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Review

Global Safety and Health: The History of High-Level Biosafety Laboratories Toward Large Scientific Facilities

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Abstract: From the perspective of the history of science and technology, this paper delves into the global development of high-level biosafety laboratories, the establishment of related legal frameworks, and the evolution of safety standards. The importance of these laboratories within the context of national security is emphasized. This paper begins with an overview of global high-level biosafety laboratories' origins and technological advancements. Then, it provides a detailed analysis of the legal and institutional frameworks that different countries have developed in the field of biosafety. By comparing the evolution of laboratory standards across nations, the paper illustrates how high-level biosafety laboratories have adapted to and addressed the international challenges posed by health security and biological threats. This study provides a broad review and analysis of the historical development and technological progress of these laboratories, offering insights into the construction and management of high-level biosafety laboratories. It also provides important historical perspectives for the formulation of future biosafety policies and international cooperation, contributing to the development of more effective strategies to address global biosafety challenges. This review demonstrates the critical role of high-level biosafety laboratories in safeguarding national security and global health, highlighting the continuous need for improving regulatory systems, upgrading standards, and fostering technological innovation.

Keywords: high-level biosafety laboratories; history of science and technology; scientific evolution

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1. Introduction

In the context of global security crises, building a human security community has highlighted the growing significance of high-level biosafety laboratories as a frontline defense in scientific research and infectious disease prevention. These laboratories, equipped with high-efficacy particulate air (HEPA) filtration systems and other advanced containment measures, are essential facilities for studying high-risk pathogens and form the core force in responding to biological threats and public health emergencies worldwide. The dual-use potential of biotechnology and the increasing risk of cross-species and transboundary pathogen transmission, exacerbated by globalization and climate change, have created a more complex and severe global biosafety landscape. High-level biosafety laboratories, as a crucial component of the biosafety domain, play a pivotal role in protecting human health, preserving biodiversity, and advancing scientific research. Therefore, understanding the historical evolution of these laboratories, developing related legal frameworks, and establishing safety standards is of great strategic importance for strengthening national and global biosafety. This paper explores the construction history of high-level biosafety laboratories globally, focusing on their technological advancements, the establishment of legal frameworks, and the formulation of safety standards, which are critical to addressing biosafety challenges. Through an in-depth analysis of their development, regulatory environment, and standardization processes, the paper highlights their critical role in national security and global health governance. By examining laboratory development cases across multiple countries, this study showcases how different nations have addressed biosafety challenges and how these challenges have driven international cooperation and the formation of global biosafety standards.

2. The Early Development of Protective Measures in High-Level Biosafety Laboratories (1941–1968)

High-level biosafety laboratories (BSL) are not only critical centers for scientific innovation but also essential defenses against biological hazards, safeguarding public health. These laboratories allow the study and handling of high-risk pathogens [1], playing a pivotal role in preventing, controlling, and responding to infectious disease outbreaks and bioterrorism. With increasing globalization and cross-border mobility, the rapid spread of infectious diseases poses a significant challenge, heightening the importance of these laboratories in global public health security networks. High-level biosafety laboratories form part of national security and a crucial component of the global health security system, ensuring that countries can respond swiftly and scientifically to biological threats.

Research on highly pathogenic microorganisms and unknown pathogens has deepened, particularly in the context of biological weapons development [2]. In 1940, the UK established the Biology Department, Porton (BDP), a covert unit within CDES led by microbiologist Paul Fildes, to study biological weapons. Its research focused on agents like anthrax and botulinum toxin. The following year, K. F. Meyer and B. Eddie published a report revealing 74 cases of Brucella infections among laboratory staff due to accidental inhalation of the bacteria while handling microorganisms or specimens (Figure 1) in 1941 [3]. These infections, caused by airborne transmission of Brucella, a pathogen responsible for zoonotic diseases such as brucellosis (also known as undulant fever or Mediterranean fever) [4], highlighted the need for strict adherence to biosafety protocols in laboratory settings.

The development of biosafety technologies was significantly driven by research on biological weapons, which raised concerns about potential biological warfare threats. During this period, efforts in biological warfare defense focused not only on protecting researchers and the public but also on safely conducting research on and storage of pathogens, especially those with potential for weaponization [5]. For instance, in 1941, under the leadership of Henry L. Stimpson, the U.S. initiated a biological weapons program, establishing the headquarters of the U.S. Army Biological Warfare Laboratories (USBWL) at Fort Detrick. Research at Fort Detrick encompassed pathogen selection, cultivation, transmission mechanisms, and the development of protective measures [6].

