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Review

From Biosafety to National Security: The Evolution and Challenges of Biosafety Laboratories

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Abstract: From the perspective of science and technology history, we review the development history and key events of global biosafety laboratories to deepen our understanding of biosafety. The construction history of biosafety laboratories reveals the complex interactions between science, social needs, public health safety, and national security. From the recognition of laboratory infection incidents in the late 19th century to the potential hazards of biological warfare and the development of biotechnology in the mid-20th century, the gradual establishment of a laboratory biosafety level system to the construction of high-level biosafety laboratories in the 21st century to respond to global infectious disease challenges, each stage of development is closely related to the social background, technological progress, public health needs and national security considerations of the times.

Keywords: biosafety laboratory; biosafety; biosafety levels; history of science and technology

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1. Introduction

Biosafety laboratories, or containment laboratories, are specialized facilities aimed at safeguarding laboratory staff, test subjects, the public, and the environment from possible biological risks. These labs work with microorganisms and biological materials that have different levels of infectivity or danger, all while prioritizing the safety of personnel, public health, and the environment. Biosafety laboratories are classified according to the potential hazard level of the biological materials they handle, with biosafety levels (BSL) ranging from BSL-1 to BSL-4. The higher the level, the greater the potential danger of the materials handled and the stricter the corresponding safety and protective measures. Biosafety laboratories play a critical role in protecting individuals and the environment, advancing scientific research, addressing public health challenges, and safeguarding national security.

2. Early Exploration of Laboratory Safety: The Rise of Microbiology and the Emergence of Biosafety Awareness (1849–1940)

In the history of microbiology, numerous laboratory-related infection incidents have occurred. In 1849, a doctor in Vienna died after contracting puerperal fever during the autopsy of a patient [1], marking the first recorded laboratory-related fatality. During the early exploration phase, laboratory safety measures were reactive and lacked sufficient attention, often driven by isolated incidents such as Robert Koch's cholera infection report in 1886 [2]. In this report, Koch pointed out the possible dangers of working with pathogens in labs and stressed the importance of implementing proper safety protocols to avoid similar occurrences. This prompted the initial ideas for biological containment. As bacteriology advanced quickly, researchers started to investigate different pathogens more thoroughly,

including Salmonella Typhi. In 1893, the first recorded laboratory infection with *Salmonella* Typhi occurred [3]. These events highlight the significance of laboratory safety to both the medical community and the public, leading to improved infection prevention and control protocols in labs.

In the early 1900s, laboratories' possible biosafety hazards started to worry researchers and public health authorities. During this time, the concept of biosafety laboratories began to take shape. The primary goal was to protect researchers from infections while preventing pathogens from spreading into the external environment and endangering public health. In 1901, Walter Reed took several preventive steps during his yellow fever studies in Cuba to protect against mosquito bites and prevent the transmission of the virus to healthy people [4]. The article aimed to control mosquito transmission in the lab setting. This involved not just comprehending how certain diseases are transmitted but also served as an early instance of biosafety protocols designed to tackle biological risks.

Charles Edward Amory Winslow developed a new method for detecting airborne bacteria, which improved the understanding of environmental microbial contamination in 1908. His creation of the impactor-type air sampler enabled scientists to better evaluate the presence of airborne microorganisms, leading to improved strategies for preventing microbial transmission and contamination [5]. In 1910, German bacteriologist Friedrich Loeffler initiated research on the foot-and-mouth disease virus at the Friedrich Loeffler Institute for Animal Disease Research, establishing it as one of the earliest locations globally to explore the biological aspects of such pathogens. The protective measures implemented during laboratory research promoted the development and establishment of biosafety laboratory facilities. This period reflects a foundational yet limited understanding of biosafety, as the focus remained on protecting researchers rather than integrating biosafety into public health infrastructure [6]. The Brucella and Rickettsia incidents in 1938 and 1939 further demonstrated the importance of biosafety management in laboratories [7,8]. These events highlighted how researchers were exposed to airborne transmission or other routes while working with pathogen samples, emphasizing the need for better laboratory design and enhanced personal protective equipment.

During this period, biosafety measures were relatively basic compared to today's advanced standards, but they represented the growing recognition of the importance of laboratory safety. These initial actions established the groundwork for the creation of more organized and stringent biosafety levels and standards in subsequent years. They also reflected the scientific community's initial efforts to protect both researchers and public health. As scientific advancements continued, these early steps evolved into the comprehensive biosafety management systems we recognize today.

3. The Construction Phase of Biosafety Barriers in Laboratories (1941–1964)

Laboratory-acquired infections (LAIs) happen when lab personnel become infected due to exposure to pathogens, which has greatly sped up the creation and enforcement of biosafety protocols. In 1941, Karl Friedrich Meyer and colleagues documented 74 cases of laboratory-associated Brucella infections, which occurred when staff inadvertently inhaled the bacteria while handling microbial specimens [9]. This emphasized the necessity for more stringent safety protocols.

A key milestone in the development of biosafety laboratories was the establishment of the U.S. Army Biological Warfare Laboratories (USBWL) in 1943. The USBWL's mission was to research biological warfare defense, decontamination, gaseous disinfection, and agent purification, aiming to provide effective biological defense strategies for the military [10]. Under the leadership of Hubert Kaempf Jr. and Dr. Arnold G. Wedum, the USBWL made groundbreaking advances, particularly in the development of the Class III biosafety cabinet prototype, designed under Dr. Wedum's guidance [11]. This advancement laid the foundation for the establishment of "cabinet-line" biosafety laboratories, where such containment systems became integral to ensuring the highest levels of safety and operational efficiency. The Class III biosafety cabinet was a highly sealed containment

system that completely isolated the operator from pathogens, maximizing protection for laboratory personnel and the environment. This development represented a major leap forward in biosafety technology and established a foundation for upcoming laboratory safety measures.

