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FEATURES

Edward McSweegan is a microbiologist in Crofton, Md.

Article Links :

- Plum Island Is Not What Many People Think

Links to Other ASM Pages:

- Table of Contents
- ASM News Issues

Hot Times for Hot Labs

The maximum containment lab building boom means more research to understand dangerous pathogens but could also heighten risks

Edward McSweegan

The news media and the Internet provide daily reminders of continuing dangers from the microbial world. New infectious agents are discovered with alarming regularity, and other more familiar diseases--some of them thought to be swept into the dustbin of history--have returned with a vengeance. Consider a partial list of recent announcements: Hendra and Nipah viruses are discovered in Southeast Asia. Mysterious hemorrhagic fevers emerge in Russia. Prions stalk Europe. Marburg, Lassa, and Ebola viruses erupt in Africa. Hantavirus lurks in the Americas. Avian flu (H5N1) strikes Hong Kong. Rumors of graveyard sources of smallpox haunt South Africa.

Authorities have been quick to respond to these developments, and experts have relied on special containment laboratories to study these infectious agents in safety. Indeed, the emergence of so many new infectious diseases has helped ignite something of a building boom in high-tech containment laboratories worldwide.

Investigations of Potent Disease Agents Are Backlogged

The laboratory building boom ``is in response to the plain fact that existing facilities are hopelessly backlogged with specimens and the increasing importations of exotic hemorrhagic fever cases," according to virologist Jack Woodall, who commented on the situation in a ProMED Internet message early during 1999.

Not too long ago, reporters and institute press releases could confidently state that there were only four or ``a handful" of high-security labs in the world. But a spate of newly built labs and upgraded facilities has erased that casual assurance of exclusivity. In fact, so many new laboratories are being built or upgraded that it is difficult to get an accurate count of them.

One reason for the confusion over the exact number of high-containment labs may lie in the definition--or definitions. What constitutes a high-containment facility?

High-Containment Lab: What's in a Name?

BMBL Section VII

Laboratories that can safely handle deadly pathogens such as the smallpox and Ebola viruses are usually designated as ``BSL-4," an abbreviation for ``biosafety level 4," that refers to a maximum containment facility. Sometimes the designation is simplified to ``BL-4," an abbreviation for ``biological level 4." And there are still other designations, such as Australia's ``PC4," which stands for ``physical containment 4," and the term ``MCL," which is what officials at the National Institutes of Health in Bethesda, Md., call the new ``maximum containment laboratory"there, which was recently made available for studying multidrug-resistant *Mycobacterium tuberculosis*.

Although falling out of favor, there is additional terminology for describing such ``hot" labs. For instance, ``P4" is an older designation for the highest ``pathogen" or ``protection level" facility. It belongs to a set of four designated safety levels for working with a full range of microorganisms, starting at P1 with the relatively safe and extending at P4 to the highly dangerous bacterial and viral pathogens requiring maximum containment and the most extreme safety precautions.

Adding to the confusion is the range of design options used in building such facilities. For instance, the maximum containment labs may be self-contained suites accessed through airlocks and decontaminating showers by researchers wearing one-piece, positive-pressure suits with their own life-support systems. On the other hand, some BSL-4 labs may consist of little more than small glove box isolators in which researchers access samples through glove-enclosed portals. Film and television dramas like *Outbreak* and the *X-Files*, and best-selling books like *The Hot Zone*, have made the former high-tech suits and suites famous. The National Aeronautics and Space Administration (NASA), on the other hand, used the latter glove box systems to handle returned Moon rocks and the Mars meteorite ALH 84001.

Regardless of the alphanumeric designation or lab design, what sets BSL-4 facilities apart from other facilities where microorganisms are routinely handled is that they provide special means for dealing with those pathogens that cause life-threatening infections or have the potential to cause serious epidemics. The Office of Health and Safety at the Centers for

Disease Control and Prevention (CDC) maintains a list of such agents that require BSL-4 conditions and special training to work with them, including Ebola and Lassa viruses, Omsk hemorrhagic fever, Central European tick-borne encephalitis, and smallpox.

