

## Laboratory Biosafety of Pathogenic Microorganisms in China

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In the past ten years, many threats from newly emerging, re-emerging, and even deliberately disseminated infectious agents have challenged the public health and infectious disease research communities worldwide. Several newly emerging pathogens, such as the SARS-associated coronavirus and avian influenza viruses; re-emerging pathogens, such as tuberculosis and the West Nile Virus; and deliberately disseminated diseases, such as the anthrax spread in attacks in the United States in 2001, have caused illness and deaths in humans and animals in China and elsewhere around the globe. Over the past decade, strains of common microbes such as *Staphylococcus aureus* and *Mycobacterium tuberculosis* have continued to develop resistance to the drugs that once were effective against them.<sup>2</sup>

The mission of China's microbiological and biomedical laboratories is to play a leading role in national efforts to develop diagnostics, vaccines, and therapeutics to combat emerging and re-emerging infectious diseases. These laboratories range in size and complexity from large, comprehensive research and clinical laboratories to the office laboratories of China's physicians. These laboratories employ many workers who could be exposed to a variety of occupational health risks due to their work with infectious materials and cultures. These types of occupational biological hazards are also present in clinical, research, and industrial production laboratories. Globally, laboratory-acquired infections are a common problem and many cases have been reported.<sup>3</sup> For instance, in China, a problem with accidental, laboratory-acquired SARS infection occurred in 2004. Exposure to infectious aerosols was considered the most common source of laboratory

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<sup>2</sup> David M. Morens, Gregory K. Folkers, and Anthony S. Fauci, "The Challenge of Emerging and Re-emerging Infectious Diseases," *Nature* 430, no. 6996 (8 July 2004):242-9; "Bad Bugs, No Drugs as Antibiotic Discovery Stagnates...A Public Health Crisis Brews," Policy White Paper (Washington, D.C.: Infectious Diseases Society of America, July 2004). Available at: [http://www.idsociety.org/pa/IDSA\\_Paper4\\_final\\_web.pdf](http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf).

<sup>3</sup> David L. Sewell, "Laboratory-Associated Infections and Biosafety," *Clinical Microbiology Review* 8, no. 3 (July 1995): 389-405.

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infection. In 1979, Pike concluded that “the knowledge, the techniques, and the equipment to prevent most laboratory infections are available.”<sup>4</sup>

Many microbiological and biomedical laboratories play an important part of China’s efforts to prevent and control infectious diseases nationwide. Good biosafety practices in these laboratories are therefore crucial. Recognizing the importance of laboratory biosafety, the Chinese government began placing a renewed emphasis on the topic in 2003. To strengthen the management of biosafety in laboratories handling pathogenic microorganisms and to protect the health of laboratory personnel and the public, the Chinese government has considerably upgraded its biosafety regulations and criteria associated with laboratory biosafety.

### **Regulations and Criteria Associated with Laboratory Biosafety in China**

A complete system of laboratory biosafety involves many different aspects, including proper laboratory procedures, sound guidelines for transfer of pathogenic microorganisms between facilities, regulations governing the correct use of certain equipment, and standards for building laboratories where personnel will work with highly infectious and/or pathogenic diseases. From 2003 to 2006, the Chinese government issued and implemented fourteen separate laboratory biosafety regulations and measures, which are summarized in Table 1.<sup>5</sup> In other words, the Chinese government has instituted a comprehensive new set of biosafety regulations and guidelines applicable to all microbiological and biomedical laboratories.

### **Classification and Management of Pathogenic Microorganisms**

The term “risk” implies the probability that harm, injury, or disease will occur. In the microbiological and biomedical laboratories, a risk assessment focuses primarily on the prevention of laboratory-acquired infections. When laboratory activities involve infectious or potentially infectious material, a risk assessment must be done.

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<sup>4</sup> R.M. Pike, “Laboratory-Associated Infections: Incidence, Fatalities, Causes and Prevention,” *Annual Review of Microbiology* 33 (October 1979): 41-66.

<sup>5</sup> A comprehensive list of China’s current laws and regulations related to biosafety, biosecurity, and genetic engineering activities can be found in the Appendix.

