

Laboratory-acquired infections and pathogen escapes worldwide between 2000 and 2021: a scoping review

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Laboratory-acquired infections (LAIs) and accidental pathogen escape from laboratory settings (APELS) are major concerns for the community. A risk-based approach for pathogen research management within a standard biosafety management framework is recommended but is challenging due to reasons such as inconsistency in risk tolerance and perception. Here, we performed a scoping review using publicly available, peer-reviewed journal and media reports of LAIs and instances of APELS between 2000 and 2021. We identified LAIs in 309 individuals in 94 reports for 51 pathogens. Eight fatalities (2.6% of all LAIs) were caused by infection with *Neisseria meningitidis* (n=3, 37.5%), *Yersinia pestis* (n=2, 25%), *Salmonella enterica* serotype Typhimurium (*S* Typhimurium; n=1, 12.5%), or Ebola virus (n=1, 12.5%) or were due to bovine spongiform encephalopathy (n=1, 12.5%). The top five LAI pathogens were *S* Typhimurium (n=154, 49.8%), *Salmonella enteritidis* (n=21, 6.8%), vaccinia virus (n=13, 4.2%), *Brucella* spp (n=12, 3.9%), and *Brucella melitensis* (n=11, 3.6%). 16 APELS were reported, including those for *Bacillus anthracis*, SARS-CoV, and poliovirus (n=3 each, 18.8%); *Brucella* spp and foot and mouth disease virus (n=2 each, 12.5%); and variola virus, *Burkholderia pseudomallei*, and influenza virus H5N1 (n=1 each, 6.3%). Continual improvement in LAI and APELS management via their root cause analysis and thorough investigation of such incidents is essential to prevent future occurrences. The results are biased due to the reliance on publicly available information, which emphasises the need for formalised global LAIs and APELS reporting to better understand the frequency of and circumstances surrounding these incidents.

Introduction

Laboratory-acquired or laboratory-associated infections (LAIs) comprise any infection acquired or reasonably assumed to be acquired by exposure to a biological agent during laboratory-related activities.¹ Accidental pathogen escape from laboratory settings (APELS) results from unintended movement of a laboratory pathogen to the outside environment following a breach of biocontainment caused by procedural or engineering failures. Clinical, research, teaching, and vaccine production facilities heavily rely on laboratories, making it crucial to understand the associated risks and necessary mitigations to prevent LAIs and APELS. LAIs and APELS have substantial consequences for laboratory staff, the broader community, and the environment, depending on the pathogen involved.²⁻⁵ They are therefore major concerns for scientists and policy makers. The risks associated with pathogen research and diagnostics should be managed within a standard biosafety and biosecurity-management framework to prevent LAIs and APELS.

Investigations aimed at determining the causes of LAIs and preventing their future occurrences have a long history. In 1941, Kisskalt and Phillips⁶ conducted the first investigation of LAIs to identify the origins of 50 laboratory-acquired typhoid fever cases dating back to 1885; six deaths were recorded, and the method of infection was known in 23 cases, of which 16 cases were caused by mouth pipetting. In 1949, Sulkin and Pike⁷ determined that 222 laboratory infections in the USA resulted in 21 deaths. Their findings led to an expanded study in 1951,⁸ wherein approximately 5000 laboratories were surveyed and 1342 LAI cases were identified that resulted in

39 deaths. 69 different pathogens responsible for LAIs were found in this expanded study, including bacteria (775 cases), viruses (265), rickettsia (200), fungi (63), and parasites (39).

Further studies were conducted to better understand the demographics and causes of LAIs in the USA.⁹⁻¹¹ Subsequently, numerous LAI occurrences were noted in the UK¹² and elsewhere worldwide,^{13,14} demonstrating a hierarchy of causal pathogens. Previous reviews of multiple surveys conducted from 1969 to 1989 showed that the most frequently reported LAIs or associated conditions were brucellosis, Q fever, hepatitis, typhoid fever, tularaemia, tuberculosis, dermatomycoses, Venezuelan equine encephalitis, psittacosis, and coccidioidomycosis.^{13,15}

Recommendations have been made for applying risk-based and evidence-based techniques to lower the likelihoods of LAIs and APELS; achieve the highest standards of biosafety, biosecurity, and biocontainment; and promote laboratory sustainability.^{1,16,17} Biosafety to ensure a safe and sustainable environment for staff and the community requires a risk-based approach that helps to identify and mitigate risks associated with pathogens, routes of pathogen transmission, and activities performed by individuals. This approach includes evaluating the layout and infrastructure of a facility and providing adequate personal protective equipment to prevent LAIs and APELS.¹⁸ This risk-based approach was adopted and described by the World Organisation for Animal Health (WOAH, formerly known as OIE) in their Manual of Diagnostic Testing Vaccines for Terrestrial Animals Biosafety and Biosecurity Standard (WOAH Terrestrial Manual)¹⁹ and by WHO in their 4th edition of the