Fueled by defense requirements, advancements like the Class III biosafety cabinet signified important progress, even though they were originally created for military use. In 1947, the National Institutes of Health (NIH) established the first peacetime research laboratory dedicated to microbial safety [12]. This facility boasted advanced biosafety measures for its time, such as air sterilization using superheated grids, nightly surface disinfection with ultraviolet light, regulated access to the laboratory through sterilization locks, and the implementation of concrete canopies in place of contaminated fabric curtains. In 1949, S. Edward Sulkin conducted the first systematic investigation into laboratory infections, identifying 222 cases of viral infections and 21 deaths [13]. These findings emphasized the risks of laboratory infections and prompted improvements in biosafety measures and standardization.

Biosafety cabinets were critical in protecting laboratory workers from infections while preventing environmental contamination with biological materials. In 1951, the Baker Company developed the world's first Class II biosafety cabinet [14], which offered both product protection through downward airflow and worker safety, something that Class I cabinets could not achieve.

The importance of laboratory safety barriers was further recognized following the American Public Health Association's 1950 conference on laboratory infections, showcasing the first protective barrier equipment for bacteriological safety [15]. In 1953, Arnold G. Wedum released a publication titled "Bacteriological Safety", which emphasizes the dangers linked to bacterial research methods like centrifugation, culturing, and inoculation. The work also presents safety protocols, including the use of bacteriological safety cabinets, precautions for centrifuge operation, and ventilated cages for animals [16].

The advancements in biosafety measures that were initially created for biological warfare labs slowly began to impact biosafety protocols globally [17]. This is evidenced by the founding of the first Biological Safety Conference in 1955. Dr. Wedum's keynote address, "The Role of Safety in Biological Warfare", opened the conference, which laid the foundation for the field of laboratory biosafety [18]. At this conference, G. Briggs Phillips presented on air biosafety, highlighting the increasing awareness of risks associated with common bacteriological techniques. The inaugural conference facilitated important conversations that propelled the creation of biosafety standards, enhanced global cooperation, and stimulated additional advancements in biosafety technology.

In 1962, W. J. Whitfield proposed the concept of unidirectional airflow, which became a key element in modern laboratory designs [19], particularly for high-level containment environments like BSL-3 and BSL-4 labs. Also called laminar flow, this airflow method ensures air moves steadily in one direction, minimizing contamination risks and safeguarding clean spaces from harmful airborne particles.

In laboratory environments, there are numerous potential biological hazards that not only pose health risks to laboratory personnel but can also threaten public health. Therefore, implementing comprehensive control measures to manage these risks is essential. In 1963, G. Briggs Phillips further explored biosafety in animal laboratories, discussing the biological hazards posed to laboratory personnel and how to mitigate them through vaccination, proper techniques, safety equipment, and laboratory design [20]. His research demonstrated that many laboratory infections could be avoided using specially designed equipment, and he stressed the necessity of a thorough biosafety program that incorporates clear safety guidelines, staff vaccinations, and the implementation of appropriately designed safety devices. Phillips' contributions were crucial in advancing biosafety practices, particularly the use of specialized equipment in both human and animal labs [21].

The years from 1941 to 1964 were crucial for establishing biosafety measures in laboratories. The foundational progress made in safety equipment, biosafety protocols, and

laboratory designs during this era set the stage for the contemporary biosafety standards that safeguard laboratory workers and public health today. The early innovations, such as the creation of Class III biosafety cabinets and unidirectional airflow, continue to shape the design and functioning of high-level containment laboratories globally.

4. Key Measures for Addressing Deadly Pathogens: Development of Biosafety Classification and Laboratory Operating Standards (1965–1982)

Laboratory infection incidents have attracted attention to the classification of pathogens to ensure the safety of the laboratory environment. R.C. Allen's Containment Criteria for Laboratories Handling Infectious Agents emphasized containment measures primarily as passive responses to potential risks in 1965 [22]. This framework became a key resource for controlling and safely handling infectious pathogens, ensuring the protection of researchers, and the prevention of biological hazards.

As laboratory technologies advanced and research on pathogens expanded, the risk of laboratory-acquired infections (LAIs) grew. In 1967, the German Marburg virus was severely infected in the laboratory. Simultaneously, Robert Paul Hanson and his team documented 428 instances of arbovirus infections linked to laboratory work, underscoring the risks encountered by scientists handling these pathogens. Their findings stressed the importance of implementing strategies like routine antibody testing for lab staff and employing passive immunity after incidents to reduce the chances of infection [23]. Although these measures improved safety, they remained heavily focused on mitigating the effects of accidents rather than minimizing the likelihood of such accidents in the first place. This research highlighted the necessity of categorizing and managing pathogens based on their risk, especially those that can be transmitted through aerosols, to minimize the likelihood of laboratory-acquired infections (LAIs). At the same time, in G. Briggs Phillips's article on Laboratory Design for Microbiological Safety, he emphasized essential elements in the design of microbiological research facilities to ensure the secure containment of infectious agents. He elaborated on the idea of primary and secondary barriers, where the primary barrier directly surrounds infectious materials, acting as the initial line of defense, while the secondary barrier consists of the laboratory's structural features that help prevent the escape or dissemination of infectious substances [24]. This approach was critical in guiding scientists, architects, and engineers in building or renovating laboratories. The article also stressed the importance of filtration, pressure balance, ultraviolet radiation, and decontamination methods in preventing accidental infections and cross-contamination.

