Appendix 4

Safety Record of Biocontainment Laboratories at BUMC and at NIAID's Intramural Facilities

The following Appendix consists of four parts.

Part 1 is entitled "Review of Laboratory Safety Record at Boston University Medical Center" and was prepared by BUMC staff.
Part 2, entitled "Biosafety at National Institute of Allergy and Infectious Diseases" was prepared by Karl M. Johnson, M.D. in October of 2003.
Part 3, entitled "Biosafety at BSL-4, More than 20 Years Experience at Three Major Facilities" was prepared by Karl M. Johnson, M.D. in October of 2003
Part 4, entitled "Biosafety Update:Short Review of BSL-3 and BSL-4 Viral Agent Laboratory Incidents Worldwide" was prepared by Karl M. Johnson, M.D. in August of 2004

Review of Laboratory Safety Record at Boston University Medical Center

The Boston University Medical Center (BUMC) is a combination of two large medical research organizations consisting of the Boston University's Medical Campus and the Boston Medical Center Corporation. BUMC comprises nearly 4 million square feet in 40 buildings and with more than over 8,000 employees. There are approximately 268 laboratories operating under dozens of Environmental Health and Safety (EHS) permits and licenses from federal, state, regional and local agencies.

As one of the nation's premier research institutions, safety is a top priority for the campus. The Office of Environmental Health and Safety's (OEHS) mission is to provide a safe and healthy work environment for all faculty, staff, and students, including complying with all local, state, and federal regulations.

The Medical Campus contains approximately 263 BSL-2 laboratories, and five BSL-3 laboratories that participate in various fields of research.

As part of the requirements to ensure worker safety, OEHS requires initial orientation, annual laboratory safety training for all research staff. This training includes the following topics: biosafety, chemical safety, regulatory requirements, spill response, waste, fire safety, disaster training, blood borne pathogen training, and security. Other training includes, but is not limited to, required annual BSL-3 laboratory training for staff working in these labs, shipping training, safety and infection control training. In 2003 and 2004 over 2,500 lab workers attended training.

All training also includes instructions on how to seek medical treatment if there is an employee injury, including who to notify and how to report an injury.

OEHS also conducts inspections of all labs to ensure compliance with all local, state, and federal regulations. In collaboration with Office of Facilities Management, OEHS works to conduct building repairs and maintenance, to ensure all building operations are functioning appropriately. In 2003 and 2004, over 280 lab inspections were conducted.

Researchers at BUMC work with a variety of BSL-2 agents, including bacteria, viruses, and toxins. The primary toxins that are studied at BUMC include Botulinum neurotoxin, Ricin, Tetrodotoxin, and Conotoxin. Bacterial agents include: *Chlamydia trachomatis*, *Borrelia burgdorferi, Brucella melitensis, Staphylococcal aureous,, Bacillus anthracis, Francisella tularensis,* and *Mycobacterium tuberculosis*. The main virus work at BUMC is on retroviruses, which include lentiviruses, and adenoviruses.

Previous and current BSL-3 research agents include the lentiretrovirus, HIV, along with the bacteria: *Brucella melitensis, Francisella tularensis,* and *M. tuberculosis*.

In 2004, three research laboratory workers at Boston University Medical Center (BUMC) were accidentally infected with tularemia bacteria in their BSL-2 lab. This incident is still under investigation by BUMC, city, state, and federal public health agencies. Corrective actions already identified and implemented include:

- Increased safety training and procedures for lab workers;
- Strengthened laboratory safety procedures;
- Unannounced safety inspections of BUMC laboratories;
- Applying additional tests and safeguards to infectious material sent to BUMC for research purposes;
- Outside, expert review of BUMC research controls and procedures; and,
- Working with the Boston Public Health Commission to improve the notification process.

Records of all reported laboratory accidents were reviewed from the past ten years, and it has been confirmed by the Occupational and Environmental Medicine Department that BUMC did not have any laboratory-acquired infections from research work at BSL-2 and BSL-3 facilities, with the exception of the incident described above. Further, there has not been any reported biosafety exposure in a BSL-3 laboratory. With approximately 14 million hours of operating time in the laboratories during this period, the following biosafety exposures, with no illness or evidence of serological exposure, were reported.