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Laboratory Biosafety Manual (WHO LBM4).^{1,20} Furthermore, the International Organization for Standardization (ISO) 35001 Biorisk standard²¹ can provide an objective standard for managing biosafety and biocontainment risks; however, successful implementation of these approaches depends on leadership commitment, a high degree of staff competency, and substantial investment in infrastructure to achieve the accreditation. Moreover, the practical implementation of this approach is challenging due to resistance to change, unfamiliarity with the associated methods, and inconsistency in risk tolerance and perception.²²

Therefore, we aimed to conduct a scoping review to create a detailed list of LAIs and APELS reported worldwide from 2000 to 2021, and to update their characteristics. We summarised relevant information such as the causal pathogens, associated pathogen-risk groups (RGs), incident causes, case numbers, and geographical locations to develop a comprehensive and contemporary collection of LAI and APELS features. Furthermore, we propose viable and sustainable control measures (including a risk-based biosafety management approach and expanded formal reporting of LAIs and APELS) on the basis of our findings.

Methods

Search strategy and selection criteria

We identified references for this Review by searching PubMed for articles published between Jan 1, 2000, and Sept 30, 2021, to examine trends in the context of the current millennium using the terms “laboratory-acquired infection”, “laboratory infection”, “LAI”, “laboratory accident”, “laboratory leak”, “laboratory escape”, “pathogen leak”, and “pathogen escape”. Peer-reviewed articles and online reports for this Review were also identified by searching the American Biological Safety Association (ABSA) International Laboratory-Acquired Infection Database, ProMED, and the Belgian Biosafety Server. We reviewed these articles and relevant references cited in them. We included articles published in English, Chinese, and German in the search.

Data extraction

Two authors (SD and MK) conducted searches individually and cross-checked information to verify correctness. The data were validated by a third author (SDB). We extracted the information and compiled it into summary tables, grouped by the incident type (LAI or APELS). For LAI variables, we recorded the following data to ascertain the characteristics of the incidents: the causal pathogen, pathogen type (ie, virus, bacteria, fungus, parasite, or prion), pathogen RG, number of cases and fatalities, cause of the incident, and geographical location (city and country). For APELS variables, we extracted information regarding the causal pathogen, pathogen type, pathogen RG, and number of community cases.

Definitions and examples

LAI/APELS cause

Broken vial	Clear evidence of a broken vial causing glass shards in a hand resulting in an LAI
Bite	Clear evidence of an animal bite resulting in an LAI
Needlestick	Clear evidence of a needlestick injury resulting in an LAI
Procedural errors	Identified or suspected breach of biosafety or risk-mitigation procedures resulting in an LAI. Examples include inappropriate selection or use of PPE or primary containment device; inadequate training; improper techniques or procedures; and mishandling of specimens, including sniffing of bacterial cultures in a petri dish or ingestion due to inappropriate handwashing following glove removal
Splash	Clear evidence of splashed infectious material into the mucous membranes resulting in an LAI
Spill	Clear evidence of a spill of infectious material inside or outside of a primary containment device
Unknown	Evidence that infectious material was present or handled, resulting in an LAI, but the source of infection was not known
Not stated	No investigation or supposition regarding the cause of an LAI

APELS location

Internal	Pathogen release outside a primary biocontainment device, such as a biological safety cabinet, but otherwise confined to the immediate laboratory environment and not breaching the secondary biocontainment barrier.
External	Pathogen release into the outside environment beyond the secondary biocontainment. Examples of external APELS might include aerosol wastewater releases due to engineering failures and leaking or inappropriately packed shipments, a staff member with an LAI who unintentionally spreads disease into the community, or any other form of release to the outside environment.

APELS=accidental pathogen escapes from laboratory settings. LAI=laboratory-acquired infection. PPE=personal protective equipment.

Table 1: Definitions of LAI/APELS causes and APELS location

Inclusion and exclusion criteria and LAI and APELS classifications

We only focused on LAIs among laboratory personnel, staff, and students working in laboratory environments. We also included LAIs that occurred in hospitals or research laboratories as part of training activities in universities and colleges. Our study also covered cases of APELS that led to infections in laboratory personnel, animals, non-laboratory personnel, and the community. Reports were excluded if they did not provide sufficient details, did not describe LAIs, or described pathogen exposures rather than LAIs or staff serological surveillance or duplication of a previously published report.

To analyse trends and similarities in the causes of LAI and APELS, we classified them on the basis of the similarity of their activities; the complete definitions are provided in table 1. We classified cases as “unknown” when the results were inconclusive or as “not stated” when an investigation was not performed or the causative agent was not explicitly mentioned. Additionally, APELS were categorised as “internal” and “external” on the basis

For more on the ABSA International Laboratory-Acquired Infection Database see <https://my.absa.org/LAI>.

For more on ProMED see <https://promedmail.org>.

For more on the Belgian Biosafety Server see <https://www.biosafety.be>.

