Interim CDC-NIH Recommendation for Raising the Biosafety Level for Laboratory Work Involving Noncontemporary Human Influenza Viruses

Excerpted from the draft *Biosafety in Microbiological and Biomedical Laboratories, 5th edition*

The *Biosafety in Microbiological and Biomedical Laboratories (BMBL)* manual is a Department of Health and Human Services (DHHS) publication that provides guidelines for the safe handling of infectious agents in various laboratory settings. The BMBL is updated and published every 5 years as a collaborative project by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). The 5th edition of the BMBL is expected to be published in early 2006. This new edition will include an updated Agent Summary Statement for Influenza that contains revised recommendations for the safe handling of influenza viruses in the laboratory. These recommendations are advisory and are intended to provide a basis for individual laboratory risk assessment of the viruses and activities used within that laboratory.

The recommended biosafety level for work with various human and animal influenza viruses, including non-contemporary human influenza A viruses, can be found below in the Draft Agent Summary Statement for Influenza for the upcoming 5th edition of the CDC/NIH *Biosafety in Microbiological and Biomedical Laboratories*.

Draft Agent Summary Statement for Influenza

INTRODUCTION

Description

Influenza is an acute viral disease of the respiratory tract. The most common clinical manifestations are fever, headache, malaise, sore throat and cough. GI tract manifestations (nausea, vomiting and diarrhea) are rare but may accompany the respiratory phase in children. The two most important features of influenza are the epidemic nature of illness and the mortality that arises from pulmonary complications of the disease (Treanor, 2005).

The influenza viruses are enveloped RNA viruses belonging to the Orthomyxoviridae. There are three serotypes of influenza viruses, A, B and C. Influenza A is further classified into subtypes by the surface glycoproteins that possess either hemagglutinin (H) or neuraminidase (N) activity. Emergence of completely new subtypes (antigenic shift) occurs at irregular intervals with Type A viruses. New subtypes are responsible for pandemics and can result from reassortment of human and avian influenza virus genes. Antigenic changes within a type or subtype (antigenic drift) of A and B viruses are ongoing processes that are responsible for frequent epidemics and regional outbreaks and make the annual reformulation of influenza vaccine necessary.

Influenza viral infections, with different antigenic subtypes, occur naturally in swine, horses, mink, seals and in many domestic and wild avian species. Interspecies transmission and reassortment of influenza A viruses have been reported to occur among, humans and wild and domestic fowl. The human influenza viruses responsible for the 1918, 1957 and 1968 pandemics contained gene segments closely related to

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those of avian influenza viruses (APHA, 2000). Swine influenza has also been isolated in human outbreaks (Dowdle & Hattwick, 1977).

Control of influenza is a continuing human and veterinary public health concern.

Occupational Infections

Laboratory-associated infections have not been routinely documented in the literature, but informal accounts and published reports indicate that such infections are known to have occurred, particularly when new strains showing antigenic shift or drift are introduced into a laboratory for diagnostic/research purposes (Dowdle & Hattwick,1977). Occupationally-acquired, nosocomial infections are documented (Stott et. al. 2002, Horcajada et.al.,2003). Laboratory animal-associated infections have not been reported; however, there is possibility of human infection acquired from infected ferrets and vice versa.

Natural Modes of Infection

Airborne spread is the predominant mode of transmission especially in crowded, enclosed spaces. Transmission may also occur through direct contact since influenza viruses may persist for hours on surfaces particularly in the cold and under conditions of low humidity (APHA, 2000). The incubation period is from one to three days. Recommendations for treatment and prophylaxis of influenza are available. (CDC, 2004).

LABORATORY SAFETY

The agent may be present in respiratory tissues or secretions of humans and most infected animals and birds. In addition, the agent may be present in the intestines and cloacae of many infected avian species. Influenza viruses may be disseminated in multiple organs in some infected animal species. The primary laboratory hazard is inhalation of virus from aerosols generated by infecting animals or by aspirating, dispensing, mixing, centrifuging or otherwise manipulating virus-infected samples. In addition, laboratory infection can result from direct inoculation of mucus membranes through virus contaminated gloves following handling of tissues, feces or secretions from infected animals. Genetic manipulation has the potential for altering the host range, pathogenicity, and antigenic composition of influenza viruses. The potential for introducing influenza viruses with novel genetic composition into humans is unknown.

Containment Recommendations

Biosafety Level 2 facilities, practices and procedures are recommended for diagnostic, research and production activities utilizing contemporary, circulating human influenza strains (e.g., H1/H3/B) and low pathogenicity avian influenza (LPAI) strains (e.g., H1-4, H6, H8-16), and equine and swine influenza viruses. Animal Biosafety Level 2 is appropriate for work with these viruses in animal models. All avian and swine influenza viruses require an APHIS permit. Based on economic ramifications and source of the virus, LPAI H5 and H7 and swine influenza viruses may have additional APHIS permit-driven containment requirements and personnel practices and/or restrictions.

