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Biosafety and Biosecurity in Veterinary Laboratories

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Abstract

With recent outbreaks of MERS-Cov, Anthrax, Nipah, and Highly Pathogenic Avian Influenza, much emphasis has been placed on rapid identification of infectious agents globally. As a result, laboratories are building capacity, conducting more advanced and sophisticated research, increasing laboratory staff, and establishing collections of dangerous pathogens in an attempt to reduce the impact of infectious disease outbreaks and characterize disease causing agents. With this expansion, the global laboratory community has started to focus on laboratory biosafety and biosecurity to prevent the accidental and/or intentional release of these agents. Laboratory biosafety and biosecurity systems are used around the world to help mitigate the risks posed by dangerous pathogens in the laboratory. Veterinary laboratories carry unique responsibilities to workers and communities to safely and securely handle disease causing microorganisms. Many microorganisms studied in veterinary laboratories not only infect animals, but also have the potential to infect humans. This paper will discuss the fundamentals of laboratory biosafety and biosecurity.

Introduction

Infectious livestock diseases pose a significant risk to global animal health, and their control is essential to preserve international trade agreements pertaining to livestock and livestock products, to support economic growth and development, to promote and foster sustainable livelihoods and food security, and to prevent zoonoses in humans [1]. Laboratory activities including pathogen research, diagnostic tool development, pharmaceutical and vaccine development, and identification and characterization of etiological agents are critical to most successful control initiatives. While many of these activities clearly benefit animal health, the handling, isolation, storage, and disposal of infectious pathogens pose inherent safety and security risks to the laboratory, the staff, the community, the environment, and even the world. As a result, laboratory biosafety and biosecurity systems must be an integral part of any laboratory working with and handling dangerous microorganisms to prevent accidental and/or intentional release. The World Organization for Animal Health's (OIE) Terrestrial Manual defines laboratory biosafety as "the principles and practices for the prevention of unintentional release of or accidental exposure to biological agents and toxins" and laboratory biosecurity as, "the physical control of biological agents and toxins within laboratories, in order to prevent their loss, theft, misuse, unauthorized access or intentional unauthorized release" [2].

Laboratory accidents and unintentional release of pathogens from veterinary laboratories can infect human and animal populations. The risk of laboratory acquired infections was first described in 1951 following a comprehensive survey of 5000 US laboratories documenting a presumed 1300 laboratory acquired infections with 39 deaths [3]. Since then, numerous laboratory acquired infections have been recorded; two notable examples include an incident in Singapore where a microbiology student contracted the Severe Acute Respiratory Syndrome (SARS) virus after working in a contaminated laboratory biosafety cabinet, and another incident where work was suspended at a US laboratory when workers contracted brucellosis and were exposed to Q fever [4; 5].

Although animal health and research laboratories handle primarily animal pathogens, many are zoonotic. Consequently, these agents pose significant risks to laboratory staff and the surrounding human and animal populations. Moreover, improperly inactivated laboratory waste containing pathogens, infected research animals, and/or contaminated laboratory staff and their possessions can contaminate the environment and infect surrounding communities and/or livestock. A notable example of such, resulting in a catastrophic outcome, occurred in August and September 2007 in Surrey, United Kingdom, when laboratory strains of foot and mouth disease virus leaked from a laboratory waste pipe, and were transmitted to local livestock by means of vehicles contaminated with the waste [6]. The virus was detected in ten farms, and resulted in severe disruptions to the livestock sector costing more than one hundred million pounds to control [6]. Given the potential consequences of accidental pathogen release, laboratory biosafety policies and practices are essential to any laboratory handling pathogens that pose a risk to human and animal health.

In addition to accidental release, deliberate dissemination of dangerous pathogens is an evolving threat. The rise in terrorist activities along with the advancements in the life sciences increases the risk that pathogens can be used for malevolent purposes [7]. Using a biological agent to inflict harm is a complex multi-step process that requires acquisition of a pure and virulent pathogen, sufficient production, followed by effective dissemination [8]. Experts suggest that terrorists are more likely to seek pathogens from bioscience laboratories because the pathogens exist in a pure form and their virulence is established, unlike acquisition from nature or naturally occurring outbreaks where the agent must be isolated and virulence determined [8-10]. Many types of research, diagnostic and pharmaceutical laboratories isolate, amplify, and retain dangerous pathogens to conduct research, diagnose disease, and establish efficacious therapies. Consequently, these pathogens are vulnerable to theft and potential misuse, and must be protected through implementation of laboratory biosecurity programs. Numerous accounts of unauthorized acquisition of biological materials from legitimate bioscience facilities for use in bio-crimes have been documented [11]. However, it was not until a laboratory strain of *Bacillus anthracis* was disseminated through the US postal system that strict guidelines to enhance laboratory biosecurity were established in several countries [8]. Laboratory biosecurity systems are necessary to ensure that pathogens, information, and technologies are protected against theft and misuse.

