Review on Biosafety and Laboratory-Acquired Infections: Mvsc Seminar

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SUMMARY

Research with pathogenic agents, such as bacteria, virus, parasites, fungi and rickettsia, or genetically modified organisms, has generated concern because of their potential biological risk to people and the environment. Hence the laboratory workers are highly prone to pathogenic microorganisms due to the nature of their work and may develop laboratory-acquired infections. Brucella, mycobacterium, salmonella and Shigella are the most common causes of laboratory acquired bacterial infections. Similarly, the hepatitis B (HBV) and C viruses (HCV), and the dimorphic fungi are accountable for the utmost number of viral and fungal-associated LAIs. These biolological agents are classified into four based on their relative risk to laboratory workers and the community. There are also containment levels 1 through 4 based on infectivity, severity and transmissibility of agents, and the nature of the work being conducted. Accidental inhation, inoculation and ingestion of biological agents are the main routes of transmission of LAIs. Even though they can pose great public health threats, there was no systematic reporting of laboratory-acquired infections. The reporting is mostly depending on the voluntary of the exposed individuals. As a result, there was no accurate number of LAIs. Laboratory biosafety is used to run the analysis of specimens safely and consequently protect the people and the environment from biological hazards.

Keywords: Laboratory biosafety, biohazards, laboratory-acquired infections

1. INTRODUCTION

Advances in biotechnology research have applications over a wide range of areas, such as microbiology, medicine, food industry, agriculture, genetically modified organisms, and nanotechnology, among others. However, research with pathogenic agents, such as virus, parasites, fungi, rickettsia, bacterial microorganisms, or genetic modified organisms, has generated concern because of their potential biological risk – not only for people, but also for the environment due to their unpredictable behaviour (Tomley and Shirley, 2009; Coelho and Garcia- Díez, 2015).

In recent years, with the continuous innovation of biotechnology and the frequent outbreak of new infectious diseases, countries around the world have continued to study infectious diseases and invested in laboratory activities such as the development of diagnostic tool, vaccine and pharmaceutical development, and identification and characterization of etiological agents, which are critical to most successful control initiatives (Brass *et al.*, 2016; Na *et al.*, 2019). Even though these activities clearly have benefits, handling, isolation, storage, and disposal of infectious pathogens pose adverse safety and security risks to the laboratory, the laboratory workers, the community, the environment, and even to the global by causing laboratory acquired infections (Brass *et al.*, 2016; Peng *et al.*, 2018).

Laboratory-acquired infections (LAI) are referred to as all infections of laboratory personnel, whether they be symptomatic or asymptomatic, acquired through laboratory or laboratory-related activities and these have been reported in scientific literature since 1897(Baron and Miller, 2008;Weinstein and Singh, 2009; Kakaraskoska-Boceska *et al.*, 2017; Siengsanan-Lamont and Blacksell, 2018). Though the precise infection risk after an exposure remains uncertain, LAIs inspections revealed that Brucella spp., Mycobacterium tuberculosis, Salmonella spp., Shigella spp., Rickettsia spp., and Neisseria meningitidis are the leading causes. Similarly, the hepatitis B (HBV) and C viruses (HCV), and the dimorphic fungi are accountable for the utmost number of viral and fungal-associated LAIs (Peng *et al.*, 2018).

laboratory-acquired infections (LAIs) have started to get a strong public health concern, as an infected laboratory worker may transmit the infectious disease to his or her colleagues, family, or community at large (Bavoil, 2005). Moreover, in recent years, there has been growing public health threat about the potential of a pandemic arising from laboratory-acquired infections as more countries are allowing gain-of-function studies, where researchers are increasing transmission and virulence of pathogens (Choucrallah *et al*. 2018).

Hence, effective control of biological risk is the cornerstone of laboratory biosafety and all laboratories that handle or process biological agents have a responsibility to their personnel and the wider community to ensure that work is done in a way that brings the potential for incidents and accidents to a minimum (Coelho and Garcia- Díez, 2015; WHO, 2020). The biosafety of laboratory is a necessary place for conducting experimental research on pathogenic micro-organisms and the prevention of infectious diseases (Na *et al.*, 2019), and it includes safe laboratory operation by implementing nationally and internationally certified protocols that include proper microbiological practices, containment devices/ apparatus, satisfactory facilities or resources, protective barriers, and specialized education and training of laboratory staffs (Coelho, and Garcia-Díez, 2015; Peng *et al.*, 2018).

In this context, clinical laboratories at large and microbiology, mycology, bacteriology, and virology-oriented laboratories, in particular, necessitate appropriate biosafety measures to ensure the safety of laboratory workers and working environment, which are likely to have direct or indirect contact/exposure to hazardous materials or organisms (Coelho and Garcia-Diez, 2015; Peng *et al.*, 2018). Despite the fact that laboratory biosafety and its associated laboratory-acquired infection (LAI) is top most priority in developed countries; it is often neglected in developing countries like Ethiopia (Jalata and Bayissa, 2020). Hence, the objective this seminar is to address laboratory-acquired infection along with their biological agents and to provide an evidence base to control and prevent laboratory acquired infections by establishing nationally and or internationally accepted biosafety systems.