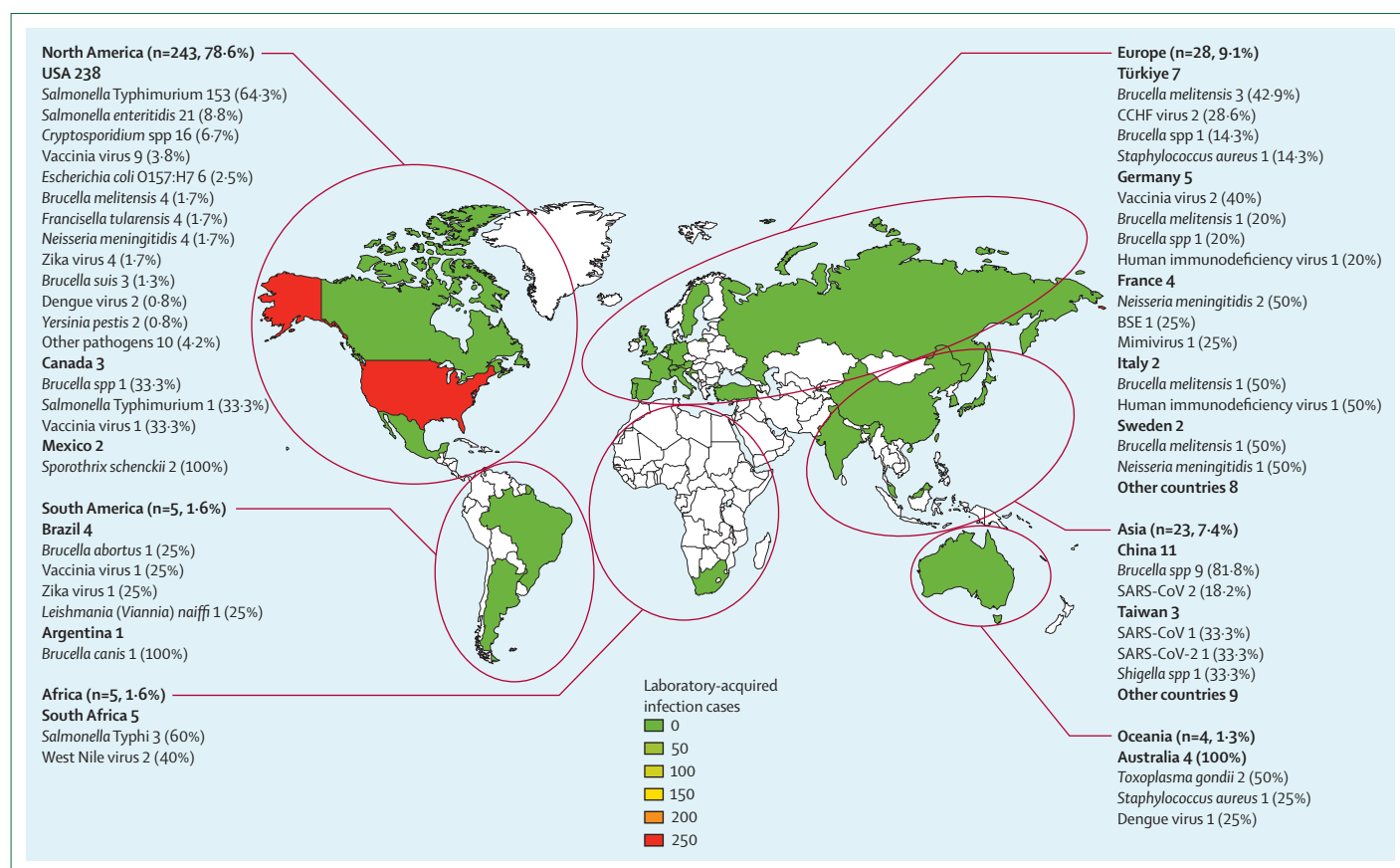


Figure 1: Laboratory-acquired infection case reports, including causal pathogens for each geographical region for the period from 2000 to 2021. Note that in 1 instance the geographic location of the LAI case was not stated.

of their cause, incident location, and extent of containment breach (table 1). Internal APELS were classified as pathogens released within the laboratory environment but contained within the primary or secondary biocontainment device or barrier. External APELS were related to pathogens released beyond the secondary biocontainment barrier into the outside environment. The RG of the pathogen was dependent on the jurisdiction, as outlined in appendix 1 pp 2–5, which was sourced from the ABSA International Risk Group Database.

Analysis

We analysed all summary tables using Stata/BE 18.0 for Mac. We performed cross-tabulations of variable data to rank causal pathogens, pathogen RGs, case numbers, geographical locations, and APELS locations to generate summary information for LAIs and APELS. We generated summary data figures using Microsoft Power BI and R software (version 4.3.1).