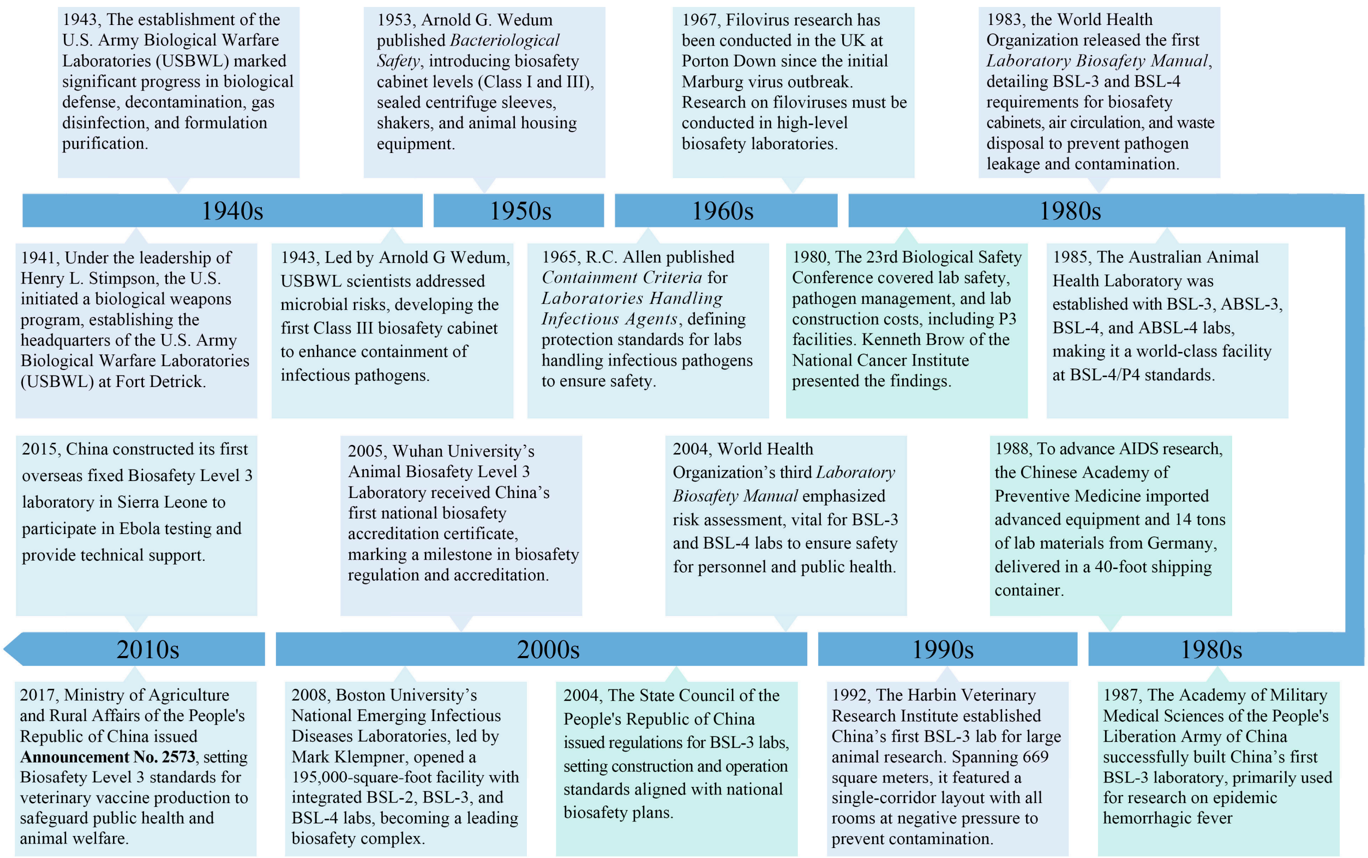

Figure 1. The development of the biosafety Level 3 laboratory.

During the 1940s, concerns over biological warfare catalyzed further advancements in biosafety. The establishment of the USBWL in 1943 marked significant progress in several fields, including biological defense, decontamination, gas disinfection, and formulation purification [7]. The emerging discipline of biosafety developed in response to biological hazards, as scientists led by Arnold G. Wedum, the modern father of biosafety at the USBWL, assessed the risks of handling dangerous microbial agents, particularly aerosols generated during microbial operations. This team developed operational protocols, designed relevant equipment, and established biosafety cabinets. Under the guidance of Hubert Kaempf Jr. and Dr. Arnold G. Wedum, the USBWL developed the prototype of the first Class III biosafety cabinet [8], which greatly enhanced laboratory safety by preventing cross-contamination and ensuring the containment of highly infectious pathogens.

In 1953, Arnold G. Wedum published the milestone paper *Bacteriological Safety*, which systematically introduced different levels of biosafety cabinets (including Class I and Class III), sealed centrifuge sleeves, shakers, and animal housing equipment [9]. The paper provided a comprehensive analysis of the potential hazards in microbiological operations, highlighting the importance of personal protective equipment (PPE), such as gloves and masks, especially when handling airborne pathogens. These advancements represented a significant stage in biosafety development and had a profound impact on subsequent laboratory safety standards. The establishment of a virology section at the UK's Microbiology Research Establishment, initially focused on poxvirus research, marked a significant milestone in the development of high-containment laboratory infrastructure in 1957 [10]. This initiative underscored the growing need for specialized facilities to handle dangerous pathogens safely. The research conducted during this period contributed to the understanding of pathogenic risks and informed the design, safety protocols, and operational standards of modern high-containment laboratories. It highlighted the importance of robust infrastructure to protect researchers and the public while advancing critical virological research.

Advancements were not only technical but also shaped by growing awareness of the global implications of biological research. As laboratory-acquired infections raised public concerns, the scientific community recognized the dual responsibility of advancing research while ensuring safety. In 1961, Wedum's paper *Control of Laboratory Airborne Infection* delved into the control of airborne infections in laboratories, emphasizing the importance of management and human factors in biosafety and the need for detailed safety protocols to mitigate the risks of infectious aerosols [11]. Wedum stressed that effective biosafety management requires more than just developing new equipment and procedures; it demands education, clear safety policies, and strict enforcement. He also discussed laboratory design and air management techniques, such as setting clean and contaminated zones, employing air disinfection methods, and designing effective air handling systems to reduce the spread of infectious particles.

In 1964, Wedum further expanded on his research into infectious aerosols with the publication of *Laboratory Safety in Research with Infectious Aerosols*, in which he designed small laboratory units for aerosol exposure experiments involving large animals, such as monkeys [12]. The paper analyzed infection pathways in laboratories, particularly those related to accidental inhalation of microbial aerosols generated during routine microbiological operations such as inoculating needles, pipettes, syringes, and centrifuges. Wedum emphasized the need for appropriate equipment, including biosafety cabinets, efficient air handling systems, and sound microbiological techniques, to mitigate the risks posed by aerosols.

As biotechnology advanced and research on highly pathogenic organisms progressed, the importance of laboratory biosafety became increasingly apparent, drawing the attention of the international community. During this period, it became clear that addressing potential biosafety risks required the establishment of uniform, stringent biosafety standards. In 1965, R. C. Allen's paper *Containment Criteria for Laboratories Handling Infectious Agents* aimed to define and establish protection standards for laboratories handling infectious pathogens, ensuring the safety of laboratory environments [13]. The paper proposed a classification system for pathogens based on their hazard levels to humans and recommended corresponding biosafety levels. It also outlined specific protection standards for different types of laboratories, such as negative pressure environments, filtered exhaust systems, glove boxes, and the sterilization of waste materials, to ensure the safety of laboratory personnel and prevent contamination of the external environment. R.C. Allen's paper profoundly impacted the development of biosafety measures and policy formulation, particularly in handling high-risk pathogens. The document emphasized the importance of safety management, including personnel training, the construction of safety facilities, accident handling procedures, and regular facility inspections. It provided a comprehensive set of operational and safety standards for biosafety laboratories, significantly influencing laboratory design, operational procedures, and safety management, particularly in safely handling high-risk pathogens.

Filovirus research has been conducted in the UK at Porton Down since the initial Marburg virus outbreak in 1967. Research on filoviruses must be conducted in high-level biosafety laboratories. This is because filoviruses, such as Ebola and Marburg viruses, are classified as high-risk pathogens, characterized by extreme infectivity and lethality, with no widely available treatments or vaccines at present. Porton Down, established in 1915 on Salisbury Plain [14], Wiltshire, to counter German gas attacks during the Great War, expanded post-war into the Microbiology Research Establishment (MRE) in 1957.

3. Risk Assessment and Establishment of Laboratory Classification System for High-Level Biosafety Laboratories (1969–1982)

During the 1960s, laboratories increasingly engaged in research involving highly infectious and dangerous pathogens, such as Brucella and Bacillus anthracis. These pathogens posed significant risks due to their transmissibility and lethality. In 1969, Arnold G. Wedum published *Assessment of Risk of Human Infection in the Microbiological Laboratory*. This work introduced four "risk indicators" that served as guiding principles for microbiological safety: the number of laboratory infections, the infectious dose for humans, the presence of infection in unvaccinated control animals, and the detection of microorganisms in the urine or feces of inoculated animals. These indicators were designed to help laboratory personnel handle microorganisms more safely. The assessment provided a comprehensive evaluation of human infection risks in microbiological laboratories. Wedum's four key risk indicators laid the scientific groundwork for biosafety operations in high-level biosafety laboratories (such as BSL-3 and BSL-4), leading to the development of stricter safety protocols and management guidelines. This work provided critical theoretical and practical guidance for the design, operation, and management of biosafety laboratories worldwide, significantly enhancing safety levels and reducing the risk of infection for both laboratory personnel and the public [15]. That same year, the U.S. Public Health Service published a booklet titled *Classification of Etiologic Agents based on Hazard*, which categorized pathogens used in laboratories into four risk groups (Class 1–4). This classification was based on the pathogens' potential dangers to public health and safety, guiding the appropriate safety levels for laboratory work.