2. BIOSAFETY AND LABORATORY-ACQUIRED INFECTIONS

2.1. Laboratory Biosafety

Laboratory biosafety is the emerging areas of safety and address the safe handling and containment of infectious microorganisms and hazardous biological materials (Gentilli, *et al*., 2016). The fundamentals of biosafety include the microbiological practices, safety equipment, and facility safeguards that protect laboratory workers, the environment, and the public from exposure to infectious microorganisms that are handled and stored in the laboratory (Wilson and Chosewood, 2007). "Biosafety" has multiple accepted definitions depending on the discipline involved (veterinary, food, medical or environmental), or even the country in which it is used. Laboratory biosafety refers to Safety with respect to the effects of biological research on humans and the environment (Merriam-Webster, 2019). World health organization also defines it as the containment principles, technologies, and practices that are implemented to prevent the unintentional exposure to pathogens and toxins, or their accidental release (WHO, 2006). Also the Office of International des Epizooties (OIE) defines it as principles and practices for the prevention of unintentional release of or accidental exposure to biological agents and toxins (OIE, 2017). On the other hand ISO defines as Practices and controls that reduce the risk of unintentional exposure or release of biological materials (ISO, 2019).

Also the term is sometimes used interchangeably with "biosecurity" but "(Laboratory)" biosecurity describes the protection, control, and accountability for Valuable Biological Material(VBM) agents and toxins within laboratories, in order to prevent their loss, theft, misuse, diversion of, unauthorized access, or intentional unauthorized release (WHO, 2006). The OIE delfines it as set of management and physical measures designed to reduce the risk of introduction, establishment and spread of animal diseases, infections or infestations to, from and within an animal population (OIE, 2017).

2.1.1. Biosafety Levels

The primary risk criteria used to define the four ascending levels of containment, referred to as biosafety levels 1 through 4, are infectivity,

severity of disease, transmissibility, and the nature of the work being conducted. Another important risk factor for agents that cause moderate to severe disease is the origin of the agent, whether indigenous or exotic (WHO, 2004).

Biosafety level 1 (BSL-1) is the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans and is used as basic teaching laboratories, whereas biosafety Level- 2 (BSL-2) is appropriate for handling moderate-risk agents that cause human disease of varying severity by ingestion or through percutaneous or mucous membrane exposure (Beeckman and Rüdelsheim, 2020). Biosafety level 3 is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious infections, are indigenous or exotic in origin and have treatment. Exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available are restricted to high containment laboratories that meet biosafety level 4 (BSL-4) standards (Table 1; WHO, 2004).

Each level of containment describes the microbiological practices, safety equipment and facility safeguards for the corresponding level of risk associated with handling a particular agent (Table 1). The facilities safeguards help protect non-laboratory occupants of the building, the public health and environment (Wilson and Chosewood, 2007). Individual workers who handle pathogenic microorganisms must understand the containment conditions under which infectious agents can be safely manipulated and secured. Application of this knowledge and the use of appropriate techniques and equipment will enable the microbiological and biomedical community to prevent personal, laboratory and environmental exposure to potentially infectious agents or biohazards (CDC, 2007; Na *et al.*, 2019).

Table 1: Summary of Biosafety Level Requirements **(**WHO, 2004)

	Biosafety Level			
	1	2	3	4
Isolation of laboratory	No	No	Yes	Yes
Room sealable for decontamination	No	No	Yes	Yes
Ventilation:				
— inward airflow	No	Desirable	Yes	Yes
— controlled ventilating system Y	No	Desirable	Yes	Yes
— HEPA-filtered air exhaust	No	No	Yes	Yes
Double-door entry	No	No	Yes	Yes
Airlock	No	No	No	Yes
Airlock with shower	No	No	No	Yes
Anteroom	No	No	Yes	—
Anteroom with shower	No	No	Yes	Yes
Effluent treatment	No	No	Yes	Yes
Autoclave:				
— on site	No	Desirable	Yes	Yes
— in laboratory room	No	No	Desirable	Yes
— double-ended	No	No	Desirable	Yes
Biological safety cabinets	No	Desirable	Yes	Yes
Personnel safety monitoring capability	No	No	Desirable	Yes

