

Highly Pathogenic Avian Influenza (HPAI) Facilities

The potential threat of avian flu and the need for appropriate facilities to work with strains of HPAI raise design issues of protection and timely development.

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We, like everyone else, have become increasingly concerned about the potential threat of an influenza pandemic over the next few years and the impact it could have on the world's health and economy. There seems to be a perception of difficulty in the design of appropriate laboratory scale and small animal facilities for work with HPAI caused by the lack of shared knowledge available on the real design issues related to containment. There is also a wide variety of responses in facilities that are currently working with various strains of HPAI. We have been working with CDC, NIH, the British Government, and others on new HPAI facilities and have been reviewing HPAI facilities in the U.S. and Asia. We find that there is not a great deal of consensus on what to do related to design issues, particularly the enhancements to BSL-3 (or ABSL-3) required for environmental protection. We felt that it would be important to share lessons learned from these experiences to assist the scientific and laboratory design community to get these facilities up and running as quickly as possible. In addition to facility development and operations, appropriate security programs must also be implemented.

It is important to note that "one size does not fit all" in biocontainment and that the information provided does not substitute for a risk assessment of the work to be undertaken and the specific facility requirements required to mitigate the risk. In particular, this should be undertaken in light of any local regulations regarding biosecurity and biocontainment. In addition, this column is focusing on HPAI facilities; requirements may be more stringent if other highly pathogenic influenzas such as the 1918 influenza virus construct are utilized. It must be clearly noted that in working with an easily transmitted, high consequence agent such as HPAI, careful attention to appropriate biosafety practices and procedures is critical, no matter how well the facility is designed and operated.

The impetus for this discussion was the ambiguity of when, where, and how to apply the regulations that govern the design of these types of spaces, particularly those designed to work with small animals housed in primary containment. Recognizing this lack of clarity in the design guidelines, the CDC is in the process of developing guidelines to address this issue. These standards will be incorporated into the 5th edition of *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) publication, which is due to be available to the general public in the spring of 2006. As

this column is not intended to replace the guidance from BMBL, it would be wise to consult this document, when available, for additional guidance on facility design criteria and appropriate procedures for HPAI laboratories.

In the U.S., the Animal and Plant Health Inspection Service (APHIS), a department of the United States Department of Agriculture (USDA), is the governing body which regulates the transport and possession of pathogens having a potential to dramatically impact the country's plant and livestock resources, including HPAI. APHIS is also the governing body that establishes and enforces the requirements for the facilities that house HPAI. The Centers for Disease Control, through their select agent program, may be the inspecting agency in lieu of APHIS. Prior to construction planning on a facility for HPAI, the risk assessment and the containment strategy should be discussed with the agency assigned to review and inspect your facility.

One element of the APHIS guidelines that is clear is the requirement by the research institution to develop and implement a written biosafety plan commensurate with the risk of the select agent under study. This requirement is reiterated in the APHIS Federal Register dated the 18th of March, 2005. The APHIS Federal Register Rules and Regulations 7 CFR331/OCFR 121 states; "*The biosafety and containment procedures must be sufficient to contain the select agent or toxin (e.g. physical structure and features of the entity, and optional and procedural safeguards)*." The information presented below is intended to assist in developing a written biosafety plan and a rational design for the facility.

BSL-3 (Enhanced) High Consequence Facilities

Risk assessment is based upon a combination of two elements, "probability" and "consequence." "Probability" is related to the potential that a given agent may be released outside the primary containment barrier through aerosolization, or some other means; the term "consequence" relates to the negative results an agent would cause should there be an accidental release into the surrounding area. As the level of both elements increases, so too does the requirement to comply with the more stringent design guidelines. Primary containment barriers used in laboratory scale research and small animal holding facilities reduce the probability of a release and, therefore, the containment requirements. The higher the degree of certainty of primary containment, the

less stringent the secondary containment can be. This article will not focus on the basic issues in BSL-3 design (such as two doors in series, self-closing/locking doors, seamless floors, monolithic ceilings, and hand-washing sinks); rather, it will focus on the enhancements to be considered for these higher risk facilities.

