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Review Article

Current status and future challenges of high-level biosafety laboratories in China

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ABSTRACT

High-level biosafety laboratories are safe and secure platforms which integrate reliable containment, well-trained personnel, and specific biosafety manuals and practices to protect researchers from being infected while manipulating microbial pathogens and prevent pathogens from being released into the outside environment. During the past decades, laboratories with different protection levels have been constructed and operated, the legal framework and a laboratory biosafety management system have been established, and these operational laboratories have played an essential role in combatting emerging and re-emerging infectious diseases in China. Here, we have summarized the significant achievements of high-level laboratory planning, construction, and operation in China, as well as the challenges that we face in the future. Additionally, we have briefly discussed the national plan for construction of high-level biosafety laboratories from 2016-2025 and "biosafety-motivated" management system. This review might be informative for further understanding the present situation and future function of high-level biosafety laboratories in China.

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1. Introduction

A biosafety laboratory (BSL) encompasses a set of precautions required for manipulating dangerous biological agents in a safe, secure, and enclosed containment setting. Primarily, a BSL consists of a primary protective barrier (safety equipment) and a secondary protective barrier (safety facilities). Based on a composite of the design features, construction, containment facilities, equipment, standard practices, and operational procedures required for working with agents of different risk groups, four biosafety laboratory protection levels are designated (BSL-1, BSL-2, BSL-3, and BSL-4).

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Among them, BSL-1 needs no special containment equipment and is generally used when working with well-characterized agents not known to cause disease in healthy adult humans and that have minimal potential hazard to the environment; BSL2 is appropriate for handling pathogenic agents associated with human disease that are rarely serious and for which preventative and therapeutic interventions are available; BSL-3 is designed for handling agents that are associated with serious or lethal disease and present high individual risk but low community risk, for which the preventative or therapeutic interventions may be available. In this type of laboratory, appropriate protective clothing and equipment are mandatory for scientists working in a negative pressure facility. Lastly, BSL-4 is the maximum containment, state-of-the-art facility constructed to handle dangerous and exotic biological agents that are likely to cause serious or lethal human disease with high individual and community risks, for which there are no preventative or therapeutic interventions usually available. This facility must be in complete isolation and the use of positive pressure personnel suit is mandatory for its staff.[4,13]

BSL-1 and BSL-2 are commonly referred to as basic laboratories while BSL-3 and BSL-4 are designated as high-level biosafety laboratories.[4,11] The main purpose of these kinds of laboratories is to protect researchers from being infected when manipulating microbial pathogens, while preventing the harmful pathogens from being released into the outside environment. Reliable containment, well-trained and knowledgeable supervisor and personnel, as well as the full execution of specific biosafety manual/standard operation practices are the pre-requisites and guarantees for the safe and secure operation of these laboratories.

Worldwide, the accepted classification systems adopted by most international organizations and countries for the different laboratory protection levels are BSL-1, BSL-2, BSL-3, and BSL-4 for facilities designed to handle suitable pathogens *in vitro*; contrastingly, ABSL-1, ABSL-2, ABSL-3, and ABSL-4 (animal biosafety laboratory) are used for facilities designed to handle suitable pathogens in *in vivo* experiments. Moreover, the containment laboratory (CL)-1–4 classification system has been adopted by some countries, such as the UK, Canada, and USA, while the physical containment (PC)-1–4 system is applied in New Zealand (Fig. 1).