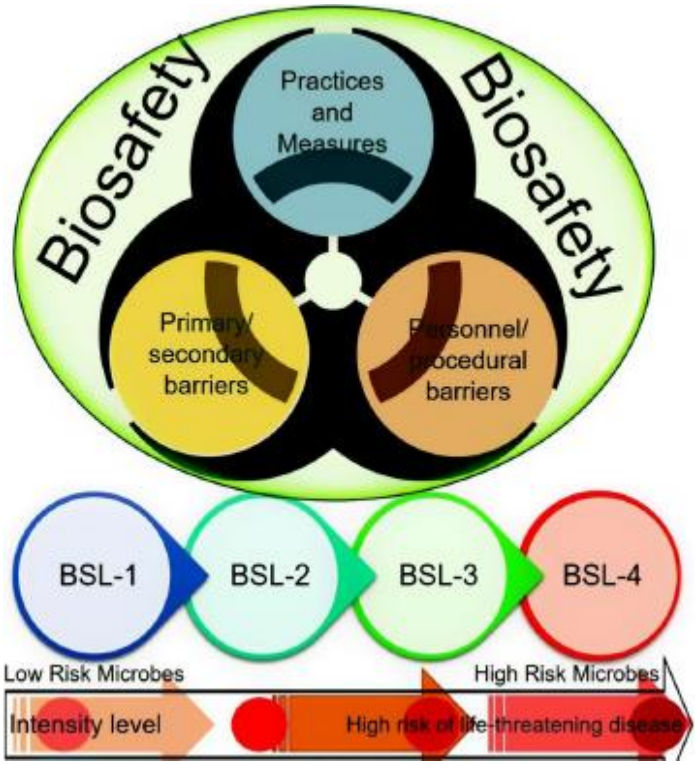


Figure 1: **S**chematic representation of a biosafety concept and four biosafety levels (BSL) with their risk intensity. (Peng *et al.*, 2018).

2.2. Biological Risk Classification

Central to biosafety programs is the concept of universal precautions and for that purpose microorganisms are containment is focused not on specific infectious agents but on standard practices for handling infectious material that will prevent the transmission of all pathogens of that risk category (Table 2; Wilson and Chosewood, 2007).

In general, the classification of biological agents are based on the following factors: (i) the virulence of the biological agent or the severity of disease (in humans), (ii) the mode of transmission (spread in the community and host range), (iii) the availability of effective preventive measures (e.g., vaccines), and (iv) the availability of effective treatment (e.g., antibiotics or antiviral drugs) (WHO, 2004) .The categorized into four biological risk categories on the basis of their relative risk to laboratory workers and the community. Subsequent risk

hazard of the infectious agent increases from risk group1, consisting of microorganisms not associated with disease, to risk group-4 (Figure1). Risk group 4 microorganisms can cause serious disease and can be readily transmitted, and effective treatments are usually not available (Wilson and Chosewood, 2007; kimman *et al*., 2008). However, there are differences in the exact definitions as used by certain countries and/or organizations (such as NIH/CDC, WHO, and European Union) which result in differences in the exact listings of biological agents in each risk category (Flemming, 2000).

Table 2: Summary of Risk Groups and Recommended Biosafety Levels for Infectious Agents (Wilson and Chosewood, 2007)

Risk Group	Bsl	Agents	Practices	Primary Barriers and Safety Equipment	Facilities 2 (Secondary Barriers)
1	1	Not known to consistently cause diseases in healthy adults.	Standard microbiological practices.	No primary barriers PPE: laboratory coats and gloves; eye, face protection,	-Laboratory bench and sink required

2	2	Agents associated with human disease -Routes of Transmission -percutaneous injury, - ingestion, mucous -membrane exposure	BSL-practice plus: -Limited access signs -Sharp precautions -Biosafety manual defining any needed waste decontamination or medical surveillance policies	Primary barriers: -BSCs or other Physical containment devices used for all manipulations of agents that splashes or aerosols of infectious materials -PPE: Laboratory coats, gloves, face and eye protection	BSL-1 plus: Autoclave
3	3	-Indigenous or exotic -agents that may cause serious or potentially lethal disease through the inhalation route of exposure	BSL-2 practice plus: -Controlled access Decontamination of all waste Decontamination of laboratory clothing before laundering	Primary barriers: BSCs or other physical containment devices used for all open manipulations of agents PPE: Protective clothing, gloves, face, eye and respiratory protection	BSL-2 plus -Physical separation from a access corridors, -Self -closing, double door access -Exhausted air not recirculated - Negative airflow into laboratory -Entry through airlock -Hand washing sink near exit
4	4	Dangerous/exotic – agents-pose high individual risk of aerosol-transmitted and frequently fatal, no vaccines or treatments.	BSL-3 practices plus: -Clothing change before entering -Shower on exit -All material decontaminated on exit from facility	Primary barriers: -All procedures conducted in class III BSCs or Class I or II BSCs in combination with full- body, air-supplied, positive pressure suit	BSL-3 plus: -Separate building or isolated zone -Dedicated supply and exhaust, vacuum, and decontamination systems

2.2.1 Biological Agent Risk Group-One

They are biological agents that pose low risk to personnel and the environment. These agents are highly unlikely to cause disease in healthy laboratory workers, animals or plants. The agents require a biosafety Level one containment (Table2). *Agrobacterium radiobacter*, *Aspergillus niger*, *Escherichia coli* strain K12, *Lactobacillus acidophilus*, *Micrococcus leuteus*, *Pseudomonas, fluorescens, Serratia marcescens* are some examples of biological agents of risk group one (WHO, 2004; Dalton, 2020).

