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Review Article

# Unlocking the Hidden Contagions: A Deep Dive into the History, Transmission, and Prevention of Laboratory-acquired Infections

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## Abstract

***Background and objectives:*** Laboratory-acquired infections (LAIs) have been documented since the first report of typhoid fever in 1885 and continue to endanger laboratory professionals despite decades of biosafety advances. This review provides a comprehensive overview of LAIs, emphasizing their history, modes of transmission, and strategies for prevention. ***Methods:*** A systematic review of historical records, case series, and biosafety guidance (1885–2025) identified documented LAIs, their transmission routes, and preventive measures. Data were extracted on pathogen spectrum, geographic distribution, incident outcomes, and the effectiveness of biosafety interventions. ***Results:*** Historical analysis identified 50 laboratory-acquired typhoid infections with six deaths from 1885 to 1915, largely due to mouth pipetting and aerosol exposure. A sharp decline in fatal bacterial infections was observed following the introduction of Class II biosafety cabinets in the 1960s. From 2000 to 2021, 309 LAIs were reported across 94 studies, most commonly Salmonella enterica (56.6%), vaccinia virus (4.2%), and Brucella species (3.9%), with Brucella responsible for over half of hospital-laboratory cases (60 per 100,000 personnel-years). In Canada during 2023, 63 exposure events occurred, including three confirmed infections despite adherence to biosafety level protocols. Environmental persistence studies underscored surface-borne risks. The most effective preventative measures included abolishing mouth pipetting, mandatory use of gloves and eye/face protection, routine Class II biosafety cabinet use for aerosol-generating procedures, surface disinfection with 0.5% sodium hypochlorite, and annual competency-based biosafety training with incident reporting. ***Conclusions:*** LAIs remain geographically widespread and pathogen-diverse. Quantitative historical trends and contemporary surveillance highlight critical transmission routes, including ingestion, inoculation, mucosal splash, and inhalation, while reinforcing evidence-based prevention strategies. Sustained investment in biosafety infrastructure, real-time exposure reporting, and pathogen-specific training is essential to further reduce LAI incidence and severity in the face of emerging antimicrobial resistance and novel agents.

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## Introduction

Laboratory-acquired infections (LAIs) include all types of symptomatic and asymptomatic infections acquired through laboratory or laboratory-related activities.[1] LAIs are as old as laboratories themselves, and their transmission rates increased as soon as microorganisms began to be cultured.[2] Such infections, as well as their modes of transmission and prevention, have not yet been fully elucidated.[3]

The spread of infectious diseases is caused by the release of microbes into the environment, which may be spontaneous, unintentional, or intentional. Regardless of the cause, such releases have the potential not only to harm human health but also to propagate throughout the affected region.[4] To prevent such scenarios, it is critical to handle these microbes in ways that minimize risk. A wide range of bacteria, viruses, fungi, and parasites have been implicated in LAIs. Although the precise risk of infection after exposure remains poorly defined, surveys of LAIs suggest that Brucella spp., Shigella spp., Salmonella spp., hepatitis viruses, human immunodeficiency virus, Mycobacterium tuberculosis, and Neisseria meningitidis are among the most common causes.[5–7] Among viruses, infections due to hepatitis B, hepatitis C, and human immunodeficiency virus are the most frequently reported viral causes of LAIs, whereas dimorphic fungi are the most common fungal causes.[2]

LAIs extend beyond occupational health hazards and represent a critical interface between biosafety and public health security. Incidents involving high-risk pathogens can lead to secondary community transmission, especially when early detection is delayed or containment measures are insufficient, increasing the risk of outbreaks originating from controlled research environments. Notably, past LAI events involving severe acute respiratory syndrome coronavirus

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(SARS-CoV) and Brucella spp. have demonstrated the capacity of such infections to breach laboratory confines and strain public health systems.[8] Economically, the fallout from LAIs can be substantial, encompassing healthcare costs, interruption of scientific operations, and long-term institutional and regulatory repercussions. For example, LAIs may trigger mandatory laboratory shutdowns, revocation of research licenses, or heightened regulatory oversight, collectively straining public resources and reducing research productivity.[9] Therefore, incorporating LAIs into broader public health planning and economic risk assessments is vital for maintaining scientific integrity while safeguarding population health.