In 1969, the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) was established, becoming the Department of Defense's only facility equipped to research hazardous viruses in positive pressure suits [25]. As the United States Army Medical Research Institute of Infectious Diseases' only facility equipped to research hazardous viruses, USAMRIID pioneered the use of advanced containment strategies, including positive pressure suits, which became a hallmark of what are now referred to as "suit lab" biosafety laboratories. Leveraging the biosafety innovations of the 1950s and 1960s, USAMRIID became a global standard for safely handling the world's most dangerous pathogens. That same year, the U.S. Public Health Service published a booklet, Classification of Pathogens by Risk, which categorized pathogens into four risk groups (Class 1–4) based on their potential hazard [26]. This classification system greatly influenced the design, operation, and management of future biosafety laboratories. The 4th edition of Classification of Etiologic Agents based on Hazard, published in 1974, continued to serve as a concise guide for general microbiological safety, emphasizing that the best way to maintain laboratory safety is through the consistent application of appropriate and cautious laboratory techniques, including effective decontamination and sterilization processes [27]. In the same year, the State Research Center of Virology and Biotechnology VECTOR of Russia was established, equipped with research facilities suitable for studying biological hazards at all levels.

The emergence of molecular biology in the 1970s, coupled with the first recombinant DNA and cloning experiments in the U.S., brought new potential risks, especially for biochemists who lacked experience in managing biological hazards compared to microbiologists [28]. In 1975, the Asilomar Conference, led by Maxine Singer and other biologists, debated the safety issues surrounding recombinant DNA [29]. The result was a provisional report that established guidelines for laboratory work, introducing the terms "Physical Containment" and "Biological Containment" as procedures to ensure pathogens are safely handled in laboratories [30]. The 1976 U.S. guidelines for recombinant DNA research, which were updated in 2016, established three biological safety levels (EK1–EK3) [31] and four physical containment levels (P1–P4) based on the risk associated with the experiments (Table 1) [32].

Table 1. Development of biosafety laboratory levels.

Year	Files	Contents
1965	Laboratory Control Standards	■ Group A–Group H ■ Pathogens are classified based on their pathogenicity to humans and animals. Groups A–D are non-pathogenic to humans but differ in their effects on animals, ranging from mild to potentially lethal. Group E is mildly pathogenic to humans, Group F occasionally causes severe disease, Group G is highly pathogenic, and Group H is extremely pathogenic and often lethal to humans.
1969	Hazard Based Etiology Classification	■ Class1–Class4 ■ Pathogens are categorized by risk levels: Class 1 poses none or minimal risk, Class 2 has ordinary potential risk, Class 3 presents special risks to individuals, and Class 4 carries a high risk to both individuals and the community.
1974	The Centers for Disease Control and Prevention of the United States formally approved the Hazard-based Classification of pathogens	■ Class1–Class4 ■ Pathogens are classified by risk level: Class 1 poses minimal or no risk, Class 2 has ordinary potential risk, Class 3 carries specific risk to individuals, and Class 4 involves high risk to both individuals and the community.
1976	Research Guide for Recombinant DNA molecules	■ Pl–P4 ■ EKI–EK3 ■ Laboratory safety levels (P1–P4) and *E. coli* containment levels (EK1–EK3) with progressively stricter controls for higher-risk experiments, from standard techniques to advanced containment measures and genetically modified strains with reduced escape potential.
1979	The World Health Organization classifies dangerous pathogens into four levels, Risk Group I-IV risk in ascending order of risk	■ Risk Group I–Risk Group IV ■ Biosafety levels from I to IV, with increasing containment measures based on risk: Level 1 involves basic teaching labs with standard practices; Biosafety Level II adds protective clothing and biohazard signs for primary health and diagnostic labs; Biosafety Level Ill introduces special clothing, controlled access, and directional airflow for high-risk diagnostics and research; and Biosafety Level IV, used for dangerous pathogens, requires airlocks, showers, and specialized waste disposal.

Table 1. *Cont.*

Year	Files	Contents
1984	Biosafety Guidelines for Microbiological and Biomedical Laboratories	■ Biosafety Level 1–Biosafety Level 4 ■ Biosafety levels from 1 to 4, increasing in containment based on risk: Biosafety Level 1 for minimal hazard agents, Biosafety Level 2 for moderate hazard agents, Biosafety Level 3 for serious or lethal diseases via inhalation, and Biosafety Level 4 for life-threatening, exotic agents.
2004	Laboratory Biosafety Manual	■ Basic-Biosafety Level 1–Maximum Containment-Biosafety Level 4 ■ Biosafety levels with progressively stricter controls: Biosafety Level 1 for basic teaching with general practices, Biosafety Level 2 for primary health and diagnostics with protective clothing and biohazard signs, Biosafety Level 3 for special diagnostics with controlled access and directional airflow, and Biosafety Level 4 for handling dangerous pathogens with airlocks, showers, and specialized waste disposal.
2015	Canadian Biosafety Standard, CBS 2nd Edition	■ CL1–CL4 ■ CL1 is suitable for low-risk work in basic labs, CL2 adds operational practices and some containment for moderate risks, CL3 includes comprehensive practices and containment, and CL4, the highest level, requires complex, self-contained facilities for maximum containment.
2020	Biosafety in Microbiological and Biomedical Laboratories 6th Edition	■ Biosafety Level 1–Biosafety Level 4 ■ Biosafety Level 1 is for low-risk agents unlikely to cause disease in healthy adults, Biosafety Level 2 is for agents with moderate risk associated with human disease, Biosafety Level 3 is for agents that may cause serious or lethal diseases through inhalation, and Biosafety Level 4 is for highly dangerous agents posing a life-threatening risk, often lacking vaccines or treatments.