2.2.2. Biological Agent Risk Group-Two

This risk group contains biological agents that pose moderate risk to individual and low to the community. If exposure occurs in a laboratory situation, the risk of spread is limited and it rarely would cause infection that would lead to serious disease. Biosafety Level 2 containment, and *Streptococcus pneumonia, Salmonella*

Effective treatment and preventive measures are available in the event that an infection occurs. The agents require

choleraesuis are examples of risk group two (Dalton, 2020)

2.2.3. Biological Agent Risk Group-Three

Biological agent classified under risk group three contains biological agents that usually cause serious disease to individual and low to community (human, animal or plant) or that can result in serious economic consequences. These agents are usually not spread by casual contact and require Biosafety Level 3 containment. *Brucella abortus, Brucella melitensis* and *coxiella burnetti* are some examples of risk group three microorganisms (Wilson and Chosewood, 2007)

2.2.4. Biological Agent Risk Group-Four

These biological agents usually produce very serious disease, both to individual and community (human, animal or plant), that is often untreatable. These agents are usually easily transmitted from one individual to another, from animal to human or vice-versa, either directly or indirectly, or by casual contact. The agents require Biosafety Level 4 containment. *Lassa virus*, *Reston ebolavirus* and *Sudan ebolavirus* are classified under risk group four microorganisms (Dalton, 2020).

2.3. Laboratory Biosafety in Ethiopia

Ethiopia ratified biosafety law firm for Genetically Modified Organism (GMO) regulation systems in 2009 and made an amendment to some of the laws in 2015. The Ethiopian biosafety law mostly focus only on protecting the environment from potential risks of GMOs, giving little attention to prevent laboratory acquired infection, and their unintended impact on human health (CMR, No.199/2013; Jalata and Bayissa, 2020). Even though Ethiopia has biosafety regulation, there is no law that enforce its implementation in the country and as a result most clients are not aware of the presence of the regulation. Also a person who carries out activity in the laboratory with pathogenic micro-organisms is not legally insured in health (Abraham, 2013; CMR, No.199/2013).

The systematic review conducted by Jalata and Bayissa revealed that most of Ethiopian laboratories, neither laboratory manual nor report incorporates biosafety issues; even the availability of laboratory safety guidelines is limited and lacks biosafety officer that supervise

laboratory safety and the working environment in all concerning biosafety questions. Biosafety training programs were inadequate for laboratory workers and there may be malpractices, which can potentially expose the personnel to pathogenic micro-organisms (Jalata and Bayissa, 2020). The laboratory personnel working with pathogenic organisms did not periodically checked-up medically and insured in health due to lack of legal enforcement. Thus, it is not possible to mention health impact of workers in such laboratories since there was no established periodical check-up and there was also no accident or injury recording and report from each laboratory and hence, the number of exposures and laboratory acquired infection cannot be estimated (Abera, 2017; Jalata and Bayissa, 2020).

2.4. Causes and Transmission of Laboratory-Acquired Infection

Before the introduction of regulations concerning biosafety levels in laboratories and good laboratory practices, laboratory manipulations, including handling of cultures of pathogenic microorganisms took place on the bench without any specific protection (Peng *et al.*, 2018). For example, it was permissible to smoke, eat or drink, 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 (Wurtz *et al.*, 2016)

Laboratory workers, especially those in microbiology, are at greater risk of becoming infected than the general population and for instance clinical diagnostic laboratories accounted for 45% of all laboratory-acquired infections (Wilson and Reller, 2013). Even though, the causative source, procedure, or breach in technique cannot be identified in approximately 50% of LAIs, inhalation of aerosols and droplets, contamination of skin and mucous membranes, ingestions and inoculations of infectious agents are common (Pence, 2018).

Laboratory activities such as pipetting, blenders, pouring, non-self-contained centrifuges, sonicators, vortex mixers, flaming a reusable loop, and catalase testing may generate airborne respirable size particles (<0.05 mm in diameter) (Wilson and Chosewood, 2007). Aerosol output and dose are impacted by procedure- aerosol burden

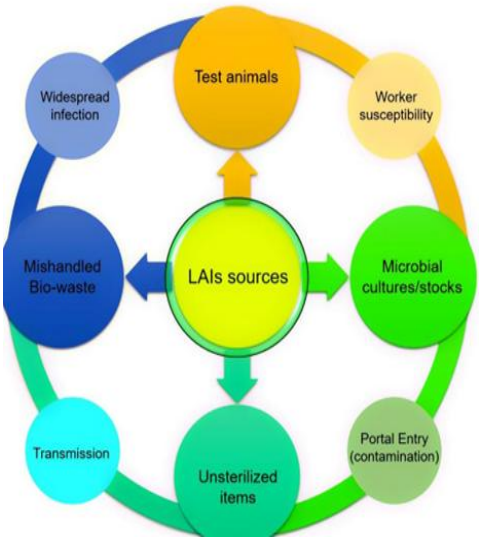
with maximal aeration is approximately 200 times greater than aerosol burden with minimal aeration. Procedures and equipment that generate respirable size particles also generate larger size droplets (>0.1 mm in diameter). These larger size droplets settle out of the air, contaminating gloved hands, work surfaces, and possibly mucous membranes of the person performing the procedure (WHO, 2004; Siengsanan-Lamont and Blacksell, 2018).

