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ORIGINAL ARTICLE

Survey of laboratory-acquired infections around the world in biosafety level 3 and 4 laboratories

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Abstract Laboratory-acquired infections due to a variety of bacteria, viruses, parasites, and fungi have been described over the last century, and laboratory workers are at risk of exposure to these infectious agents. However, reporting laboratory-associated infections has been largely voluntary, and there is no way to determine the real number of people involved or to know the precise risks for workers. In this study, an international survey based on volunteering was conducted in biosafety level 3 and 4 laboratories to determine the number of laboratory-acquired infections and the possible underlying causes of these contaminations. The analysis of the survey reveals that laboratory-acquired infections have been infrequent and even rare in recent years, and human errors represent a very high percentage of the cases. Today, most risks from biological hazards can be reduced through the use of appropriate procedures and techniques, containment devices and facilities, and the training of personnel.

Introduction

Laboratory-acquired infections (LAIs) are defined as all infections acquired through laboratories or laboratory-related

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activities, whether they are symptomatic or asymptomatic in nature. LAIs due to a wide variety of bacteria, viruses, fungi, and parasites are described in the literature. The largest survey of infections was reported in 1976 by Pike [1], who found that 4079 LAIs were caused by 159 biological agents, although ten agents caused infections accounting for 50 % of cases (brucellosis, Q fever, hepatitis, typhoid fever, tularemia, tuberculosis, dermatomycoses, Venezuelan equine encephalitis, psittacosis, and coccidioidomycosis). There were no distinguishable accidents or exposure events identified in more than 80 % of the reported cases. During the 20 years following the Pike and Sulkin publications, a worldwide literature review by Harding and Byers revealed 1267 cases of infections, with 22 deaths [2]. Five deaths were fetus abortions as consequences of a maternal LAI. *Mycobacterium tuberculosis*, *Coxiella burnetii*, hantaviruses, arboviruses, hepatitis B virus, *Brucella* spp., *Salmonella* spp., *Shigella* spp., hepatitis C virus, and *Cryptosporidium* spp. accounted for 1074 of the 1267 infections. Like Pike and Sulkin, Harding and Byers reported that only a small number of the LAIs involved a specific incident. These studies reported cases of old infections and refer to periods with practices and types of exposure which have since considerably evolved, especially with the introduction of high-containment laboratories.

More recently, Henkel et al. presented data reported to the Centers for Disease Control and Prevention (CDC) from 2004 to 2010 following the implementation of a nationwide program for monitoring the potential theft, loss, or release of biological select agents and toxins (BSATs) [3]. In total, 11 LAIs associated with BSAT releases were reported in an average annual population of approximately 10,000 individuals with approved access to BSATs. No cases of fatality or secondary human-to-human transmission was reported. These LAIs were associated with exposures to *Brucella* species (six cases), *Francisella tularensis* (four cases), and *Coccidioides immitis*/*posadasii* (one case) [4, 5]. They resulted from either unrecognized exposures or presumptive exposure to BSAT aerosols. These observations are consistent with Pike's and Harding's studies [1].

Two publications in science magazines have provided recent information about LAIs. The current Ebola crisis reveals that priority must be given to infectious diseases because of the potential consequences to individuals and society [6]. Some researchers argue for the need to increase research on Ebola virus to develop treatments, while others focus on recent incidents in biosafety facilities and the possible dissemination of these dangerous pathogens in the general population [6]. A recent example, in 2004, was the mishandling of the severe acute respiratory syndrome virus that resulted in tertiary infections and the death of an attending physician in China [7]. Lipsitch found that government data on US biosafety labs reveal accidents estimated to be between 100 and 275 potential releases of pathogens each year in labs that deal with select agents between the years 2008 and 2012; however, these reports include banal accidents like spills and record-keeping errors, and very few workers were infected [8].

However, until now, the true risk posed to laboratory workers after potential exposure to an infectious agent has been difficult to determine, in part because of the lack of systematic reporting of laboratory infections. It may vary greatly according to the pathogen and also the type of exposure considered. Currently available data are limited to retrospective and voluntary postal surveys, anecdotal case reports, and reports about selected outbreaks with specific microorganisms.