Porton Down received the initial Ebola virus samples in 1976 during the first confirmed outbreak in Africa. Today, it houses some of the world's most dangerous pathogens, including Ebola, anthrax, and plague, and plays a key role in the UK's research on viral inoculations.

The establishment of BSL-4 laboratories became a necessity as advancements in molecular biology and bioweapons defense emphasized the importance of secure containment. In 1977, the 20th American Biological Safety Conference proposed the establishment of BSL-4 laboratories, and Orley Bourland discussed the reasons behind the U.S.'s decision to build P4 facilities in a report by the Frederick Cancer Research Center (FCRC) (Figure 2). These facilities were intended to continue research on high-risk microorganisms and provide platforms for external researchers [16]. Everett Hanel provided a history of the modular BSL-3 biosafety cabinets designed by the engineering and safety divisions at Fort Detrick, which were installed by Blickman Corporation in Building 550 at Fort Detrick in 1954. These cabinets were used for research on highly infectious microorganisms, including Helicobacter simiae, Coccidioides immitis, Mycobacterium tuberculosis, Coxiella burnetii, and others, until the facility underwent extensive renovations in January 1977 to accommodate recombinant DNA research at P4 levels. Stephen Pijar described the tests conducted at the P4 facility and the challenges encountered during the process.

The U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) completed the construction of the first BSL-4 laboratory in the U.S. in 1978 [17]. This facility implemented rigorous protective measures including full-body positive pressure suits, sealed working environments, HEPA filter systems, and multiple safety door systems to isolate different zones. These measures aimed to prevent the escape of highly pathogenic microorganisms and cross-contamination, ensuring the safety of both laboratory personnel and the public. All personnel were required to undergo extensive training to master the use of advanced protective equipment and the skills necessary to handle potential hazards. The design and operation of this facility demonstrated a high level of attention to extreme biosafety risks, making it a pioneering institution for global biosafety research. That same year, the Birmingham smallpox laboratory accident was a pivotal moment in the history of laboratory biosafety in the UK and globally [18]. This incident, where smallpox virus escaped from a laboratory and caused a fatal infection, led to significant changes in the UK's approach to laboratory safety. The aftermath of this event resulted in the establishment of the Advisory Committee on Dangerous Pathogens (ACDP) the following year. The ACDP played a critical role in guiding laboratory biosafety policies, including the development of the "Approved List of Biological Agents" which aligns with the EU biosafety classification system. This framework has since become a cornerstone of biosafety practices in the UK and serves as a model for international standards.

Figure 2. The evolution of the biosafety Level 4 laboratory.

The 1980s marked a pivotal moment as zoonotic diseases and laboratory-acquired infections (LAIs) began escalating in frequency and severity. The 23rd Biological Safety Conference held in Lexington, Kentucky, in 1980, covered several important biosafety topics, including the latest advancements in laboratory safety, infectious disease handling, and strategies for managing transmissible pathogens in laboratories. Kenneth Brow from the National Cancer Institute (NCI) analyzed the time and costs associated with constructing or renovating small laboratories, animal research facilities, P3 laboratories, and large multi-story buildings. Howard Larsh from the University of Oklahoma described procedures for using wooden safety cabinets in a hospital in Chester, Missouri, to isolate and identify Mycobacterium tuberculosis as well as pathogenic systemic fungi such as Histoplasma capsulatum and Blastomyces dermatitidis. Arthur DiSalvo introduced a 93,000-square-foot public health laboratory in South Carolina that featured unidirectional airflow systems and separate air systems for animal areas. Stanley Nagle from the National Institutes of Health (NIH) discussed the extensive renovations required to build a P4 laboratory in Building 550 at Fort Detrick [19]. Sol Miller from Abbott Laboratories introduced new safety laboratories, each module equipped with airlocks for entry and exit, HEPA-filtered supply air, and HEPA and activated carbon-filtered exhaust systems.

As global awareness of biosafety increased and microbial research deepened, the demand for studying high-risk pathogens also grew. P4 laboratories, or BSL-4 laboratories, were specifically designed to research highly contagious and lethal pathogens for which no known treatments exist, such as the Ebola and Marburg viruses. In March 1981, Japan's National Institute for Infectious Diseases (NIID) established its own BSL-4 laboratory [20]. This facility, with a total area of 145 square meters, included two Class III biosafety cabinets—one for pathology research and the other for in vitro experiments. A third BSL-4 laboratory, measuring 87 square meters, housed two Class I biosafety cabinets, one used for small animals like mice and rats and the other for medium-sized animals such as monkeys and rabbits, capable of holding six monkey cages simultaneously. In addition to the BSL-4 laboratories, the facility also featured BSL-3 laboratories designed to handle serious pathogens that typically have preventive or treatment methods. The institute supported infectious disease research and daily operations with additional facilities such as cell culture rooms, management offices, a washing room, and two machine rooms [21]. The establishment of these facilities not only strengthened Japan's capabilities in handling and researching infectious diseases but also made significant contributions to global infectious disease prevention and control.

4. Institutionalization and Standardization of High-Level Biosafety Laboratories (1983–2003)

Governments and international organizations gradually recognized the importance of biosafety and began to establish relevant policies and regulations. In 1983, the World Health Organization (WHO) released the first edition of the *Laboratory Biosafety Manual* [22]. This manual set forth specific requirements for BSL-3 and BSL-4 laboratories regarding facilities and equipment, including types and uses of biosafety cabinets, air circulation systems, and waste disposal procedures. These guidelines ensured that laboratories handling high-risk pathogens were equipped to prevent pathogen leakage and environmental contamination [23]. For instance, BSL-3 laboratory designs had to ensure physical isolation, with entry through dual-door systems, including airlocks and buffer zones. Laboratories were required to maintain negative pressure to ensure that air flowed from clean areas toward contaminated areas, and all exhaust air had to pass through HEPA filters to prevent contaminants from escaping into the environment. Laboratory waste, including biological waste and sharps, had to be sterilized on-site before removal. Class II or Class III biosafety cabinets were mandated to provide a protective barrier, shielding laboratory personnel from aerosols and droplets. The operational guidelines required personnel to wear appropriate protective gear, such as lab coats, gloves, and face protection, with strict biosafety training for all individuals working in BSL-3 labs. A negative pressure filtration system ensured that lab air was filtered and released safely, preventing pathogen escape.