Exposure within BSL-2 Laboratories	Number of incidents
Animal (including bites)	9
Percutaneous (skin penetration/needle stick)	16
Eye splash	2
Total	27

BUMC has a database of all employee accidents and potential injuries including an OSHA 300 log of all OSHA-reportable employee injuries, as required by the Occupational Safety and Health Administration. Accidents and injuries are also reported to the Office of Occupational and Environmental Medicine, an accident/exposure reporting form is completed, and the information is forwarded to the Office of Environmental Health and Safety (OEHS). OEHS compiles this information into a database and follows up with individual exposures as appropriate with safety training and education to prevent reoccurrences.

.

Biosafety at National Institute of Allergy and Infectious Diseases:

1982-2003

Karl M. Johnson, M.D.
October 15, 2003

Biosafety at National Institute of Allergy and Infectious Diseases

1982-2003

The National Institutes of Health and the Centers for Disease Control (NIH/CDC) first promulgated National Guidelines for safe work with a broad range of infectious organisms in 1980. Four levels of physical containment and work practices were designated for agents with different virulence for humans and relative risk of infection from aerosols induced by laboratory manipulation. Biosafety Level 3 (BSL-3) is reserved for organisms that cause serious disease and which are known to be infectious via the respiratory route. Examples include Mycobacterium tuberculosis and West Nile virus. For such agents all procedures must be carried out in biosafety cabinets (BSC) fitted with high efficiency filters (HEPA). Centrifuges require sealed rotors so that aerosols that ensue if a tube breaks during spinning runs will be contained until the rotor is opened under the BSC. Air in such laboratories is maintained at negative pressure relative to hallways and cannot be blended with air to other laboratories and offices in order to prevent potential infection to others in the building. More and more such laboratories also have HEPA filters on laboratory room exhaust.

In addition to agents known to be aerosol transmitted, microbiological science continues to confront newly discovered viruses and bacteria for which aerosol infectiousness is uncertain. The NIAID has adopted a policy for such organisms that stipulates BSL-3 equipment and practices in BSL-2 laboratories with negative pressure. Work with the Human Immunodeficiency Virus (HIV) in the early 1980s led to adoption of that strategy for HIV and its close animal virus relatives, a policy that continues. Similar standards were initiated for work with hepatitis viruses at request of senior investigators, largely because new agents that cause hepatitis continue to emerge and little is known in early years regarding their infectiousness as aerosols.

This review is limited to work done during the past two decades by scientists at intramural laboratories of NIAID located on the Bethesda campus, at a neighboring facility in Rockville, MD, and at the institute's Rocky Mountain Laboratories in Hamilton, Montana.

Senior scientists were interviewed to ascertain agents studied, the variety of research programs that evolved over two decades, animals employed, if any, laboratory space, daily number of workers in the laboratories, and specific histories of laboratory accidents and consequences. Problems with function of facilities also were solicited and recorded.

Independent records of reported laboratory accidents that might expose workers to infection were reviewed. During the past 21 years all such accidents were to be reported quickly to the NIH Occupational Medical Service (OMS) for epidemiologic and medical evaluation as

well as immediate prophylactic treatment if indicated. Invasive wounds in course of laboratory work and clinical care of persons with chronic HIV infection are of continuing concern. The OMS is now able to provide antiviral therapy within two hours of an accident on a 7day/24 hour basis when circumstances indicate the need for therapy.

Intake records of all accidents on the NIH campus were initially paper documents. Copies were forwarded to the Occupational Safety and Health Branch (OSHB) in the Director's office for to follow up circumstances of an accident and for remedial action when indicated. In addition to such immediate reaction to accidents and facility emergencies, the OSHB has developed standardized protocols for periodic review of all laboratories for compliance with NIH safety practices. Laboratories at BSL-3 level are reviewed at six month intervals; all others annually. For the past decade, all records are computerized and electronic copies go from OMS to OSHB instantly. Records for this 21-year interval were cross-checked for details by staff of both Offices, together with specific scientist memory, in constructing the biosafety record for NIAID since 1982. Records for the Rocky Mountain Laboratories were reviewed with biosafety and scientific staff at that facility.