This article aims to provide a comprehensive overview of the history, transmission mechanisms, and prevention strategies of LAIs, emphasizing the importance of biosafety measures and highlighting gaps in current knowledge to guide future research and practice.

## Historical context of LAIs

### *Early reports and recognition (1885–1917)*

Typhoid fever was reported as the first LAI in 1885. The first survey of LAIs was published by Kisskalt in 1915, who identified 50 instances of typhoid fever between 1885 and 1915, six of which were fatal. Aerosol production, cuts from sharp objects, ingestion, mouth pipetting, and splashes onto mucosal membranes were among the modes of transmission.[10] From 1907 to 1917, several LAIs were reported in laboratory personnel working with pathogens of cholera, plague, and typhoid fever.[11]

### *Development of biosafety measures (1940–1960)*

Van der Ende published the first official description of a biosafety cabinet (BSC) in 1943, but the first stainless-steel cabinet with an exhaust fan and a glass viewing front was not manufactured until 1948.[12] In their 1951 survey, Sulkin *et al*. described several instances of laboratory-acquired brucellosis, Q fever, and tuberculosis, among other LAIs.[13] Furthermore, in 1957, Reid reported on the incidence of tuberculosis in laboratory workers. Chief technicians had the lowest incidence, whereas junior and student technicians had the highest.[14]

### *Advancements and outbreaks (1961–1990)*

The risks associated with biohazards has steadily decreased since 1965 due to the improved awareness of biohazards and the introduction of containment facilities and BSCs.[2] According to reports by Pike and Sulkin, and serial investigations conducted by Grist from 1979 to 1989, the most prevalent LAIs were typhoid (3.2%), brucellosis (2.1%), salmonellosis (11.6%), hepatitis (20%), shigellosis (27.4%), and tuberculosis (25.3%).[15–18] In 1966, Phillips and Bailey demonstrated that using syringes and needles could produce significant aerosols, particularly when there was pressure inside the syringe, and advised using forceps to remove the needle.[19] Additionally, pipettes produced aerosols, especially when the last few drops were expelled.[19] In 1979, increased biosafety measures became necessary after a Venezuelan equine encephalitis outbreak in a Panamanian laboratory resulted in several infections.[20]

### *Modern era and new threats (1990–present)*

Laboratory practices and knowledge of infectious diseases have significantly influenced the incidence and prevalence of LAIs. Hungarian physician Ignaz Semmelweis was the first to observe that women receiving care from medical students had a relatively higher risk of developing puerperal fever than those managed by midwives. His emphasis on hand hygiene laid the groundwork for modern infection prevention and control practices and highlighted the critical need for cleanliness in laboratories.[21]

The emergence of new pathogens in the second half of the twentieth century increased the risk of LAIs among laboratory personnel. Accidents such as the release of anthrax spores in Sverdlovsk in 1979 and the handling of smallpox samples at the Centers for Disease Control and Prevention (CDC) in 2014 highlighted inadequacies in laboratory security.[11,22] In the 2000s, high-risk pathogen-related LAI incidents prompted stricter oversight and regulation of high-containment laboratories.[23] The significance of biosafety and biosecurity measures was further underscored by the anthrax cases in the USA in 2001.[24]

## Current challenges in LAIs

### *Importance of LAIs in biosafety*

Acquiring knowledge of LAIs is critical for implementing appropriate biosafety and biosecurity measures to ensure the safety of laboratory workers and their working environments, which may be exposed directly or indirectly to hazardous materials or organisms.[1] LAIs are a significant biosafety concern in clinical laboratories; therefore, the comprehensive collection and dissemination of information about LAIs is essential for laboratory personnel training and represents an important component of laboratory biosafety management. This information assists in selecting appropriate experimental protocols, safety equipment, and protective measures.[25] Studying typical LAI cases provides insights into the effectiveness of current safety norms, benefiting national and regional biosafety programs.[26] Education and training for laboratory personnel are required to ensure an appropriate level of awareness when handling biologically hazardous materials in accordance with internationally recognized protocols.