The WHO *Laboratory Biosafety Manual* became a critical global guide in the field of biosafety, offering laboratory workers worldwide comprehensive guidance on biosafety principles, operational procedures, and management requirements. Following this, in 1984, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) in the U.S. collaborated to release the Biosafety in Microbiological and Biomedical Laboratories (BMBL) guidelines [24]. Building on the WHO manual, the BMBL adapted the guidelines to the U.S. context, providing a national-level biosafety guide that included detailed specifications on laboratory design, construction, operation, and management for various microbiological laboratories. This guide aimed to offer U.S. laboratory workers practical and specific safety and management instructions for conducting experiments in secure environments. It outlined precise requirements for BSL-3 and BSL-4 laboratory facilities, emphasizing the importance of proper engineering and design features. For example, BSL-3 laboratories were designed to work with local or exotic pathogens that could cause serious or potentially lethal diseases via inhalation [25] (Table 1). Laboratory personnel had to undergo specialized training in handling such pathogens and were supervised by experienced scientists. All procedures involving infectious materials had to be conducted in biosafety cabinets or other physical containment devices or by personnel wearing appropriate personal protective equipment (PPE). The BMBL guidelines provided standardized operating procedures, strict facility design and equipment requirements, systematic training and education, and detailed emergency response and incident-management guidelines, contributing significantly to the construction and management of high-level biosafety laboratories.

Table 1. The categorization of laboratory facilities and protection between Biosafety Level 3 (BSL-3) and Biosafety Level 4 (BSL-4) laboratories.

Types	Standard Microbiological Practices	Special Practices	Safety Equipment	Laboratory Facilities
Biosafety Level 3 laboratory	✓ Lab supervisors enforce safety, provide training, and ensure health screenings. PPE, careful sharps handling, and decontamination are required. ✓ Food/drink is restricted; only authorized animals/plants are allowed. ✓ Pest control is maintained.	✓ Lab entry is restricted; medical evaluations and training in BSL-3 practices are required. ✓ Incidents are reported and documented. Infectious materials are double-contained, and work is performed in containment devices. ✓ Routine decontamination of equipment and waste is mandatory, with full lab decontamination after major events. ✓ Decontamination processes are regularly verified.	✓ Lab workers wear solid-front protective clothing, changed if contaminated and not worn outside. ✓ Additional PPE, like eye, face, respiratory protection, and double gloves, are used as needed. For work with animals, PPE is adjusted based on risks, including protection against allergens.	✓ BSL-3 labs have restricted access, self-closing doors, handwashing sinks, and eyewash stations. ✓ HEPA-filtered airflow ensures containment. ✓ BSCs and equipment prevent aerosol escape, with full decontamination capability. ✓ Enhanced controls and emergency communication are provided as needed.
Biosafety Level 4 laboratory	✓ Lab supervisors ensure safety, training, health checks, and PPE use. ✓ Biohazard signs, restricted food, safe sharps handling, and lab access controls are enforced. ✓ Procedures minimize spills, aerosols, and contamination; surfaces and waste are decontaminated. ✓ Pest control is maintained; only approved animals/plants allowed.	✓ BSL-4 labs require strict entry protocols, training, health checks, and decontamination. ✓ Only essential personnel access, following controlled entry/exit and logging. ✓ Infectious materials, waste, and equipment are securely contained and decontaminated. ✓ Daily inspections ensure containment.	✓ In a Class III Biological Safety Cabinet, all infectious work is contained within the BSC using double-door autoclaves, ✓ HEPA filters, and regular decontamination. ✓ Suit labs use BSCs and positive pressure suits; HEPA filtration controls aerosols. ✓ Strict decontamination and exit protocols are followed.	✓ BSL-4 labs have restricted access, ✓ HEPA-filtered ventilation, and backup power. Hands-free sinks and sealed surfaces for decontamination. ✓ Negative pressure and alarms ensure containment, and waste is treated before disposal. ✓ Emergency communication and annual testing maintain safety.

The establishment of high-containment laboratories such as Australia's Australian Animal Health Laboratory (AAHL) in 1985 reflected a growing emphasis on managing zoonotic diseases and global health security. This facility, equipped with BSL-3, ABSL-3, BSL-4, and ABSL-4 laboratories, represented a significant advancement in biosafety infrastructure [26]. This facility made AAHL one of the world's highest-standard animal health laboratories, reaching BSL-4/P4 levels. AAHL was designed specifically to study pathogens that pose extreme danger to animals and potential threats to human health. Its establishment significantly enhanced Australia's ability to research and respond to animal diseases, especially those with zoonotic potential, such as rabies and foot-and-mouth disease. The facility included advanced isolation and containment technologies to ensure absolute biosafety within and outside the laboratory. Through its state-of-the-art biosafety facilities and stringent management systems, AAHL provides vital support for global research and control of high-risk pathogens [27].

In response to these public health challenges, the Academy of Military Medical Sciences of the People's Liberation Army of China, successfully built China's first BSL-3 laboratory, primarily used for research on epidemic hemorrhagic fever caused by hantaviruses in 1987 [28]. The laboratory was equipped with non-standard exhaust filtration systems, autoclaves, pass-through windows, wastewater treatment facilities, and observation areas, and it established detailed operating procedures. This BSL-3 lab significantly advanced China's research on hemorrhagic fever and provided valuable experience for the construction and management of higher-level biosafety laboratories in the country.

To advance AIDS research, the Chinese Academy of Preventive Medicine (now the Chinese Center for Disease Control and Prevention) imported advanced equipment and technology from Germany in 1988. This equipment, including 14 tons of laboratory construction materials, arrived in China via a 40-foot shipping container [29]. Two German engineers also participated in the laboratory's construction. These efforts facilitated the establishment of a BSL-3 laboratory, providing a critical research platform for AIDS and other infectious diseases.

Starting in 1992, China entered an exploratory phase in the field of high-level biosafety laboratories. That year, the Harbin Veterinary Research Institute of the Chinese Academy of Agricultural Sciences established the country's first BSL-3 laboratory dedicated to large animal research. Covering 669 square meters, the laboratory featured a single-corridor design, with all rooms maintained at negative pressure to prevent airborne contamination. The facility included a receiving room, a dissection room, two large animal laboratories, two small animal laboratories, and two isolation rooms [30]. The lab's internal design ensured the strict separation of personnel, materials, and animals, and a clean processing system maintained environmental hygiene. All contaminated materials were sterilized in the laboratory to ensure decontamination. The Harbin Veterinary Research Institute, as the host institution for this lab, was committed to advancing research on animal disease prevention and control, contributing significantly to the development of animal disease control technologies in China and globally.

Under the circumstances of the Cold War's end in the early 1990s, Russia sought to pivot its extensive biological research infrastructure toward peaceful applications. This shift was driven by international pressure to curtail bioweapons programs and an increasing recognition of the need for global collaboration in addressing emerging infectious diseases. In 1994, Russia consolidated the All-Soviet Molecular Biology Research Institute, established in 1974, with other institutions to form the "State Research Center of Virology and Biotechnology VECTOR" [31]. This center brought together leading experts from molecular biology, virology, genetic engineering, epidemiology, and ecology. VECTOR achieved notable success in researching various viral diseases, including hepatitis, influenza, tuberculosis, rubella, measles, HIV/AIDS, herpes, and Crimean-Congo hemorrhagic fever. The center also housed high-risk virus samples, including those of smallpox, Ebola, and severe acute respiratory syndrome (SARS).