Construction of the Containment Barrier

Most HPAI facilities in the U.S. are conventional construction as appropriate for the facility type (typically metal studs with gypsum board for laboratories and small animal holding areas with dry husbandry, or concrete masonry units for larger animal holding areas). The containment barriers are well sealed but are not of pressure decay tested construction. Sealing should be appropriate to allow gaseous decontamination. Doors are conventional doors with sufficient air gaps to allow directional inward airflow. Consider barometric dampers in the room walls to allow sufficient directional airflow as an alternative if door seals or drop bottoms are used to limit infiltration, provide a means to achieve a minimum differential pressure, and/or reduce areas for vermin to enter the facility.

Airflow in a BSL-3 (or ABSL-3) facility should be directed from the cleanest area, or area of least hazard potential, toward spaces of greatest hazard potential. We would recommend providing a minimum of 50 cubic feet per minute (CFM) of doorway infiltration as recommended in the USDA ARS biosafety design criteria as well as providing interlocks on the anteroom doors. Based on our current work, in addition to providing “directional airflow” as described in the BMBL, we’ve adjusted the HVAC systems to further enhance and minimize risk by setting room airflows and installing door seals to maintain pressure differentials between .03 and .05 inches of water column at the doors. With a 4-foot wide door, this could drive the transfer airflow rate at the door to between 100 and 150 cfm.

Personnel Showers

Gown-in, shower-out protocols have been utilized at all HPAI facilities we have encountered. These personnel shower facilities are utilized as a means for workers within the lab and animal holding areas to remove any hazardous material prior to donning street clothes. The showers should be designed so that they must be passed through upon exit from the facility and should be located between an inner, potentially contaminated changing area and an outer clean changing area to eliminate the possibility of cross contamination from dirty to clean clothing. Under this condition, the containment barrier should be considered at the exit opening of the shower stall. Most work with HPAI requires respiratory protection equipment such as powered air purified respirators (PAPRs). Space for storage, battery charging, and decontamination of this equipment should be provided within this area. Standard operating procedures for the decontamination of the PAPR units must be thoroughly worked out and reviewed prior to determination of appropriate location for change-out, maintenance, battery charge, storage, and disposal of the PAPR unit.

HEPA Filtration at the Containment Barrier

HEPA filtration is mandatory and should be provided on the

exhaust system with sealed ductwork from the containment barrier to the filter. The filter units must be fabricated to permit the in-place scan testing of the filters after installation, and to permit filter decontamination before removal. To reduce the length of contaminated ductwork, HEPA filters should be located as near as possible to the containment barrier. Bioseal dampers should be provided in the exhaust ductwork to facilitate decontamination.

Supply HEPA filtration has been a norm in USDA BSL-3 facilities; however, some large HPAI facilities do not have supply HEPA filtration. Supply HEPA filtration does not have a significant impact on containment if directional inward airflow through the entry doors is maintained. There are three possible conditions: 1) Normal operation with directional inward airflow. 2) Exhaust system failure accompanied by supply system shutdown, so that the room becomes static. 3) Supply system failure with continuation of exhaust allowing some inward airflow through the supply system. During this scenario, we suggest re-setting the exhaust system airflow to a reduced quantity in order to prevent excessive negative pressurization of the containment lab. Should a momentary reversal of flow occur in any of the cases, the air will flow out through the air gaps under the doors making supply HEPA filtration ineffective.

Supply and exhaust air handling systems must be interlocked such that the supply air system would shut down in the event of an exhaust system failure; this will prevent reversal of inward directional airflow should the containment space become positively pressurized during an exhaust system failure. This reversal in air flow would occur through doorways and other unsealed openings, possibly contaminating adjacent spaces.

While independent air supply and exhaust systems are ideal for HPAI facilities, some large facilities experienced with this work have systems that are isolatable from other areas, but are not independent. When a new facility is being considered, independent systems for BSL-3 areas are recommended. In addition, while laboratories are permitted to be shut down in the event of a systems failure, animal facilities, at a minimum, must remain operational at a reduced level as required by the *Guide for the Care and Use of Laboratory Animals*. N+1 capacity or 100% redundant supply and exhaust systems are strongly recommended for containment laboratories, and especially for animal welfare. This could be handled in several ways, such as providing multiple fans in a single air handling unit or by utilizing multiple air handling units tied to a manifolded distribution system. In either case, supply and exhaust air fans should be connected to an emergency power network, with consideration for UPS power to prevent any possible chance of pressurization loss during a transfer from normal to emergency power, and vice versa. Note that this transfer of power, and its effect on the laboratory, is a normal occurrence, as the emergency generator is required to be exercised, typically on a monthly basis.