The detailed report is organized by Laboratory within the NIAID Division of Intramural Research. Agents, research agendas, containment levels, animal use, location and space for laboratories are presented in tabular form, together with histories of laboratory accidents and of facility problems that have affected work in those laboratories.

By any measure, the safety record at intramural NIAID laboratories, where work is done with the Institute's most pathogenic agents, is outstanding. No agent has escaped from any laboratory to cause infection in adjacent civilian communities. Indeed, this record stretches to almost 70 years at RML where several agents now on the national "Select List" have been studied for decades.

If one takes the number of 8-hour person days estimated by senior research staff during direct conversations and translates these into 2000 person hours per year in exposure to microbial organisms, impressive numbers emerge as shown in the following Table.

PERSONNEL HOURS WORKED AND OUTCOMES OF ACCIDENTAL EXPOSURES TO INFECTIOUS AGENTS: INTRAMURAL NIAID 1982-2003

HOURS AT RISK			
	BENCH	Animal	Total
BSL-3	553,000	81,500	634,500
BSL-2/3 P	2,235,500	360,200	2,555,200
Total	2,788,500	441,700	3,189,700

OUTCOMES OF ACCIDENTAL EXPOSURES			
	Clinical Infections	Silent Infections	Other Exposures, No infections
BSL-3	1	2	9*
BSL-2/3 P	0	2	15
Total	1	4	24

* One HIV invasive accident treated with anti-retroviral drugs. No infection ensued.

One clinical infection without sequelae and four silent infections in more than three million hours of exposure is a remarkable record, especially when continuous exposure of personnel to fluids containing HIV virus over many years is a significant part of that record. Indeed, only a single instance was considered worthy of immediate prophylaxis for that agent and no infection occurred.

Biosafety in NIAID laboratories demands, and receives, constant vigilance. I recommend, however, better documentation of communication between the OSHB and NIH Division of Engineering Services. I was unable to find very many records of specific facility problems and their outcomes. It might be well to have a brief computerized form for registry of each event that requires action, together with follow-up reports that find their way to OSHB.

Another concern is design and function of air handling systems for BSL-3 laboratories. In both Building 10 and the new Building 50, BSC IIB cabinets directly ventilated externally are an essential part of the overall exhaust system that always must be greater than the input air. If room negative pressure diminishes, the BSCs also shut down, a poor condition if aerosols are being generated in course of the work. Much better would be to have IIA BSCs as workstations. These would continue to capture aerosols regardless of overall room negativity. Hoods would not have to run continuously and room failure would not also release aerosols into the laboratory. The Uninterrupted Power Supply installed in Building 50 was a prudent decision. I hope that these questions will be/have been considered in the current renovation of Twinbrook III as BSL-3 laboratory. Finally, it was a pleasure to receive frank, careful responses from all the scientists I approached. They willingly turned from their particular microbial environments to candidly discuss the history of their work from a safety perspective.

This report is included in the Final Environmental Impact Statement of the Integrated Research Facility.

Biosafety at BSL-4
More than 20 Years Experience at Three Major Facilities

Karl M. Johnson, M.D.

October 15, 2003

Biosafety at BSL-4:
More than 20 Years Experience at Three Major Facilities

WHAT IS BSL-4, AND HOW DID WE GET THERE?

Special containment for work with infectious microbes in the United States originated during World War II in response to intelligence that the German army had a program for development of biological, in additional to chemical weapons that had been used during the first World conflict. Temporary facilities were established in a suburb of Frederick, Maryland, later to become the permanent Fort Detrick. During the 1950s and 1960s several agents, most notably the bacteria that cause plague and anthrax and the rickettsial organism that causes so-called Q fever, were produced in large quantities and in forms with properties that make highly infectious tiny particles in the air. The term used was, and is, 'weaponized.'