The risk of cross-border transmission of infectious diseases increased significantly. Emerging zoonotic diseases such as Ebola and Marburg further underscored the necessity for high-containment facilities capable of managing these threats. In response to these global challenges, Canada opened the Canadian Science Centre for Human and Animal Health (BSL-4) at the National Microbiology Laboratory (NML) in 1998 [32]. This facility was specifically designed for research on pathogens that pose an extremely high risk to human health, such as Ebola and Marburg viruses. The establishment of the BSL-4 laboratory significantly bolstered Canada's capacity to handle the world's most dangerous pathogens, strengthening its leadership in infectious disease research and responses to global health crises. The NML's core responsibilities include identifying, monitoring, controlling, and preventing infectious diseases in humans. In addition, the lab is responsible for surveillance, reference testing, applied and developmental research, outbreak warning, and emergency response. It also provides foundational biological education, disease surveillance, and prevention training and participates in global pathogen detection initiatives [33].

In 1999, France completed the construction of the Jean Mérieux/INSERM BSL-4 Laboratory in Lyon, and it was officially opened to scientists in 2001. This project represented a milestone in biosafety [34]. The laboratory was designed to provide a safe environment for researching highly pathogenic agents such as the Ebola and Lassa viruses. Its construction and operation enhanced France's and the world's ability to manage severe infectious disease outbreaks and biological threats, making it a key hub for global biosafety research.

Initially serving military research purposes, Porton Down's facilities evolved, and the site was divided into two entities. It hosts two key agencies: the Defence Science and Technology Laboratory (DSTL), established in 2001 and the Health Protection Agency (HPA), established in 2003. DSTL is part of the UK Ministry of Defence, while the HPA primarily focuses on preparing for public healthcare emergencies and providing epidemiological services and screening. In 2013, the HPA was merged into Public Health England (PHE) as part of a restructuring of public health services in England. Later, in October 2021, PHE was replaced by the UKHSA, which was created to focus more specifically on health protection and emergency response, particularly in the context of the COVID-19 pandemic and future pandemic preparedness.

In the context of the 2003 SARS outbreak, the world became increasingly aware of the critical importance of infectious disease prevention and biosafety. The epidemic exposed significant gaps in many countries' capabilities to respond to emerging infectious diseases and underscored the urgency of strengthening high-level biosafety laboratories and establishing relevant standards. Against this backdrop, U.S. President George W. Bush announced the launch of the "BioShield" initiative to safeguard against potential bioterrorist attacks. A central component of the initiative was the construction of BSL-4 laboratories to store and study the most hazardous viruses. This marked a significant shift in the global approach to biosafety, leading to a surge in the construction of high-level biosafety laboratories worldwide. With the implementation of the BioShield initiative and the growing international awareness of biosafety, more countries and regions began investing resources in constructing such facilities. This not only helped raise global biosafety standards but also provided a stronger defense against emerging biological threats. Additionally, in the same year, France completed an innovative project—the "LaboMobil" mobile microbiology laboratory developed by the Directorate for Preventive Medicine [35]. Although smaller and less equipped than fixed BSL-3 and BSL-4 laboratories, the mobile labs were closely related in function and purpose. These labs were designed to improve France's and its global partners' ability to rapidly diagnose and respond to infectious disease outbreaks on-site. Equipped with all the necessary biosafety measures, advanced laboratory equipment, and data analysis tools, these mobile labs were especially suited for deployment in outbreak areas or remote regions, significantly enhancing the speed and efficiency of responses to public health emergencies and providing robust technical support for infectious disease control.

5. Challenges and Strategies for High-Level Biosafety Laboratories in the Prevention and Control of Highly Pathogenic Agents (2004–)

Laboratories worldwide were increasingly handling dangerous agents, driven by the need to address emerging infectious diseases, respond to bioterrorism threats, and enhance global pandemic preparedness, necessitating updated biosafety protocols to address these evolving risks. The World Health Organization (WHO) released the third edition of the *Laboratory Biosafety Manual*, providing more comprehensive global guidance on laboratory biosafety in 2004. This edition placed special emphasis on risk assessment, offering detailed methodologies for evaluating potential risks in laboratory operations. Such systematic risk assessments are particularly important for BSL-3 and BSL-4 laboratories, where the pathogens handled are highly infectious and lethal. Accurate risk assessments ensure that appropriate safety measures are implemented to protect both laboratory personnel and public health. Additionally, several biosafety practices were updated, including stricter contamination control techniques and operational procedures. For BSL-3 and BSL-4 laboratories, these updates included improved personal protective equipment (PPE) usage, refined biosafety cabinet protocols, and more stringent engineering controls, all aimed at minimizing biohazards within and outside laboratories. The manual further elaborated on design and safety recommendations for high-level biosafety laboratory facilities, covering laboratory layouts, air handling systems, and waste disposal mechanisms. These detailed guidelines helped laboratory designers and managers establish advanced biosafety laboratories that meet international standards [36]. By offering technical and policy guidance, the third edition of the *Laboratory Biosafety Manual* significantly improved global standards for the safe operation and design of high-level biosafety laboratories, with far-reaching impacts on biosafety practices worldwide.

In parallel, the Chinese State Council issued the Regulations on Biosafety Management of Pathogenic Microorganism Laboratories, a directive serving as a cornerstone for the construction and operation of biosafety laboratories in China [37]. These regulations mandated that newly built, renovated, or expanded BSL-3 laboratories comply with the national biosafety laboratory system plan and the relevant approval standards. The regulations comprehensively outlined pathogen classification and management, laboratory establishment and operation, infection control measures, supervision, and legal liability for violations. To further strengthen laboratory biosafety regulations and enhance protection for laboratory personnel, the Chinese State Council revised these regulations in 2016 and 2018. These revisions aimed to improve the enforcement of biosafety management and enhance safety protections, ensuring the effective implementation of biosafety measures and safeguarding the health and safety of relevant personnel. Moreover, the General Administration of Quality Supervision, Inspection and Quarantine (AQSIQ) and the Standardization Administration of China jointly issued the country's first national biosafety laboratory standard, General Requirements for Laboratory Biosafety (GB 19489—2004) [38]. This standard provided systematic guidance on biosafety management, including biosafety levels, facility and equipment configuration, and requirements for personal protection and safe operations. It classified biological agents into four risk levels, with Level III (high individual risk, low community risk) including pathogens that cause severe disease in humans or animals but are not typically transmissible between individuals and can often be treated with antibiotics or antiparasitic drugs. Level IV (high individual and community risk) includes pathogens that cause very severe diseases, are difficult to treat, and are easily transmissible between humans and animals. For BSL-3 laboratories, the standard required facilities to be in isolated buildings or zones within a building, with clear separation into clean, semi-contaminated, and contaminated areas. Buffer zones were to be used between these areas to reduce cross-contamination risks. Laboratory design emphasized structural integrity, with smooth, corrosion-resistant surfaces that were easy to clean and disinfect. All seams had to be sealed, and critical ventilation systems were to operate independently, controlling airflow and pressure to ensure that air flowed from clean to contaminated areas, with exhaust air filtered through high-efficiency particulate air (HEPA) filters before being released. Laboratories also had to be equipped with appropriate biosafety cabinets and PPE to manage various biosafety risks. Additionally, BSL-3 laboratories were required to have emergency alarm systems to monitor environmental changes and ensure the maintenance of negative pressure, thus guaranteeing safe laboratory operations and preventing contamination spread. These regulations provided a solid foundation for managing high-risk biological agents in China.