**Table 1: Chinese Regulations, Standards, Codes, and Lists Pertaining to Laboratory Biosafety.**

<b>Responsible Government Organization</b>	<b>Area of Authority</b>	<b>Identification Number of Measure</b>	<b>Date of Issuance/ Implementation</b>
State Council	Management of biosafety in laboratories working with pathogenic microorganisms	424-2004	5 November 2004
Ministry of Health	General biosafety standards for microbiological and biomedical laboratories	WS233-2002	December 2002/August 2003
Ministry of Agriculture	Code for biosafety management of veterinary laboratories	302-2003	October 2003
General Administration of Quality Supervision, Inspection, and Quarantine and the Standardization Administration	General biosafety requirements for laboratories	GB19489-2004	April 2004/October 2004
Ministry of Construction and the General Administration of Quality Supervision, Inspection, and Quarantine	Architectural and technical code for biosafety in laboratories	GB50346-2004	August 2004/September 2004
State Council	Managerial regulations for the treatment of medical wastes	308-2003	June 2003
Ministry of Agriculture	Regulations for the biosafety management, examination, and certification for zoo laboratories handling highly pathogenic microorganisms	52-2005	2005
Ministry of Agriculture	List of pathogens contagious to animals	53-2005	2005
Ministry of Agriculture	Regulations for the packaging and transport of pathogenic bacteria, viruses, and other pathogenic microorganisms that are contagious to animals	503-2005	2005
State Food and Drug Administration	Regulations for the proper installation and performance of biosafety cabinets	YY0569-2005	July 2005/January 2006

**Table 1: Chinese Laboratory Biosafety Regulations and Measures (Continued).**

<b>Responsible Government Organization</b>	<b>Area of Authority</b>	<b>Identification Number of Measure</b>	<b>Date of Issuance/ Implementation</b>
Ministry of Health	Regulations for the packaging and transport of pathogenic bacteria, viruses, and other pathogenic microorganisms that are contagious to humans	45-2005	December 2005
Ministry of Health	List of pathogens contagious to humans	Not applicable	January 2006
State Environmental Protection Administration	Managerial regulations for laboratories working with pathogenic microorganisms to safeguard the exterior environment	32-2006	March 2006
Ministry of Health	Regulations for the management, examination, and certification for laboratory biosafety and laboratory activities involving work with highly pathogenic microorganisms that are contagious to humans	50-2006	September 2006

The purpose of a risk assessment is to help choose the appropriate biosafety levels for facilities, equipment, and laboratory practices to reduce to an absolute minimum the risk of exposure to facility workers and the environment. In general, the more infectious and pathogenic the material, the higher the biosafety level to be applied. Another general rule of thumb is that when the infection risk of the material is unknown, conservative or high biosafety containment levels should be applied until the exposure risk is determined.

The factors of interest in a risk assessment include the *pathogenicity* of the infectious or suspected infectious agent, including disease incidence and severity (i.e., mild morbidity versus high mortality, acute versus chronic disease). The *route of transmission* (e.g., parenteral, airborne, by ingestion or aerosol route), which may not be definitively established for newly isolated agents, is also taken into consideration. The *agent stability*, which involves not only aerosol infectivity but also the agent's ability to survive over time in the environment, is contemplated (e.g., from spore-forming bacteria), along with the *infectious dose* of the agent. The infectious dose can vary from one to hundreds of thousands of units. The complex nature of the interaction of microorganisms and the host presents a significant challenge even to the healthiest immunized laboratory worker and may pose a serious risk to those with lesser resistance.

The *concentration*, or number of infectious organisms per unit volume, will be important in determining the risk, as is the volume of concentrated material being handled.

Also critical to a risk assessment is the *origin* of the potentially infectious material. The biohazard level of the material needs to be understood by the receiving facility so that personnel can choose the appropriate biosafety level to handle that material.<sup>6</sup> Moreover, the *availability of data from animal studies*, in the absence of human data, may provide useful information in a risk assessment. Information about the pathogenicity, infectivity, and route of transmission in animals may provide valuable clues for the behavior of the microorganism in humans. Finally, the established *availability of an effective prophylaxis* or therapeutic intervention is another essential factor to be considered. The most common form of prophylaxis is immunization with a proven vaccine, hence, the availability of effective immunizations and/or other medications (e.g., antibiotics, antivirals) that could be applied in the event of infection to mitigate the disease is also considered.