Exotic creatures require exotic cages. The growing menagerie of exotic microbes collected from world jungles and steppes has stretched the limits of the handful of labs that can--or will--work with such microorganisms. However, a number of new BSL-4 labs have been or are being built, and still others are in the planning stage (Table 1).

Hot Zones in the Cold Zones

Table 1

In June 1999, the Canadian government opened its first BSL-4 research facility (see p. 736). Located in Winnipeg, Manitoba, the Canadian Science Center for Human and Animal Health is a state-of-the-art complex for studying dangerous infectious diseases. The Center is unique among BSL-4 labs in being able to handle both human and animal diseases, infected livestock, and zoonotic agents that can jump from animals to people.

France has built a new BSL-4 lab over the top of the former Institut Pasteur building in Lyons. This ultramodern construct of metal, glass, and plastic rests on concrete stilts and will complement Europe's oldest BSL-4 lab at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany.

Farther to the north, Sweden is building its first BSL-4 lab at the Institute for Infection Control in Solna. The United Kingdom has two such labs under construction. One is at the National Institute for Medical Research in London, and the other is a Ministry of Defence facility at Porton Down called the Chemical and Biological Defence Establishment. When those new facilities are completed, U.K. researchers will have five hot labs capable of handling nature's most dangerous microbes.

The hot-lab building boom is also evident in the United States, where one new BSL-4 lab has opened and two more are under construction. The recently opened Maximum Containment Lab at NIH consists of a BSL-4 suite of three modular labs isolated from the rest of the suburban campus by its bunker-like architecture, airlocks, showers, autoclaves, and high-efficiency particulate air (HEPA) filters. The MCL replaces an older, cumbersome glove box facility. Unlike the larger labs at the CDC and the Department of Defense (DoD) facility in Frederick, Md., however, the MCL will handle only one pathogen at a time.

Right now, that microbe is a strain of multidrug-resistant *Mycobacterium tuberculosis*.

Elsewhere in the United States, the not-for-profit Southwest Foundation for Biomedical Research in San Antonio, Texas, is building a small BSL-4 facility; it is expected to be completed by the end of 1999. Like the MCL, the Southwest lab will be a full positive-pressure suit system to replace an older glove box arrangement. The University of Texas Medical Branch (UTMB) in Galveston is building a state-of-the-art maximum containment lab, too. The Galveston lab should be online by 2002. Both Texas labs will be studying viral diseases from the Americas, but UTMB may be looking even farther afield for exotic agents--maybe all the way to Mars.

NASA is planning a Mars sample-return mission for sometime around the year 2005. Any returned rock and soil samples from the Red Planet would, according to a recent NASA study, be ``quarantined and treated as potential biological hazards until they are proven safe." The nearest place to do that might be UTMB, only 45 miles from the Johnson Space Flight Center in Houston. Given the theoretical dangers of returning Martian microbes, and the proximity to a high-containment research facility, NASA and UTMB signed a December 1998 memorandum of understanding to collaborate on ``extraterrestrial biohazard containment strategies."

Meanwhile, many more earthly but dangerous infectious agents seem to be located in and around the tropical forests of the Southern Hemisphere. Yet, most of the BSL-4 labs built to study them are located in the Northern Hemisphere. This asymmetry is slowly being corrected. Down under, two high-security (PC4) labs in Australia played critical roles in identifying new and deadly diseases caused by the Hendra and Ross River viruses. A lonely outpost in Gabon (see Table) serves central Africa. But the whole of South America, which is home to several obscure but highly dangerous viruses such as Junin, Machupo, Sabia, and Guanarito, currently lacks a BSL-4 lab. However, a facility is being built in Botucatu, Brazil, according to ProMED moderator Jack Woodall.

Healthy Competition or a Race That Risks Serious Mishaps?

The new maximum containment labs will provide more opportunities for international collaboration and should help curtail epidemics by speeding up the detection and isolation of unusually pathogenic viruses, rickettsia, and bacteria. The special features of some of these labs should also enable users to conduct studies that complement the work being done at other

such sites.