Proper knowledge and training for LAI prevention can mitigate the hazards associated with biological materials through the correct execution of certified protocols, including proper microbiological practices, containment devices, adequate facilities and resources, protective barriers, and specialized education and training for laboratory personnel.[4,27]

### *Epidemiology of LAIs*

Recent epidemiological data underscore the ongoing threat posed by LAIs, highlighting both regional and pathogen-specific trends. A comprehensive scoping review by Blacksell *et al*.[28] documented 309 LAI cases reported across 94 articles between 2000 and 2021, with most incidents occurring in North America, Europe, and Asia. The most frequently identified pathogens were Salmonella enterica serovar Typhimurium (49.8%), Salmonella enteritidis (6.8%), vaccinia virus (4.2%), and Brucella spp. (3.9%), underscoring the predominance of enteric and zoonotic agents in LAI events.[28] Similarly, the Public Health Agency of Canada reported 63 confirmed laboratory exposure incidents in 2023, three of which resulted in LAIs, demonstrating that occupational exposures continue to occur despite rigorous biosafety protocols.[29] In hospital-based laboratories, Brucella spp. remains a leading cause of LAIs, accounting for 55.5% of all reported cases, with an estimated incidence rate of 60 per 100,000 laboratory personnel annually.[30] These data emphasize the persistent need for robust biosafety measures, real-time exposure reporting systems, and pathogen-specific training to reduce the incidence and severity of LAIs, particularly in high-risk settings.

### *Emerging risks from antibiotic-resistant pathogens in laboratory settings*

The rising prevalence of antibiotic-resistant pathogens represents a critical emerging risk in laboratory environments, demanding urgent attention in biosafety protocols. Laboratories working with multidrug-resistant organisms, such as carbapenem-resistant Enterobacterales, methicillin-resistant Staphylococcus aureus (MRSA), and azole-resistant Aspergillus fumigatus, face heightened transmission risks due to these pathogens' ability to evade conventional treatments.[31,32] For instance, MRSA strains, historically linked to hospital-acquired infections, have evolved into community-associated variants capable of causing severe skin and soft tissue infections even in healthy individuals, underscoring their adaptability and persistence in diverse settings.[33] Similarly, drug-resistant Mycobacterium tuberculosis poses dual threats: primary resistance from airborne transmission and secondary resistance due to inadequate treatment regimens, both of which complicate containment in laboratory workflows.[34] Recent studies highlight alarming resistance patterns, such as gram-negative pathogens exhibiting near-total susceptibility only to last-resort antibiotics like imipenem, while showing >80% resistance to first-line agents like ampicillin.[35] These trends necessitate revised safety measures, including enhanced personal protective equipment (PPE) standards, real-time genomic surveillance using whole-genome sequencing, and strict adherence to the CDC's Antimicrobial Resistance Laboratory Network guidelines for rapid detection and response.[31] Collaborative frameworks between clinical and research laboratories, exemplified by the Antimicrobial Resistance (AMR) Laboratory at Institute of Bacterial Infections and Zoonoses (IBIZ), further emphasize the integration of molecular diagnostics and inter-institutional data sharing to mitigate cross-contamination risks.[31,36] Addressing these challenges requires a paradigm shift toward proactive monitoring of resistance gene transfer and tailored decontamination protocols to prevent LAIs in an era of diminishing therapeutic options.

### *Emerging pathogens and contemporary laboratory safety challenges*

The rapid emergence of novel pathogens, such as SARS-CoV-2, Ebola virus, and Zika virus, has introduced unprecedented complexities to laboratory biosafety protocols, necessitating adaptive strategies to mitigate evolving risks.[37,38] These agents often exhibit poorly characterized transmission dynamics, high virulence, or novel routes of infection, as demonstrated by the aerosol stability of SARS-CoV-2 and the hemorrhagic complications of Ebola.[37,39] For instance, LAIs with West Nile virus occurred via percutaneous inoculation during necropsies, underscoring the critical need for enhanced PPE and procedural safeguards even in biosafety level (BSL)-2/3 environments.[37] Similarly, clusters of SARS-CoV-2 infections among laboratory staff, linked to both community exposure and potential sample handling, highlight the dual challenges of managing workplace transmission risks alongside community outbreaks.[39] Emerging pathogens further complicate risk assessments due to gaps in data on environmental stability, infectious dose, and therapeutic countermeasures, as observed during the early stages of the COVID-19 pandemic.[37] The World Health Organization now emphasizes integrated biorisk management frameworks that address cybersecurity threats, genetic modification risks, and infrastructure vulnerabilities during emergencies, reflecting the multidimensional nature of modern laboratory hazards.[40] Proactive measures, including dynamic risk reassessment, stringent aerosol control protocols, and institutional biosafety committees, are essential to safeguard personnel and prevent unintended pathogen release. These adaptations ensure laboratories remain resilient against both naturally evolving pathogens and those engineered through advanced biotechnologies.[37,38]