At a minimum, eight different factors are taken into account in a risk assessment for work with a microorganism and weighed against each other to determine what level of risk the microorganism presents. The next segment of this essay describes how the results of a risk assessment are categorized. In turn, the risk group in which an individual microorganism is placed informs the appropriate biosafety containment precautions warranted for the planned activities with that microorganism.

### **Risk Categorizations for Microorganisms**

The results of the risk assessment help to classify etiologic agents in groups according to the level of hazard they present to humans, animals, the environment, and community. Appropriate government authorities classify pathogenic microorganisms into four categories determined by the infections they cause and the seriousness of their harm to the individual and the community as a whole. These risk group categories guide decisions about the level of biosafety appropriate for work with infectious pathogens.

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<sup>6</sup> Appropriate precautions should always be taken when opening a sample. For example, strict precautions might be taken with material originating directly from field samples (e.g., environmental, human, animal) where the biohazard level has not been firmly established.

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These classifications presume ordinary circumstances in a research laboratory, or growth of the microorganism in small volumes for diagnostic and experimental purposes.

Pathogenic microorganisms in **Risk Group 1** are considered of high risk to the individual and to the community. Such microorganisms usually cause serious human or animal disease and can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available. For example, the causative agents for Marburg virus, Ebola virus, Congo-Crimean hemorrhagic fever virus, and Jenin virus (visceral leishmaniasis) fall into Risk Group 1.

Pathogenic microorganisms are categorized in **Risk Group 2** if they present high individual risk, but low risk to the community. Pathogens in this group usually cause serious human or animal disease but do not ordinarily spread from one infected individual to another. Sometimes, effective treatment and preventive measures are available for these diseases. *Mycobacterium tuberculosis*, *Coxiella burnetii*, St. Louis encephalitis virus, and Hantavirus are in Risk Group 2. Working from this system of classification, pathogenic microorganisms in Risk Groups 1 and 2 are jointly referred to as the “highly pathogenic microorganisms.”

The third category of pathogenic microorganisms poses a moderate risk to the individual and a limited risk to the community. **Risk Group 3** refers to pathogens that can cause human or animal disease but are unlikely to be a serious hazard to laboratory workers, the community, livestock, or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of further spread of infection is limited. To illustrate, Hepatitis B virus, *Salmonella*, and *Toxoplasma* spp are classified in Risk Group 3.

Pathogenic microorganisms in **Risk Group 4** present low risk to the individual and the community. Risk Group 4 pathogens are unlikely to cause disease in healthy workers or animals. The fourth risk group includes microorganisms such as *Bacillus subtilis*, *Naegleria gruberi*, and infectious canine hepatitis virus.

Among other actions, the 2004 State Council regulation on the management of laboratory biosafety resulted in the formulation, publication, and implementation of lists of pathogenic microorganisms capable of spreading to humans and to animals. These lists are used to guide decisions related to biosafety risk assessments as well as decisions

about the appropriate biosecurity precautions to be taken with specific pathogens.<sup>7</sup> Laboratories that plan to work with these listed human and animal pathogens must have specific permission to do so. Otherwise, laboratories that are not permitted to work with these microorganisms have a grace period to destroy historical reference strains or send any samples of these pathogens that might be in their institutional culture collections to facilities certified to possess such materials.

### **Biosafety Containment Levels**

Another major component of biosafety is the containment level established to indicate the grade of containment required for handling the microorganism safely in a laboratory setting. The biosafety containment level includes the engineering, operational, technical, and physical requirements for manipulating a particular pathogen. Each pathogen has different inherent characteristics, but, as described above, a risk assessment makes it possible to group pathogens into risk levels. The biohazard level of microorganisms determines the biosafety containment level to be employed. Prior to the establishment of new laboratory biosafety standards in China, a Biosafety Level (BSL)-3 laboratory in China was roughly equivalent to BSL-3 laboratories in the United States or Europe. Based largely on the standards of the World Health Organization and the guidelines used in the United States and Canada, the Chinese government has established four grades of containment for work involving pathogenic microorganisms.<sup>8</sup> With the revised biosafety standards, a BSL-3 laboratory in China is somewhere between a BSL-3 and a BSL-4 facility in Europe or the United States. As a general rule, laboratories in the Biosafety Level 1 and 2 shall not perform experimental activities with highly pathogenic microorganisms.