Parenteral inoculation of infectious materials with syringe needles or other contaminated sharps such as blades and broken glassware and or spills, sprays, and splashes into eyes, mouth, or nose and hand-to-face actions, onto skin cuts, abrasions, and dry, inflamed skin are potential routes of transmission of Pathogens. Mouth pipetting and transfer of organisms to the mouth from contaminated items such as pencils or fingers (figure 2). In addition, the Consumption of food or drink in the laboratory and accidental splashes into the mouth can cause significant transmission of biological agents (Wurtz *et al.* 2016; Pence, 2018)

There are several factors that impede the application of laboratory-related biosafety measures within the facility and in turn they contribute for the occurrence of LAIs. These may include, but not limited to: the absence of a technical document containing specific biosafety guidelines, poor biosafety skills (for example, on spills management) because of lack of training, the continuous presence of laboratory hazards and increased vulnerability due to poor execution of bio-risk assessment, reduction, and management activities, use of substandard laboratory supplies and poor equipment maintenance (WHO, 2004; Pence, 2018).

In addition to the above factors, when biosafety guidelines are more likely to be poorly implemented in facilities because of poorly written guidelines, including the adoption of generic, nonspecific procedures, unclear roles and responsibilities for each staff involved, lack of review and updating process of existing guide, and poor dissemination and access to such guidelines are the predisposing factors for the transmission and occurrence of laboratory acquired infections (Pence, 2018).

Figure 2: Laboratory-acquired infections (LAIs) sources and route infection (Peng *et al.*, 2018).



3. STATUS OF LABORATORY-ACQUIRED INFECTIONS

Laboratory acquired infections are referred to as all infections of laboratory personnel, whether they are symptomatic or asymptomatic, acquired through laboratory or laboratory-related activities (Baron and Miller, 2008; Weinstein and Singh, 2009; Siengsanan-Lamont and Black sell, 2018).

Bacteria, viruses, rickettsiae, fungi, and parasites have been described as the causes of laboratory acquired infections (Baron and Miller, 2008). A world wide literature review conducted by Harding and Byers showed 1267 cases of laboratory infections and out of these (1267) infections, 1074 were caused by Mycobacterium tuberculosis, Coxiella burnetii, hantaviruses, arboviruses, hepatitis B virus, Brucella species, Salmonella spp., Shigella spp., hepatitis C virus, and Cryptosporidium species (Harding and Byers, 2006).

Furthermore, LAIs inspections done by Peng *et al.* revealed that Brucella spp., Mycobacterium tuberculosis, Salmonella spp., Shigella spp., Rickettsia spp., and Neisseria meningitidis are the leading causes (Peng *et al.*, 2018). In a 2002–2004 inspection of clinical laboratory directors, who participated in *ClinMicroNet*, an online forum sponsored by the American Society of Microbiology, approximately 33% of laboratories stated the incidence of at least one LAI (Baron and Miller, 2008). Among these infections, brucellosis, shigellosis, and salmonellosis were found to be the most common LAIs (Peng *et al.*, 2018). Similarly, the survey done by Choucrallah, *et al.* revealed 89 exposure incidents to human pathogens and five suspected and one confirmed laboratory-acquired infections. This was approximately twice the number of exposure incidents that were reported in 2017 (n=44) and 2016 (n=46) (Choucrallah *et al.* 2018).

On the other hand, a search for Laboratory acquired infections and zoonoses in the Asia-Pacific region using online search engines revealed 27 LAI reports which were published between, 1982 and 2016. The most common pathogens associated with these LAIs were dengue virus, Brucella spp., Mycobacterium spp., Rickettsia spp., and Shigella spp. and 78% (21/ 27 LAI reports) occurred in high-income countries (i.e., Australia, Japan, South Korea, Singapore, and Taiwan) where laboratories were likely to comply with international biosafety standards. Two upper-middle income countries (China (2), and Malaysia (2)) and one lower-middle income country (India (2)) reported LAI incidents. The majority of the reports (52% (14/27)) of LAIs occurred in research laboratories while 5 were from clinical or diagnostic laboratories that are considered at the frontier for zoonotic disease detection (Siengsanan-Lamont and Black sell, 2018).

Also retrospective study of historical data done from 1976 to 2010 by National Institute of Health of US America to identify and characterize the types of incidents, accidents, exposures, and subsequent infections that have occurred since the inception of biotechnology and oversight by NIH showed a total of 139 occupational exposures from 88 NIH-funded institutions reporting. They identified 42 different biological agents that resulted in a total of 14 LAIs and all of which were self-limiting or easily treated, with a 79% known source of exposure (Campbell, 2015).The greatest number of occupational exposures occurred while working with lentivirus (21), followed closely by vaccinia virus (19), and then adenovirus (15). Of the 19 occupational exposures to vaccinia virus, over 50% resulted in a laboratory acquired infection, some of which were caused by recombinant viruses (Table 3).