The aim of this survey was to gather information on LAIs in biosafety level 3 and 4 laboratories around the world and to assess possible underlying causes of these infections, in order to identify real current risks and to propose preventative procedures.

Materials and methods

In this study, 119 private or public institutions with notified containment level 3 or 4 laboratories were contacted by email to complete a survey about LAIs. The mailing list was established by investigators in Marseille. In total, 15 questions were addressed to each respondent, consisting of single-answer questions and multi-answer questions, most of the questions being mandatory (see below).

We also performed a literature analysis. To determine the worldwide number of LAIs, a systematic review of articles published during the period 1980–2015 was performed. The inclusion criterion was the presence of an accidental infection in workers or students in research laboratories working with French select agents. The following academic Internet search systems were used: PubMed, Google Scholar, and ISI Web of Knowledge. They were searched with the keywords "laboratory acquired infection", "laboratory accident", and with the list of the different French select agents.

Survey of recently laboratory-acquired infections (BSL-3-BSL4)

1. **Which types of laboratories exist in the organization that you work for? (Multiple answers possible)**

- ☐ BSL-3, Biosafety level 3 laboratory
- ☐ BSL-4, Biosafety level 4 laboratory
- ☐ A3, animal facility of containment level 3
- ☐ A4, animal facility of containment level 4
- ☐ G3, greenhouse of containment level 3
- ☐ G4, greenhouse of containment level 4
- ☐ I don't know
- ☐ Other: [ ]

2. **Which type of activities are carried out in your organization? (multiple answers possible)**

- ☐ Cell Culture
- ☐ Animal care
- ☐ Animal experiments

please specify the species:

- ☐ Entomology
- ☐ Microbiology
- ☐ Lyophilization
- ☐ Virology
- ☐ Parasitology
- ☐ TSE/Prion research or diagnosis
- ☐ Microscopy
- ☐ Education (practical lessons)
- ☐ Serology or hematology
- ☐ Maintenance, managment of collection
- ☐ Cloning
- ☐ Other: [ ]

3. What type of personal protection is set up in your lab? (Multiple answers possible)

- ☐ nitrile gloves
- ☐ goggle or face protection
- ☐ latex gloves
- ☐ waterproof coverall or gown
- ☐ two pair of gloves
- ☐ overboot or overshoe
- ☐ filtering facepiece respirator FFP2
- ☐ hygiene cap or hood
- ☐ filtering facepiece respirator FFP3
- ☐ Powered air-purifying
- ☐ vaccination against specific pathogen
- ☐ post-exposure prophylaxis
- ☐ specific medical team
- ☐ Other, please specify

4. Are you aware of or do you know of any LAI's (laboratory acquired infections), resulting from a contamination of 1 or more employees in your organization?

Please choose only one of the following:

- ☐ Yes
- ☐ No

5. How many LAI's are you aware of?

Please write your answer here:

6. Which organisms or biological agents were involved in the LAI(s)?

Please write your answer here (list all biological agents):

LAI-1 :

LAI-2 :

LAI-3 :

LAI-4 :

LAI-5 :

…

7. Who was contaminated? Where did the LAI(s) occur?

Please choose the appropriate response for each item:

	Who was contaminated?							Where did the LAI occur?			
	Laboratory technician	Researcher	Student for short period(<1month)	Student for longer period(>1month)	Animal care taker	I don't know	Other (specify)	Biosafety level 3 laboratory	Biosafety level 4 laboratory	A3 Animal facility of containment 3	A4 Animal facility of containment 4
LAI-1											
LAI-2											
LAI-3											
LAI-4											
LAI-5											
…											

8. About the contaminated person, do you know if:

	she has been vaccinated previously against the pathogen involved (if the vaccine exists)	A treatment post-exposition has been proposed (if a treatment exists)	she has a reinforced medical surveillance
LAI-1	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know
LAI-2	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know
LAI-3	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know
LAI-4	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know
LAI-5	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know	☐ Yes ☐ No ☐ I don't know
…			

9. Which type of activity was being carried out when the LAI(s) occurred?

Please choose the appropriate response for each item:

	Cell culture	Anima l care	Animal experiments	Entomology	Lyophilization	Microbiology	Virology	Parasitology	TSE/prio n research	Microscopy	Education	Serology hematology	Maintenance Management of collection	Cloning	Other activity Please specify
LAI-1															
LAI-2															
LAI-3															
LAI-4															
LAI-5															
…															

10. Do you know if it was transmitted to another person (e.g., family member, colleague, etc.)?

Please choose the appropriate response for each item:

	YES	NO	Don't know
LAI-1			
LAI-2			
LAI-3			
LAI-4			
LAI-5			
…			

11. Do you know if the LAI(s) that occurred was due to one of the incidents cited below? If yes, please describe.

Please choose the appropriate response for each item:

	Spills	Cut with broken glass	Needle accident	Bites and scratches (animals)	Splashes	Centrifuge accident	Falling of recipient	Breaking of recipient	Not wearing personal protections	Technical failure of equipment	Technical failure of infrastructure	Other	Description of the incident
LAI-1													
LAI-2													
LAI-3													
LAI-4													
LAI-5													
…													

12. Do you know the route of transmission of the pathogen involved in the LAI(s)? Please describe

Please choose the appropriate response for each item:

	Airborne transmission	Cutaneous contamination	Percutaneous transmission	Mucocutaneous contamination	Oral contamination	Description of the incident
LAI-1						
LAI-2						
LAI-3						
LAI-4						
LAI-5						
…						

13. What were the consequences for the contaminated person? (Multiple answers possible)

	Death	Sequels	No consequences	Other consequences
LAI-1				
LAI-2				
LAI-3				
LAI-4				
LAI-5				
…				

14. A bio-incident is often the result of several different factors. In your opinion, what is the cause of the incident that occurred? (different answers are possible)

	Not enough experience	Not enough training	Not enough follow-up	Too much work	Lack of space	Lack of adapted equipment, materials	Lack of knowledge of the risks	Lack of attention	Not respecting certain biosafety practices	Not very clever	Fear of informing the boss after exposure	Other, please specify
LAI-1												
LAI-2												
LAI-3												
LAI-4												
LAI-5												
…												

15. This is the end of the survey. If you have some remarks or suggestions about this survey, you are invited to write them here.

Please write your answer here:

Results

The experience of two skilled researchers

Prof. X, director of a laboratory dealing with rickettsial diseases in the United States, pointed out that he had not had any laboratory infections with biosafety level 3 rickettsial agents since 2000. He specified that he had personal experience with laboratory infections with rickettsial agents (particularly *Rickettsia*) in the USA, but these infections generally occurred before the implementation of biosafety level 3 laboratories and the exclusive handling of infectious agents in class II biosafety cabinets. He remembered one *C. burnetii*-related infection caused by a needle stick while the involved person was working with a previously infected mouse. However, at present, all work with *C. burnetii* is performed in a specific laboratory, and requires vaccination of the laboratory workers and the use of a powered air-purifying respirator in the biosafety level 3 laboratory.

Prof. Didier Raoult established the Rickettsia Unit at Aix Marseille University in 1984. Since 2008, he has been the director of the "URMITE", the research Unit in Infectious and Tropical Emergent Diseases, and employs 450 personnel (with 80 national and international students and PhD students). The laboratory coordinates European and international networks, and serves as a leader in research on several infectious diseases, including rickettsial diseases, Q fever, and arboviral diseases, and is directly involved in defense against bioterrorism and highly contagious diseases. In the 1980s, the laboratory had three LAI cases from skin wounds caused by the manipulation of glass tubes broken after centrifugation of an infectious suspension. The involved biological agents were *Rickettsia* species (including *R. australis*, *R. conorii*, and *R. japonica*). The persons exposed received appropriate antibiotic treatment and recovered without sequelae. These incidents occurred before the publication of regulatory procedures for biosafety level 3 and 4 laboratories and good laboratory practices.

Analysis of the survey

A total of 23 of the 119 contacted laboratories accepted to participate to this survey, of which five were biosafety level 4 laboratories. As shown in Fig. 1, this survey was conducted on a global basis. Most of the questioned laboratories routinely use the following personal protective equipment: latex gloves (86 %), nitrile gloves (68 %), two pairs of gloves (77 %), FFP3 masks (64 %), goggle or face protection (81 %), waterproof coverall or gown (68 %), overboots or overshoes (90 %), and hygiene cap or hood (54 %) (Fig. 2).

