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International Consultant Della-Porta Challenges BSL-3 and BSL-4 Standards

Provides Insight on Best Practices in Design, Operations, and Training

According to Tony Della-Porta, Ph.D., an independent biosecurity and biocontainment consultant based in Australia, recent SARS-Coronavirus infections within laboratories should dramatically underscore the need for safer operations, improved standards, and better staff training. The SARS virus is just one example of the many potentially deadly infectious agents handled by BSL-3 and BSL-4 laboratories.

Della-Porta led the World Health Organization (WHO)/CDC team that investigated the 2003 SARS laboratory infection in Singapore, and assisted with the WHO investigation of the 2004 SARS laboratory infection case in Taiwan.

The Singapore SARS incident occurred in August-September of 2003 involving a doctoral student working with the West Nile virus in a BSL-3 lab that also contained the SARS virus. Three days after working in the lab, the student developed a fever and symptoms consistent with SARS.

“In this case, the evidence strongly points to infection through laboratory contamination since the student did not have contact with any known SARS case or travel to any SARS affected areas,” says Della-Porta. “After reviewing the case it was discovered that the frozen specimen the student worked with tested positive for both West Nile and SARS.”

The investigators also documented a variety of shortcomings within the laboratory that most likely contributed to the incident. These included inadequate record-keeping procedures, totally inadequate training, a variety of structural problems including no magnahelic gauges to indicate the pressure differentials, and an overall lack of security.

In December-January 2004 another SARS laboratory contamination occurred, this time in Taiwan where a principal researcher in a military BSL-4 lab used 70 percent ethanol to decontaminate a spill in a Class III isolator chamber. The researcher opened the isolator to clean the spill, thereby exposing himself to the SARS virus, which had not been inactivated with the 70 percent ethanol. The following day he traveled to Singapore for several days. On return, he developed a fever and respiratory problems (which he believed was influenza), stayed at home for six days, and was then subsequently hospitalized with SARS.

This laboratory was also found to have violated many safety and record-keeping standards. For example, this researcher regularly worked long shifts (12 to 14 hours) usually alone and there was no timely procedure in place for reporting incidents. In addition, there was no record of him actually working in the laboratory since he had recently lost his building access card and was using a borrowed card on the date of the incident.

Della-Porta explains that the recommended procedure for decontamination of the isolation cabinets used in the Taiwan facility is the use of a hydrogen peroxide generator, which takes several hours. He adds that a short cut of 70 percent ethanol for 10 minutes is completely inadequate. In addition, there were inadequate standard operating procedures and Taiwan was without guidelines or regulations related to biological safety.

“This case is extremely indicative that Taiwan needs a legislative basis requiring stricter standards in biosafety labs,” says Della-Porta. “I feel that the standards should include a tracking system for importation and exportation of infectious agents to and from Taiwan.”

Improving U.S. Standards

Similarly, Della-Porta feels there are numerous problems within the U.S. regarding biosafety standards. Specifically, he views the CDC/NIH publication *Biosafety in Microbiological and Biomedical Laboratories* (BMBL) as merely a set of recommendations and guidelines, not a true standard since it contains no physical measurable tests for containment.

The BMBL, now in its fourth edition, was first issued by the CDC/NIH more than two decades ago. The publication outlines four categories or biosafety levels of laboratory operation pertaining to selected agents infectious to humans. Each level (BSL-1 through BSL-4) relates to the operations performed, the documented or suspected routes of transmission of the infectious agents, and the laboratory function or activity.

“Rather than merely defining the biosafety levels, I feel that all countries need to create a structure for laboratory certification and reporting on both structural integrity and operating procedures within BSL-3 and BSL-4 labs,” says Della-Porta. “Lab certifications could be renewed annually, and could monitor issues such as standard operating procedures, safety and emergency procedures, and recommended laboratory operations and maintenance. In the U.S., this is done to some extent when the CDC conducts audits of laboratories that handle Select Agents.”

Della-Porta adds that he believes self-monitoring by internal biological safety committees is sufficient for BSL-2 facilities since the risk from these agents is minimal.

Design and Operation of Level 3 & 4 Facilities

“When designing Level 3 and Level 4 facilities, it is essential to consider what viruses will be handled within the facility, the characteristics of the virus, and any potential routes of infection that can occur,” says Della-Porta. “This ensures that the proper barriers and safety equipment will protect lab personnel and the environment from exposure to potentially infectious agents.”