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<sup>7</sup> China. Ministry of Agriculture, "List of Animal Pathogenic Microorganisms," Regulation 53-2005 (Beijing: 13 May 2005); Ministry of Health, "Directory of Pathogenic Microorganisms Transmissible Between Humans," (Beijing: 11 January 2006).

<sup>8</sup> Switzerland. World Health Organization, *Laboratory Biosafety Manual*, 3<sup>rd</sup> ed. (Geneva: 2004); The United States. Centers for Disease Control and Prevention and National Institutes of Health, *Biosafety Microbiological and Biomedical Laboratories*, 4<sup>th</sup> ed. (Washington, D.C.: U.S. Government Printing Office, May 1999); *Biosafety Microbiological and Biomedical Laboratories*, 3<sup>rd</sup> ed. (Toronto: Health Canada, 2004).

### **Biosafety Containment Level 1**

The practices, safety equipment, and facility design and construction of BSL-1 facilities are appropriate for undergraduate and secondary educational training and teaching laboratories, and for other laboratories in which work is done with defined and characterized strains of viable microorganisms that are not known to consistently cause disease in healthy human adults. A BSL-1 facility has four major characteristics. First, this type of laboratory requires no special design features beyond those suitable for a well-designed and functional laboratory. Second, biological safety cabinets are not required in a BSL-1 facility. Work may be done on an open bench top. Third, containment is achieved through the use of practices normally employed in a basic microbiology laboratory. Fourth, laboratory personnel have specific training in the procedures conducted in the laboratory and work under the supervision of a scientist with general training in microbiology or a related science. Although there are some differences, Chinese laboratory biosafety practices are modeled largely on those of the World Health Organization.

### **Biosafety Containment Level 2**

The practices, equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, and other laboratories that work with Risk Group 3 microorganisms. A BSL-2 facility has several major characteristics. To begin with, access to the laboratory is limited or restricted at the discretion of the laboratory director when experiments are in progress. A biohazard sign must be posted on the entrance to the laboratory when etiologic agents are in use. Another major characteristic of a BSL-2 laboratory are the precautions taken to limit work with sharp objects to a minimum. Needles, syringes, or other sharp instruments should be used only when there is no alternative, such as parenteral injection, phlebotomy, or aspiration of fluids from laboratory animals and diaphragm bottles. In addition, plastic ware should be substituted for glassware whenever possible. Another defining characteristic of a BSL-2 facility is the presence of properly maintained biological safety cabinets, preferably Class II. If biosafety cabinets are not present, personnel must employ other appropriate personal protective equipment or physical containment devices when conducting procedures with

a potential for creating infectious aerosols or splashes and when high concentrations or large volumes of infectious agents are used. In the event of an accident, BSL-2 facilities must have an eyewash station readily available. Finally, according to the size of the facility, one or more autoclaves to decontaminate infectious materials are essential in all BSL-2 facilities.

### **Biosafety Containment Level 3**

The practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, teaching, research, or production facilities conducting work with large volumes and high concentrations of Risk Group 3 microorganisms and/or with Risk Group 2 microorganisms, where the risk of aerosolization is high and the consequences of subsequent infection are life-threatening. Construction of BSL-3 laboratories must follow specific guidelines.<sup>9</sup> BSL-3 laboratories should be registered or listed with national or other appropriate health authorities. This category of laboratory has several defining characteristics.