Table 3: Summary of biological agents association with occupational exposures
(Campbell, 2015).

Agent	**Occupational Exposures**	**Laboratory-acquired infections reported**
Lentivirus	21	0
Vaccinia virus	19	10
Adenovirus	15	1
Toxoplasma gondii	9	0
Escherichia coli	7	1
Mycobacterium spp.	4	0
Leishmania spp	3	0
Shigella flexneri	2	1

Bacillus anthracis	1	1
Francisella tularensis	1	0
Hepatitis B virus	1	0
Herpes simplex virus	1	0
Neisseria meningitides	1	1

4. SPECIFIC LABORATORY-ACQUIRED INFECTIONS

4.1. Laboratory-Acquired Brucellosis

Brucellosis is caused by pathogenic *Brucella* spp., of which *Brucella abortus*, *Brucella melitensis*, and *Brucella Suis* are the most commonly affecting humans. The primary sources of human infection are consumption of unpasteurized dairy products consumed in or imported from a country where brucellosis is endemic ((Traxler *et al.*2013), contact with meat or tissues of infected wild animals (CDC, 2007) and laboratory exposures to *Brucella* isolates (Harding and Byers, 2006).

Brucella is one of the main causes of laboratory-acquired infection (Harding and Byers, 2006; Batsukh and Battsetseg, 2014). Brucella pose the highest risk to the worker (Table 4) and its attack rate has been reported to be 30%–100%, depending on the inoculums involved, the physical location of the workers, and the source at the moment of the exposure (Flori *et al.*, 2000; El-Jaouhari *et al.*, 2022). Between 1979 and 2015; brucellosis was reported as causing 378 LAIs (Byers, 2017). Brucella is recommended that to be handled according to level 3 biosafety precautions because of its aerosolization, which is the primary mechanism of transmission (El-Jaouhari *et al.*, 2022)

In 2013, a study by Traxler *et al.* showed 167 Brucella exposed workers, and 71 of them developed laboratory-acquired brucellosis. Among these, 18 (11%) exposures were due to laboratory accidents, 147 (88%) were due to aerosolization of organisms during routine identification activities, and the circumstances of 2 (1%) exposures were unknown; and 80% of them were caused by *Brucella melitensis* (Traxler *et al.*, 2013).

In the United States, Brucella infection is one of the most common laboratory-acquired infections, accounting for 24% of laboratory-acquired bacterial infections and 11% of deaths due to laboratory infection (Harding and Byers, 2000). Brucellosis is also endemic in the Asia-Pacific region, and the predicted prevalence of the

disease in livestock ranges between 3% for South East Asia and 16% for South Asia, posing a high risk of exposure to veterinary laboratory workers (Garin-Bastuji, 2014).

Table 4: Laboratory-associated infection and relative risk of infection, compared with the risk among the general population.

Microorganisms	Number of cases of infections	Relative risk of Infections
Shigella species	15	1
Brucella species	7	8012.5
Salmonella species	6	0.08
Neisseria meningitidis	4	40.8
Cocidioides species	2	8.6

Data are for the years 2002–2004 (Baron and Miller, 2008).

4.2. Laboratory-Acquired Tuberculosis

Initial inspections of laboratory-acquired tuberculosis documented the prevalence of pathogenic *Mycobacterium tuberculosis* three to nine times higher amongst laboratory employees compared with the general population (Weinstein and Singh, 2000). Though Laboratory associated tuberculosis is extremely challenging to recognize owing to the wide-environmental dissemination of the microorganisms and chronicity of the infection, the extreme menace of LAI for laboratory staffs handling *M. tuberculosis* is related to the aerosols generation. Also, the literature survey revealed some M. tuberculosis cases occurred due to inadequate isolation techniques and high capacities of specimens handled. It is important to handle mycobacterium in class II or III BSC to avoid their associated possible LAI (Weinstein and Singh, 2000; Peng *et al.*, 2018).

4.3. Other Bacterial-Associated LAIs

In addition to Brucellosis and Tuberculosis, other several bacteria have also been reported to causing LAIs with infrequently. For instance, *Francisella tularensis* is a fastidious, gram negative coccobacillus that is infrequently encountered in the clinical microbiology laboratory, but it has gained increased importance because of its possible use as a bioterrorism agent (Dennis *et al.*, 2001). Tularaemia is a zoonotic infection and there are some reported cases of F. tularensis mediated LAIs in the literature and the greatest hazard to laboratory workers is from exposure to infectious aerosols from manipulation of bacterial cultures rather than on infected animals or clinical material (Dennis et al., 2001; Weinstein and Singh, 2009).