Canada's maximum containment facility, for example, can handle large animals. Two other maximum containment facilities-one run by DoD in Frederick, Md. and the other run by the Bernhard Nocht Institute in Germany-can treat patients who are infected with unusual or particularly dangerous pathogens in strict isolation. The facility at CDC has at its disposal a vast collection of pathogens, antigens, and antisera for diagnostic and epidemiological studies.

Some experts, such as the director of the World Health Organization Emerging Diseases Program, say they support the current proliferation of such facilities because they will lead to increased research involving unusual pathogens. Other experts are not so sure. A few of them seem to be worried about a possible hot-lab race.

Where international prestige and technical prowess once were measured by missiles and spacecraft, the trend may now be toward genetic engineering and the risky bravado of the hot lab. It can be dangerous to race with things that can bite back. Some nations may lack the money to build and maintain complicated and expensive facilities needed to handle level 4 microorganisms. Equally as bad, they may lack the specially trained personnel needed to safely maintain the equipment and handle the sudden appearance of an unknown, life-threatening pathogen.

Global Standards Are Far from Uniform

OhASIS Biosafety Documents

In the United States, the CDC determines standards of design, construction, equipment, and safety procedures for BSL-4 labs (see page 741). Moreover, the shipping of infectious materials is regulated by the CDC, the Department of Transportation, and the International Air Transport Association Dangerous Goods Regulations. CDC and the U.S. Department of Agriculture also conduct inspections of laboratory facilities.

However, that level of regulation and oversight is not available worldwide. In addition, concerns about and, in some cases, an interest in biological warfare and bioterrorism may be driving some of the recent hot-lab construction. The once-unthinkable use of microbes as weapons has apparently become thinkable, and some countries may be upgrading and building labs as a defensive--and even offensive--measure.

A few national facilities seem to be intended for a more offensive

than defensive purpose in regard to biological warfare. Iraq had BSL-4 facilities purportedly for studying agricultural pathogens, but it was widely believed that the facilities were part of the Iraqi biological weapons program. Following the 1991 Persian Gulf War, weapons inspectors representing the United Nations destroyed the Iraqi facilities. Ken Alibek, a former director at Vector in Siberia who now works as a biowarfare defense consultant in the United States, has described how he and his colleagues in the former Soviet Union developed industrial-scale production of ``weaponized" microbes in his recently published book, *Biohazard.*

Meanwhile, several other nations, including Libya and North Korea, are assumed to have some type of BLS-4 facilities. These countries do not disclose much if anything about their facilities--even if they acknowledge their existence--so our current picture of worldwide BSL-4 labs must be considered incomplete.

Still, it is reassuring to know that many of the maximum containment labs being built or upgraded are also being publicly acknowledged. These carefully designed, well-built, and professionally staffed labs often serve as sentinel sites against the appearance of new and recurring infectious diseases. They will offer new opportunities for international collaborations and research training. Moreover, the vaccines and antiviral agents to protect against some of the most dangerous pathogens are likely to be developed in these new facilities. Positioned around the world, the men and women willing to staff these facilities will be the first responders against unexpected outbreaks of many of the most dangerous infectious diseases--natural or otherwise.

Plum Island Is Not What Many People Think

A Century of Science / Plum Island

Many people assume that the U.S. Department of Agriculture (USDA) Plum Island Animal Disease Center on a small island off Long Island is equipped with a BSL-4 maximum containment laboratory. Not so.

This research facility atop a flat piece of rock and sand, a mile and a half off the tip of Long Island, is steeped in Cold War mythology and is cloaked in rumors of biological warfare. New York gamblers catching the Orient Point ferry to Connecticut casinos pass close enough to see the guards and the signs warning boaters not to land. It even is the subject of a best-selling murder mystery.

The truth about this USDA facility is less dramatic, however.

Plum Island houses the foreign animal disease diagnostic laboratory (FADDL), which serves as a diagnostic and vaccine source for dangerous animal diseases, including the economically devastating foot-and-mouth disease. To keep dangerous pathogens from escaping, the FADDL relies on BSL-3 precautions, its isolated geography, and offshore breezes.

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Email: webmaster@asmusa.org