior to exiting recommended but not required	<ul style="list-style-type: none">•Protective sleeves over gown when working in a biosafety cabinet.•Spray or wipe down of PPE with a disinfectant with activity against influenza virus (e.g. 70 % ETOH) prior to leaving containment•Shower required•In order to promote adherence to proper practices, including proper removal of PPE, and reporting of any loss of containment or exposures, at least two individuals should be in the lab at all times when research is ongoing and during removal of PPE

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1(6)

Current <i>NIH Guidelines</i>	Additional Enhancements for Mammalian -Transmissible HPAI H5N1
Laboratory worker personal protective devices and practices: Training	
As proper training of laboratory workers is an essential component of biosafety, retraining and periodic reassessments (at least annually) in BL3 enhanced practices, especially in the proper use of respiratory equipment, such as PAPRs, and clothing changes is required.	By signing this document the laboratory worker acknowledges their understanding of and intent to adhere to biosafety, biosecurity, and occupational health requirements This document shall include a statement that the laboratory worker agrees to report any exposures or accidents, including those observed by the laboratory worker

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1(7)

Current <i>NIH Guidelines</i>	Additional Enhancements for Mammalian -Transmissible HPAI H5N1
Occupational Health	
<p>Seasonal flu vaccine is required unless medically contraindicated</p> <p>Influenza strain specific vaccine is recommended if available</p>	<p>Baseline serum samples should be stored for all laboratory workers</p> <p>For research with HPAI H5N1 that is mammalian-transmissible by respiratory droplet, if a licensed virus-specific vaccine is available and there are no medical contraindications, it should be taken by all laboratory workers, and if given, a post vaccination serum sample should be collected, assessed for immune response and stored.</p>
	<p>Researchers shall not have contact with susceptible avian species for a minimum of five days after engaging in work with the virus</p>

Summary of Additions to Biosafety Level 3 Enhanced for Mammalian Transmissible HPAI H5N1(8)

Current <i>NIH Guidelines</i>	Additional Enhancements for Mammalian -Transmissible HPAI H5N1
Occupational Health	
An occupational health plan is in effect that has provisions for reporting of incidents, monitoring for influenza-like illness, and isolation of laboratory workers with exposure to HPAI H5N1 virus that carries a high risk of exposure	High risk exposures to mammalian transmissible HPAI H5N1 require isolation outside of the community as is done for 1918 H1N1 Antivirals for exposures shall only be provided after medical evaluation, home supplies shall not be given