Infections among those working with these and other microbes were a recurrent problem. Under the inspired leadership of the late Dr. Arnold G. Wedum, recognized today throughout the world as the "Father of Biosafety," Fort Detrick borrowed technology from the nuclear industry to prevent such infections, especially those induced by small aerosols that arose during the course of routine laboratory manipulations. Stainless steel cabinets (termed Class III) were constructed and assembled in continuous airtight lines. Each had at least one pair of sealed glove ports to allow manipulation of hazardous materials in a sealed-off environment. Incubators, microscopes, and doors leading directly to autoclaves and to animal cabinets were integral to the cabinet line. The cabinets had a constant supply of filtered air and filtered exhaust fans to remove any particles generated during the work sessions. Air pressure in cabinet lines was negative to the laboratory room and the exhaust was filtered. The room itself also was negative to the rest of the building, and exhaust air was filtered before release to the environment. Thus workers, others in the building, and the outside community, were all protected against aerosol infection from agents otherwise intended for battle.

During these same two decades, new organisms with serious human pathogenicity were discovered in nature on several continents. Most of these, all of which were viruses, caused a syndrome (with variations) known as acute viral hemorrhagic fever (VHF). There was no specific treatment or vaccine available for any of them, except for the classical virus that causes yellow fever. That disease is now recognized as the prototype of VHF. Even more disturbing was the fact that aerosols were infectious for laboratory staff for most of these agents. Virology at Fort Detrick quickly entered the Class III cabinet habitat.

The recognition of Marburg virus in 1967 propelled the Centers for Disease Control (CDC) into this arena. That agency was asked to help with field studies designed to uncover the African reservoir for the virus, and it was decided that diagnostic reagents were needed.

Visions of travelers returning from parts of the globe endemic for HF agents became a chronic concern. A small Class III cabinet laboratory was established in 1970 at the CDC. It had about 70 linear feet of cabinet line and a staff of two persons who tested samples from wild animals for infection and made diagnostic reagents for Marburg and other viruses of concern.

One year previously (1969), President Richard Nixon unilaterally terminated the national program of offensive biowarfare at Fort Detrick. Most of the buildings were given over to the National Cancer Institute. But the Army now expanded its defensive program. A new facility was constructed that became the principal laboratory of the U. S. Army Medical Research Institute for Infectious Diseases (USAMRIID). It opened in early 1971 with a mission to develop technology for detection and identification of potential biowarfare agents, to understand pathogenesis of the new VHF agents, to search for specific antiviral therapies, and to develop vaccines.

Another VHF agent, Lassa virus, appeared in Nigeria in 1969. When Marburg virus attacked two young Australians traveling in southern Africa in 1975, CDC Director David Sencer decided that it was time to reinforce the nascent Special Pathogens Branch. A surplus large trailer was obtained from NIH and outfitted as a new laboratory for work with VHF agents. It had a Class III cabinet line. Space previously used as offices was redesigned as the first completely suited laboratory and animal room. Workers wore special positive pressured suits that could be hooked up to hoses from the ceiling that provided clean breathing air. Suits came in several sizes and each worker was now able to have gloves that truly fit their hands. All work was to be done in movable Class II laminar flow biosafety cabinets (BSC) that pulled air across the work surface then filtered it, with about half recirculated in the box and the rest released into the laboratory. Similar filtered enclosures were employed to house infected animals. Laboratory exhaust air was twice filtered before release to the environment, all solid wastes were autoclaved in double-door machines installed through a laboratory wall, and all liquid wastes were pressure cooked at high temperature before cool down and released to sanitary sewers. Workers leaving the laboratory stood in a chemical shower to decontaminate the "space" suits before doffing scrub suits and showering before leaving the facility. Various alarms and redundant systems were installed to ensure that power, continuous negative pressure, and breathing air were always available in emergency. Needles and scalpels were used as infrequently as possible and plastic ware replaced glass for almost all procedures.

The new CDC laboratory was opened at the end of 1978. Laboratories utilizing positive pressure suits also were ready at USAMRIID within months. These configurations allowed convenient installation and maintenance of new instruments and other equipment that was being developed for molecular work on viruses. The principles of biocontainment were: (1) capture each small particulate aerosol immediately where it is generated, (2) ensure that workers have functional hands, life support, minimum exposure to invasive accidents, and ready access to the tools required for research, and (3) make sure that systems for

prevention of escape of aerosolized viruses to the environment are redundant. The BSC cabinets were the primary containment, the exhaust-filtered laboratories were the secondary, and even these were redundant.