2. Construction of high-level biosafety laboratories in China

In the early 1980s, the Chinese Academy of Military Medical Sciences built the first modern BSL-3 laboratory for studying the transmission mechanisms of epidemic hemorrhagic fever viruses. Subsequently, several other laboratories were built for working on Hantavirus, HIV, arboviruses, and human bacterial pathogens in national institutions. These operational laboratories provided safety platforms for research and development to study the etiology and therapeutic approaches of infectious diseases, and they also provided valuable knowledge and experience for the development of biosafety management systems for laboratories later.[2,12]

The unprecedented severe acute respiratory syndrome (SARS) epidemic that affected 37 countries including China from 2002–2003, resulting in 8098 cases and 774 fatalities, highlighted the urgent necessity of strengthening the country's public health system.[14] After the epidemic and several lab-acquired infection events worldwide, biosafety became a major priority for Chinese central and local governments and a series of 'biosafety-motivated' policies were enacted to promote legislative processes and the subsequent construction of more biosafety laboratories. From that moment, a new chapter on the sustainable operation of high-level biosafety laboratories and harmonious implementation of biosafety management was opened in China.[2,3,12,16,18]

In 2004, China's central government launched a national BSL program that aimed at building a national BSL network comprising high-level BSLs as the nodes. High-level BSLs were then constructed and successfully operated.[2] As of December 31st 2013, 53 BSLs, including 42 BSL-3s, had been fully accredited in China[1] and more laboratories have completed the accreditation in recent years. In addition, more than 1000 BSL-2 labs are currently being operated in universities, research institutions, hospitals and R&D entrepreneurship centers.[2,9,12] In addition, four mobile BSL-3 laboratories were imported from Labover (Montpellier, France) and distributed to institutes in Beijing, Shanghai, and Guangdong for the nation-wide surveillance of pathogens and the emergency response of post-disaster and global public health events.[8] In addition, a self-designed and self-constructed mobile BSL-3 was composed of two 9125 mm containers and met the biosafety requirements for pathogen diagnosis. A new and improved model of BBS-3 was installed in Freetown, Sierra Leone and used for diagnosis of the Ebola virus infection.[6,8] In parallel, a specific regulation, "Mobile Laboratory – General Requirements for Biosafety (GB27421-2015)", was issued and applied.[5]

On January 31st 2015, the first Chinese BSL-4 laboratory (National Biosafety Laboratory, Wuhan) constructed by the Chinese Academy of Sciences was physically completed.[7,15] After several years of commissioning and validation by relevant local and international authorities, the facility was finally accredited by the Chinese National Accreditation Service for Conformity Assessment (CNAS) and fully certified by the National Health Commission for manipulating the Ebola, Nipah, and Crimean-Congo hemorrhagic fever viruses, and the laboratory became operational in early 2018.[15] The operation of this laboratory marked the preliminary establishment of a national high-level biosafety network.

Fig. 1. Left: Staff celebrating the physical completion of the laboratory in 2015, Wuhan, China; Right: Two technicians performing scientific research activities under positive pressure protection in the laboratory.

Simultaneously, China has also created and promulgated a series of laboratory biosafety management regulations, norms, and standards to guide the construction, management, and safety operations of laboratories.[17] As early as 2003, China's then Ministry of Health promulgated "General Guidelines for Biosafety in Microbial and Biomedical Laboratories (WS233-2002)," which marked the beginning of the standardized management of laboratory biosafety. Later on November 12th, 2004, the State Council promulgated "Regulations on Biosafety Management of Pathogenic Microorganism Laboratories," which marked the beginning of the legalization of laboratory biosafety management.[11,16]

To implement the regulations, several ministries separately or jointly issued policy documents, such as "Measures for the Management of Biosafety Environments in Pathogenic Microorganism Laboratories," and "General Guidelines for Biosafety in Microorganism and Biomedical Laboratories," "General Requirements for Biosafety in Laboratories and the Technical Regulations for the Construction of Biosafety Laboratories." Technical guidelines and documents, such as "Measures for Examination of Construction of High-level Pathogenic Microorganism Laboratories," "Code for Biosafety Management of Veterinary Laboratories," "General Requirements for Biosafety of Laboratories (GB19489-2004, 2008)," and "Technical Code for Construction of Biosafety Laboratories (GB50346-2004)" provided detailed provisions on all aspects related to laboratory design, construction, accreditation, and management. The standardization of laboratory biosafety management in China provides legal and technical guaranteed on-set operations.[11,16,17]

