Thoughts on Strengthening the System Planning for High-Containment Biosafety Laboratories in China (Postprint)

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Abstract

In recent years, with the continuous emergence of epidemics such as avian influenza, tuberculosis, and Ebola, an increasing number of healthcare workers and scientific researchers worldwide have been engaged in activities related to the diagnosis, detection, research, development, production, and teaching of dangerous pathogenic microorganisms—activities that must be conducted within high-level biosafety laboratories. This article compares the development status and characteristics of domestic and international high-level biosafety laboratory systems, analyzes existing problems in China' s high-level biosafety laboratory system regarding overall layout, funding investment, and the construction of management and support systems, and proposes recommendations for improving laboratory construction layout, increasing funding investment, strengthening management and support system construction, and enhancing information and resource sharing, thereby promoting the development of China' s high-level biosafety laboratory system and providing support for the country' s response to emerging and re-emerging infectious disease outbreaks.

Full Text

Considerations on Strengthening the Planning of China' s High-level Biosafety Laboratory System

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Abstract

In recent years, with the continuous emergence of epidemics such as avian influenza, tuberculosis, and Ebola, an increasing number of medical workers and researchers worldwide have been engaged in activities related to dangerous pathogenic microorganisms, including diagnostics, detection, research, development, production, and teaching. All these activities must be conducted within high-level biosafety laboratories. This paper compares the development status and characteristics of high-level biosafety laboratory systems both internationally and domestically, analyzes existing problems in China' s high-level biosafety laboratory system regarding overall layout, funding, and the construction of management and support systems, and proposes recommendations to improve laboratory construction layout, increase capital investment, strengthen management and support systems, and enhance information and resource sharing. These measures aim to advance the construction of China' s high-level biosafety laboratory system and provide support for responding to emerging and re-emerging infectious disease outbreaks.

Keywords: high-level, biosafety, laboratory

1. Development History of Biosafety Laboratories

In 1886, Koch published a report on laboratory-acquired cholera infection, which is recorded as the world' s first report on laboratory biosafety. During the 1940s, the United States conducted extensive research on biological weapons, using numerous highly infectious pathogens for laboratory weaponization and field testing, which led to frequent laboratory-acquired infections. By the 1960s, European and American countries began paying attention to laboratory biosafety issues, with the United States establishing the first biosafety laboratories, followed by the United Kingdom, the former Soviet Union, Canada, Japan, and other developed countries that subsequently built biosafety laboratories with various protection levels. In 1974, the U.S. Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) jointly published *Classification of Etiologic Agents on the Basis of Hazard*, which for the first time categorized pathogenic microorganisms available for human research and corresponding laboratory activities into four risk levels. Subsequently, in the 1980s, the World Health Organization (WHO) also classified global biosafety laboratories into levels 1–4, promoting basic biosafety concepts through the 1983 publication of the *Laboratory Biosafety Manual* and encouraging countries to develop operational guidelines for the safe handling of pathogenic microorganisms in their laboratories, while clarifying requirements for biosafety management and laboratory hardware and software [Figure 1: see original paper]. In 1993, the CDC and NIH collaborated again to launch *Biosafety in Microbiological*

and Biomedical Laboratories, which has reached its 4th edition by 1999 and is currently recognized internationally as the "gold standard" for biosafety laboratories. Since then, biosafety laboratories worldwide have had unified guidelines and have embarked on a path of stable development.

Since the beginning of the 21st century, the 2001 anthrax letter attacks and the 2003 global SARS outbreak have accelerated the pace of biosafety laboratory construction worldwide. For example, the United States launched the "Bioshield" program in 2003 to promote biosafety laboratory construction. The United States and the United Kingdom built the first BSL-4 laboratories in the earliest days, and subsequently, the former Soviet Union, Australia, South Africa, Japan, Canada, France, Germany, Italy, Sweden, Spain, the Netherlands, Denmark, Brazil, India, Gabon, China, and others have successively constructed BSL-4 laboratories. By 2007, it was known that 60 institutions in 22 countries and regions worldwide possessed BSL-4 laboratories. This demonstrates that countries around the world have regarded the construction of high-level biosafety laboratories as an important means to enhance national strategic capabilities, vigorously promoting their development to form comprehensive, collaborative national and regional biosafety laboratory systems that play crucial roles in responding to public health emergencies and bioterrorism incidents.