The absence of coordinated laboratory networks capable of handling high-risk pathogens across member states was seen as a critical vulnerability in regional public health security. In 2005, the European Union launched the European High-Level Biosafety Laboratory (EHSL4) program [39]. This initiative aimed to establish and coordinate a network of laboratories across the EU capable of safely handling the most dangerous pathogens. Through this program, the EU sought to strengthen cooperation and resource sharing among member states in the field of biosafety laboratories, improving the union's ability to respond to biological threats and infectious disease outbreaks. The EHSL4 program focused not only on the physical construction and technical equipment of laboratories but also on implementing unified operational standards, personnel training, research collaboration, and emergency response mechanisms. Laboratories under this program primarily involved BSL-4 facilities designed to handle pathogens that pose extreme risks to public health, such as the Ebola and Marburg viruses. By enhancing biosafety and biosecurity capabilities, the EHSL4 program ensured that laboratory staff were protected and that pathogens were contained. The program also emphasized the establishment of cross-border monitoring and rapid response networks, enabling member states to share information and resources quickly and collaborate in the event of a biological crisis. This integrated approach strengthened regional public health security and contributed to global biosafety. As a result, the EU further consolidated its leadership in global public health security. That same year, Wuhan University's Animal Biosafety Level 3 Laboratory received China's first national biosafety laboratory accreditation certificate, marking a milestone in the institutionalization and legal regulation of biosafety laboratory accreditation in China [40].

Biorisk Management: Laboratory Biosecurity Guidance was published by the World Health Organization in 2006 [41]. The document aims to expand the laboratory biosecurity concepts introduced in LBM3, and to strike a balance between the biosafety procedures and practices described in LBM3 and the more recently introduced and broader biosecurity concepts. It also presents the comprehensive "bio-risk management" framework, developed through thorough analysis of existing practices, international standards, recommendations, and ethical considerations.

The Defence Science and Technology Laboratory (Dstl) operates two types of Level 4 containment laboratories: an in vitro laboratory with a cabinet line for virus growth, enumeration, and assays, and in vivo/aerobiology laboratories using rigid half-suit isolators for animal infections and aerosol studies. Each lab has double HEPA-filtered air systems. The in vitro laboratory began working with filoviruses in late 2005, and the in vivo laboratory conducted its first animal infection with filoviruses in 2007. All work is conducted within primary containment either within cabinet lines (for in vitro work) or large rigid half-suit isolators (for in vivo work). A unique aspect of the UK's biosafety practices is its reliance on Biological Safety Cabinets (BSCs) as the primary form of engineered protection in BSL-4 laboratories. This approach differs significantly from that of other nations, such as the USA, Canada, and France, which predominantly utilize air-fed positive pressure suits for worker protection. The UK's strategy reflects the principle that engineered controls—such as BSCs—are higher in the hierarchy of hazard controls compared to personal protective equipment (PPE). This distinction underscores a fundamental difference in biosafety philosophy and highlights the adaptability of laboratory designs to meet specific operational needs.

In 2008, Boston University's National Emerging Infectious Diseases Laboratories (NEIDL) established a BSL-4 laboratory under the leadership of Mark Klempner [42]. The laboratory, part of a 195,000-square-foot facility, was one of the most advanced biosafety complexes in the world, combining BSL-2, BSL-3, and BSL-4 laboratories. NEIDL received final approval from the National Institutes of Health (NIH) in February of that year. The laboratory was built to conduct research on infectious diseases and develop drugs, vaccines, and treatments for deadly natural and intentionally released pathogens as part of the U.S. national biodefense agenda. At the time, NEIDL also housed the world's only BSL-4 simulator, designed to replicate the exact conditions of a BSL-4 laboratory for training and preparedness purposes [43].

Several countries have not only focused on researching high-risk pathogens endemic to their regions but also invested heavily in studying exotic pathogens from abroad, establishing dedicated institutions for this purpose. Some countries have also cooperated with others to build advanced biosafety laboratories overseas. For example, in 2009, the Canadian government invested $30 million to establish a BSL-4 biosafety laboratory in Kyrgyzstan. The main goal of this project was to ensure that high-risk pathogens left behind by the former Soviet Union, such as Bacillus anthracis and Yersinia pestis, did not fall into the hands of terrorists, thus enhancing biosafety and preventing bioterrorism. That same year, the National Institute of Allergy and Infectious Diseases (NIAID) in the U.S. completed a facility supporting BSL-3 and BSL-4 pathogen research [44]. In addition, Makerere University built the BSL-3 laboratory for tuberculosis research [45]. In April 2010, the U.S. government announced a collaboration between the Defense Threat Reduction Agency and Kazakhstan to build Central Asia's largest virus laboratory and monitoring station, where extensive research, preservation, and monitoring of high-risk viral samples would be conducted [46].

Under the circumstances of the devastating West African Ebola epidemic, the international community recognized the need to overhaul global biosafety practices. The epidemic revealed that many countries could not handle high-risk pathogens safely and efficiently, resulting in delays in diagnostics and containment efforts. It also exposed the dangers of under-resourced laboratories in outbreak-prone regions, where breaches in biosafety could exacerbate already dire public health crises. Saudi Arabia announced plans to build its first BSL-4 laboratory while upgrading existing BSL-3 facilities to address the challenges of MERS-CoV and other emerging pathogens. These investments aimed to strengthen the country's research capabilities, enabling detailed studies on coronaviruses and improving its outbreak response mechanisms in 2013 (Figure 3). During the Ebola outbreak in West Africa, Nigeria built a BSL-3 laboratory for rapid diagnosis and control of the epidemic. Later, China assisted Sierra Leone in constructing its first fixed BSL-3 laboratory as part of its efforts to support Ebola testing and provide technical assistance [47]. Covering 383 square meters, with a 126-square-meter BSL-3 work area, this laboratory was the first fixed biosafety laboratory in Sierra Leone to meet WHO standards. Named the China-Sierra Leone Friendship Biosafety Laboratory, this facility not only supported Ebola virus detection but also strengthened the country's public health system and capacity to prevent infectious diseases. The guiding principle behind this effort reflects the philosophy of transnational medical assistance and international collaboration long championed by Henry Norman Bethune. His belief that "medicine has no borders" aligns with the mission of this biosafety laboratory, which is not merely a facility for detecting and controlling infectious diseases but a symbol of global cooperation in addressing health crises [48]. This biosafety laboratory is not just a facility for detecting and controlling infectious diseases; it also represents the kind of transnational scientific research cooperation and technology sharing that Bethune advocated for in his lifetime. This collaboration is essential in tackling major global health challenges, and it reflects a core goal of biosafety laboratory systems today: to enhance global health security and foster international cooperation in the fight against emerging infectious diseases. That same year, the Robert Koch Institute in Germany established a BSL-4 laboratory (P4), built to airtight standards based on the Canadian biosafety guidelines (Canada Biosafety Standards, 2015) [49]. The Robert Koch Institute's P4 laboratory featured state-of-the-art design and technical configurations, including independent air handling systems and multiple safety barriers to ensure that all operations were conducted in a fully sealed environment. The airflow within the laboratory was meticulously designed to maintain a negative pressure environment, preventing pathogen leakage. Additionally, HEPA filters were used to ensure that all incoming and outgoing air was thoroughly purified. This P4 laboratory not only enhanced the institute's ability to conduct high-risk pathogen research but also bolstered Germany's leadership in global infectious disease research and control.