3. Challenges in the development of high-level biosafety laboratory systems

In China, the constant establishment of different BSLs has greatly promoted the accumulation of knowledge on laboratory design and construction, development of key biosafety facilities and equipment, as well as laboratory management. The overall capability of laboratories has been greatly improved to deal with public health and biosafety emergencies. However, we have encountered some challenges; there are insufficient laboratories in industry and in clinical units, an unbalanced distribution of regions and associations, a lack of proper national coordination and resource sharing management, as well as an uncertainty about the financial support for laboratory construction, operation, and maintenance.[9,12,16] These bottlenecks hamper the capacity of well-established laboratories to quickly respond to public health emergencies.

3.1. Unbalanced national distribution

Presently, the national BSL network, with the BSL-4 laboratories as its core units, has not yet been completely established. The existing laboratories are mainly concentrated in economically developed regions, whereas some remote regions lack even a single laboratory facility. Indeed, most of these laboratories are designed mainly for pathogen detection and scientific research, but not for specialized manipulations such as industrial testing and pathological anatomy analyses. In addition, the majority of these laboratories are installed in universities and scientific research institutions, with a limited number in clinical hospitals and industrial production units. Therefore, this unbalanced distribution among regions and industries leads to a contradictory scenario between the current actual use and arising demands.

3.2. Inadequate biosafety management systems

Since the promulgation and implementation of "Regulations on Biosafety Management of Pathogenic Microorganism Laboratories," issued by State Council in 2004, a series of other regulations have been formulated by different ministries and local governments. These have considered the examination and approval of laboratory construction and accreditation, authorization of research activities, as well as pathogen, waste, and laboratory animal management regulations. Although these regulations wholesomely cover all aspects of construction, management, and eventual operation of BSLs, their enforcement still needs to be strengthened. Furthermore, due to different investment sources, affiliations, and management systems, the implementation of these laboratories faces difficulties converging objectives and cooperation workflows. This scenario puts laboratory biosafety at risk since the implementation efficiency and timely operations are relatively compromised.

3.3. Insufficient resources for efficient laboratory operation

Depending on the size and location, building a modern BSL costs millions of US dollars, and in China the funds for construction are typically raised by the state, local governments, upstream authorities, and institutions. Additionally, 5–10% of construction costs are needed for annual operation. However, the maintenance cost is generally neglected; several high-level BSLs have insufficient operational funds for routine yet vital processes. Due to the limited resources, some BSL-3 laboratories run on extremely minimal operational costs or in some cases none at all.[12]

3.4. Deficiency of professional capacity

In the process of BSL construction, operation, and management, highly skilled professional teams from diverse disciplines such as architectural science, materials science, aerodynamics, automatic controlling, environmental science, microbiology, botany, biosafety, and systems engineering are required. In addition, biosafety measures and practices are vital in daily laboratory operations hence a highly qualified, motivated, and skilled biosafety supervisor is needed not only for overseeing solid containment but also in laboratory risk management. Currently, most laboratories lack specialized biosafety managers and engineers. In such facilities, some of the skilled staff is composed by part-time researchers. This makes it difficult to identify and mitigate potential safety hazards in facility and equipment operation early enough. Nonetheless, biosafety awareness, professional knowledge, and operational skill training still need to be improved among laboratory personnel.

4. The future outlook of biosafety laboratories in China

In 2016, the National Development and Reform Commission and the Ministry of Science and Technology jointly issued the "Planning for the Construction of High-level BSLs across China (2016–2025)".[10,16] The initiative targets the five aspects of monitoring, detecting, eliminating, preventing, and treating severe infectious diseases, with the strategic aim of strengthening the overall capacity of BSLs to meet national demands of microbial resource preservation, scientific research, environmental protection, and industrial application in human and animal health, inspection, and quarantine. Accordingly, the national high-level BSL network with a rational layout will be formed and operated by 2025.