In 1977, during the 20th American Biosafety Conference, the construction of Biosafety Level 4 (BSL-4) laboratories was proposed and discussed. In a report by Orley Bourland at the Frederick Cancer Research Center (FCRC), the rationale and consequences of establishing P4 facilities were explored [33]. These labs, designed to handle the most dangerous pathogens, required the highest levels of biosafety precautions. The construction of BSL-4 labs involved strict safety protocols to ensure that researchers and the surrounding environment were not exposed to dangerous agents. Such facilities were crucial for studying high-risk microbes that seriously threatened public health. The establishment of these labs and the international standardization that followed played a key role in bolstering global public health security and in enabling countries to better prepare for and respond to potential biological threats.

The rapid development of biomedical research, the increased risk of laboratory communication, the rise of genetic engineering technology, and the international community's attention to global biosecurity have been significant factors. In this context, these laboratories provide necessary guarantees for the safe handling and research of high-risk pathogens. In 1981, Japan's National Institute for Infectious Diseases constructed a biosafety facility (Building 8) in Musashi Murayama City, approximately 40 km from Tokyo [34]. The facility spans a total area of 1112 square meters. Its first floor houses a Biosafety Level 4 (BSL-4) laboratory as its centerpiece, alongside a Biosafety Level 3 (BSL-3) laboratory.

In the 1970s, Multiple countries and organizations established risk-level classification standards for handling pathogenic microorganisms in laboratories, laying the groundwork for the classification of biosafety laboratories. The progress in laboratory biosafety demon-

strates a growing awareness of the need for advanced containment technologies and strict safety measures to protect researchers and the public.

5. Standardized Development of Biosafety Laboratories: Progress and Advancements (1983–1998)

The increased risk of laboratory-acquired infections (LAIs) in biotechnology highlights the need for standard biosecurity practices. In 1983, the World Health Organization (WHO) released the first edition of the Laboratory Biosafety Manual, marking an important progress in the field of biosafety [35]. This manual establishes global guidelines, including classifying laboratories according to biosafety levels (BSL) from BSL-1 to BSL-4, based on the biohazard level of the pathogens being processed. Each level defines safety measures for managing biological materials to protect staff, the environment, and the public. This classification system not only promotes the systematic and orderly construction of biosafety laboratories but also ensures that corresponding safety measures can accurately match different risk levels.

Biosafety guidelines and standards have greatly improved the construction of biosafety laboratories. The WHO's manual offers international biosafety guidelines that stress the importance of global cooperation, guiding laboratories everywhere. In 1984, the U.S. CDC and NIH jointly published the Biosafety in Microbiological and Biomedical Laboratories (BMBL). While it focused on U.S. practices, BMBL guidelines gained international acceptance, particularly in countries without their biosafety measures [36]. The BMBL defines four biosafety levels for handling infectious agents, from basic precautions in BSL-1 to maximum containment in BSL-4 for agents with severe risks and no available treatments. By then, the classification of biosafety levels had become globally recognized, creating a consistent framework for laboratory development. Around the same time, the American Biological Safety Association (ABSA) was established, playing a crucial role in promoting biosafety education and training and raising awareness among lab staff and leaders [37].

The Australian Animal Health Laboratory (AAHL) became a pioneering biosafety facility, purpose-built to contain and study animal pathogens in 1985. As the first BSL-4 facility for such research, it was equipped to handle high-risk pathogens safely, advancing studies on diseases with potential impacts on both animal and public health. This marked a major investment in biosafety infrastructure for Australia, positioning the country at the forefront of biosafety research. This marked a major investment in biosafety infrastructure for Australia, positioning the country at the forefront of biosafety research [38]. Similarly, in 1987, China established its first BSL-3 laboratory, a significant step forward in its biosafety capabilities [39]. This facility bolstered China's research for handling moderately dangerous pathogens and supported the development of public health and scientific research.

Since the publication of the first Biosafety in Microbiological and Biomedical Laboratories (BMBL) in 1984, biotechnology advanced rapidly, particularly in genetic engineering, molecular biology, and pathogen research. Figure 1 summarizes the development history of standards and laws for global biosafety laboratories. These advancements increased the complexity and diversity of microbial and biological materials handled in labs. In 1993, the CDC and NIH published the third edition of the Biosafety in Microbiological and Biomedical Laboratories [40]. This edition refined the biosafety level classism and provided more specific guidelines for laboratory design and operation. It represented a significant advancement in ensuring lab safety and making progress while strengthening international collaboration. In 1997, Georgia State University called for research on the B virus, emphasizing the need for high-level biosafety research in a university environment [41]. This highlighted the growing recognition of the unique, specific, high-risk pathogens in research settings.

This period saw the global standardization of biosafety practices, with the WHO's 1983 Laboratory Biosafety Manual and the 1984 BMBL laying the foundation for biosafety levels (BSL) classifications and safety protocols. Key developments included the establishment of pioneering BSL-4 labs, such as the AAHL in Australia, and advancements in laboratory

design to handle increasingly complex biological materials. The refinement of biosafety standards, particularly in the 1993 BMBL edition, further strengthened international collaboration and addressed emerging challenges in pathogen research, underscoring the growing importance of biosafety in scientific advancement.