In 2016, China released its High-Level Biosafety Laboratory System Construction Plan (2016–2025), marking a significant advancement in biosafety and high-level biosafety laboratory development [50]. The plan aimed to improve biosafety management by constructing and upgrading several BSL-3 and BSL-4 laboratories across the country to meet international standards. It also sought to establish a comprehensive biosafety management system, refine relevant laws and regulations, and ensure the safe operation of laboratories. The plan emphasized the cultivation of professional technical personnel in the biosafety field and the improvement of emergency response capabilities through enhanced technical training. By promoting scientific innovation in biosafety-related fields, China aimed to participate actively in international biosafety cooperation and address global public health challenges. The construction of a rapid and efficient emergency response mechanism under this plan significantly enhanced China's ability to respond to sudden biosafety events, greatly improving its comprehensive capabilities in biosafety and public health protection and providing robust support for safeguarding public health and national security [51].

With the rapid progress of biotechnology and the continuous growth of the global veterinary vaccine market, strengthening biosafety management in vaccine production has become a critical issue. In response, China's Ministry of Agriculture issued Announcement *No. 2573 in 2017, Biosafety Level 3 Protection Standards for Veterinary Vaccine Production Enterprises*. This standard aimed to enhance biosafety levels in veterinary vaccine production enterprises, ensuring biosafety during vaccine production to protect public health and animal welfare [52]. The standard provided detailed guidelines on the construction and management of production facilities, requiring that all vaccine production workshops not only comply with national building codes but also adopt designs that effectively prevent contamination [53]. Additionally, interior materials for workshops were to be selected for easy cleaning and disinfection to maintain hygiene and cleanliness. Laboratories were required to be equipped with advanced ventilation systems and waste disposal facilities to ensure that harmful gasses and waste were safely and effectively treated while maintaining optimal air quality and circulation within the laboratory. The implementation of the standard not only improved the quality and safety of vaccine products but also significantly enhanced the protection of public health and animal health, further promoting the healthy development of the veterinary vaccine industry and boosting the sector's international competitiveness.

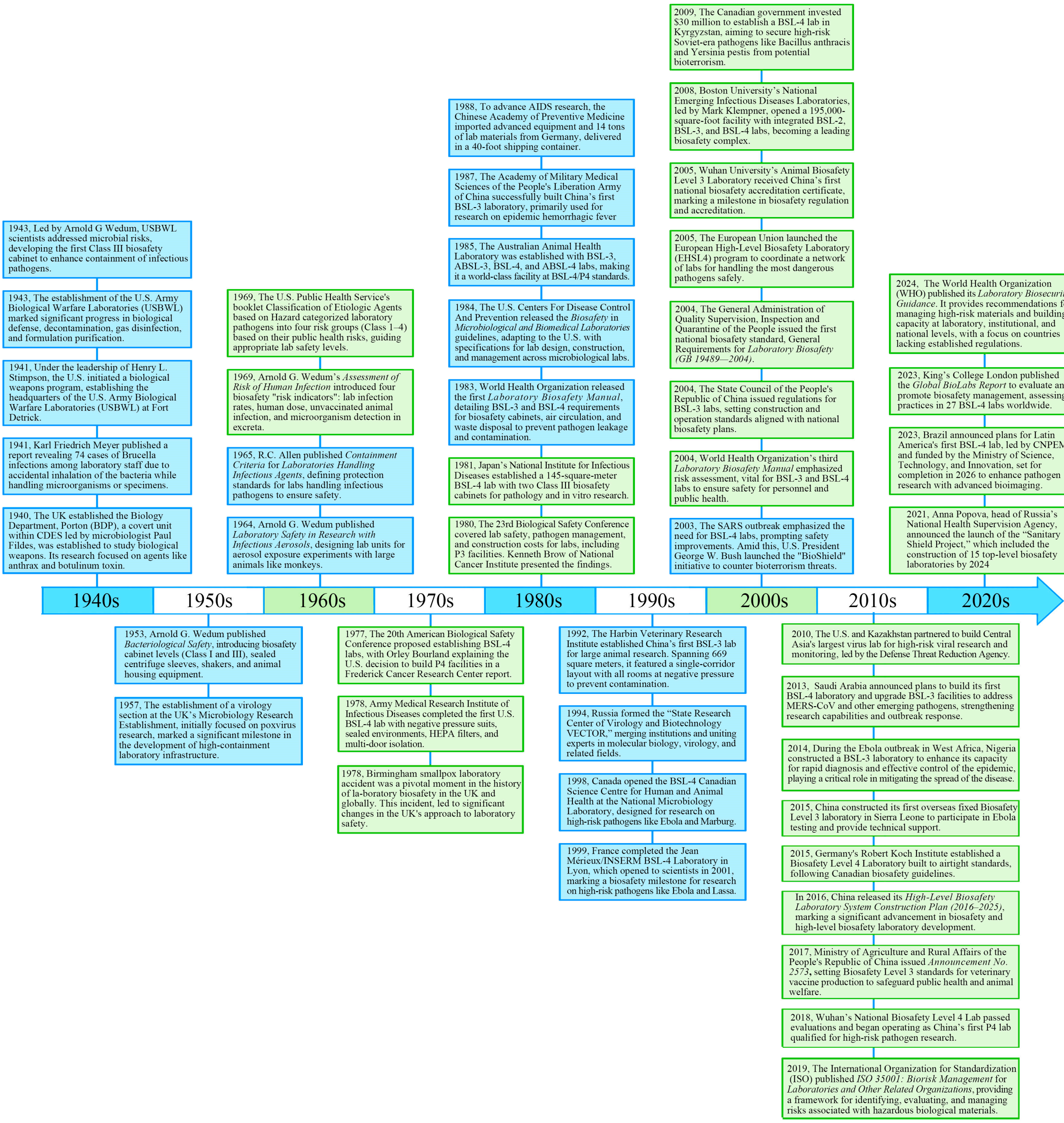

Figure 3. Global history of high-level biosafety laboratories.