Microorganisms such as Salmonella or Shigella belonging to Enterobacteriaceae have also been recognized to cause LAIs (Baron and Miller, 2008). Salmonella species is among the most commonly reported bacterial causes of laboratory-acquired infections. In South Africa over the period 2012 to 2016, three cases of laboratory-acquired Salmonellosis had reported and all cases were most likely the result of lapses in good laboratory practice and laboratory safety (Smith *et al*., 2017).

Shigella species are among the frequently identified agents of laboratory-acquired infection (Baron and Miller, 2008). Large number of laboratory- acquired shigellosis had reported because of that *Shigella* species are more virulent and require much lower inoculums to cause illness. However, it is also probably true that microbiology laboratory staffs that develop diarrhoea are more likely to attempt to establish a cause for their illness, compared with the general population (Weinstein and Singh, 2009). A number of other enteric pathogens have also been identified as less common causes of laboratory-acquired infection, including *Clostridium difficile* and *Escherichia coli* (Bouza *et al*., 2005; Baron and Miller, 2008).

Bacillus anthracis is also an important pathogen causing LAI at high infective doses but it can be prevented by personal protective measures and adequate training in laboratory biosafety (Rusnak *et al*. 2004; Odetokun *et al*. 2017). Although the 2011 Chicago anthrax infection was the most recent laboratory-researcher infection by anthrax-producing bacteria, there were two earlier and larger clusters of infections, one each associated with government laboratories in the USA and in Russia, where *B. anthracis* spores were produced and tested (Silver and Cole, 2014).

The most familiar one was the American 2001 bioterrorism scare when *B. anthracis* spores were sent through the mail to multiple recipients (Rasko *et al.*, 2011), and as a result of the posting of anthrax spores by a deranged person (and not research-related) who mailed letters containing anthrax spores in the US post, 22 people were infected, 11 with cutaneous anthrax (Jernigen *et al.* 2001) and 11 with inhalation anthrax (Johnson 2005). Five of the inhalation-

infected people died (Jernigan *et al.*, 2001; Johnson 2005).

4.5. Laboratory-Acquired Viral Infections

Researchers studying both cellular and viral disease agents in the laboratory have become infected since the early days of microbiology 150 years ago. However, in the early 21st century, new concerns about bioweapons being used to generate terror and also with a series of newly emerging or newly understood disease-causing virus have resulted in infections and deaths of workers studying these microbes in the laboratory to gain understanding and to develop treatments and vaccines (Silver and Cole, 2014)

Now days, virus research is associated with widespread applications in biotechnological sectors, such as viral diseases, the development of novel vaccines, or GMOs. Despite scarce research investigation concerning virus associated LAIs, West Nile Virus, Dengue, or Marburg virus have been reported (Gaidamovich,*et al.*, 2000; Britton, *et al.* 2011; Wei, *et al.*, 2014). Viral agents transmitted through blood and body fluids are responsible for most of the LAIs amongst the employees in diagnostic laboratories (Silver and Cole, 2014). Even though, the viral hemorrhagic fevers provoke the greatest fear; these viruses are rare causes of laboratory infection and among the common blood-associated viruses, HBV is the leading cause of LAIs and the incidence of HBV infection in the United States is approximated to be 3.5–4.6 infections per 1000 workers (CDC, 2006). Lack of implementation of universal precautions while handling specimens, puncture by needle, and lack of vaccination are the factors that contributes to HBV- laboratory infection (Peng, *et al.*, 2018). During 2005–2006, there were 802 confirmed cases of HCV reported to the Centers for Disease Control and Prevention, with five occupational exposures to blood (Wasley, *et al.* 2006). However, very few data were found on the occurrence of HCV among laboratory employees with only one case in the US and UK (Peng, *et al.*, 2018). Therefore, correct biosecurity and biosafety procedures, immune control approaches, education and training, and specialized laboratory facilities should be adopted to reduce the potential risk of LAIs or viral-associated diseases (Lipsitch and Bloom, 2012).

4.6. Parasites Associated LAIs

Among laboratory-acquired infections caused by the parasites, Leishmaniasis, Fascioliasis, Malaria, Toxoplasmosis, Trypanosomiasis, or Schistosomiasis have been found to be the most adverse forms (Kinoshita-Yanaga, *et al.*, 2009; Felintode-Brito, *et al.*, 2012). Nearly, 313 cases of LAIs, with a variety of blood and intestinal protozoa, have been reported (Herwaldt, 2001; Weinstein and Singh, 2009). Many of these cases occurred in reference and research laboratories and a total of 52 malaria cases have been reported, with 34 cases reviewed by Herwaldt. Out of these, 10, 9, and 15 cases were caused by *Plasmodium cynomolgi, P. vivax and P. falciparum*, respectively (Herwaldt, 2001. The direct contact or exposure to parasites in the laboratory presumably increases the potential risk for acquiring parasitic infections. Several causes including needle stick injuries, barehanded work in the open field are the common means associated with parasitic LAIs. Since parasitic diseases are commonly characterized by a prolonged asymptomatic period, laboratory employees working with parasites are advised to be tested intermittently (Herwaldt, 2001; Lopes, *et al.*, 2012). Additionally, exceptional attention must be taken for child bearing women due to the hereditary transmission of some protozoan parasites (Lopes, *et al.*, 2012).