A BSL-3 laboratory should be separated from other areas of the facility that are open to unrestricted traffic flow within the building. To accomplish this, a BSL-3 laboratory should consist of the clean area, the potentially contaminated area, and the contaminated area. The clean area and the potentially contaminated area are linked by an air lock, and the potentially contaminated area and the contaminated area are linked by a second air lock. The structure of the BSL-3 laboratory is called “three areas and two buffers.” The author first proposed this concept of “three areas and two buffers” in the 2004 general biosafety requirements for laboratories.<sup>10</sup> Additional buffers are established with the use of biosafety cabinets. While Class II biological safety cabinets are normally used in BSL-3 laboratory, a Class III biological safety cabinet may be needed for high-risk procedures involving Risk Group 2 microorganisms, in accordance with national

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<sup>9</sup> China. Chinese General Administration of Quality Supervision, Inspection and Quarantine and Chinese Standardization Administration, *General Biosafety Requirements for Laboratories*, Regulation GB19489-2004 (Beijing: 2004); China. Chinese Ministry of Construction and Chinese General Administration of Quality Supervision, Inspection, and Quarantine, *Architectural and Technical Code for Biosafety Laboratories*, Regulation GB50346-2004 (Beijing: 2004).

<sup>10</sup> China. Chinese General Administration of Quality Supervision, Inspection and Quarantine and Chinese Standardization Administration, *General Biosafety Requirements for Laboratories*, Regulation GB19489-2004 (Beijing: 2004).

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rules. Biological safety cabinets should be situated away from areas of high foot traffic and out of cross-currents from doors and ventilation systems. A final buffer for laboratory workers is personnel protective equipment and other physical protective equipment, which must be used in BSL-3 laboratories.

BSL-3 facilities also have stricter requirements for the control of air and other materials exiting the area. The ventilation system must establish a directional air flow from the clean area into the contaminated area. At all times, staff must ensure that proper directional air flow into the contaminated area is maintained. The building ventilation system must be also constructed so that air from the BSL-3 laboratory is not recirculated within that laboratory or to other areas within the building. Exhaust air from the BSL-3 laboratory (other than from biological safety cabinets) must be filtered through high-efficiency particulate air (HEPA) filters and must be discharged outside of the building. Exhaust air outtakes are separate from air intake vents and from occupied buildings. The exhaust air from Class II and/or Class III biological safety cabinets must be passed through individual HEPA filters for each biosafety cabinet and must be discharged in a way that avoids interference with the air balance of the cabinet or the exhaust system for the building. All HEPA filters for the biosafety cabinet(s) and general BSL-3 laboratory must be installed in a manner that permits gaseous decontamination and testing. For liquid and solid materials, an autoclave for the decontamination of waste material must be available in the BSL-3 laboratory. Autoclaves are to be installed in the wall between the clean area and the potentially contaminated area so that all autoclaved materials can be removed in the clean zone. All laboratories that meet the construction, equipment, and other pertinent biosafety standards for BSL-3 are to be accredited by the proper authorities working on behalf of the State Council. The certificate of accreditation is valid for a five-year period.

### **Biosafety Containment Level 4**

The practices, safety equipment, and facility design and construction are applicable to clinical, diagnostic, research, or production facilities in which work is performed with Risk Group 1 microorganisms and/or with large volumes and high concentrations of Risk Group 2 microorganisms, where there is a high risk of aerosol

spread and subsequent life-threatening consequences from infection. As of yet, there are no BSL-4 laboratories in China. For the time being, Risk Group 1 microorganisms are being studied in BSL-3 laboratories using BSL-4 practices and strengthened individual protection for the personnel working with these pathogens.

### **The Management of Specific Work within a BSL-3 Laboratory**

A variety of procedures can be performed in a laboratory; some procedures generate a low or very restricted risk of accidental exposure, others create a higher risk of exposure. To illustrate, a Risk Group 3 virus being grown in liter-sized cultures to make reagents or to deactivate it for the manufacture of a vaccine might require BSL-3 biosafety precautions. Also, careful attention must be taken selecting the appropriate biosafety measures for procedures (e.g., grinding, centrifugation) that create a risk of micro-aerosolization of the pathogenic microorganism or that involve the handling of dry forms of Risk Group 2 microorganisms that are electrostatic. A combination of the type of laboratory procedures to be done and the Risk Group of the pathogenic microorganism(s) are used to select specific biosafety measures for work within a BSL-3 laboratory. Such factors are used to determine the size of the BSL-3 facility required, the proper class of biosafety cabinet and other physical containment devices, and the personal protective equipment needed for specific procedures. Following the risk assessment, a biosafety plan specific to each proposed experiment can be created.