4.1. Deployment and implementation of the national high-level biosafety laboratory program

Considering regional distribution and actual demand, especially in regions that are facing increased domestic and international challenges of fatal infectious diseases, the operation of 5–7 BSL-4 laboratories has been scheduled. In Harbin, Heilongjiang province, The Chinese Academy of Agricultural Sciences will oversee operations of a comprehensive research platform on important animal zoonotic infectious diseases; in Southwestern China, a high-level biosafety facility jointly built by the Chinese Academy of Medical Sciences and the Chinese Academy of Sciences in Kunming, Yunnan Province, will focus on non-human primate infection experiments. The Wuhan National Biosafety Laboratory (NBL, Wuhan), located in the Hubei Province in central China, will function as a comprehensive research and international cooperation platform for highly pathogenic microorganisms and at the same time will aim to be a reference laboratory for the World Health Organization. In Northern China, the China Center for Disease Control and Prevention will build a high-level BSL as a comprehensive platform for research on prevention and control of infectious diseases. Thereafter, the construction of other maximum biocontainment facilities in South, East, and Northwest China will be considered in accordance with domestic and international demands.

The public BSL-3 laboratories are located in government-affiliated institutions and finally form a network that plays a pivotal role in meeting the public health requirements that concern human and animal health, inspection, and quarantine, as well as environmental protection. Furthermore, these facilities essentially serve as primary platforms for scientific research on microbe analysis and detection, strain preservation, and human and animal anatomy studies. At the same time, government- and non-government-affiliated institutions, universities and private enterprises are encouraged to construct and operate non-public BSL-3 laboratories to satisfy their diversified needs. Specific containment facilities will also be constructed in research institutions engaging in special fields (deep-sea, space, polar and other special environments).

4.2. Improvement of the efficiency of laboratory operations and management

We should promptly revise the existing regulations, guidelines, norms, and standards of biosafety and biosecurity. The experimental verification and industrialization development of existing and newly developed containment equipment should be the main direction in the establishment of a research and development system for verification, standardization, and intellectual property protection for core technology and key components. Finally, this system would form a value chain from the development of facility and personnel protection equipment to their evaluation, certification, and use. Relying on the operational and simulated BLS-3 and BSL-4 laboratories, theoretical and practical training, evaluation, and recording systems will be perfected and applied.

5. Establishment of multi-funding input mechanisms

Overall, the coordination of pre-research, construction, upgrading, operation, and scientific research in high-level BSLs should be strengthened. Financial investments from central and local governments should be increased, while entrepreneurial grants and other sources of funding are strongly encouraged for eventually forming a diversified investment model for the program. We need to streamline investment management to strengthen performance evaluation and to improve the efficiency of funds. In order to continue making progress, we will increase the financial support for construction of public laboratories, support and guide competent enterprises to build private ones independently, and encourage enterprises to develop key technologies and equipment for BSLs.

5.1. Enhancing information and resource sharing

Establishing a management system for all classified information generated in laboratories and biological resource centers entails building an information database and a biological resource bank, standardizing data collection, processing, and storage, as well as forming a hierarchical information- and resource-sharing system oriented toward scientific research and innovation.

The staff should regularly collect, monitor, and analyze information on the situation of high-level BSL development while improving their information dissemination mechanisms, continuing relevant policy research on BSLs, monitoring international development trends, and performing advanced research on major issues in BSL development considering national and social developments.

5.2. Strengthening laboratory personnel training

In line with the construction of high-quality BSLs, the ready availability of skilled, dedicated, talented, and well-trained personnel is paramount in successful laboratory operation. From the design phase to the actual construction, management, and operation of BSLs, the provision of qualified personnel is compulsory. Therefore, BSL management and operation should be continuously strengthened so as to attract local and international high-level talents. The national and regional biosafety centers and other high-level BSLs should be autonomous to invent, improve, and conduct personnel trainings. Perfecting this talent classification assessment, the evaluation and incentive mechanisms should meet the characteristics of high-level BSLs and guarantee professional staff in laboratory management and operations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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