Results

Summary and demographics

In this study, we identified 164 reports, of which 94 reports detailing 309 LAIs were eligible for inclusion (appendix 1

pp 2–5). Of the 94 reports, 85 (90.4%) were from peer-reviewed journals and accounted for 143 LAI cases, whereas the remaining nine reports (9.6%; 166 LAI cases) were obtained from online articles. Of the 94 LAI reports, most were from North America (n=43, 45.7%), Europe (n=25, 26.6%), or Asia (n=14, 14.9%), with the majority of the reports originating from the USA (n=39, 41.5%). Of the 309 individual LAI cases, most occurred in North America (n=243, 78.6%), followed by Europe (n=28, 9.1%) and Asia (n=23, 7.4%), with the majority of the reports originating from the USA (figure 1). The majority of the LAI cases reportedly occurred in academic (n=118, 38.2%), unspecified or unclear locations (n=77, 24.9%), research (n=61, 19.7%), hospital (n=29, 9.4%), vaccine (n=22, 7.1%), and veterinary laboratories (n=2, 0.6%; figure 2).

LAI pathogens

In this Review, we identified 309 individual LAI cases caused by 51 pathogens. Of the 309 LAI cases, the majority were caused by *Salmonella enterica* Typhimurium (S Typhimurium; n=154, 49.8%), *Salmonella enteritidis* (n=21, 6.8%), *vaccinia virus* (n=13, 4.2%), *Brucella* spp (n=12, 3.9%), or *Brucella melitensis* (n=11, 3.6%; table 2). Of the 309 reported LAI cases, eight fatalities (2.6% of all LAIs) were

See Online for appendix

For more on the **International Risk Group Database** see <https://my.absa.org/tiki-index.php?page=Riskgroups>.

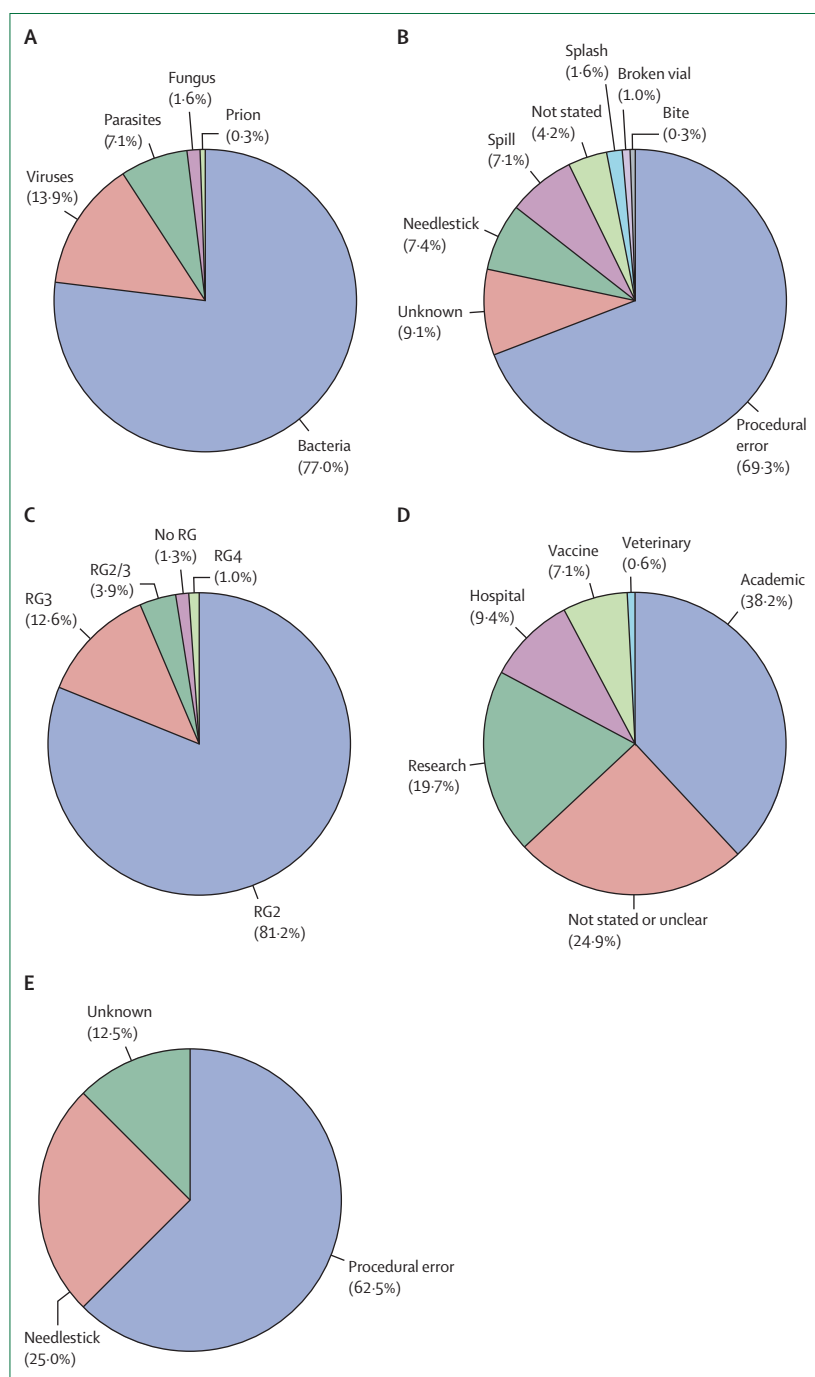


Figure 2: Summary details for laboratory-acquired infection case reports for the period from 2000 to 2021
The details include the (A) pathogen type, (B) incident cause, (C) pathogen-risk group (RG), (D) type of laboratory where the incident occurred, and (E) incident cause resulting in a fatal LAI case.