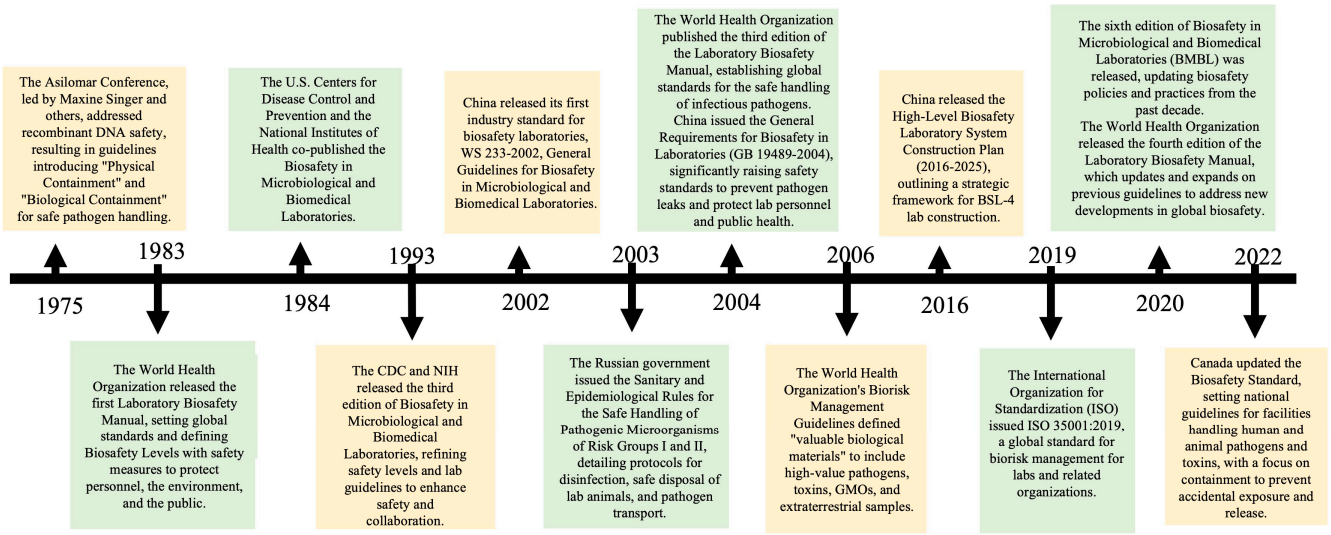


Figure 1. History of standards and guidelines for global biosafety laboratories.

6. Frontline Exploration of Biosafety Laboratories in Tackling Emerging Pathogens and Global Infectious Disease Challenges (1999–Present)

In the late 1990s, the world began to pay more attention to biosecurity due to concerns about bioterrorism and emerging infectious diseases. The National Microbiology Laboratory (NML) of Canada, equipped with BSL-4 facilities, officially opened in 1999 [42]. In partnership with the Public Health Agency of Canada (PHAC) and the Canadian Food Inspection Agency (CFIA), NML plays a key role in public health through research, surveillance, emergency preparedness, and diagnostic services, greatly supporting global disease prevention efforts. During this period, the U.S. Centers for Disease Control and Prevention (CDC) and the Association of Public Health Laboratories (APHL) jointly launched the Laboratory Response Network (LRN). This network aimed to standardize laboratory testing procedures, enhance communication and collaboration among laboratories, and improve the capacity to handle high-risk pathogens and toxins.

The Jean Mérieux Laboratory BSL-4 lab in Lyon, France, was completed in 1999 and opened to scientists in 2001 [43]. This milestone project was designed to provide a safe environment for researching highly pathogenic agents such as Ebola and Lassa fever. Its establishment strengthened France's and the global capacity to address infectious disease outbreaks and biological threats, becoming a key hub for global biosafety research.

In 2002, China released its first industry standard for biosafety laboratories, WS 233-2002, General Guidelines for Biosafety in Microbiological and Biomedical Laboratories. This standard outlined the fundamental principles of biosafety protection, laboratory classification, and the basic requirements for different levels of laboratories. It was intended to serve as the minimum requirement for disease control agencies, healthcare facilities, and research institutions [44]. The release of this standard marked an important step in China's laboratory biosafety management, offering clearer guidelines and norms to reduce the risk of laboratory-acquired infections and protect laboratory workers and the external environment from biohazards. By standardizing laboratory design, operations, and personnel training, this standard helped improve laboratory safety and fostered healthy development in the bioscience sector.

The 2003 outbreak of severe acute respiratory syndrome (SARS) and subsequent laboratory-acquired infections underscored the importance of establishing and managing BSL-4 laboratories

within global research institutions. This led to an international surge in the construction of high-containment laboratories, further fueled by the U.S. government's announcement of the "BioShield" initiative aimed at countering biochemical terrorist attacks through the creation of multiple BSL-4 facilities for studying the deadliest viruses [45].

In response to these challenges, the Russian government issued the Sanitary and Epidemiological Rules for the Safe Handling of Pathogenic Microorganisms of Risk Groups I and II in 2003. This regulation detailed protocols for disinfection procedures, the safe disposal of laboratory animals, and pathogen transport [46]. It required all research institutions handling Risk Group I and II pathogens to develop comprehensive laboratory procedures, subject to review and approval by biosafety committees, to ensure operational safety. The regulation also emphasized the importance of personnel safety training, mandating that all staff working with these pathogens undergo professional biosafety training to heighten awareness and response capability. Through these measures, Russia aimed to establish a robust biosafety management system, reducing health and safety risks in laboratory work and safeguarding public health.

In 2004, the WHO published the third edition of the Laboratory Biosafety Manual, establishing global standards for the safe handling of infectious pathogens [47]. This version introduced risk assessment and expanded the scope of biosafety to include laboratory biosecurity, reflecting a growing awareness of the broader implications of biosafety. That same year, China issued the General Requirements for Biosafety in Laboratories (GB 19489–2004), which significantly contributed to elevating laboratory safety standards by preventing pathogen leaks and protecting laboratory personnel and public health. Additionally, China's Technical Specifications for Biosafety Laboratory Construction (GB 50346–2004) outlined specific technical standards for laboratory construction, ensuring compliance with biosafety requirements [48]. Subsequently, the Technical Specifications for Construction of Biosafety Laboratories (GB 50346–2004) further detailed the construction requirements for biosafety laboratories. This specification provided specific technical standards for the architectural design, construction, and acceptance of laboratories, ensuring that laboratory facilities and equipment met biosafety requirements, thereby enhancing the overall safety performance of the laboratories [49]. In November, China's Regulation on the Biosafety Management of Pathogenic Microorganism Laboratories, the first law in the country's biosafety domain, was enacted to regulate various aspects of laboratory biosafety management, including laboratory establishment, record-keeping, activity management, and emergency responses [50]. Meanwhile, the Shope Laboratory, part of the Galveston National Laboratory at the University of Texas Medical Branch, established a BSL-4 biosafety laboratory.