### *Potential limitations and biases in reporting LAIs*

A critical limitation in the literature on LAIs is the significant underreporting of cases. This underreporting is widely acknowledged and attributed to factors such as fear of reprisal, stigma, and a litigious environment, which discourage laboratories and personnel from disclosing incidents.[3] Most available data on LAIs rely on voluntary reporting or case studies, resulting in incomplete and potentially biased datasets that do not capture the true incidence or diversity of LAIs worldwide.[3] Furthermore, mandatory reporting systems are often insensitive, focusing primarily on acute symptomatic infections and neglecting asymptomatic or subclinical cases, which may lead to an underestimation of exposure risks.[41] The lack of a systematic, comprehensive surveillance system complicates accurate risk assessment and the development of evidence-based biosafety guidelines. Additionally, the voluntary nature of many surveys and the limited number of participating laboratories introduce selection bias, as some laboratories may be reluctant to report accidents due to regulatory or reputational concerns.[1] These reporting biases highlight the need for improved surveillance, standardized reporting protocols, and a culture that encourages transparent incident disclosure to enhance the understanding and prevention of LAIs.

## Routes of transmission of LAIs

LAIs can be acquired through several transmission routes, including contamination of skin and mucous membranes, inoculation, ingestion, inhalation, persistence on surfaces, and mobile phone-mediated spread, each posing specific risks to personnel working with infectious agents. Table 1 summarizes the documented mechanisms of LAI transmission along with representative case examples, geographic locations, and years, highlighting the diversity and persistence of these infection pathways.

### *Contamination of skin and mucus membranes*

Workers in biological laboratories are exposed when spills, splashes, or contaminated surfaces come into direct contact with their skin or mucosal membranes. Open bleeding wounds are particularly prone to infection if they come into contact with fluids containing pathogens. A laboratory technician in North Carolina, USA, was reported to acquire dengue virus infection after preparing a high-titer viral suspension. Inappropriate glove removal and an exposed finger wound were determined to be the cause of infection in this case.[42] Furthermore, Noviello *et al*.[43] described two cases of laboratory-acquired brucellosis following two separate biological incidents.

### *Inoculation*

Blood-borne pathogen infections caused by animal scratches and puncture wounds from sharp objects are examples of illnesses following direct inoculation. Exposure to as little as 0.004 ml of blood contaminated with pathogens due to sharp

**Table 1. Documented routes of transmission of laboratory-acquired infections**

| Transmission route | Mechanism | Documented case(s) | Country | Year |
|---|---|---|---|---|
| Ingestion | Hand-to-mouth contact; contaminated hands or food | Helicobacter pylori infection from finger-to-mouth contact | France | 1995 |
| Inoculation | Needle-stick injuries, animal bites, or scratches | Lymphocytic choriomeningitis virus (LCMV) via needle injury | USA | 2017 |
| | | Vaccinia virus infection via guinea pig bite | Brazil | 2013 |
| Mucosal/skin contamination | Splash onto mucosa or broken skin during procedures | Dengue virus infection via exposed finger wound during glove removal | USA | 2018 |
| | | Brucella exposure via mucosal splash | USA | 2004 |
| Inhalation (Aerosols) | Inhalation of aerosols during lab procedures or equipment failure | Brucella outbreak from unsterilized vaccine fermenter at veterinary lab | China | 2019 |
| Surface contact | Indirect contact via contaminated lab benches and/or instruments | Persistence of Methicillin-resistant Staphylococcus aureus (MRSA) for up to 7 months and Mycobacterium tuberculosis for up to 5 months on surfaces | Germany | 2020–2023 |
| Mobile phones | Use of personal electronic devices in contaminated zones | Bacterial colonization on phones of healthcare/lab staff | Saudi Arabia | 2021–2024 |

injuries may lead to infection. In 2017, a female researcher contracted lymphocytic choriomeningitis virus after accidentally puncturing her left index finger while disposing of used syringes in a full sharps container.[44] Furthermore, a bite from a guinea pig infected with vaccinia virus led to an LAI in a researcher from Brazil.[45] In Nigeria, dengue virus infection was reported in a laboratory worker who handled mice and cleaned their cages.[46]