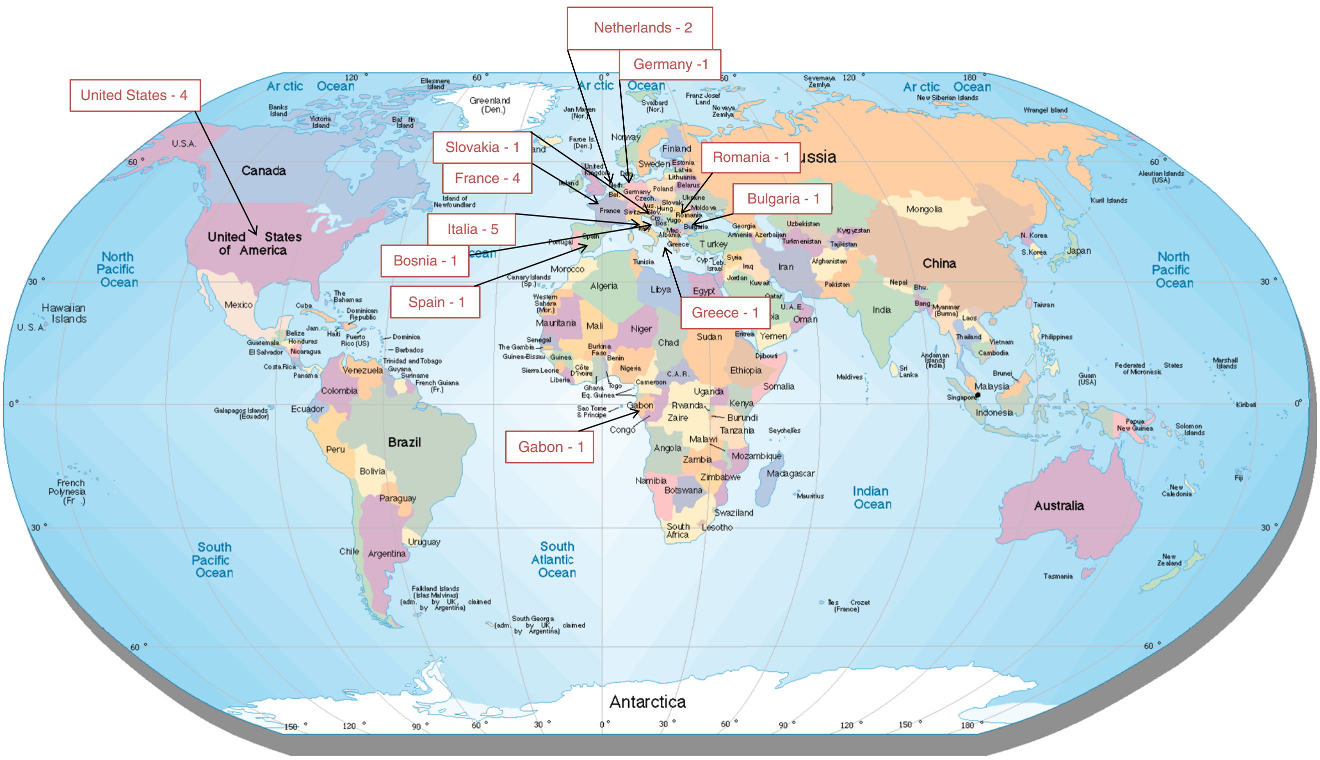

Fig. 1 Worldwide repartition of the laboratories that responded to the survey. Retrieved from http://www.jimmymack.org/worldmap.html

Only four of the 23 surveyed laboratories reported 15 LAIs caused by four different pathogenic organisms. Bacterial infections predominated, particularly biosafety level 3 bacteria belonging to the following species: *Mycobacterium tuberculosis* (ten cases), *Coxiella burnetii* (two cases), and *Brucella melitensis* (two cases) (Table 1). The remaining case was caused by a biosafety level 2 virus (foamy virus). The majority of the LAIs (73 %) occurred in a biosafety level 3 laboratory in the context of microbiology activities (42 %), followed by microscopy (22 %) and cell culture (22 %) (Fig. 3).