In 2006, the WHO introduced the concept of "valuable biological materials" (VBM) in its Biorisk Management Laboratory Biosafety Guidelines [51]. This term was meant to encompass a range of biological materials with special economic, historical, or hazardous significance, including pathogens, toxins, non-pathogens, vaccine strains, genetically modified organisms, and extraterrestrial samples. Proper management of VBMs requires consideration of both direct risks, such as theft or misuse, and potential risks associated with dual-use research. Effective biorisk management strategies must be implemented to address these concerns. Through a unified management framework, VBM ensures consistent safety measures across countries when handling biologically hazardous materials, particularly in biomedicine, public health responses, and technological innovation. It also strengthens the regulation of materials that could be misused, thereby reducing the risks associated with biological weapons and other malicious applications. This comprehensive approach helps promote global cooperation, safeguards scientific progress, and enhances overall biosafety standards.

In 2008, the National Emerging Infectious Diseases Laboratories (NEIDL) at Boston University completed the construction of its BSL-4 laboratory [52], which began receiving pathogens for study in 2018 [53]. This laboratory was established to research highly infectious and potentially lethal pathogens, such as the Ebola virus, adhering strictly to biosafety regulations to ensure the safety of both personnel and the public. NEIDL's BSL-4

facility further bolstered Boston University's capabilities in infectious disease research, contributing significantly to the global response to emerging infectious diseases.

In 2015, Germany's Robert Koch Institute completed the construction of its BSL-4 laboratory, which became fully operational in 2018 [54]. This lab enhanced Germany's capacity for infectious disease research and prevention. That same year, China completed and passed the acceptance of the first overseas fixed BSL-3 laboratory in Sierra Leone, designed to support the region's diagnostic and research capabilities in response to the Ebola outbreak. Figure 2 depicts the establishment of global biosafety laboratories and the advancement of protective measures [55]. This facility marked a major contribution by China to global public health security and strengthened international cooperation in biosafety.

In 2016, China's National Development and Reform Commission and the Ministry of Science and Technology released the High-Level Biosafety Laboratory System Construction Plan (2016–2025), outlining a strategic layout for BSL-4 laboratory construction [56]. Through this plan, China established a series of complementary regulations and standards to support research, disease prevention, and industrial development in biosafety. This strategic plan reflects a proactive approach to public health by ensuring the capability to research and contain the most dangerous pathogens. It underscores China's commitment to enhancing disease prevention, emergency response, and biotechnology development while fostering industrial growth in biosafety. By establishing clear regulations and standards, the plan aims to safeguard public health, prevent future pandemics, and enhance global biosafety cooperation.

In 2019, the International Organization for Standardization (ISO) issued ISO 35001:2019, biorisk management for laboratories and other related organizations [57]. This standard provided systematic guidelines covering risk assessment, operational control, compliance, and continuous improvement, aiming to help institutions effectively manage biosafety risks [58].

In 2020, the sixth edition of the Biosafety in Microbiological and Biomedical Laboratories (BMBL) was updated, reflecting changes in biosafety policies and practices over the previous decade. It introduced new sections and appendices addressing topics such as large-scale biosafety, clinical laboratory safety, pathogen inactivation, and laboratory sustainability. This edition not only ensured the continued protection of laboratory workers and the public from biological hazards but also promoted sustainable and safe laboratory practices [59]. At the same time, the WHO released the fourth edition of the Laboratory Biosafety Manual, which updates and expands on previous guidelines to address new developments in global biosafety [60]. This edition details requirements for design, operation, oversight, and safety measures across biosafety levels BSL-1 to BSL-4, providing specific guidance on layout, ventilation, PPE, and cleaning protocols to ensure the highest safety standards for various pathogen risk levels. The release of this edition is a significant step forward in biosafety laboratory construction. It updates standards for design, air handling, contamination control, and safety while emphasizing sustainability and energy efficiency. By offering risk assessment methods and management strategies, the manual enhances laboratories' capacity to address emerging diseases, providing essential guidance for global biosafety standardization. This strengthens labs' collective response to biosafety challenges, encourages international collaboration, and supports ongoing scientific research and public health.

The Canadian Biosafety Standard was updated in 2022, defining the national standard for facilities handling regulated human and terrestrial animal pathogens and toxins [61]. This version emphasized containment strategies to prevent accidental exposure and release of these substances, ensuring the safety of workers and the public. In summary, CBS specifies the minimum physical containment, operational practices, and performance and validation testing requirements for facilities handling and storing RG2 (Risk Group 2), RG3, and RG4 human or terrestrial animal pathogens or toxins [62].

In 2023, a report from King's College London highlighted the growing number of BSL-4 laboratories worldwide, raising concerns about insufficient oversight and the risks associated with biological safety and security. The report assessed 27 BSL-4 laboratories and found that only seven had high standards of biorisk management, emphasizing the need for

WHO oversight and external audits to ensure compliance with international standards [63]. The report calls on the World Health Organization to strengthen its guidance and urges countries to agree to external expert audits to ensure their laboratories meet international standards. The report emphasizes that, with the growing number of BSL-4 laboratories, concerns about accidents in these facilities have also increased, particularly in countries planning to open their first BSL-4 lab, where biosafety management scores are lower. Globally, 51 BSL-4 laboratories are currently in operation, with an additional 18 in planning or construction. The report also includes an analysis of national biosafety and biosecurity scores and provides recommendations for improvement.