BSL-3 labs contain indigenous or exotic agents with a potential for transmission, which may cause serious and potentially lethal infection, and their release could have a serious community impact. Examples include *Mycobacterium tuberculosis*, SARS-Coronavirus, Japanese encephalitis, *Bacillus anthracisis*, and *Coxiella burnetii*. Primary hazards to personnel working with these agents relate to autoinoculation, ingestion, and exposure to infectious aerosols.

Special considerations for BSL-3 facilities include:

- The lab should be physically separated by double-doors from other areas.
- The lab should be able to operate continuously, even when workers are not present, in order to maintain negative air pressure regions within the facility.
- Air should be filtered through HEPA filters to minimize the release of infectious aerosols.
- All infectious work must be done in biosafety cabinets or other enclosed equipment, such as gas-tight aerosol generation chambers.
- Only a minimal amount of material should be kept in biosafety cabinets so that it does not interfere with proper airflow.
- Bunsen burners should never be used in biosafety cabinets.
- Rather than lab coats, workers should wear gowns that fasten at the back so they can easily slip out of the gowns if there is a spill.

BSL-4 labs also contain dangerous and exotic agents that pose a high individual risk of life-threatening disease. However there is usually no available vaccine or therapy for BSL-4 agents, and personnel are at high risk for exposure to infectious aerosols, mucous membrane or broken skin exposure to infectious droplets, and autoinoculation.

Special considerations for BSL-4 facilities include:

- The facility itself should be in a separate building or completely isolated.
- All work should be done in Class III biosafety cabinets or in fully contained suits using Class I or Class II BSC.
- Suits should be decontaminated with a chemical shower.
- Specialized HEPA filtered ventilation requirements and waste management systems should be used to prevent release of viable agents to the environment.
- The facility must be air tight and under negative air pressure to facilitate decontamination and containment of agents.

A Box within a Box

“Ideally, BSL labs should be designed using the principle I call a box within a box,” says Della-Porta. “This means that the BSL lab will be fully contained within the main building so that at least one of the lab walls is not an exterior building wall. This creates a

"shell" around the lab, allowing correct pressure differentials to be maintained thereby containing the risk of leaks."

Della-Porta explains that this configuration ensures that the highest risk areas are at the lowest possible pressure and prevents pathogens from escaping into the surrounding no-risk spaces. It also allows the pressure-controlled hollow exterior wall space to serve as the zero pressure reference point.

"It is a much safer alternative to trying to maintain pressure difference measured against outside air pressure," says Della-Porta. "It is critical that pressure differentials are sufficient to ensure that a reversal of pressures cannot occur and that an adequate differential is maintained even when the air lock is opened."

He feels that many laboratories in the U.S. have too small a pressure differential to ensure that no reversal occurs, especially since some standards require that the pressure be maintained at -50 pascals between areas and within $\pm$ 25 pascals when doors are opened.

Della-Porta and his team of consultants are currently applying this design principle at the University of Hong Kong, where they are working on the medical school's new Influenza Center. The facility is targeted for completion in 2004 and will include several BSL-3 labs, animal rooms, a flexible film isolator (Class III biological safety cabinet) room, and a decontamination chamber. The decontamination chamber is large enough to allow continuous operation, meaning equipment and materials can be moved in and out of the facility without having to close it down.

According to Della-Porta, the air pressure within the Influenza Center labs will be at -100 pascals. An airlock leading into the dirty corridor will drop down another 50 pascals. All animal rooms will have the air pressure kept at -250 pascals. The same is true for the decontamination chamber, which will have doors with rubber seals to seal in air during the decontamination process. There are magnehelic gauges outside laboratories to indicate the pressure within the rooms and these are replicated with meters on a panel outside the facility to enable checking before staff can enter the facility.

"Since the center is being designed to handle high-virulence influenza, it is imperative that it meets the most rigorous of safety standards," says Della-Porta. "Researchers will most likely study high-risk agents such as the SARS virus, as well as the bird flu virus, which is currently affecting China, Thailand, Vietnam, and several other countries. Bird flu has a mortality rate of nearly 60 percent."

Training and Security

"Having the proper personal protective equipment within a lab is important, but it is even more important to take the time to properly train staff in the equipment's use," says Della-Porta. He points to a lack of staff training as a leading cause of safety-related

incidents within labs and adds that labs should develop appropriate training standards that are competency based.