By 1976, some leading molecular microbiologists became worried that new technology could potentially create novel organisms that might conceivably become Andromeda strains. The Director of the National Institutes of Health (NIH) ordered new guidelines for standards of microbiological safety for diverse agents with known properties of human pathogenicity and modes of transmission, as well as for newly discovered agents. The first edition of the NIH/CDC guidelines was published in 1980. Most work could be done in ordinary laboratories at BioSafety Level 2 (BSL-2). Others that cause more serious illness in humans, and/or for which no treatment is available, were assigned to BSL-3. All work was to be done in Class II biosafety cabinets. Room air was to be under negative pressure relative to hallways with no recirculation to other space in the building.

BSL-4 was reserved for VHF agents, certain tick-borne encephalitis viruses, and a simian herpesvirus for which human infection is almost universally fatal. At the time, this meant USAMRIID and CDC Special Pathogens, but authorities in South Africa were progressively concerned about VHF on their continent. Ebola virus, an even more virulent relative of Marburg, had been discovered in 1976. Rift Valley fever virus had caused its first-ever epidemic that included hemorrhagic fever. Crimean-Congo virus was a new concern. To meet these challenges, a BSL-4 laboratory, modeled on the Detrick and Atlanta prototypes, was constructed outside Johannesburg and commissioned in 1980. It had both suit and cabinet-line laboratories.

These three laboratories were virtually the sites of BSL-4 viral work during the past 22-30 years. With experience over time, most investigators chose to work primarily in the positive-pressure suit environment. Indeed, at the end of the1980s, CDC moved into new large laboratories that were almost devoid of Class III cabinet lines. Moreover, the Johannesburg laboratory, now part of the National Institute for Communicable Diseases (NICD), recently removed its Class III cabinets in order to expand positive-pressure suit space. Only the British BSL-4 laboratories continue to depend on Class III cabinet line configurations. All recently constructed Level 4 facilities in other countries, as well as those proposed for ours, are positive-pressure suit labs. Accordingly, this review will not include biosafety at the Porton Down facility. We are concerned principally with the track record of, and a risk analysis for, BSL-4 positive-pressure suit laboratories.

That record is exemplary. Most individuals who begin work in BSL-4 suites are already experienced microbiologists. Specific training for use of the positive-pressure suits and for safe execution of all procedures is standard practice at all of the laboratories. In context of current international concern regarding potential use of some of these viruses as weapons of terror, access to the facilities and to individual laboratories is carefully controlled. At two of the facilities in the United States individual security clearance is required to qualify for work

at the BSL-4 level. The viruses under study do not escape, neither by accident nor by covert design. Reviews of individual facilities are summarized below.

USAMRIID — 1972-2003

Persons Interviewed:

Drs. Peter Jahrling, Chief Civilian Scientist; Gerald Eddy, retired Chief, Virology Division.

Research Program:

Pathogenesis of viral infections in animal models, including clinical and anatomical pathology. Quantitative susceptibility of animals to aerosol infection by VHF pathogens. Development of diagnostic assays and air sampling detectors. Molecular anatomy and genetics of agents. Drug screening program in search of antiviral compounds. Development of live attenuated, inactivated, and recombinant vaccines.

Agents Studied:

Machupo, Junin, Guanarito, Sabia, and Lassa arenaviruses; Marburg and Ebola; Rift Valley fever and Crimean-Congo hemorrhagic fever viruses; Tick-Borne encephalitis virus. Yersinia pestisand Bacillus anthracis.

Animals Used:

Mice, hamsters, guinea pigs, non-human primates, wild rodents, lambs,

Site:

Two buildings, Fort Detrick, Maryland. Total BSL-4 space: about 6500 sf. One third is animal space and suit/cabinet ratio of lab space is about 2:1.

Time Devoted in BSL-4 Space:

Approximately 343,980 hours. (6.5 persons/8 hour day x 1680 hours/year x 31.5 years).

Laboratory Accidents and Outcomes:

During early years when work was completely in cabinets, invasive accidents resulted in treatment with human plasma containing specific antibodies to virus in question, as well as confinement in an isolation suite in one building that was also set up as an intensive care facility in event that a worker became ill after accidental exposure to an agent. Two invasive accidents were of most concern:

November 1979. Accidental finger puncture with needle on a syringe loaded with Lassa

virus. Ribavirin and immune plasma were given. (This was an experimental therapy for monkeys under development at the Institute.) No illness or serological evidence for infection occurred.