Non-contemporary human influenza (H2N2) strains

Non-contemporary, wild-type human influenza (H2N2) strains should be handled with increased caution. Important considerations in working with these strains are the number of years since an antigenically related virus last circulated and the potential for presence of a susceptible population. Biosafety Level 3

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and Animal Biosafety Level 3 practices, procedures and facilities are recommended with rigorous adherence to additional respiratory protection and clothing change protocols. Negative pressure, HEPA-filtered respirators or positive air-purifying respirators (PAPRs) are recommended for use. Cold-adapted, live attenuated H2N2 vaccine strains may continue to be worked with at BSL-2.

1918 influenza strain

Any research involving reverse genetics of the 1918 influenza strain should proceed with *extreme* caution. The risk to laboratory workers is unknown at the present time but the pandemic potential is thought to be significant. Until further risk assessment data are available, the following practices and conditions are recommended for manipulation of reconstructed 1918 influenza viruses and laboratory animals infected with the viruses. These practices and procedures are considered minimum standards for work with the fully reconstructed virus.

- Biosafety Level 3 and Animal Biosafety Level 3 practices, procedures and facilities
- Large laboratory animals such as nonhuman primates should be housed in primary barrier systems in ABSL-3
- Rigorous adherence to additional respiratory protection and clothing change protocols
- Use of negative pressure, HEPA-filtered respirators or positive air-purifying respirators (PAPRs)
- Use of HEPA filtration for treatment of exhaust air
- Amendment of personnel practices to include personal showers prior to exiting the laboratory.

Highly pathogenic avian influenza (HPAI)

Manipulating highly pathogenic avian influenza (HPAI) viruses in biomedical research laboratories requires similar caution because some strains may pose increased risk to laboratory workers and have significant agricultural and economic implications. Biosafety Level 3 and Animal Biosafety Level 3 practices, procedures and facilities are recommended along with clothing change and personal showering protocols. Loose-housed animals infected with HPAI strains must be contained within BSL-3 (Ag) facilities. Negative pressure, HEPA-filtered respirators or positive air-purifying respirators are recommended for HPAI viruses with potential to infect humans. The HPAI are agricultural Select Agents requiring registration of personnel and facilities with the lead agency for the institution (CDC or USDA-APHIS). An APHIS permit is also required. Additional containment requirements and personnel practices and/or restrictions may be added as conditions of the permit.

Other influenza recombinant or reassortant viruses

When considering the biocontainment level and attendant practices and procedures for work with other influenza recombinant or reassortant viruses the local Institutional Biosafety Committee should consider but not limit consideration to the following in the conduct of protocol-driven risk assessment. If adequate risk assessment data are not available, a more cautious approach utilizing elevated biocontainment levels and practices is warranted.

- The gene constellation used
- Clear evidence of reduced virus replication in the respiratory tract of appropriate animal models, compared with the level of replication of the wild-type parent virus from which it was derived
- Evidence of clonal purity and phenotypic stability
- The number of years since a virus that was antigenically related to the donor of the hemagglutinin and neuraminidase genes last circulated.

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There may be specific requirements regarding the setting of containment levels if your institution is subject to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

SPECIAL ISSUES

Occupational Health Considerations

Institutions performing work with HPAI and avian viruses that have infected humans; non-contemporary wild-type human influenza strains, including recombinants and reassortants; and viruses created by reverse genetics of the 1918 pandemic strain should develop and implement a specific medical surveillance and response plan. At the minimum these plans should 1) require storage of baseline serum samples from individuals working with these influenza strains; 2) strongly recommend annual vaccination with the currently licensed influenza vaccine for such individuals; 3) provide employee counseling regarding disease symptoms including fever, conjunctivitis and respiratory symptoms; 4) establish a protocol for monitoring personnel for these symptoms; and 5) establish a clear medical protocol for responding to suspected laboratory-acquired infections. Antiviral drugs (e.g., oseltamivir, amantadine, rimantadine, zanamivir) should be available for treatment and prophylaxis, as necessary (CDC). It is recommended that the sensitivities of the virus being studied to the antivirals be ascertained. All personnel should be enrolled in an appropriately constituted respiratory protection program.

Influenza viruses may require USDA and/or USPHS import permits depending on the host range and pathogenicity of the virus in question.

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or call CDC at 800-CDC-INFO (English and Spanish) or 888-232-6348 (TTY).