

DHH OBA Notice of changes to the NIH Guidelines (*Federal Register* 74:48275-48280, 22Sep09).
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Section III–D–7.

Experiments Involving Influenza Viruses

Experiments with influenza viruses generated by recombinant methods (e.g., generation by reverse genetics of chimeric viruses with reassorted segments, introduction of specific mutations) shall be conducted at the biosafety level containment corresponding to the risk group of the virus that was the source of the majority of segments in the recombinant virus (e.g., experiments with viruses containing a majority of segments from a RG3 virus shall be conducted at BL3). Experiments with influenza viruses containing genes or segments from 1918–1919 H1N1 (1918 H1N1), human H2N2 (1957–1968) and highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1) shall be conducted at BL3 enhanced containment (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses) unless indicated below.”

Section III–D–7–a.

Human H2N2 (1957–1968).

Experiments with influenza viruses containing the H2 hemagglutinin (HA) segment shall be conducted at BL3 enhanced (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses). Experiments with the H2 HA gene in cold-adapted, live attenuated vaccine strains (e.g., A/Ann Arbor/6/60 H2N2) may be conducted at BL2 containment provided segments with mutations conferring temperature sensitivity and attenuation are not altered in the recombinant virus. Experiments with Risk Group 2 influenza viruses containing genes from human H2N2 (1957–1968) other than the HA gene can be worked on at BL2.

Section III–D–7–b.

Highly Pathogenic Avian Influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1).

Experiments involving influenza viruses containing a majority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced containment, (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses). Experiments involving influenza viruses containing a minority of genes and/or segments from a HPAI H5N1 influenza virus shall be conducted at BL3 enhanced unless a risk assessment performed by the IBC determines that they can be conducted safely at biosafety level 2 and after they have been excluded pursuant to 9 CFR 121.3(e).

Section III–D–7–c.

1918 H1N1.

Experiments involving influenza viruses containing any gene or segment from 1918 H1N1 shall be conducted at BL3 enhanced containment (see Appendix G–II–C–5, Biosafety Level 3 Enhanced for Research Involving Risk Group 3 Influenza Viruses).

Section III–D–7–d.

Antiviral Susceptibility and Containment.

The availability of antiviral drugs as preventive and therapeutic measures 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, alternative antiviral

agents if available, etc. Experiments with 1918 H1N1, human H2N2 (1957–1968) or HPAI H5N1 that are 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. As per Section I–A–1 of the NIH Guidelines, if the agent is a Select Agent, the NIH will defer to the appropriate Federal agency (HHS or USDA Select Agent Divisions) on such experiments.

Appendix B.

Classification of Human Etiologic Agents on the Basis of Hazard

Orthomyxoviruses

—Influenza viruses types A, B, and C (except those listed in Appendix B–III–D (RG3)).

—Tick-borne orthomyxoviruses. The following is added to Appendix B–III–D. Risk Group 3 (RG3)—

Viruses and Prions

—Influenza viruses 1918–1919 H1N1 (1918 H1N1), human H2N2 (1957–1968), and highly pathogenic avian influenza H5N1 strains within the Goose/Guangdong/96-like H5 lineage (HPAI H5N1).

Appendix G–II–C–5–a.

Containment, Practices, and Training for Research with Risk Group 3 Influenza Viruses (BL3 Enhanced)

Appendix G–II–C–5–a–(1).

In addition to standard BL3 practices, the following additional personal protective equipment and practices shall be used:

(1) Powered Air-purifying Respirators (PAPR) are worn.

(2) Street clothes are changed to protective suit (e.g., wrap-back disposable gown, olefin protective suit).

(3) Double gloves are worn.

(4) Appropriate shoe coverings are worn (e.g., double disposable shoe coverings, single disposable shoe coverings if worn with footwear dedicated to BL3 enhanced laboratory use, or impervious boots or shoes of rubber or other suitable material that can be decontaminated).

(5) Showers prior to exiting the laboratory should be considered depending on risk assessment of research activities.

Appendix G–II–C–5–a–(2).

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

Appendix 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.

Appendix G–II–C–5–a–(4).

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

(1) 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.

(2) Tissue cultures with these viruses shall be conducted at separate times (temporal spacing) in the same room.

(3) Separate reagents shall be used to minimize risk of cross contamination.

(4) 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.

(5) 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.

(6) 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.

(7) 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.)

Appendix G–II–C–5–a–(5).

Continued susceptibility of the reassortants 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.

Appendix G–II–C–5–b.

Containment for Animal Research Guidance provided in Appendix G–II–C and Appendix Q–II–C is applicable with the following emphasis on standard BL3 or BL3–N containment or additional enhancements.

Appendix 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 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.

Appendix G–II–C–5–b–(2).

Large animals such as non-human primates shall be housed in primary barrier environments according to BL3–N containment requirements (see Section Q–II–c).

Appendix G–II–C–5–b–(3).

Specialized training and proven competency in all assigned practices and procedures shall be required for laboratory staff, including staff involved in animal care.

Appendix G–II–C–5–b–(4).

For HPAI H5N1 research, the NIH Guidelines defer to USDA/APHIS recommendations for biocontainment practices for loose housed animals.

Appendix G–II–C–5–c.

Occupational Health. 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.

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, and 24-hour contact numbers for the principal investigator and institution's occupational health care provider(s).

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 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;
- (3) Reporting of all respiratory symptoms and/or fever (i.e. influenza like illnesses); and
- (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. For exposures to viruses containing genes from 1918 H1N1 or the HA gene from human H2N2 (1957–1968), specimens shall be sent to the CDC for testing (RT–PCR and confirmatory sequencing).

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. A laboratory worker performing research with either an influenza virus containing the HA gene from human H2N2 or an influenza virus containing genes and/or segments from 1918 H1N1, 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 testing (e.g., negative RT–PCR for 1918 H1N1 or human H2N2 (1957–1968)) of appropriately timed specimens. 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.

Appendix G–II–C–5–c–(4).

Influenzalike illness. If a laboratory worker, who had recent exposure (within ten days) to influenza viruses containing the human H2N2 HA gene or any gene from the 1918 H1N1 or HPAI H5N1 viruses, or to 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.

Appendix G-II-C-5-c-(5).

For 1918 H1N1 research, the use of antiviral agents (e.g., oseltamivir) for preexposure prophylaxis shall be discussed with laboratory workers in advance including a discussion of the data on the safety of long term exposure to these agents and their ability to reduce the risk of clinical disease and the limits of the data regarding protection of close contacts and the community.

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.