December 1982. During autopsy, a bone fragment of a monkey infected with Junin virus punctured a finger. Immune plasma was used and no clinical or subclinical infection ensued.

CDC SPECIAL PATHOGENS

Persons Interviewed: Senior Scientists and Author Research Program:

Development of diagnostic methods and reagents for diagnosis of all BSL-4 agents. Pathogenesis of viral infections in animal models, including natural wild reservoirs. Molecular anatomy and genetics of VHF agents. Limited vaccine development work. Response to VHF epidemics in natural settings. Diagnosis, clinical pathology and virology, discovery of new agents.

Agents Studied:

Five arenaviruses, Marburg, Ebola, Crimean-Congo HF virus, Rift Valley fever virus, Nipah and Hendra viruses, Russian spring summer encephalitis and Tick-Borne encephalitis viruses, Omsk and Kyasanur Forest disease viruses, Hantavirus (animal work only).

Animals Employed:

Mice, hamsters, guinea pigs, non-human primates, rats, five wild rodent species for rodent-borne agents.

Sites:

Building A: 1970-78. About 70 linear feet of Cabinet line.

Building B: 1979-1989. About 900 sf with 30 ft cabinet line, 300 sf positive-pressure suit lab and 200 sf of positive-pressure suit animal space.

Building C: 1990-2003. About 5000 sf of which approximately 30% is animal space. Laboratory is entirely positive-pressure suit operated.

Time Devoted in BSL-4 Space:

120,560 hours.

Laboratory Accidents and Outcomes:

Animal bite; Hantavirus infected rodent, no infection.

Animal bite; animals being inoculated with Hantavirus. Pre-inoculation bite from rat.
Needle stick to worker prior to setting up an inoculum with mouse-adapted Ebola virus. No infection.
Autoclave door interlock failed and a load not autoclaved was opened, but not handled. No infections resulted.
Multiple events over the years of outer gloves or suits developing tears or holes detected during work. Such incidents are evaluated and followed up. No treatments were ever used and no infections resulted.

Facility/System Failures: None of note that caused interruption of work.

National Institute for Communicable Diseases

Johannesburg, South Africa, 1980-2003

Person Interviewed:

Dr. Robert Swanepoel, BSL-4 Laboratory Director

Research Program:

Diagnostic reagents and support for all HF outbreaks in Africa and neighboring regions when requested,; pathogenesis of infections in animals, especially candidate wild reservoir species; clinical virology; molecular biology of selected hemorrhagic fever viruses; field investigations of natural history of disease outbreaks; and seroepidemiology of infections in humans and animals.

Agents Studied:

Marburg and Ebola viruses, Rift Valley fever virus, Crimean-Congo HF virus, ten hantaviruses.

Animals Employed:

Mice, guinea pigs, rabbits, bats, tortoises, pigeons, snakes, roaches, spiders, frogs, millipedes, snails, 20 species of wild rodents, hares, hedgehogs, guinea fowl, chickens, etc. Much animal work was devoted to a search for wild reservoirs of Marburg and Ebola viruses.

Site:

Rietfontein, 4500 sf. Space divided into 721 sf positive-pressure suit lab and 222 sf similar animal holding room, plus cabinet lab of 999 sf (now defunct). Remaining 1443 sf devoted to change rooms, showers, and service corridors.

Time Devoted in BSL-4 Space:

Approximately 40,000 hours in nearly 23 years.

Laboratory Accidents and Outcomes:

Bat bite through double gloves. No infection.

Multiple other accidents. Those exposed are monitored closely for 21 days, during which time they are not permitted to leave town—as are all employees after their last day of work inside BSL-4 space. No infections recorded.

Facility/System Failures:

Only one that caused shutdown of operations. About 5 liters of highly concentrated Marburg virus was suddenly aerosolized when worker opened chamber to add a bit more fluid without closing the nitrogen pressure tank and bleeding off pressure. Laboratory was mopped for several hours with glutaraldehyde, and finally decontaminated with formaldehyde gas. No infection occurred in two "exposed" workers. There was no breach in BSL-4 containment, and no infections occurred in neighboring open-air monkey colonies on the campus. This was a maximum challenge to BSL-4 containment, and I am aware of no other event remotely comparable in terms of concentration and volume of a highly lethal virus.