In 2024, the WHO released an updated Laboratory Biosafety Guideline to assist countries, especially those lacking relevant regulations, in establishing frameworks for biorisk management. The new guidelines cover cybersecurity, handling of confidential information, genetic modification, AI-related risks, and laboratory safety during emergencies. It emphasizes the role of national biosafety oversight committees. The guideline provides best practices aimed at protecting communities from pathogen threats while ensuring the safety and sustainability of legitimate biomedical research.

Since 1999, biosafety laboratories have shifted from reacting to laboratory-acquired infections (LAIs) to proactively preventing biological risks. This evolution has made them essential in tackling new pathogens and global infectious disease issues. Ongoing advancements and standardization in biosafety practices improve global public health security and encourage international cooperation against biological threats.

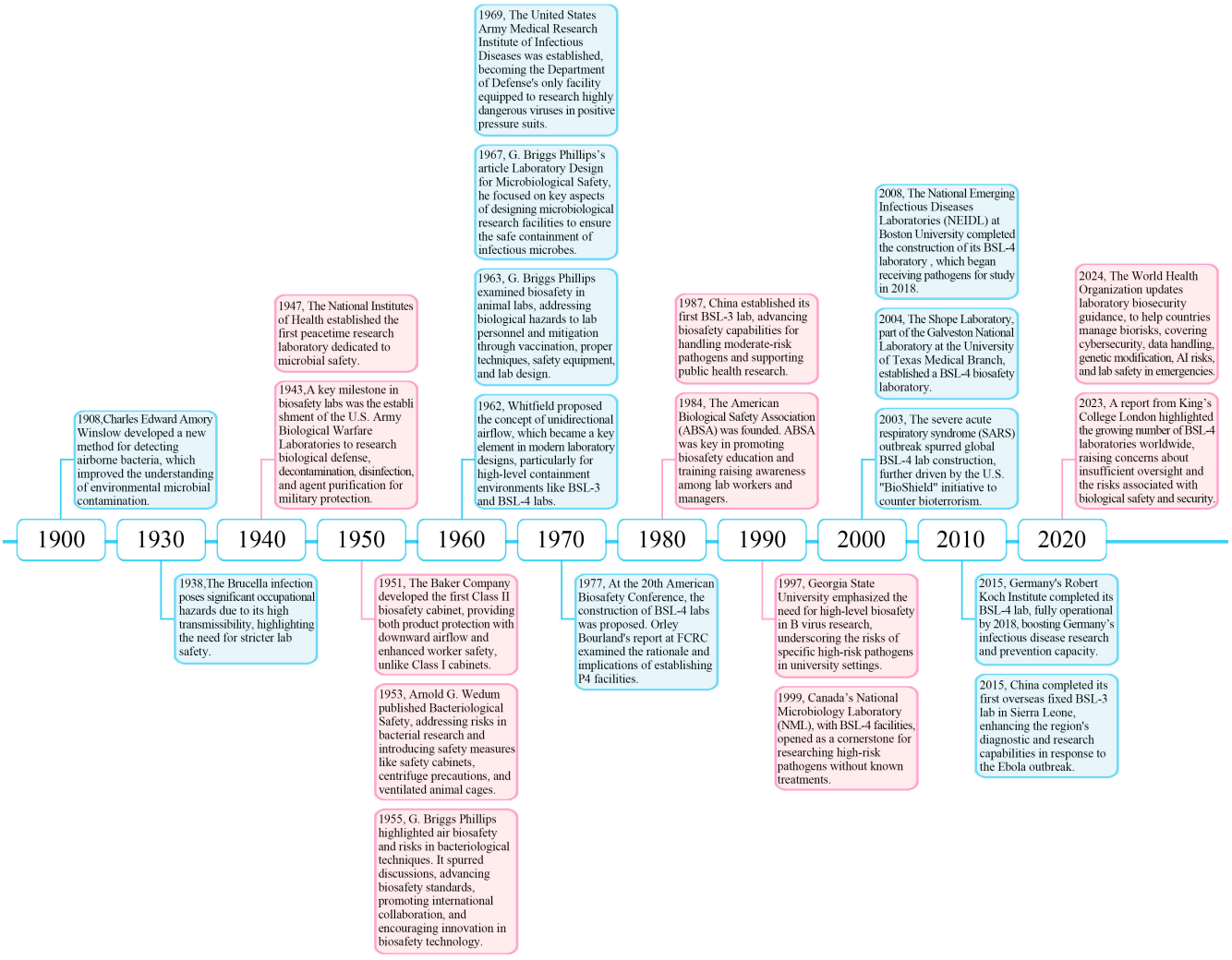


Figure 2. Establishment of global biosafety laboratories and advancement of protective measures.

7. Discussion

The biosafety laboratories have gradually developed, from the initial awareness of protection, to protect laboratory personnel from being infected by pathogens and to protect public health and the environment from biological hazards. Figure 3 shows Evolution of global biosafety laboratories. The U.S. Army Biological Warfare Laboratory (USBWL) set the stage in 1943, followed by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in 1969, two important milestones in the history of biosafety laboratory development. These institutions have helped stimulate advances in protective measures like biosafety cabinets, vastly enhancing the capacity to manage high-risk pathogens. With biotechnology development, the dual use of biotechnology has led to an ever-increasing need for biosafety laboratories. That involved a new focus on something called "biosafety" at the Asilomar Conference in 1975. In 1983, the World Health Organization (WHO) published the Laboratory Biosafety Manual, where risk assessment and safe practices were highlighted, and recommendations for the classification of biosafety laboratories were provided globally. In such a context, early 21st-century threats posed by emerging infectious diseases have underscored the pivotal role of high-level biosafety laboratories in epidemic response and disease research. Countries like the US, Canada, Russia, and China were faced with these threats and responded to them with strict biosafety standards and regulations, confirming that biosafety laboratories are increasingly regarded as important infrastructure for global health security. Biosafety laboratories are not only the main force of disease prevention and biomedical research but also an important part of national security. They are essential to enhancing public health security, advancing scientific progress, and preparing for bioterrorism threats.