### *Ingestion*

LAIs can be acquired through accidental ingestion of biological hazards, often as a result of inappropriate hand-to-face contact or poor hand hygiene. A female gastroenterologist was reported to acquire Helicobacter pylori infection after accidentally placing her pathogen-exposed finger in her mouth.[47] Other instances include cases of anthrax in laboratory personnel handling cultures while smoking. Mislabeling of food has also resulted in LAIs among laboratory personnel.[10]

### *Inhalation*

Aerosol inhalation is a common cause of LAIs, as pathogens can remain airborne for extended periods and propagate through the atmosphere. Surveys suggest that inhalation could account for 35–65% of LAI cases, primarily due to scientists not adhering to necessary biosafety protection protocols.[41] In 2019, several individuals in China tested positive for anti-Brucella antibodies after a fermenter was inadequately sterilized using expired disinfectants during the production of the S2 veterinary vaccine.[41] Aerosol exposure can sometimes result in unexplained LAIs with considerable morbidity despite adherence to safety practice guidelines.

### *Persistence of pathogens on surfaces*

The survival of pathogens on inanimate surfaces is a critical factor in LAI transmission. Studies have shown that clinically significant microorganisms can persist on surfaces for extended periods, increasing the risk of indirect transmission in laboratory environments. For instance, Staphylococcus aureus (including MRSA) can survive from seven days to seven months, while Mycobacterium tuberculosis can persist for up to five months under suitable conditions.[48] Enveloped viruses such as SARS-CoV-2 can remain viable on plastic and stainless-steel surfaces for up to 72 h, depending on temperature and humidity.[49] These findings underscore the importance of rigorous surface decontamination protocols and regular disinfection practices in preventing LAIs, reinforcing the need for heightened vigilance and tailored biosafety procedures in laboratory settings.

### *Spread via mobile phones*

Using mobile phones during laboratory work can significantly increase the risk of LAIs. Mobile devices can serve as vectors for pathogens, transferring microbes from contaminated surfaces or hands to the user. This risk is heightened in laboratory settings, where exposure to hazardous biological agents is common.[50] When a laboratory worker uses a cell phone, they may inadvertently contaminate it with infectious agents, which can then be transferred to their face, mouth, or other surfaces outside the laboratory. This compromises sterile environments and safety and can lead to the spread of infections, underscoring the importance of strict adherence to 'No-Phone' policies in laboratory settings.[51]

## Prevention of LAIs

### *Use of PPE*

Ensuring the proper use of PPE is critical in a laboratory. Staff should be trained in correct techniques for donning and doffing PPE to prevent LAIs. The importance of wearing gloves should be emphasized repeatedly, as they serve as the first barrier protecting bare skin from contact with any biological specimen.[52]

### *Engineering controls*

Several engineering controls should be implemented to minimize the risk of LAIs. These include using BSCs for aerosol-generating procedures to prevent the spread of pathogens such as Mycobacterium tuberculosis, SARS-CoV-2, influenza virus, and respiratory syncytial virus.[53] Furthermore, proper maintenance of ventilation and air filtration systems, as well as regular servicing of laboratory equipment, is essential to prevent mechanical failures. Automated systems can also be used for sample processing to reduce direct handling of potentially infectious materials. Work with high-risk pathogens should always be conducted in contained and sealed environments.

### *Administrative controls*

Developing and enforcing Standard Operating Procedures for all laboratory activities, particularly those involving infectious materials, is vital.[54] Laboratory access should be restricted to authorized personnel only. Additionally, establishing a system for reporting and investigating accidents, exposures, and near misses will help prevent future incidents.

### *Good Laboratory Practices*

Aseptic techniques, hand hygiene, and environmental cleaning are primary methods to protect laboratory and healthcare workers from acquiring infections from patients or clinical specimens. Regular handwashing with soap and water, especially before and after handling infectious agents, is essential. Work surfaces, equipment, and waste should be regularly decontaminated to eliminate infectious agents. Techniques that minimize spills, splashes, and aerosol generation should be employed when handling infectious materials. Eating, drinking, smoking, applying cosmetics, or storing food for human consumption should be strictly prohibited.[55]

### *Waste management*

Following protocols for the safe disposal of biohazardous waste, including using autoclaves for decontamination, is critical. Sharps containers should be used for the disposal of needles, blades, and other sharp objects to prevent injuries.[56]

### *Emergency preparedness*

Laboratory staff should be trained and prepared to respond to spill incidents, eye splashes, and needle-stick injuries.[55] It is prudent to maintain an updated list of emergency contacts and resources, including local health departments and infection control departments, should be maintained.