Similarly, Della-Porta points to a lack of security as another shortcoming among many BSL-3 and BSL-4 labs. He recommends a thorough evaluation of security issues and that the following actions be taken regarding lab security:

- Access to BSL-3 and BSL-4 labs should be properly documented and monitored.
- Minimal precautions include the use of personal access cards with photo ID or electronic keypads with a code that changes regularly.
- Higher risk labs should use biometric devices such as palm scanners or iris scanners, instead of keypads or keypads with a personal access card.
- Inventory records should be computerized and closely monitored.
- Prolonged, continuous work hours in the laboratory should be discouraged.
- An emergency response plan must be developed and staff trained to handle spills and laboratory incidents.

Della-Porta also points to the monitoring and control of high-risk organisms within BSL-3 and BSL-4 labs as another key security issue.

He feels that currently there are too many molecular biologists around the world allowed to handle high-risk agents who have had no training in infectious diseases. In addition, Della-Porta recommends that the occupational health component of incident reporting should be clearly defined for all labs working with infectious agents.

“Currently the U.S. is the only country that maintains a Select Agent list, but unfortunately I find the list somewhat excessive because it does not actually represent real risk,” says Della Porta. “There probably are only half a dozen high consequence pathogens and biological toxins that need to be properly controlled because they represent significant potential for terrorists to use, not the forty or so on the Select Agent list.

“The critical issues are related to proper training of staff and management, staff taking responsibility for safety and biocontainment (not leaving it to safety and engineering staff,) an openness in reporting incidents and discussing safety concerns, and seeing safety as a culture (the way to work) rather than as an imposed obligation. Unfortunately there are few labs that meet these requirements and I would expect to see further

incidents, infections, and possibly the release of agents into the community, as happened recently with SARS in Beijing."

Biography

Tony Della-Porta, Ph.D., worked for Australia's Commonwealth Scientific and Industrial Research Organization from 1972 to 2003 in the fields of virology, infectious disease of livestock, biocontainment, and biological safety. This included serving as program manager and deputy head of the animal health laboratory in Geelong, Victoria. In 2003, Dr. Della-Porta became an independent biosecurity and biocontainment consultant. In that capacity, he led the World Health Organization/CDC team that investigated the fall 2003 SARS laboratory infection in Singapore, and he assisted with the WHO investigation of the January 2004 SARS laboratory infection case in Taiwan. He has also advised the New Zealand Ministry of Health and Biosecurity on their needs for the next ten years, and is providing advice to Hong Kong University on the construction and operation of a biocontainment facility to handle high virulence influenza. He holds a doctorate in virology from Monash University and has published extensively on the subject of operating high-containment facilities.

This report is based on a presentation Dr. Della-Porta gave at the Tradeline *International Conference on Biocontainment Facilities* conference in April 2004.

For More Information

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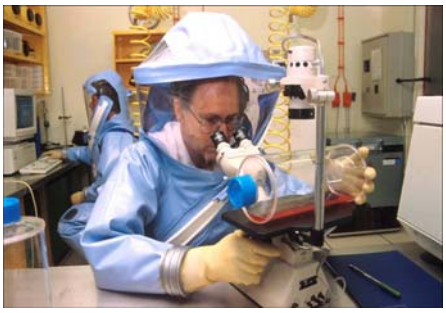
Resources

Biosafety in Microbiological and Biomedical Laboratories (4th Edition)
http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm.

Biosafety and SARS Incident in Singapore (September 2003) Report
http://www.wpro.who.int/sars/docs/pressreleases/mr_24092003.pdf

Select Agent List: http://www.nih.gov/od/ors/ds/pubs/appendxa,html



For BSL-4 labs, which require the highest safety standards, lab personnel should work in fully encapsulated suits. The positive pressure suit shown here is decontaminated using a chemical shower. (*Photo courtesy of Tony Della-Porta.*)

One lab at the University of Hong Kong's Influenza Center will include flexible film Class III biosafety cabinets, which are used extensively throughout Europe, Asia, and Australia but have not yet been adopted in the U.S. Like other isolation cabinets, flexible film cabinets operate under negative air pressure. However, unlike traditional cabinets, flexible film cabinets can easily be demounted and decontaminated giving researchers the flexibility to easily convert a BSL-3 lab into a laboratory that can handle level 4 agents (particularly for diagnostic and small scale work) and back again when necessary. (*Photo courtesy of Tony Della-Porta.*)