Laboratory technicians were most commonly infected (87 % of the cases), while in only 7 and 6 % of the cases, respectively, the infected person was an animal caretaker or a researcher. It should be noted that laboratory technicians are more numerous than researchers worldwide, and also probably more often exposed to biological agents. All 15 LAI cases recovered from their infection, without sequelae in 13 persons (87 %), but with sequelae in two patients. Fortunately, no deaths were reported. Notably, for 93 % of the cases, post-exposure treatment was prescribed. A small percentage of exposed persons had only reinforced medical surveillance

Fig. 2 Personal protective equipment in the laboratories

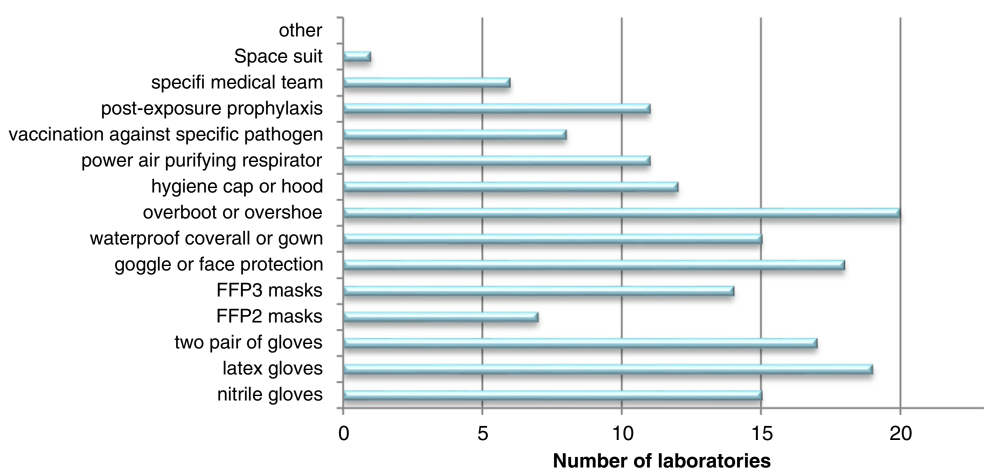

Table 1 Biological agents involved in laboratory-acquired infections (LAIs)

Species	Biosafety level	Number of LAIs
Coxiella burnetii	3	2
Foamy virus	2	1
Brucella melitensis	3	2
Mycobacterium tuberculosis	2	10

(13 %), and only 40 % were vaccinated against the involved pathogen prior to exposure. Regarding the potential transmission routes involved in LAIs, 87 % of the cases were airborne infections, while the others were percutaneous infections. In none of the LAIs was the infection transmitted to another person. Half of the cases were related to technical failures in equipment and infrastructure. However, these cases occurred in a single laboratory where the environment was not safe. Consequently, the laboratory was closed after this incident. For the remaining cases, three contaminations occurred because of not wearing personal protective equipment. Other incidents leading to LAIs were animal bites and scratches (two cases), splashes (one case), inadequate compliance with safety rules (one case), and spills (one case) (Fig. 4). Not respecting certain biosafety practices (eight cases), lack of attention (six cases), lack of appropriate equipment and materials (four cases), and insufficient training (four cases) seem to be the principal causes of LAIs (Fig. 5). Therefore, human error accounted for 78 % of the underlying causes of LAIs.

Discussion

LAIs represent an occupational hazard unique to laboratory workers, especially those working in microbiology laboratories. Before the introduction of regulations concerning biosafety levels in laboratories and good laboratory practices, laboratory manipulations, including the handling of cultures of human pathogens, took place on the bench, without any specific protection. For example, it was permissible to smoke, eat, or drink in such laboratories, to conduct an olfactory examination of the cultures, or to perform mouth pipetting of infectious suspensions, all practices that are now well known to be associated with a high risk of laboratory infections. Therefore, many LAIs occurred, as described by Pike [1].