### *Incident reporting*

A system should be implemented for reporting and investigating laboratory incidents, exposures, and infections. Findings from incident investigations should be used to improve safety practices and prevent recurrence. Regular review and analysis of these reports are crucial for identifying trends and areas needing improvement.[57]

## Future directions in LAI prevention and biosafety

### *Policy and regulatory evolution*

Prevention of LAIs relies on recognizing the pathogenicity, source, and method of transmission of organisms in the laboratory, as well as identifying susceptible hosts. The risk of infection can then be reduced through the appropriate use of safe practices and procedures, protective barriers, containment, vaccination, and post-exposure prophylactic therapy.

The most effective way to reduce transmission is to adopt precautionary measures. Most LAI-associated pathogens can be safely handled in a BSL-2 laboratory, while some require the more advanced containment of a BSL-3 laboratory.[58] Preventive strategies may vary among laboratories; however, the basic measures remain consistent.

Biosafety protocols should be regularly reviewed and updated based on the latest guidelines and best practices. Continuous education and training programs should be implemented to keep laboratory staff informed of current biosafety practices. This ongoing process ensures that safety measures remain up-to-date and effective in mitigating risks.

### *Education and training*

Continuous training and education are essential components of a biosafety program. All laboratory personnel should receive initial training and periodic refresher training on biosafety, infection control practices, and emergency response procedures. Regular assessment of staff competency in following safety protocols should also be conducted to ensure effective prevention of LAIs.[59]

### *Proactive monitoring and surveillance*

Medical surveillance programs should be implemented to monitor laboratory personnel for signs of infection and provide timely medical intervention when needed. Regular health screenings are essential to detect early signs of infection. Ensuring that staff are vaccinated against relevant pathogens, such as hepatitis B and influenza, is also important. Protocols for immediate response and treatment following potential exposures should be established.

Additionally, regular safety audits should be conducted to ensure compliance with protocols and identify areas for improvement. Routine maintenance and calibration of safety equipment, such as BSCs, autoclaves, and ventilation systems, are necessary.[60] Rigorous implementation of these strategies can significantly reduce the risk of LAIs and ensure a safer working environment for all personnel.

## Limitations

While this review offers a broad historical and thematic synthesis of LAIs, several limitations temper the strength and generalizability of its findings. First, incident reporting for LAIs remains largely voluntary and heterogeneous across jurisdictions; underreporting, driven by reputational concerns and disparate surveillance infrastructures, almost certainly masks the true incidence of events. Second, the review relied predominantly on English-language publications and readily accessible grey literature, potentially skewing geographic representation toward North America and Europe while overlooking data from low-resource regions with weaker biosafety oversight. Third, inconsistencies in case definitions, diagnostic modalities, and study designs across the 1885–2025 time span limited direct comparisons and precluded robust meta-analysis of incidence trends or intervention effectiveness. Fourth, publication bias is likely, as unusual or severe incidents are more often documented than commonplace exposures or near misses, inflating the apparent proportion of high-consequence pathogens. Finally, key denominator data, such as the number of full-time laboratory personnel, hours of pathogen handling, or biosafety level distribution, were frequently absent, restricting the ability to calculate standardized incidence rates or quantitatively evaluate specific preventive measures. Consequently, the recommendations presented here rest on triangulation of imperfect evidence rather than graded effect estimates.

## Conclusions

LAIs remain a persistent challenge, evolving alongside advances in science and technology. By understanding their historical context, recognizing current challenges, and proactively preparing for future threats, laboratories can safeguard personnel and the broader community. Continuous improvement in biosafety protocols, training, and surveillance will be key to minimizing the risk of LAIs in the years to come.

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## Author contributions

Study concept and design (MAK), acquisition of data (NJ, SM), analysis and interpretation of data (MAK, NJ, SM), drafting of the manuscript (NJ, SM), critical revision of the manuscript for important intellectual content (MAK), and study supervision (MAK). All authors have approved the final version and publication of the manuscript.

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