Double Door Autoclave in Lab

Autoclaves serving HPAI laboratories and animal facilities should be of the pass-thru double door type, with the doors interlocked to provide protection against the passage of poten-

tially contaminated particulate matter through the chamber. A bioseal must be installed and maintained around the face of the unit at the containment barrier to seal the space. The best design is to position the main body of the autoclave outside the containment barrier to allow maintenance and repair personnel to work on the unit in a safe environment with unrestricted work conditions.

If effluent decontamination is warranted by the risk assessment, consider an autoclave with an integral effluent decontamination cycle. When biologically hazardous material is placed within the chamber of the autoclave during its initial loading, a potential exists to release particulate matter into the atmosphere of the chamber due to the operation of most steam sterilizers. At the beginning of the sterilization cycle, steam is introduced into the chamber. The potentially contaminated air, not yet sterilized, is purged from the chamber into the atmosphere or drain, unless aerosolized particulates are captured through filtration. During the purging process, the temperature inside the chamber increases, moisture in the un-sterilized air condenses on the interior face of the chamber walls. The condensation then flows from the chamber drain into the building's sanitary system or an effluent decontamination system, if one is provided. Many autoclave manufacturers offer effluent decontamination cycles that sterilize chamber air and waste water prior to their being released into the atmosphere and drain. Relatively new to the autoclave industry is the use of filter housings to trap the potentially infectious material prior to its release into the waste streams. Depending upon the make and model of the autoclave that will be available for sterilization, a thorough review of the various options must be completed to determine an appropriate process to ensure that the effluent from the autoclave chamber is not released into the municipal sanitary system without being adequately heat and pressure treated.

Effluent Decontamination

There is evidence of increasing environmental stability of recent strains of H5N1 HPAI. In July, a paper published by *Nature* indicated that the 2004 virus seems to have become more stable, surviving in the environment for six days at a temperature of 37°C, compared to two days for older strains. There is not a consistent opinion or practice in existing HPAI facilities on the issue of decontamination of liquid effluents coming from the facility, particularly waste water from the personnel showers. Systems sized to decontaminate showers are expensive and cumbersome to operate, particularly for smaller facilities. The need for effluent decontamination of shower waste water may be reduced or eliminated with effective primary containment. Some large facilities experienced in the handling of HPAI do not routinely utilize effluent decontamination systems. CDC select agent inspectors do not seem to be requiring them as a norm when appropriate primary containment systems and practices are in place.

Additional steps to reduce the need for these systems can be taken:

- Minimize or eliminate the effluent from the laboratory or animal holding areas or decontaminate the effluent at the source.
- Where liquid effluent cannot be avoided, such as from

hand washing sinks, consider sinks that collect the waste in autoclavable containers for daily decontamination, or use of hand washing products that do not require the use of water to rinse prior to exiting the laboratory or animal holding rooms.

- Liquid decontamination by chemical means is also an effective treatment before discharge to the sanitary sewer.

If decontamination treatment of shower effluent is deemed necessary, the cost for redundant (if animals are present and must be cared for) automated heat treatment systems to allow 6-10 showers a day will be on the order of \$1,000,000 - \$2,000,000. Effluent waste from personnel showers and toilets is permitted to be decontaminated under certain circumstances through the use of chemical disinfectants that are targeted specifically to the agent being studied; however, chemical tank systems can also be problematic and require large volumes of chemicals. These fully automated systems can be cost and operationally prohibitive in small facilities; therefore, an option may be to install large holding vessels or sump pits below a grating system in the floor of each shower stall. Prior to a worker entering the shower, he or she would release a pre-determined quantity of chemical disinfectant into the holding vessel either manually or through a reservoir and pump system. The waste water from the shower would ultimately drain into the vessel and mix with the disinfectant. The amount of flow from the worker's shower would be controlled by means of an automatic shut-off timer permitting only a pre-determined quantity of waste to accumulate in the holding system. Upon the completion of the worker's shower and a proven period of time, the contents of the vessel would be released into the sanitary system through a series of control valves. Because effluent is disinfected prior to being released into the sanitary system, it is not necessary to have visual access to drainage piping for purposes of monitoring. Depending upon the space available, this could be sized for several shower events.