Currently, the global status and development of high-level biosafety laboratories exhibit several notable characteristics: (1) Most developed countries have incorporated high-level biosafety laboratory construction into their national strategic plans, deploying corresponding platform and research programs around laboratory operations and establishing comprehensive regulations and systems for personnel management, research activity management, and pathogen management; (2) The vast majority of high-level biosafety laboratories are affiliated with government agencies or research institutions, with operational funding primarily from fiscal appropriations, while also encouraging non-profit organizations and enterprises to establish corresponding biosafety facilities to meet their research and development needs for biological products; (3) Developed countries have initiated a global layout of high-level biosafety laboratories, aiming to advance the frontlines of infectious disease prevention and biosecurity while effectively controlling and acquiring strategic resources; (4) Laboratory network systems have been established with high-level biosafety laboratories as the core, such as the U.S. Laboratory Response Network (LRN), National Biosafety Laboratory System (NBL), Regional Biosafety Laboratory System (RBL), and the European High-level Biosafety Laboratory Program (EHSL4). Additionally, complete biosafety laboratory supervision systems and timely responses to safety hazards are also important features. For instance, to address recent frequent laboratory safety incidents, the United States issued a memorandum on *Further Enhancing Biosafety and Biosecurity in the United States* in October 2015, and the Federal Experts Security Advisory Panel (FESAP) and Fast Track Action Committee (FTAC) proposed implementation recommendations on biosafety and biosecurity, all of which put forward requirements, implementation measures, and suggestions for strengthening safety supervision of biosafety labora-

tories. Subsequently, on April 19, 2016, the U.S. Government Accountability Office (GAO) pointed out that safety management of high-level biosafety laboratories in five departments and nine agencies (including the CDC) had loopholes, and proposed a series of recommendations, including developing and updating biosafety policies, ensuring supervision results are reported to senior officials, and establishing timelines for completing safety recommendations.

2. Current Status of Foreign High-level Biosafety Laboratory Systems

Biosafety is an important component of national security, closely related to core national interests, and has received increasing attention from governments worldwide. Many countries have incorporated biosafety into their national strategies and established complete biosafety technology support systems. High-level biosafety laboratory network systems constitute the core component and fundamental platform of biosafety technology support systems, enabling three main functions: microbial strain resource preservation, scientific research, and industrial application transformation. They address five key aspects of highly infectious disease pathogens: monitoring and early warning, detection, disinfection, prevention and control, and treatment. By conducting research on pathogen isolation and identification, pathogen-host interaction mechanisms, infection model establishment, vaccine development, and biopreparedness, these systems provide important scientific and technological support for controlling highly infectious diseases, public health emergency response, and new drug development.

The United States has established multiple high-level biosafety laboratory systems according to its needs. Although different laboratories belong to different departments with clear functional divisions, they have also established efficient coordination and cooperation mechanisms. The LRN is guided and operated by the CDC, while the NBL and RBL are funded by the NIH. The LRN consists of a three-tier structure: the top tier comprises three high-level biosafety laboratories responsible for verifying and confirming major infectious disease pathogens and training professional and technical personnel for the national laboratory network; the second and third tiers consist of 150 and 25,000 testing laboratories, respectively, responsible for rapid diagnosis and submitting data to upper-level laboratories [Figure 2: see original paper]. The NBL comprises two BSL-4 laboratories whose core mission is to conduct basic pathogen research and provide resources and information support for national rapid mobilization and response to public health emergencies. The RBL consists of 12 BSL-3 laboratories across the United States, responsible for providing resources and information support for rapid mobilization and coordination of regional and local systems in response to public health emergencies [Figure 3: see original paper].

To better utilize high-level biosafety laboratory resources and promote cooperation and resource sharing among different laboratories, the European Union has established the European High-level Biosafety Laboratory Program (EHSL4).

The French National Institute of Health and Medical Research (Inserm) is responsible for coordinating this program. Laboratories within the system are distributed across Europe with varying scales and functions (including diagnostics, research, animal experiments, and professional training). On this basis, the EU will continue to support laboratory construction to meet research needs for emerging highly virulent viruses and drug-resistant bacteria. Meanwhile, the EHSL4 program will promote and coordinate basic and clinical research, improve the EU' s pathogen diagnostic capabilities, provide biosafety and reliability training for researchers, and establish a management or coordination body.

From the perspective of established high-level biosafety laboratory systems and their operations, the main characteristics are emphasis on improving overall system capabilities with sustained investment, attention to division of labor and cooperation within the system, and emphasis on resource and information sharing within the system.

3. Development Status of China' s High-level Biosafety Laboratory System

China' s construction of high-level biosafety laboratories can be traced back to the 1980s, when China's first modern BSL-3 laboratory was built at the Academy of Military Medical Sciences in 1987 to study the transmission mechanism of epidemic hemorrhagic fever virus. Subsequently, China introduced and built a number of biosafety laboratories approaching BSL-3 standards, which played important roles in the prevention and control of infectious diseases in China and provided valuable experience for the development of China' s biosafety management system.