4.7. Fungi- Associated LAIs

An intensive search of literature through several search engines revealed that dimorphic fungi, such as *Blastomyces dermatitidis, Coccidioides immitis,* and *Histoplasma capsulatum* are responsible for the maximum number of laboratory-acquired mycoses (LAM). Coccidioidomycosis caused by *C. immiitis* and dermatophytosis caused by *Trichophyton mentagrophytes* are the commonest laboratory acquired fungal infections (Lim *et al.*, 2004; Gugnani and Randhawa, 2020). Dermatophytes can be involved in laboratory acquired infections and cutaneous infections occur by accidental inoculation (Lim *et al.*, 2004). In the 2009 Weinstein and Singh reported that dimorphic fungi were responsible for the greatest number of Laboratory-acquired fungal infections (Weinstein and Singh, 2009). Aerosols of these fungi produced in various ways are probably the most frequent causes of laboratory-associated infections and accidental infections have also resulted while pipetting, and from the spills by the

use of a needle and syringe (Gugnani, and Randhawa, 2020). The risk of fungal infection is probably lower in the mycology laboratories, because specimen handling is carried out in laminar-flow biological safety cabinets (BSCs), and culture plates are also sealed to avoid accidental opening (Weinstein and Singh, 2009).

5. CONTROLAND PREVENTIONS OF LAI

Many LAIs occur because laboratory personnel do not appreciate the increased exposure risk associated with an incorrect or delayed identification of a highly infectious agent that often leads to performing aerosol-producing procedure outside of the Biosafety cabinet (BSC) (Peng *et al.* 2018). The keys to the prevention of LAIs are knowledgeable personnel who are aware of the potential hazards, understand the various modes of transmission within the workplace, and are proficient in safe microbiological practices and techniques, and a laboratory-specific safety manual (Swell,2005).

Training of employees about the possible causes and transmission of LAIs is used the employees as they practice standard precautions at all times, process specimens in a BSC, use of appropriate containment equipment and safety barriers when necessary, decontaminate work surfaces at least daily and following a spill, and properly dispose of biological hazardous waste, which in turn used to minimize and prevent the occurrence of laboratory acquired infections (CLSI, 2005). Hence,

before performing any laboratory test, the provision of required training on biosafety to the laboratory workforce is vital, either as a focused training program or as part of the training curriculum for certain laboratory procedures (Whistler *et al.*, 2016).

The integration of the monitoring of biosafety practices and laboratory processes also used as a means of preventions. Certain indicators that indirectly assess the overall biosafety include an updated procedure manual and work instructions, a list of trained staff with regular competency or proficiency tests, and regular quality control and laboratory equipment maintenance are also used to prevent the employees from biohazards (Rim and Lim, 2014; Whistler *et al.*, 2016). Vaccination and regular medical consultation of laboratory personnel can early detect the risk of infection and used for controlling of the diseases (Rim and Lim, 2014).

Moreover, the presence of laboratory signage such as a biohazard symbol to recommended sites of the facility, with a well-organized mechanism for disposal of wastes, can significantly minimize the risk of accidents and incidents both inside and outside the laboratory are most importantly used to prevent the possible occurrence of Laboratory acquired infections (CLSI, 2005; Rim and Lim, 2014)

6. CONCLUSIONS AND RECOMMENDATIONS

Laboratory-acquired infection represents an occupational hazard unique to laboratory workers, especially those in the microbiology laboratory. Bacteria, viruses, fungi and parasites are potential causes, and exposures may occur inadvertently, or may result from lapses in technique leading to accidental inoculation. The LAIs are mostly associated with lack of consistent biosafety system with allocated resources for regular training of laboratory personnel. The accurate number of laboratory acquired infection is unknown because there is no systematic reporting system that monitors the number of laboratory-related exposures and infections, even in developed countries. These can pose a serious, life-threatening risk of disease transmission and/or spread over from infected laboratory staff to communities and the environment.

Based on these conclusions the following recommendations are forwarded:

- Comprehensive biosafety programs including appropriately designed, built and maintained containment facilities are effective in facilitating the safe and responsible conduct of research.
- Efforts to promote biosafety are vital and must include training and education programs for scientists and support staff (including facility engineers and animal care technicians), as well as funding for infrastructure maintenance, which is particularly important in developing countries.
- Surveillance should be done to determine the status laboratory-acquired infections (LAIs) and associated biological risks.
- The establishment of strong and appropriate biosafety systems, and training the laboratory staffs concerning the causes and transmission and the prevention methods of pathogenic microorganisms are needed.
- The laboratory workers should be encouraged to record and report the accidental exposures and as well as laboratory-acquired infections.
- Every laboratory personnel should follow strictly biosafety guidelines and procedures when they go to run any test or analysis.
- Vaccination and strong medical monitoring of laboratory workers is necessary.

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