recorded as being caused by *N meningitidis* (n=3, 37.5% of all deaths), *Yersinia pestis* (n=2, 25%), *S Typhimurium* (n=1, 12.5%), Ebola virus (n=1, 12.5%), or bovine spongiform encephalopathy (BSE; n=1, 12.5%; table 2).

Bacterial pathogens were the leading cause of LAIs, accounting for 77.0% of all cases (n=238), followed by

viruses (n=43, 13.9%), parasites (n=22, 7.1%), fungi (n=5, 1.6%), or the prion agent that causes BSE (n=1, 0.3%; table 2 and figure 2). The majority of LAI pathogens were classified as members of RG2 (n=251, 81.2% of all individual pathogens), followed by RG3 (n=39, 12.6%), RG2/3 (depending on the jurisdiction; n=12, 3.9%), an unassigned RG (n=4, 1.3%), or RG4 (n=3, 1.0%; appendix 1 pp 2–5 and figure 2).

Procedural errors represented the leading cause of LAIs, accounting for 69.3% of cases (figure 2), followed by unknown causes (9.1%), needlestick injuries (7.4%), spills (7.1%), not stated (4.2%), splashes (1.6%), broken vials (1.0%), or animal bites (0.3%). Among these causes, procedural errors were also the most common cause of fatal outcomes (62.5%), whereas the remainder of cases were caused by needlestick injuries (25.0%) and unknown exposures (12.5%).

Geographically, the majority of the cases in the USA were caused by *S Typhimurium* (n=153), *S enteritidis* (n=21), or *Cryptosporidium* spp (n=16; figure 1). China had 11 reported cases (3.5% of all cases), which were caused by *Brucella* spp (n=9) or SARS-CoV (n=2).

Risk assessments for different pathogen groups

Of the bacterial pathogens that caused LAIs, *S Typhimurium* was the most common (n=154/309, 49.8%), followed by *S enteritidis* (n=21, 6.8%), *Brucella* spp (n=12, 3.9%), *B melitensis* (n=11, 3.6%), and *N meningitidis* (n=7, 2.3%; table 2; appendix 1 pp 2–3).

Of the 154 reported cases of *S Typhimurium* LAIs, one resulted in a fatality. The largest outbreak of *S Typhimurium* (n=109) occurred among students in microbiology teaching laboratories and employees in clinical microbiology laboratories across 38 states in the USA.²³ Illnesses were also reported among children living with someone who worked or studied in a microbiology laboratory, and although these cases technically qualified as APELS, no distinction was made between student or staff and family cases. Of the *S Typhimurium* infections, 150 (97.4%) were caused by procedural errors, and four (2.6%) had unknown routes. All 21 cases of *S enteritidis* were caused by spill incidents. Of the seven *N meningitidis* LAIs, four (55.1%) were caused by procedural errors, and three (42.9%) had unknown causes, with three fatalities associated with procedural errors. Of the 28 *Brucella* spp LAI cases attributable to *B abortus*, *B melitensis*, *B canis*, or *B suis*, 21 (75.0%) were caused by procedural errors, and the causes of the remaining cases were unknown or unstated (n=7, 25.0%; appendix 1 p 2).

Of the 43 LAIs caused by viral pathogens, vaccinia virus (n=13/309, 4.2% of all LAIs), Zika virus (n=5, 1.6%), and dengue virus and SARS-CoV (n=4 each, 1.3%) were the most common (figure 1). Of the 13 vaccinia virus LAIs, none were associated with fatalities, and all were either acquired in academic research laboratories or the source was not stated. Most of these LAIs were caused by sticks with needles (n=9/13, 69.2%) contaminated with recombinant vaccinia virus vectors¹⁶ (appendix 1 p 4).