Since the outbreak of SARS in China in 2003, the Party Central Committee and the State Council have attached great importance to the construction of high-level biosafety laboratories. In 2004, China issued its national biosafety laboratory construction system plan, which planned to build a nationwide biosafety laboratory system with high-level biosafety laboratories as nodes, accelerating the pace of high-level biosafety laboratory construction. On January 31, 2015, the Wuhan National Biosafety Laboratory of the Chinese Academy of Sciences was completed in Wuhan, marking that China' s first BSL-4 laboratory would soon be operational [Figure 4: see original paper]. In addition, as of August 31, 2013, 42 BSL-3 laboratories in China had been accredited, and a number of BSL-2 laboratories were operating safely, indicating that a nationwide biosafety laboratory system had initially taken shape in China. Meanwhile, China has formulated and promulgated a series of regulations, norms, and standards for laboratory biosafety management to guide laboratory management and safe operation. In 2003, the Ministry of Health issued China' s first standard on laboratory biosafety management, the *General Biosafety Guidelines for Microbiological and Biomedical Laboratories* (WS233-2002), marking the beginning of standardized management of laboratory biosafety in China.

On November 12, 2004, the State Council promulgated the *Regulations on the Administration of Biosafety in Pathogenic Microbiology Laboratories* (hereinafter referred to as the *Regulations*), marking the beginning of legalized management of laboratory biosafety in China. In conjunction with the implementation of the *Regulations*, ministries and commissions including the Ministry of Environmental Protection, the former Ministry of Health, the Ministry of Agriculture, the General Administration of Quality Supervision, Inspection and Quarantine, the Ministry of Construction, and the Ministry of Science and Technology respectively issued supporting regulations and standards such as the *Administrative Measures for Biosafety Environment of Pathogenic Microbiology Laboratories*, *General Biosafety Guidelines for Microbiology and Biomedical Laboratories*, *General Requirements for Laboratory Biosafety*, *Technical Code for Biosafety Laboratory Construction*, *Review Measures for High-level Pathogenic Microbiology Laboratory Construction*, *Veterinary Laboratory Biosafety Management Norms*, *General Requirements for Laboratory Biosafety* (GB19489-2004, 2008), and *Technical Code for Biosafety Laboratory Construction* (GB50346-2004, 2011). These documents provide detailed provisions for all aspects of laboratory biosafety management, offering legal and technical guarantees for standardizing laboratory biosafety management in China.

The promulgation of China' s biosafety laboratory system plan and the construction of laboratories have not only promoted progress in laboratory design, construction techniques, and technology, improved the localization level of key facilities and equipment, and gathered and cultivated a group of high-end scientific and technological talents as well as high-level engineering and management personnel, but have also played important roles in the prevention and control of emerging infectious diseases such as SARS, H5N1 avian influenza, severe fever with thrombocytopenia syndrome, influenza A (H1N1), H7N9 avian influenza, and Ebola, greatly improving China' s ability to respond to public health emergencies and biological threats.

However, China still faces certain problems in the construction and management of its high-level biosafety laboratory system. Currently, only one BSL-4 laboratory has been completed nationwide, and the management and maintenance of its key equipment, as well as personnel mastery of standardized operating procedures (SOPs) for BSL-4 laboratories, are not yet mature. Among the batch of BSL-3 laboratories that have been built, the distribution across regions is uneven, and many laboratories suffer from low utilization rates due to insufficient construction and operational maintenance funds. Overall, the problems in China' s high-level biosafety laboratory system are mainly manifested in: (1) Regarding overall layout, insufficient consideration has been given to industrial and economic development needs and requirements in special fields, with more laboratories for scientific research and fewer for emergency response; (2) Regarding funding mechanisms and operational mechanisms, long-term stable construction investment, operational mechanisms, and sharing and cooperation mechanisms have not yet been formed, lacking stable operational funding support, with a disconnect between construction and operation that results in laboratories either

not being completed or being unable to operate normally after completion; (3) Regarding management and support system construction, the laws, regulations, and standard systems for high-level biosafety laboratories urgently need further improvement, supporting research condition platforms such as information resources and experimental data lag behind, and the construction of engineering technology, management, and strategic research teams needs strengthening.

4. Considerations for Strengthening China' s High-level Biosafety Laboratory System

Based on the experience of developed countries in constructing high-level biosafety laboratory systems and China' s actual conditions, China needs to coordinate the development planning of high-level biosafety laboratories to serve the strategic goal of China' s "overall national security concept," addressing strategic needs for national security, population health, animal health, economic development, and the development of biosafety-related science and technology. With basic research, applied basic research, applied research, and industrial development as the main research directions, China should aim to enhance overall biosafety capabilities including laboratory construction, operation, maintenance, management, talent cultivation, and equipment development, and plan to build a nationwide high-level biosafety laboratory platform system and a management system for safe operation and resource sharing.