Dunk Tanks and Pass-Thru Chambers

Dunk tanks and pass-thru chambers in BSL-3 and other high containment facilities are included for the convenience of those working in the rooms as a means to move samples and products through the lab that may be heat and steam sensitive. This option may not be applicable if no such items will be used in the lab or be transferred outside the lab to other BSL-3 environments.

Primary Containment

Laboratory scale work can be safely done in Class II Type A1 biological safety cabinets (BSCs). These BSCs discharge cabinet air back into the laboratory or animal procedure room through HEPA filters. Certification (by qualified personnel) of BSCs must be done when initially installed and at least annually thereafter. Any BSC that requires hard ducting to the building exhaust system has a potential built-in problem. Since these BSCs rely on the building exhaust system to function properly, any exhaust failure will compromise biocontainment and place workers and/or animals at risk of exposure to the agents being manipulated in the cabinet. If limited diagnostic work is anticipated, consider a small standard Class III BSC

for handling and manipulation of HPAI; however, use of a Class III BSC requires specific training and ongoing maintenance of the system.

Particular attention should be given to equipment or procedures that are likely to produce an aerosol of infectious particles. Such procedures (e.g., vortex mixing, tissue grinding, or homogenization) should be done inside a BSC. All centrifuges should be equipped with bioseal rotors or containment holders; exhaust vents found on larger centrifuges should have in-line HEPA filters. In-line HEPA filters should also be used to protect vacuum systems and piped-in gases. Special primary containment devices are available for cage dumping activities or to house larger aerosol-generating equipment.

Primary containment for animal use may be more difficult, considering the wide spectrum of animal species that may be used in influenza research activities (e.g., mice, ferrets, various bird species, and pigs). Some facilities hold animals in isolators with characteristics similar to Class III BSCs. These can be difficult for animal care and husbandry. Carefully consider these issues when selecting or designing an isolator. For rodents, there are new individually ventilated biocontainment caging systems available that provide positive containment and secure transport from the cage rack to the BSC for cage changing. Think of animal holding and husbandry as a system and, to minimize the potential for aerosols outside of primary containment, make your animal care system as much of a closed system as possible.

Special Practices

Each facility needs to conduct a specific risk assessment based on the nature of the work planned or anticipated and then develop appropriate risk management procedures. Necessary components of the biosafety program include having a biosafety officer, a biosafety committee, a site-specific biosafety manual, and focused training. Persons entering areas where work with HPAI viruses is conducted should receive seasonal influenza immunizations and, when available, applicable avian flu immunizations. They should wear full body protective single-use clothing, gloves, respirators (N95 or equivalent), and eye protection. For two weeks after leaving these facilities, they should be restricted from visiting farms or other locations housing pigs, horses, or birds. An occupational health program should include respirator fit-testing, having suitable antivirals available for employees, and medical surveillance.

Methods for Fast Facility Development

Obviously it is important to get these facilities in place as quickly as possible to allow research and development to progress. The following are suggestions to expedite the construction of your HPAI facility.

- Do not combine the HPAI facility with a large project unless the large project is well under construction. These projects by nature take significant time to complete and can experience delays that can put off occupancy. However, if you have a large project over half complete, consider adding the HPAI facility to the project to expedite completion.

- Minimize complexity wherever possible as it increases both the cost of the facility and the time required for completion.
- Minimize impacts that require significant modification of existing infrastructure.
- Use a “Design Build” approach with a contractor and A/E team experienced in BSL-3 facilities to allow overlap of the design and construction process.
- Use a “best value” approach selecting subcontractors based on their qualifications and experience as well as cost.
- Obtain approval for biocontainment and biosecurity plans from regulatory agencies as early as possible.
- Align expectations (see *Animal Lab News*, November/December 2005, pp. 50-56) on small facilities for additional detail.

We hope the above information allows you to complete your facility rapidly and successfully. Feel free to e-mail the authors if you have any questions or comments.

References:

- Richmond, Jonathan Y. and McKinney, Robert W., editors. *CDC/NIH Biosafety in Microbiological and Biomedical Laboratories*, May 1999.
- United States Department of Agriculture (Animal and Plant Health Inspection Service) 7 CFR Part 331 and 9 CFR Part 121, *Agricultural Bioterrorism Protection Act of 2002, Possession, Use and Transfer of Select Agents and Toxins, Final Rule*, March 2005.
- United States Department of Agriculture, Agricultural Research Service, *ARS Facilities Design Standards*, Publication 242 1M-ARS, July 2002.

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