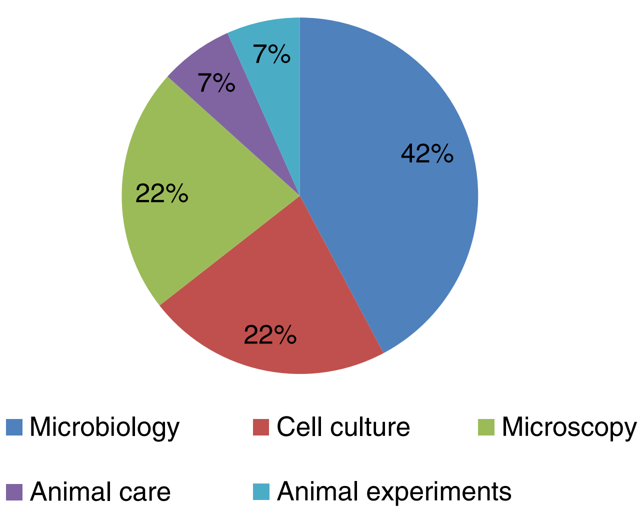

Fig. 3 In which context did the infection happen?

The actual risk of LAIs is difficult to quantify because there is no systematic reporting system. Because of this lack of information, control measures are proposed and implemented by competent authorities, and regulations are increasing dramatically, which, in turn, profoundly affect research [9]. The additional, sometimes draconian, measures for laboratories working with highly pathogenic microorganisms have been implemented without solid evidence that they will provide additional public or laboratory safety.

We performed a comparison of three different sources on the number of LAIs due to biological select agents: this survey, the reference [3] dealing with LAIs due to select agents in United States between 2004 and 2010, and a literature review of LAIs over the last 35 years (Table 2). It is evident that 23/119 (19 %) laboratories responding to our questionnaire present a limited proportion of laboratories and we understand that it is a limitation of this work. However, with the strengthening of regulations, we believe that some laboratories are reluctant to expose their accidents. However, due to the long period of survey for several investigators, we believe that the obtained results are a good reflection of the frequency and cause of accidents. Overall, this analysis allows us to conclude that LAIs have been infrequent with highly pathogenic microorganisms (two in our survey, ten in reference [3], and 220 during the last 35 years), and even rare in recent years. This phenomenon is almost certainly due to the improvement of working conditions, particularly the biosecurity measures implemented during this time. This is especially true with biosafety level 4 laboratories, in which no accident was observed in the five laboratories participating in this work. Moreover, with the exception of a case of a technician accidentally inoculated with Ebola virus who did not develop hemorrhagic fever [10], we could not find any LAI reports in biosafety level 4 laboratories (Table 2). As accidents in this kind of laboratories are likely to become publicized, we do not believe we missed any information. Recent incidents in the USA involving BSATs have focused attention on the need to improve and maintain a culture of biosafety and biosecurity in the life sciences. Notable incidents included the discovery of vials labeled “variola”, the virus responsible for smallpox, in a storage room in a Food and Drug Administration laboratory located on the Bethesda campus of the National Institutes of Health, the potential exposure of staff members at the CDC to *Bacillus anthracis*, and the inadvertent cross-contamination