It is of great significance to study the construction of biosafety laboratories from the perspective of the history of science and technology. The history of biosafety laboratories is a history of scientific advancement and technological innovation, as well as a history of humanity's growing comprehension of, response to, and governance of biological hazards. A systematic review and analysis of the developmental trajectory, technical evolution, management model, and policy from the history of biosafety laboratories enhances our understanding of biosafety as a discipline and provides a foundation for the construction of the knowledge system of biosafety laboratories. Furthermore, the history of biosafety labs in the world has demonstrated the delicate relationship between science, societal needs, health security, and national security. Each stage of the development of laboratory safety, from the first realization of the need for laboratory safety in the late 19th century through the establishment of the biosafety level system in the mid-20th century to the construction of high-level biosafety laboratories in response to 21st-century global infectious disease threats, is closely linked to the social context, technological advances, public health demands, and national security concerns of the times in which it developed. This historical evolution reflects the complex relationship between science and society and shows how humans use technological advances to respond to new challenges. At the same time, historical research can also reveal the role of biosafety laboratories in national security and biodefense and help evaluate and enhance the country's ability to respond to bioterrorism. It provides valuable historical experience and lessons for the development of effective biosafety strategies. In addition, studying the development of biosafety laboratories allows us to understand how these facilities adapt and innovate to respond to new biological hazards and public health challenges.

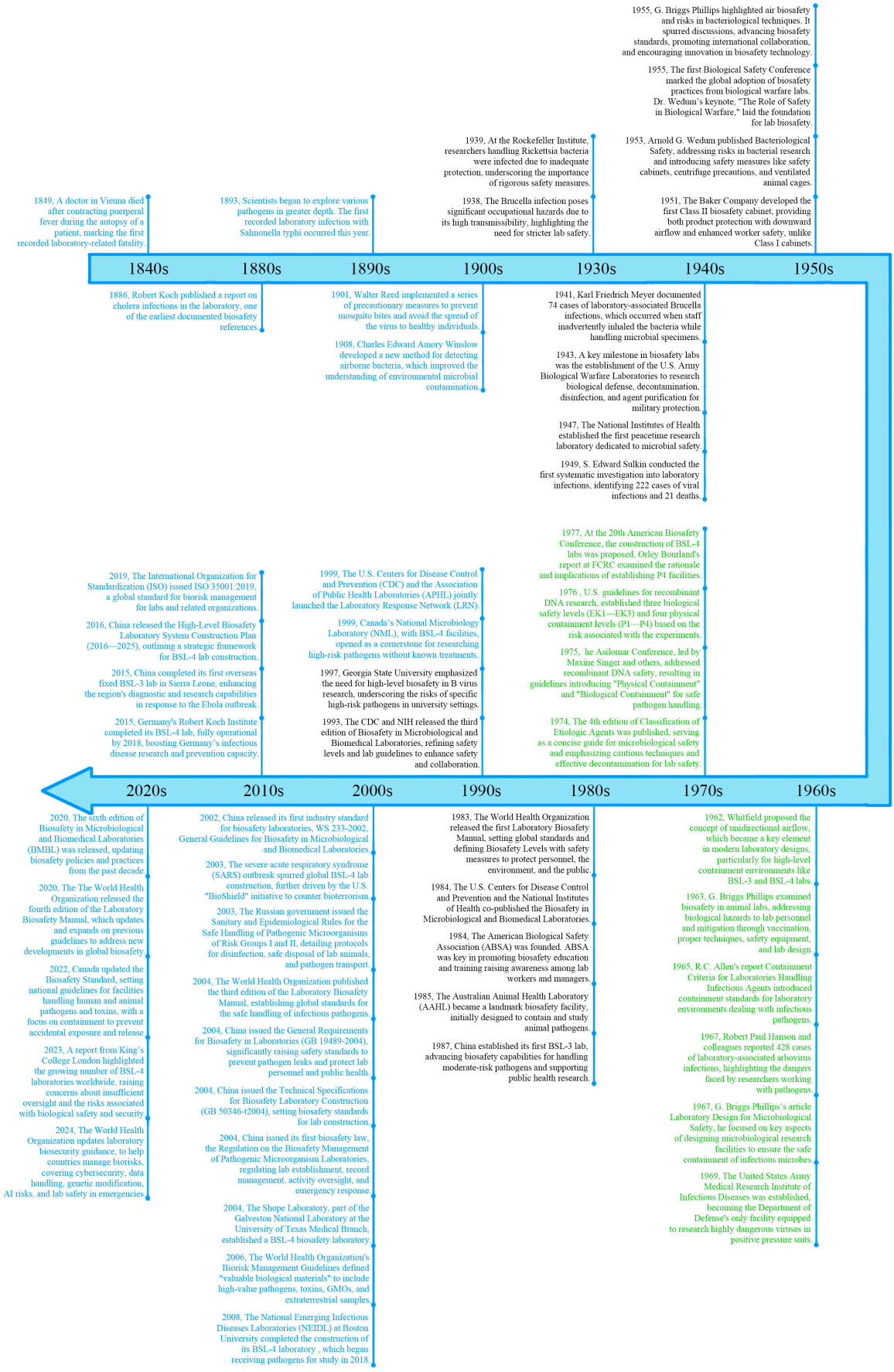


Figure 3. Evolution of global biosafety laboratories.

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