	N cases	N fatalities [†]
Bacteria		
<i>Salmonella</i> Typhimurium	154 (49.8%)	1 (12.5%)
<i>Salmonella enteritidis</i>	21 (6.8%)	
<i>Brucella</i> spp*	12 (3.9%)	
<i>Brucella melitensis</i>	11 (3.6%)	
<i>Neisseria meningitidis</i>	7 (2.3%)	3 (37.5%)
<i>Escherichia coli</i> O157:H7	6 (1.9%)	
<i>Francisella tularensis</i>	4 (1.3%)	
<i>Brucella suis</i>	3 (1.0%)	
<i>Salmonella</i> Typhi	3 (1.0%)	
<i>Staphylococcus aureus</i>	2 (0.7%)	
<i>Yersinia pestis</i>	2 (0.7%)	2 (25.0%)
<i>Bacillus anthracis</i>	1 (0.3%)	
<i>Bacillus cereus</i>	1 (0.3%)	
<i>Brucella abortus</i>	1 (0.3%)	
<i>Brucella canis</i>	1 (0.3%)	
<i>Burkholderia mallei</i>	1 (0.3%)	
<i>Campylobacter jejuni</i>	1 (0.3%)	
<i>Klebsiella (Enterobacter) aerogenes</i>	1 (0.3%)	
<i>Leptospira</i> spp	1 (0.3%)	
<i>Mycobacterium tuberculosis</i>	1 (0.3%)	
<i>Neisseria gonorrhoeae</i>	1 (0.3%)	
<i>Orientia tsutsugamushi</i>	1 (0.3%)	
<i>Shigella</i> spp	1 (0.3%)	
<i>Vibrio cholerae</i>	1 (0.3%)	
Sub-total	238 (77.0%)	6 (75.0%)
Virus		
Vaccinia virus	13 (4.2%)	
Zika virus	5 (1.6%)	
Dengue virus	4 (1.3%)	
SARS-CoV	4 (1.3%)	
HIV	3 (1.0%)	
Crimean Congo haemorrhagic fever virus	2 (0.7%)	
West Nile virus	2 (0.7%)	
Buffalo pox virus	1 (0.3%)	
Cowpox virus	1 (0.3%)	
Ebola virus	1 (0.3%)	1 (12.5%)
Influenza virus	1 (0.3%)	
Lymphocytic choriomeningitis virus	1 (0.3%)	
Mimivirus	1 (0.3%)	
Norovirus	1 (0.3%)	
Poliovirus	1 (0.3%)	
Recombinant raccoonpox virus	1 (0.3%)	
SARS-CoV-2	1 (0.3%)	
Subtotal	43 (13.9%)	1 (12.5%)
Parasite		
<i>Cryptosporidium</i> spp	16 (5.2%)	
<i>Toxoplasma gondii</i>	3 (1.0%)	
<i>Echinococcus</i> spp	1 (0.3%)	
<i>Leishmania (Viannia) naiffi</i>	1 (0.3%)	
<i>Plasmodium vivax</i>	1 (0.3%)	
Sub-total	22 (7.1%)	0

(Table 2 continues in next column)

	N cases	N fatalities [†]
(Continued from previous column)		
Fungus		
<i>Sporothrix schenckii</i>	2 (0.7%)	
<i>Arthroderma benhamiae</i>	1 (0.3%)	
<i>Coccidioides</i> spp	1 (0.3%)	
<i>Histoplasma capsulatum</i> var <i>capsulatum</i>	1 (0.3%)	
Subtotal	5 (1.6%)	0
Prion		
Bovine spongiform encephalopathy	1 (0.3%)	1 (12.5%)
Total	309 (100.0%)	8 (100%)

LAI=laboratory-acquired infection. *The *Brucella* species causing the LAI was not stated in the report. †Derived from LAI case report.**Table 2: Causal pathogens for the LAI cases and fatalities**

Of the LAIs caused by parasites, infections with *Cryptosporidium* spp (n=16/309, 5.2% of all LAIs) and *Toxoplasma gondii* (n=3, 1.0%) were most common. In terms of LAIs caused by fungal pathogens (n=5, 1.6%), *Sporothrix schenckii* (n=2, 0.5%) showed the highest number of reported cases (table 2). One LAI was caused by a prion agent that causes BSE (n=1).

Summary of APELS and related pathogens

16 APELS incidents were reported between 2000 and 2021 (table 3 and appendix 2 pp 2–4) that involved bacterial (n=6, 37.5%) and viral (n=10, 62.5%) pathogens, comprising *Bacillus anthracis* (n=3, 18.8%), SARS-CoV (n=3, 18.8%), poliovirus (n=3, 18.8%), *Brucella* spp (n=2, 12.5%), foot and mouth disease virus (n=2, 12.5%), variola virus (n=1, 6.3%), *Burkholderia pseudomallei* (n=1, 6.3%), and influenza virus H5N1 (n=1, 6.3%; table 3). Generally, APELS did not cause infections, although cases of possible exposure were reported for staff members, the surrounding community, or animals. However, APELS were responsible for disease outbreaks in some cases, such as the 10 528 brucellosis infections linked to a *Brucella* vaccine production facility in Lanzhou, China.⁵

The majority of APELS involved RG3 (n=12, 75.0%) pathogens, with the remaining cases being caused by RG2 (n=3, 18.8%) and RG4 (n=1, 6.3%) pathogens. Most APELS were external (n=12, 75.0%). The majority of APELS occurred in research or university laboratories (n=11, 68.8%), followed by vaccine production facilities (n=4, 25.0%); the purpose of one laboratory (n=1, 6.3%) was unspecified. Geographically, the majority of reported APELS occurred in the USA (n=7, 43.8%), followed by the UK and China (n=2 each, 12.5%), Belgium, Singapore, India, the Netherlands, and Taiwan (n=1 each, 6.3%).