As globalization accelerates, the risk of cross-border transmission of infectious diseases continues to rise, with highly virulent pathogens like Ebola and SARS posing severe threats to global public health security. To effectively address these challenges and elevate its role and influence in global public health security, China strategically initiated the construction of a P4 laboratory. In 2018, the Wuhan National Biosafety Level 4 Laboratory passed on-site evaluations by the National Health Commission for high-risk pathogenic microorganism research activities and officially began operations, becoming the first P4 laboratory in mainland China with research qualifications [54]. Initially launched in 2003 by the Chinese Academy of Sciences as a major national scientific project, the Wuhan P4 laboratory was a critical infrastructure project. Since its completion in 2015, the Wuhan P4 laboratory has provided foundational and technical support for enhancing China's ability to prevent and control emerging infectious diseases and its capacity for antiviral drug and vaccine research and development [55]. It marked a new era for China in high-level biosafety research, providing a full suite of facilities and technical capabilities for advanced biosafety research. The laboratory's design incorporated comprehensive safety measures, including airtight seals, highly efficient air filtration systems (HEPA), and air handling systems that maintain a stable negative pressure environment [56]. The facility also featured chemical shower units and independent life support systems to enhance safety. Laboratory personnel were required to wear full-body protective suits with independent breathing systems, providing the highest level of safety protection for operators. These stringent safety and protection measures ensured the safe conduct of high-risk pathogen research within the laboratory, preventing any potential pathogen leakage. The establishment of this laboratory not only enhanced China's capacity to research and respond to global infectious diseases but also marked rapid development and maturity in the country's high-level biosafety laboratory infrastructure.

The International Organization for Standardization (ISO) published *ISO 35001: Biorisk Management for Laboratories and Other Related Organizations in 2019* [57]. This standard outlines a process to identify, evaluate, control, and monitor risks associated with hazardous biological materials. It is applicable to laboratories and organizations that handle, store, transport, or dispose of such materials. The document is designed to complement existing international laboratory standards.

On 17 August 2021, Anna Popova, head of Russia's National Health Supervision Agency, announced the launch of the "Sanitary Shield Project" which included the construction of 15 top-level biosafety laboratories by 2024 [58]. These laboratories, all BSL-4 facilities, were designed to enhance the country's ability to handle highly dangerous pathogens [59]. By 2024, these laboratories will form part of Russia's national biosafety infrastructure, significantly increasing its capacity to manage biological threats.

The COVID-19 pandemic underscored the critical role of biosafety in responding to global health crises. The high-level biosecurity laboratories are the basic supporting platform of the national biosecurity system. Countries worldwide invested in upgrading and expanding their BSL-3 and BSL-4 facilities to enhance diagnostic and research capabilities. These laboratories were pivotal in the rapid identification and characterization of SARS-CoV-2, facilitating the development of diagnostics, therapeutics, and vaccines at an unprecedented pace. For example, in 2023, Brazil announced plans to build Latin America's first BSL-4 laboratory, scheduled for completion in 2026. This project, led by the Brazilian Energy and Materials Research Center (CNPEM) and funded by Brazil's Ministry of Science, Technology, and Innovation (MCTI), will include high-level biosafety laboratories and research stations, utilizing synchrotron light sources for bioimaging studies to enhance pathogen research capabilities [60]. This facility will also be the world's first biosafety laboratory connected to a synchrotron light source [61].

Given the importance and potential risks of BSL-4 laboratories, ensuring that these facilities operate according to the strictest international safety and management standards is critical. To evaluate the current state of biosafety management in BSL-4 laboratories worldwide and promote the standardization and improvement of global biosafety practices, King's College London published the 2023 *Global BioLabs Report*, which assessed biosafety management in 27 global BSL-4 laboratories [62]. The report provided an in-depth analysis of biosafety management practices and outcomes, highlighting key strategies and measures for maintaining biosafety and preventing biological threats. The evaluation covered laboratory infrastructure, operational procedures, personnel training, emergency response capabilities, and integration with global biosafety networks. The report aimed to offer a comprehensive perspective on the global capacity of high-level biosafety laboratories to prevent disease outbreaks and bioterrorism threats, while identifying areas for potential improvement. Furthermore, the report presented a series of recommendations to enhance the safety and responsiveness of global biosafety laboratories, better preparing them to address future biosafety challenges. This report was significant for scientists and provided the public with critical information, fostering transparency and international cooperation in global biosafety.

Considering the increasing global challenges posed by emerging infectious diseases, and rapid advancements in biotechnology, The World Health Organization (WHO) published its *Laboratory Biosecurity Guidance* in 2024 to provide comprehensive recommendations for working safely and securely with high-consequence and biosecurity-relevant materials [63]. This document focuses on building capacity at laboratory, institutional, and national levels to effectively address biological risks. It is particularly beneficial for countries without established regulations, offering a framework to develop or enhance systems for handling high-risk pathogens.

6. Conclusions and Perspectives

This paper reviews the development of high-level biosafety laboratories worldwide from the perspective of the history of science and technology, focusing on the importance of these laboratories in biosafety and global health management. By comparing the development paths and legal regulations of biosafety laboratories in different countries, the paper reveals how high-level biosafety laboratories effectively respond to biosafety threats and biological risks. The selection of laboratories in this study is based on their historical significance, contributions to global health security, and representation of diverse regional contexts, ensuring a balanced analysis of key milestones in biosafety development. By comparing the development paths, operational practices, and legal regulations of biosafety laboratories in different countries, the paper reveals how these facilities effectively respond to biosafety threats and biological risks.

High-level biosafety laboratories play a pivotal role in addressing global health challenges and advancing international biosafety initiatives. Their contributions are multifaceted, encompassing the rapid response to emerging infectious diseases, the promotion of international standards, and the reduction in inequities in health infrastructure. During the COVID-19 pandemic, these laboratories were at the forefront of global efforts to combat the virus. They provided critical support for diagnostic innovation, vaccine development, and therapeutic research, while collaborating across borders to share data and methodologies. This international cooperation underscores their global responsibilities, enabling countries to respond collectively to health crises and preventing the escalation of biological threats. The responsibilities of high-level biosafety laboratories also encompass ethical considerations, particularly in the context of emerging technologies and dual-use research. These laboratories are more than national assets; they are integral components of a global network dedicated to protecting public health, advancing scientific knowledge, and mitigating biological risks. By examining their evolving roles and responsibilities, this study highlights the indispensable contributions of biosafety laboratories to the collective pursuit of global health security.

The development of high-level biosafety laboratories globally shows that technological advancement and the improvement of safety standards are key elements. In the early stages, countries mainly strengthened protective measures within laboratories, such as biosafety cabinets, air handling systems, and sealed isolation technologies, to address laboratory infection incidents. As research on highly pathogenic microorganisms deepened, safety measures gradually upgraded to adapt to more complex biological threats and pathogen studies. Particularly in the face of emerging infectious diseases and bioterrorism threats, the construction and management of high-level biosafety laboratories have become critical. Experience from various countries demonstrates that a sound legal framework and safety standards are essential to the safe operation of these laboratories. A series of standardized documents from international organizations and countries, such as the World Health Organization's *Laboratory Biosafety Manual* and the U.S. Centers for Disease Control and Prevention's *Biosafety in Microbiological and Biomedical Laboratories*, provide unified guidelines for high-level biosafety laboratories globally. By adhering to stringent technical standards and management systems, these laboratories are better equipped to respond to sudden biosafety incidents, ensuring the safety and effectiveness of pathogen research. The paper emphasizes that high-level biosafety laboratories not only play a crucial role in addressing national biosafety challenges but also make significant contributions to international public health cooperation. Biosafety laboratories across countries can jointly tackle global biological threats, driving the establishment and improvement of international biosafety standards. This underscores the importance of international collaboration and policy support in laboratory safety management and provides valuable historical insights for developing more effective biosafety strategies in the future.

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