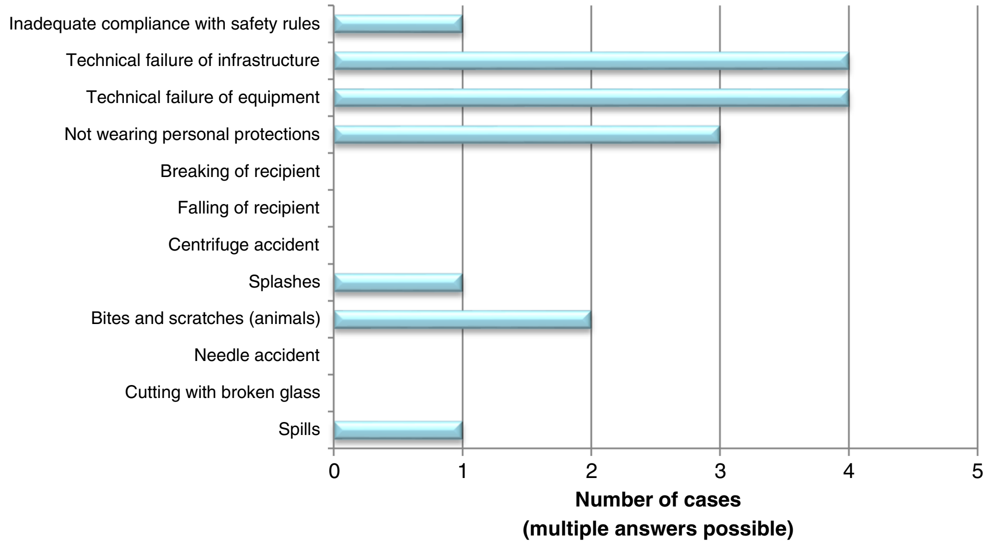

Fig. 4 Type of incident involved in the infection

of a low pathogenic avian influenza A (H9N2) virus sample with a highly pathogenic avian influenza A (H5N1) virus and subsequent shipment of the contaminated culture to an external high-containment laboratory. None of these events resulted in human contamination, but suggested an inadequate compliance with existing regulations, policies, and procedures [11, 12]. After these events, the White House published a report dealing with national biosafety and biosecurity in order to protect the nation's health and in order to prevent, detect, and respond to infectious threats around the world, resulting in a set of recommendations in terms of biosafety and associated biosecurity [11]. Fortunately, none of these events resulted in a casualty.

One important point that could improve safety in laboratories working with highly pathogenic agents is the training of personnel to reduce LAIs caused by human error, and, in particular, to avoid the involvement of people with psychological problems in research on highly pathogenic agents by means of a regular medical follow-up. An example of a failure in medical monitoring was provided during the anthrax attacks that occurred in the USA in 2001 [36, 37]. Dr. Ivins was working in a military laboratory at Fort Detrick, Maryland on the development of anthrax vaccines. He had mental health and professional problems because his work on anthrax vaccine was unsuccessful. An apparent lack of careful oversight allowed him to send letters containing anthrax spores to various offices and senators, resulting in the deaths of five people and infections in 17 others [38].

When examining actual biological hazards, human errors represent a very high percentage of LAIs. If in the past, as observed in laboratory number 3 of the present work, cases could be related to technical failures in equipment and infrastructure, today, most risks from biological hazards for

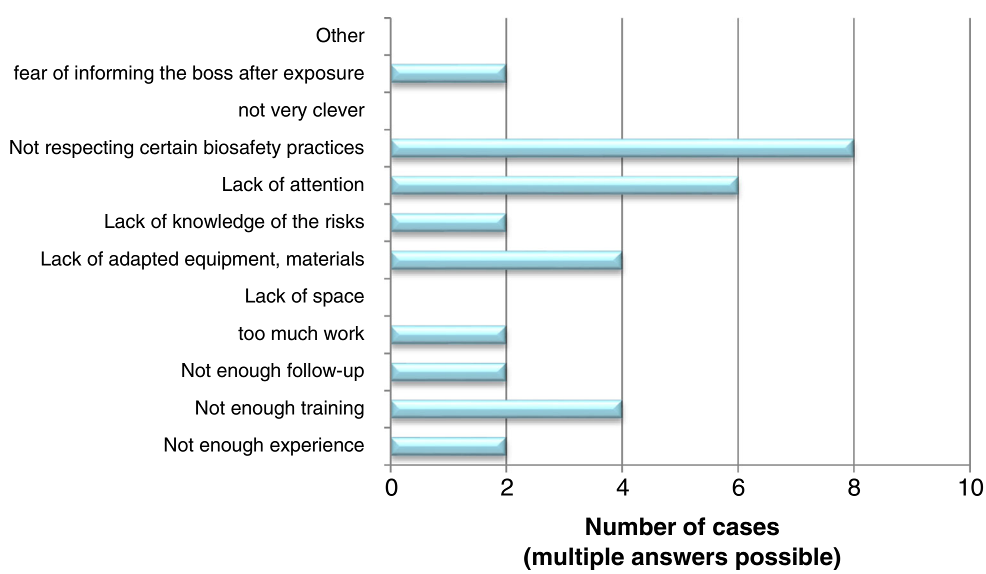

Fig. 5 Probable causes of the incident

Table 2 Number of LAIs caused by French select agents according to three different sources (this survey, reference [3], and literature reviews)