Discussion

The findings of this scoping review show that LAIs and APELS periodically occur, and the information collected in LAI and APELS reports enables regulators, biosafety professionals, and laboratory management to perform

	Date	Location	Facility	APELS category	Exposures (n)	Cases (n*)	Cause	Reference(s)
<i>Bacillus anthracis</i>	June, 2014	US Centres for Disease Control and Prevention, Bioterrorism Rapid Response and Advanced Technology, GA, USA	Research	Internal	Not stated	0	Procedural error	²⁴
	April-May, 2015	Dugway Proving Ground, UT, USA	Research	External	Not stated	0	Procedural error	^{25,26}
	May, 2012	Animal Health and Veterinary Laboratories Agency, Surrey, UK	Research	External	2	0	Procedural error	^{27,28}
SARS-CoV	August, 2003	National University of Singapore and Environmental Health Institute of Singapore, Singapore	Research	External	84	1	Procedural error	^{3,29,30}
	December, 2003	Taiwan Military Institute of Preventive Medical Research of the National Defence University, Sanxia, Taiwan	Research	External	74	1	Procedural error	^{3,29,31}
	April, 2004	Chinese National Institute of Virology, Beijing, China	Research	External	747	11	Procedural error	^{3,29,32}
Foot and mouth disease virus	June, 2004	Plum Island Animal Disease Center, NY, USA	Research	Internal	Not stated	6 cattle/pigs	Not stated	³³
	August, 2007	Pirbright, Surrey, UK	Research	External	Not stated	Not stated	Engineering	^{2,34}
<i>Brucella</i> spp	Mid-2019	Lanzhou, China	Vaccine	External	Not stated	10 528	Procedural error	^{5,35,36}
	2018	USA, location unknown	Not stated	External	Not stated	Not stated	Not stated	³⁷
Influenza virus	January, 2014	Southeast Poultry Research Laboratory, GA, USA	Research	External	Not stated	0	Procedural error	³⁸
Variola virus	July, 2014	National Institutes of Health, MD, USA	Research	Internal	Not stated	0	Procedural error	³⁹
<i>Burkholderia pseudomallei</i>	Mid-January, 2015	Tulane National Primate Research Center, LA, USA	Research	Internal	Not stated	2 primates	Procedural error	⁴⁰
Poliovirus	September, 2000; November, 2002–February, 2003	India	Vaccine	External	Not stated	8 or 10	Not stated	^{41,42}
	September, 2014	Belgium	Vaccine	External	Not stated	Not stated	Not stated	⁴³
	April, 2017	Netherlands	Vaccine	External	2	0	Not stated	⁴⁴

APELS=accidental pathogen escape from laboratory settings. *If not stated explicitly, the data presented refer to human cases.

Table 3: Pathogens associated with internal and external APELS

root cause analysis to identify the basis of the incidents. Lessons from such research inform the risk-based bio-safety and biosecurity approach that supports specific regulations and methods designed to control pathogens in laboratory settings while promoting safety for staff members, the community, and the environment.

The composition and hierarchy of pathogens causing LAI cases (ie, *S Typhimurium*, *S enteritidis*, vaccinia virus, *Brucella* spp, and *B melitensis*) and LAI reports (ie, any *Brucella* spp, vaccinia virus, *S Typhimurium*, *N meningitidis*, dengue virus, and *F tularensis*) appear to have changed, with an increase in the dominance of RG2 pathogens being documented over the last 50 years. The dominance of RG2 pathogens as leading causes of LAIs and fatalities is consistent with data recorded with the Canadian Laboratory Incident Notification Canada surveillance (LINC) system.^{45–47} Furthermore, Baron and Miller⁴⁸ made similar observations of LAIs occurring from 2002 to 2004, where the most common causes were *Shigella*, *Brucella*, *Salmonella*, and *Staphylococcus aureus*. RGs are used as biosafety shorthand to quantify the inherent hazard associated with different pathogens. Individual countries often assign RGs on the basis of their intrinsic hazard and other local factors such as endemicity. Several hypotheses could explain the increase in RG2-pathogen LAIs, including: (1) increased

RG2-pathogen exposure due to greater prevalences in clinics, hospitals, teaching laboratories, and diagnostic laboratories; (2) the perception of a lower risk when working with RG2 pathogens; and (3) shifting research priorities. The lower number of reported RG3 and RG4 pathogen LAIs (less than half that of RG2) might be attributable to stricter regulatory requirements requiring higher levels of biorisk infrastructure and increased facility requirements for handling RG3 and RG4 agents, which naturally reduces the number of people who could potentially be exposed.