For all experiments with highly infectious human or animal pathogens, an accredited laboratory must present a plan for the experiments that is in conformance with the biosafety regulations of the appropriate authorities (e.g., veterinary for animal pathogens). BSL-3 laboratories must also ensure that the staff that will be involved in these experiments are trained appropriately in the practices, procedures, and biosafety requirements for the proposed experiments. If these preconditions are met, the appropriate national health or veterinary authorities will review suitability of the proposed experiment.

In conjunction with the facility's biosafety capacities, two aspects of the research plan are closely evaluated. First, the laboratory must have attained the appropriate corresponding level of biosafety to be able to apply for acquisition of a highly pathogenic

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microorganism. A BSL-1 laboratory, therefore, cannot apply to work with a microorganism in Risk Group 3 unless and until the laboratory is certified as having completed the required improvements to bring its infrastructure, laboratory equipment, biosafety management, biosafety practices and standard operational procedures, personnel training, and personal protective gear up to BSL-3 standards. Second, the laboratory must state a scientific research requirement for the proposed work with highly pathogenic microorganisms.

If there is a scientific need for the research and all of the requisite biosafety requirements have been met, then the relevant health or veterinary authorities will grant the requesting BSL-3 laboratory credentials to proceed with the proposed experiment(s) and will also give approval to receive the seed culture for the highly pathogenic microorganism(s) from a central culture collection. At the conclusion of the experiment(s), a report describing the work undertaken and its results must be filed with the relevant authorities.

### ***Institutional Management of BSL-3 Laboratories***

An institution that establishes a BSL-3 laboratory is responsible for overseeing laboratory biosafety so that the required national standards for strict scientific, technical, and managerial regulations are implemented and updated, as needed, for the BSL-3 facility. Under this managerial system a National Accreditation Service for Conformity committee, consisting of biosafety experts, was established. This committee conducts initial and periodic inspections to ensure the implementation of the biosafety regulations and the proper maintenance and repair of the BSL-3 facilities, equipment, and material. The Ministries of Health and of Agriculture, which oversee pathogenic human and animal microorganisms respectively, are also engaged in authorizing specific activities in BSL-3 laboratories.

The institution with a BSL-3 laboratory shall create a three-tiered system for biosafety management that consists of the Institutional Biosafety Committee (IBC), the BSL-3 laboratory director, and the principal investigators (PIs) for various programs conducted within the laboratory. The IBC has four major responsibilities. First, the IBC is accountable for establishing biosafety policies, procedures, and regulations that are

consistent with national and international laws, regulations, and standards and making sure that these are carried out in the institution. If personnel at the BLS-3 propose projects involving biohazardous substances that are not specifically listed in the risk groups, the IBC has the authority to review, approve, and oversee the execution of such projects. The IBC is also responsible for guaranteeing that the institution's Biosafety Office makes biosafety information services, training programs, and emergency assistance available. Finally, the IBC is to supervise and assist the institution's Biosafety Officer and his support staff in carrying out their responsibilities.

Concurrent with the IBC, the director of the BSL-3 laboratory holds primary responsibility for laboratory biological safety. The BSL-3 director reviews and renews the certificates for the proper operation of laboratory safety equipment, facilities, and personnel training. To underscore this responsibility, these certificates bear the laboratory director's personal signature. Assessments of the potential safety and environmental hazards of proposed research programs and procedures are the responsibility of the laboratory director, who also develops standard operating procedures specific to the laboratory and, if needed, for individual projects. In sum, the laboratory director supervises the biosafety of all experiments and practices within the BSL-3 facility and sees that all personnel comply with all applicable regulations and guidelines.

The laboratory director is also responsible for seeing that there is adequate surveillance of the health of laboratory personnel. Given the potentially hazardous nature of the work, BSL-3 laboratories are not to employ individuals who are highly susceptible to disease (e.g., pregnant women,<sup>11</sup> immuno-compromised individuals). The objective of the surveillance is to monitor for occupationally acquired diseases. Appropriate health surveillance activities include the mandatory medical examination of all BSL-3 laboratory personnel, beginning with a detailed medical history and a physical examination. After a satisfactory clinical assessment, the examinee should be provided with a medical contact card that the individual is always to carry that contains their picture and identifies them as an employee of a BSL-3 laboratory. During the initial examination, a baseline serum sample should be obtained and stored for future reference.