Biological select agent	**Biosafety level class [13]**	**LAIs identified in the survey**	**LAIs identified in (3)**	**LAIs identified by literature review in the last 35 years**	
Yersinia pestis	3	0	0	1 (1)	[14]
XDR-TB*	3	0	0	0	-
Lassa virus	4	0	0	0	-
Machupo virus	4	0	0	0	-
Sabia virus	4	0	0	2	[15, 16]
Andes virus	unclassified	0	0	0	-
CCHF† virus	4	0	0	0	-
Ebola virus }	4	0	0	3(1)	[10, 17, 18]
Marburg virus	4	0	0	2(1)	[19, 20]
Hendra virus	4	0	0	0	-
Nipah virus	unclassified	0	0	0	-
Smallpox virus	4	0	0	0	-
Monkeypox virus	3	0	0	0	-
SARS-CoV‡c	3	0	0	4(1)	[21–23]
MERS-CoV§	3	0	0	0	-
Bacillus anthracis	3	0	0	1	[24]
All *Brucella*, except *Brucella ovis*	3	2	6	71	[25]
Burkholderia mallei	3	0	0	2	[26, 27]
Burkholderia pseudomallei	3	0	0	1	[28]
Clostridium botulinum	3	0	0	0	-
Francisella tularensis	3	0	4	5	[29–31]
Rickettsia prowazekii	3	0	0	0	-
Rickettsia rickettsii	3	0	0	0	-
Junin virus	4	0	0	0	-
Guanarito virus	4	0	0	0	-
Lujo virus	unclassified	0	0	0	-
Chapare virus	unclassified	0	0	0	-
Whitewater Arroyo virus	unclassified	0	0	0	-
RVF¶ virus	3	0	0	0	-
Sin Nombre virus	3	0	0	0	-
Hantaan virus	3	0	0	126	[32]
Seoul virus	3	0	0	1	[33]
Laguna Negra virus	unclassified	0	0	0	-
Dobrava-Belgrade virus	3	0	0	0	-
Choclo virus	unclassified	0	0	0	-
KFD# virus	3	0	0	0	-
OHF** virus	3	0	0	0	-
Influenza A virus subtype H5N1	2	0	0	0	-
Influenza A virus subtype H7N7 and H7N3	2	0	0	0	-
Poliovirus	2	0	0	1	[34]

The biological agents colored in red belong to annex 1 of the French regulation concerning select agents [35] (Highly pathogenic microorganisms presenting the highest risk to public health)

The biological agents colored in green belong to annex 2 of the French regulation concerning select agents [35]

(): number of deaths

*XDR-TB: extensively drug-resistant tuberculosis

† CCHF: Crimean-Congo hemorrhagic fever

‡ SARS-CoV: severe acute respiratory syndrome coronavirus

§ MERS-CoV: Middle East respiratory Syndrome coronavirus

¶ RVF: Rift Valley fever

KFD: Kyasanur forest disease

**OHF: Omsk hemorrhagic fever virus

} unique case of class 4 pathogen contamination in a biosafety level 4 laboratory humans can be reduced through the use of appropriate procedures and techniques, containment devices, and facilities. It should be noticed that humans are not the unique possible victims of biological hazards; cattle were affected by an outbreak of foot-and-mouth disease in the UK in 2007 that was later suspected to be due to a cracked pipe from two laboratories working on this virus in their vicinity [39]. The control measures used in the laboratories questioned are designed to protect employees and the public from exposure to infectious agents, and these measures seem to be sufficient. The consequence of not respecting such measures is that many of the laboratories will simply abandon the study of critically important biohazardous agents. The biosafety procedures adopted so far have greatly contributed to reducing the burden of LAIs in recent years, and data from this survey contribute to improving the balance between the need to facilitate research activities and assuring appropriate biosafety and biosecurity procedures. Tim Trevan recommended that scientists working with hazardous materials take lessons from the nuclear industry, hospitals, and other sectors that have established a safety culture [40]. In conclusion, there is still a need to implement a culture of biosafety in the life sciences, rather than strengthen regulations.

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Compliance with ethical standards

Funding None.

Ethical approval Not applicable.

Informed consent Not applicable.

Conflict of interest The authors declare that they have no conflict of interest.

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