Summary

No clinical infections occurred at three institutions during work with BSL-4 agents, mostly hemorrhagic fever viruses during the past 31 years. Almost half a million hours of laboratory (and field) exposure have been recorded, the majority of which was time spent in positive pressure suits. Nor have there been major defects or incidents in operation of the physical facilities. No escape of any agent with clinical consequences for neighboring communities occurred.

Invasive injuries were infrequent, eloquent testimony to the awareness of the dangers and the daily care observed by workers who volunteer for such duty. One laboratory inadvertently carried out a maximum aerosol challenge to BSL-4 containment with a highly pathogenic hemorrhagic fever virus. Virus did not escape the laboratory, nor was a worker infected.

The zero numerator of infections in these three laboratories and the huge denominator of exposure hours make it impossible to provide a number for 'risk of infection' to either laboratory workers or outside communities. Nevertheless, that number must be small. When the value of diagnosis, treatment, and control of deadly outbreaks of hemorrhagic fever over the past three decades is added to this equation, risk/benefit clearly comes out in favor of continued operation of BSL-4 laboratories.

Indeed, considering new challenges posed to the world community by these agents, it is fair to conclude that more such facilities are needed. Better therapeutic agents are desperately needed. High priority also must go to the development of vaccines that can protect laboratory and hospital personnel in countries where natural epidemics occur, as well as first responders to intentional aerosol attack on any community.

This report is included in the Final Environmental Impact Statement of the Integrated Research Facility

Biosafety Update:
Short Review of BSL-3 and BSL-4 Viral Agent Laboratory Incidents Worldwide

Karl M. Johnson, M.D.
August 28, 2004

In March of 2003, the global health community was alerted to a new respiratory infection that is deadly and readily transmissible. The disease became known as severe acute respiratory syndrome (SARS), and now is believed to have originated in China in the fall of 2002. Cases quickly were reported from Vietnam, China, Hong Kong, Singapore, and Canada. On July 5 2003, the World Health Organization announced that the disease had been contained, and although only four months had passed since the first report, more than 7,000 cases were confirmed and 774 attributable deaths were recorded. Intensive study revealed that the infection is caused by a corona virus, now known as SARS corona virus (SARS-CoV). .

BSL-3 Laboratory Infections
SARS

Since the primary epidemic of severe acute respiratory syndrome (SARS) in Asia and Canada was terminated in early summer of 2003, there have been three instances of laboratory clinical SARS infections.

- Singapore: August 26, 2003.
  A university graduate student worked on attenuated strains of West Nile virus and obtained a virulent recent New York strain of the virus. To work on the virus, he was sent to an Institute in Singapore that had BSL-3 laboratories. After minimal training, and with help of an Institute technician, several passages of the new virus were made in Vero E6 cells. This line also was used by the Institute to grow the SARS coronavirus. The student sickened with fever and myalgia on August 26. On September 3, he was admitted to hospital with a dry cough and signs of pulmonary inflammation. He was transferred to an isolation hospital, and had a moderately severe evolution of the disease. Supplemental oxygen was not required. Surveillance, even quarantine, was maintained on several dozen contacts, but no secondary infections occurred.

  It was discovered that supernatant fluids of the virulent West Nile virus that was to become stock for further experiments was significantly contaminated with the SARS strain of corona virus under investigation in the Institute laboratory. The student and the technician prepared storage vials of the West Nile harvest on August 26 and this work is thought to have been point of exposure, albeit the technician did not become infected with the corona virus, and had no antibodies to signify past infection.

- Taipei, Taiwan: December 10, 2003
  A senior research scientist at the National Defense University worked with the SARS virus to screen compounds for antiviral activity in a Class III cabinet (BSL-4). On December 6, he noticed that waste fluid placed in a tightly docked transfer chamber had leaked onto the floor of that attached unit. From inside the main cabinet he sprayed alcohol into the chamber, waited 10 minutes, then undocked the chamber, opened and sprayed more alcohol into it, then physically cleaned up the spill. Next day he went to Singapore to a SARS meeting. The evening of return on December 10 he noted fever and fatigue. These symptoms progressed to include dry cough and severe myalgia. He was finally hospitalized on December 16 and experienced only moderately severe clinical illness. Contacts, especially a number of passengers on the plane with him from Singapore on December 10 were monitored or quarantined. No secondary infections occurred.