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<sup>11</sup> For the safety of mother and child, pregnant women are restricted from engaging in certain activities with biohazardous agents for the duration of their pregnancy.

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Health monitoring allows for the provision of active or passive immunization against one or more diseases, where indicated, and of effective personal protection equipment and procedures.<sup>12</sup>

The PIs in a BSL-3 laboratory are to assess the risks of their experiments and, if required, to submit proposed experiments for initial review and approval by the IBC, other relevant managerial departments of the institution, and subsequently by the appropriate national authorities. PIs must register the following types of experiments for institutional and national biosafety oversight: 1) recombinant DNA activities; 2) work with infectious agents; 3) experiments involving the use of human blood or other potentially infectious materials, such as unfixed human tissues, primary human cell lines, and certain body fluids; and, 4) work animal and plant pathogens. Other major biosafety duties of the PI are to ensure the safe operation of their laboratory; to establish plans and capacities for emergency treatment in the event of an accident; to train their personnel in safe work practices; and to comply with all applicable state and local or institute regulations and guidelines.

The institution with the BSL-3 laboratory or the laboratory itself is to provide initial and annual training to laboratory personnel to ensure their mastery of the standardized laboratory technology, operational procedures, and biosafety precautions, knowledge, and operational and technical know-how. All laboratory personnel are to be evaluated on their knowledge of these matters before beginning work in the laboratory, and only those assessed as having the requisite knowledge will be permitted to resume their duties.

Finally, all institutions with BSL-3 laboratories are to have a general system of safety and security for the BSL-3 laboratory and take specific additional measures to ensure that the BSL-3 laboratory guards strictly against the theft, misplacement, and/or unauthorized diversion of the pathogenic microorganisms in its possession. These security measures are to be reviewed and improved, as needed. In case of any theft, misplacement, or diversion of a microorganism from a BSL-3 laboratory, the incident must be reported to the appropriate authorities.<sup>13</sup> The BSL-3 laboratory is also to advise

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<sup>12</sup> This type of health monitoring would also be required for personnel working in a BSL-4 laboratory, but not for those working in BSL-2 or BSL-1 laboratories.

<sup>13</sup> See Article 17, in China's *Managerial Regulation Governing the Biosafety in Laboratories Working with Pathogenic Microorganisms*, Regulation 424-2004 (Beijing: State Council, 2004).

local law enforcement agencies of its activities related to highly pathogenic microorganisms and is to accept their counsel and supervision on matters of facility security.

Laboratory accidents and instances of regulatory noncompliance at microbiological or biomedical laboratories in China are to be reported to the management of the institution and, as appropriate, to the national authorities overseeing the laboratory's activities. Depending on the seriousness of the accident or noncompliance, an investigation would be conducted. If the situation involves laboratory-acquired infection, the laboratory would be closed during the investigation of the incident. Once the cause of the problem is understood, a new standard operating procedure or guideline would be established to address the problem, or perhaps the governing regulation would be revised. The laboratory where the incident occurred would have to be recertified to work at the appropriate biosafety level prior to resuming operations.

### **Concluding Observations**

In recent years, the Chinese government has made considerable revisions to its regulations and standards for laboratory biosafety. Additional improvements to China's laboratory biosafety measures will certainly be made in the future. For the time being, the issue of concern for laboratory biosafety in China relates to a shortage of officials, experts, and scientists who specialize in laboratory biosafety. This dearth of professionals has made it a challenge to implement the new regulatory system in a timely and complete manner. Furthermore, this personnel shortage has also made it difficult to review and compare China's existing regulations with the upgraded standards and technologies of other countries to help determine where China's regulations might be even further improved. To augment China's expertise in biosafety, the Chinese government has begun to send scientists to work in laboratories overseas to gain first-hand experience with practices in other countries. To continue building on the recent improvements that have been made, individuals involved in laboratory biosafety in China welcome cooperation with specialists in other countries and from the World Health Organization on matters of laboratory biosafety. Areas of potential collaboration include

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biosafety training in universities, research laboratories, and other facilities; institutional management of biosafety; novel laboratory biosafety technologies; new laboratory biosafety concepts; and biosecurity.