(1) Improve Laboratory Construction Layout. Targeting frontier scientific research and major national strategic needs, and based on the overall development trends of international high-level biosafety laboratories combined with domestic development environments and foundations, China should gradually improve its high-level biosafety laboratory system from four aspects: preliminary research, new construction, promotion, and upgrading. Fully considering the characteristics of China' s economic and industrial development, and following the approach of demand-based setup, rational layout, and synchronous construction, China should intensify the construction of high-level biosafety laboratories for emergency response on the basis of existing facilities to achieve a scientific and rational layout. For high-level biosafety laboratories that already have certain research foundations and advantages, they should actively carry out research on key and difficult issues in the biosafety field. For high-level biosafety laboratories that have been initiated but not yet completed, efforts should be intensified in project management and technical research to strive for early completion and operation. For high-level biosafety laboratories that have been put into operation but still have considerable development potential, technical indicators and comprehensive performance should be further improved and upgraded to fully play their roles.

(2) Increase Capital Investment. Adapting to situational needs and actively creating conditions, China should strengthen investment in high-level biosafety laboratory construction through multi-channel, multi-level, and multi-form fund-

raising to form a diversified investment pattern and multi-party joint construction mechanism. Strengthening coordination among preliminary research, construction, upgrading, operation, and scientific research of high-level biosafety laboratories, China should increase financial investment from central and local governments and encourage investment from other sources such as enterprises to form a diversified investment pattern. Standardizing investment management and strengthening performance evaluation will effectively improve the efficiency and effectiveness of fund utilization. China should gradually increase the support of fiscal science and technology funds for public welfare laboratory construction, establish special funds, and leverage the guiding role of fiscal funds to encourage financial capital to increase investment in high-level biosafety laboratory construction. China should support and guide capable enterprises to independently build high-level biosafety laboratories and encourage enterprises to develop key technologies and equipment for biosafety laboratories.

(3) Strengthen Management and Support System Construction. China should improve the legal and regulatory framework, technical standards, ethics review, and supervision and management systems. It should promptly study, formulate, and revise relevant laws, regulations, or departmental rules such as the *Administrative Measures for High-level Biosafety Laboratories* and the *List of Pathogenic Microorganisms Infectious to Humans*. Based on the National Pathogenic Microbiology Laboratory Biosafety Expert Committee, a National Laboratory Biosafety Management Committee and Expert Committee should be established by law and incorporated into the leadership system of the National Security Commission. A Biosafety Laboratory Operation Management Standardization Technical Committee should be established to effectively promote the construction and effective operation of China' s biosafety laboratory standard system. China should strengthen ethics review and supervision of laboratory research activities, establish and improve a research ethics review and supervision system, improve norms and operational procedures for sample transport, storage, and testing, formulate emergency plans, and improve laboratory assessment, protection level accreditation, and activity approval processes. It should strengthen quality control and whole-process supervision of laboratory biosafety protection, enhance talent cultivation, and establish talent evaluation systems and incentive mechanisms.

(4) Enhance Information and Resource Sharing. Additionally, China needs to break down sectoral barriers and establish a scientific information and data classification storage and hierarchical sharing system. For public welfare biosafety laboratories, especially those with key national layouts, long-term accumulated resources, information, and scientific data should be organized, submitted, and databased to achieve standardization and normalization of data collection, processing, and preservation. On this basis, with government investment as the main source, a sharing service system for the laboratory system should be formed. China should improve information collection, monitoring, statistics, and analysis of the development situation of high-level biosafety laboratory systems, improve the information release mechanism for high-level

biosafety laboratories, and perfect the personnel biosafety training system, training effectiveness evaluation system, and personnel training management system. Systematic training should be provided for laboratory operation and maintenance, biosafety management, scientific research personnel, and third-party service agency personnel to ensure safe laboratory operation and reduce infection risks for relevant personnel. China should continue to conduct policy research related to biosafety laboratories, comprehensively monitor international development trends, and carry out forward-looking and tracking research on major issues in biosafety laboratory development in combination with national and social development dynamics to provide policy recommendations and consulting advice.

(5) Establish a National Biosafety Innovation Center. Relying on high-level biosafety laboratories with rich operation and management experience, China should establish a National Biosafety Innovation Center. The National Biosafety Center should be responsible for providing support services for biosafety management and personnel training for high-level biosafety laboratories nationwide, becoming a resource and information sharing center and information release platform for the national high-level biosafety laboratory system. Regional biosafety centers should provide support services for biosafety management and personnel training for high-level biosafety laboratories within their regions, becoming regional nodes for resource and information sharing and emergency response within the national high-level biosafety laboratory system.

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Note: Figure translations are in progress. See original paper for figures.