  Environmental samples obtained from his laboratory on December 18 revealed SARS corona virus nucleic on the handle of an alcohol bottle kept on top of the transfer chamber and on the light switch of the Class II cabinet. It is postulated that the scientist grossly contaminated his hands during the waste mopping of the transfer chamber after an incomplete inactivation step using alcohol spray.

- Beijing, China: February and April 2004
  Two SARS workers at the National Institute of Virology sickened and were diagnosed with that disease two weeks apart in April. The identity of these infections was not recognized until the mother of one of the workers also sickened. She died. Six other persons in contact with these two individuals also acquired the disease. During the course of intense investigation at the laboratory, two other workers were discovered to have experienced SARS-compatible illness in February 2004. These individuals had antibodies to the etiologic coronavirus. Details regarding likely sources of these laboratory infections have not been published to date.

Subsequent to the October 15, 2003 report, "Biosafety at BSL-4: More than 20 Years Experience at Three Major Facilities," there have been three reported laboratory-acquired infections with BSL-4 viruses, one fatal ebola lab infection in 2004 and two Marburg infections, 1988 and 1990, as reported by ProMed-mail and detailed below. ProMed is the Program for Monitoring Emerging Infectious Diseases, a public service internet-based reporting system dedicated to rapid global dissemination of information on outbreaks of infectious diseases and acute exposures to toxins that affect human health.

BSL-4 Laboratory Infections

- Fatal Ebola Lab Infection: May 19, 2004:
  On May 5, 2004, a 46-year-old female employee at Vektor, the leading BSL-4 laboratory complex in Novosibirsk, Russia, was admitted to hospital with fever and severe myalgia. Several days previously she had accidentally stuck a finger with a needle during experiments with guinea pigs infected with the Zaire strain (most virulent) of Ebola virus. Despite all measures she died on May 19.

  Informal verbal information from a colleague who works on viral hemorrhagic fevers is that the Institute did not have any proper needle disposal boxes at the time of the accident. Workers had apparently been instructed to replace the plastic sheaths on needles after use. This was purportedly the maneuver that resulted in her injury, although such detail is omitted in the Special Committee report of the Russian Federation Ministry of Health.

- Two Infections (with One Fatality) of Marburg Virus: 1988
  In the same ProMed report concerning the fatal Ebola case, it is mentioned without further detail that two Marburg virus clinical laboratory infections occurred in the past at the same laboratory, Vektor in Novosibirsk, Russia. One of these was fatal. A second worker survived Marburg disease.

These experiences demonstrate that working with certain viruses carries significant risk to workers, and further indicates that facility, equipment, and adherence to sound protocols for worker safety are all important in minimizing infections. The secondary SARS infections in China, moreover, raise the question of whether those working with that corona virus should also wear respirators. Respirator use for this virus is justifiable as the virus is transmissible from person to person and secondary infections in the general population have already proven to be international emergencies.

Data Sources

SARS

Lingappa JR, McDonald LC, Simone P, Parashar UD. Wresting SARS from uncertainty. Emerg Infect Dis 2004 Feb. Available from: URL: http://www.cdc.gov/ncidod/EID/vol10no2/03-1032.htm

Singapore

Lim PL, Kump A, Gopalakrisha G, et. al. Laboratory acquired severe acute respiratory syndrome. N Engl J Med 2004. 350:1740-5.

Taiwan

Normile D. Second lab accident fuels fears about SARS. Science 2004. 303:1126.
ProMed v2004, number 014 January 9, 2004

China

ProMed v2004.n247 July 4, 2004

Filoviruses

Russia

ProMed v2004,n334 August 24, 2004

ProMed

http://www.promedmail.org/pls/askus/f?p=2400:1001:11281378051439518103::NO::F2400_P1001_BACK_PAGE,F2400_P1001_PUB_MAIL_ID:1000,26482, Accessed September 2004.

Click here to view Appendix 5