Many of the LAIs reported in this Review resulted from operator-related errors, with the majority being reported as procedural errors or needlestick injuries. Many LAIs were reported to result from an unknown cause. Many laboratory errors, either LAI or APELS, can be attributed to human mistakes, which can arise due to insufficient training, low competence, inadequate understanding of the implications of poor laboratory practices, or a combination of these factors. Examples of procedural errors include: (1) the discovery of historical variola virus ampoules in cold storage during a move of laboratories at the National Institutes of Health campus in Bethesda, MD, USA in July, 2014,³⁹ which highlighted weaknesses in managing inventories and transferring institutional knowledge and (2) the shipment of live anthrax cultures

from US Department of Defense laboratories following incomplete inactivation,⁴⁹ which underscored the need to adhere to laboratory procedures and management processes. Wurtz and colleagues¹⁴ presented evidence indicating that most LAI incidents involved technical infrastructure and equipment failure, with the most probable causes cited as poor biosafety practices and insufficient attention due to a breakdown in good microbiological principles and practices (GMPP).¹ Data from the Canadian LINC system, which are published in an annual report on LAIs, showed that poor adherence to procedures was often the cause of laboratory incidents.^{46,47,50}

The APELS documented in this Review highlight potential fallibilities including human errors (caused by individuals or groups), engineering problems, or combinations of both. APELS were primarily caused by procedural errors, as shown by the large-scale *Brucella* APELS in Lanzhou, China, which was reported to be caused by using expired disinfectants when manufacturing vaccines.³⁵ Engineering failures were less common, such as the escape of foot and mouth disease virus-contaminated wastewater from old, damaged drainage pipes, resulting in the contamination of nearby farms in the UK in 2007.³⁴ A dominance of RG3 pathogens was found, which reflects their high transmissibility potentiated by the activity performed (eg, large-scale vaccine production), although this might have been due to the inherent bias associated with voluntary reporting.

The study has some limitations. The summary of LAI and APELS data presented here should be interpreted with caution due to potential biases in voluntary reporting. A crude examination of the summary results suggests that the frequencies of LAIs and APELS have decreased since the studies of Sulkin and Pike and others were conducted,^{10–15} possibly due to improved laboratory practices, advanced diagnostic technologies, and increased awareness of biological hazards. However, without globalised formal reporting requirements, the data summarised here could only represent the tip of the iceberg.⁵¹ Furthermore, the reports included in this study might be biased towards more severe or high-consequence occurrences. The possibility also exists that LAIs could be under-reported because of an inability to discriminate between community-acquired infections or LAIs, especially when high levels of transmission are present in the community,⁵² such as with SARS-CoV-2 or *Mycobacterium tuberculosis*. Another limitation is the possible misclassification of LAIs or APELS due to difficulties in discerning LAIs and external APELS, given that LAI-affected individuals would typically leave the laboratory, potentially spreading the infection in the community, as occurred with SARS-CoV^{3,29,32} and the *Brucella* vaccine infections in China.^{5,35} Another limitation is inconsistent or few details related to the causes of LAIs or APELS, necessitating broad classifications rather than the conventional route of infection. Nevertheless, the large number of needlestick injuries and other operator error-

related causes highlights the need to focus on staff training and promoting GMPP. Finally, in the case of *Brucella* LAI reports, we observed inconsistency in the amount of detail of the causative pathogen (ie, *Brucella* spp vs *B melitensis*, *B canis*, or *B abortus*).

Improved understanding of the causes of LAIs and APELS and implementation of suitable preventive steps and actions (including continuous improvement through formalised LAI and APELS reporting and root-cause analysis) will mitigate future occurrences.

Incorporating robust institutional leadership, laboratory design, and risk-based practices appropriate for working with known biohazards, especially those known to cause LAIs and APELS, into laboratory management, will mitigate LAI and APELS occurrences; however, it is important to recognise that human errors are often the primary cause and should be carefully managed.

An integrated and sustainable biorisk management approach should be applied to promote a positive and transparent biosafety culture in life science laboratories, including facility and engineering controls, administrative controls, effective training and competency, and leadership support. Best practice guidance for GMPP in the laboratory is detailed in the WOAHP Terrestrial Manual;¹⁹ the WHO LBM4;¹ and nationally by the USA,¹⁷ Canada,⁵³ and Belgium. Furthermore, the release of the ISO 35001 Bio-risk standard²¹ can provide an objective standard for biosafety and biocontainment risk management; however, successful implementation depends on substantial investment in infrastructure to achieve the accreditation.

Contributors

SDB, KH, and AMB conceived the study. SDB, SD, MK, and KKL collected the data. SDB and SD verified the underlying data. SDB, SD, and KKL analysed the data and interpreted the results. SDB, KKL, and SD produced the figures. SDB and SD wrote the first draft of the manuscript. KS, JO'K, SSA, IS, CMS, AA, AMB, KK, KH, JPK, ZMM, and DRH participated in the review and editing of the manuscript. KH and SDB acquired the funding. All authors had full access to all the data in the study, provided essential review and revision of the text, approved the final version, and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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For more on **Service Biosafety and Biotechnology**, see <https://www.biosafety.be/>.

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