Laboratory Biorisk Management Systems

Biorisk management (BRM) is a system of processes and procedures used to reduce safety and security risks associated with the handling, storage, and disposal of biological agents and toxins in laboratories [12]. Laboratory biosafety and biosecurity are essential components of biorisk management that should be employed in all biological research laboratories based on the biorisk, or the probability that an adverse event, such as accidental infection or intentional release, will occur, and the consequences of that event. Laboratory biosafety systems consist of engineering controls, standard work practices, and personal protective equipment, and biosecurity systems consist of physical security, personnel security, information security, transportation security, and material control and accountability. While separate concepts, it is important to recognize that both are complementary and both share a common goal: to keep the laboratory, the community, and the environment safe and secure.

The OIE's Terrestrial Manual, *Biosafety and Biosecurity: Standard for Managing Biorisks in Veterinary Laboratory and Animal Facilities*, describes the components of biorisk management as a) biohazard identification, b) biological risk assessment, c) risk management, d) risk communication, and f) verification with continual improvement [2].

Biohazard and Asset Identification

Before a laboratory's risks can be fully assessed and characterized, biohazards and assets must be identified. Hazard and asset identification answers the question: What can go wrong? More specific questions can be asked and include: What is the risk of infection? What is the risk to individuals (humans/animals) outside of the laboratory? What is the risk of theft of biological materials or equipment? What is the risk of selling or destroying biological materials, equipment, intellectual property, or personnel information for personal gain? Animal handling injuries, burns, punctures from sharps, exposure to hazardous chemicals, and other non-biological risks from work with biological materials must be taken into account as well.

When identifying biosafety biorisks, it is important to identify the biological hazards that could cause harm. The biological characteristics of each agent are used to determine how hazardous the agent is including routes of infection, infectious dose, mortality/morbidity rates, stability in the environment, virulence, documented laboratory acquired infections, host range, and the availability of preventative and therapeutic treatments. At risk hosts are those vulnerable to infection who may be inside or outside the laboratory and may include, humans, wildlife, livestock, and other domestic animals.

When identifying biosecurity biorisks, it is important to identify all assets, including anything of value to the institution or an adversary such as biological material, equipment, intellectual property, and possibly even laboratory animals. Identification of assets should consider the impact to the facility (financial, reputation, or potential scientific impact) from theft or destruction of the asset and the potential impact to the environment or the facility of misuse of the asset. Assets can be determined based upon attractiveness to an adversary who may pursue those assets. Thus, adversarial types, motive, means, opportunities and potential attacks should be considered.

Biological Risk Assessment

The backbone of laboratory biosafety and biosecurity is the biorisk assessment [13]. Because each laboratory is unique, its risks will be unique. Thus, all risks should be considered and prioritized for each laboratory. A standardized and repeatable risk assessment process is necessary to identify changes over time, to facilitate clear risk communication, and to ensure compliance with biorisk management best practices. Many biorisks may exist, including accidental or intentional exposure of staff, the community, and/or the environment, and the risk of theft of biological materials, laboratory equipment, or information. The questions posed to understand risk include: a) What can go wrong? b) How likely is it to happen and how likely can we anticipate it? c) What are the consequences? [17]. A biosafety and biosecurity risk assessment should be performed to ensure awareness of all of the risks faced by a laboratory or biomedical facility and their mitigation.

Collecting data for a laboratory biosafety and biosecurity risk assessments should be a shared responsibility between principal investigators, scientists, researchers (or a risk assessment team), and biorisk management advisors. After the information necessary to conduct a risk assessment has been gathered, an overall characterization of biorisk is conducted. In terms of biosafety, the likelihood and consequences of an infection or contamination event is determined. For biosecurity, the likelihood and consequences of theft or acquisition is the focus. Considering the consequences of adverse events is critical to risk characterization. The health effects, potential to spread, and/or economic effects of a release (intentional or accidental) must be considered. This is often location specific; for example, the release of an agent into a region where the disease is enzootic can have less severe consequences than if released into an area where the disease has been eradicated. Depending on the situation, the facility should decide if the work with biological materials can proceed with safeguards or if the work should be refused.

Risk Management

Risk management can be described in terms of mitigating identified laboratory biorisks, and refers to actions and control measures put into place to reduce or eliminate the risks associated with biological agents and toxins based on the laboratory risk assessment. The assessed and accepted risks determine the actions and control measures that will be most effective in reducing and eliminating those particular risks. Monitoring the performance of the chosen mitigation measures is also required to ensure the mitigation controls are reducing risks to an acceptable level.

Biosafety risk mitigation systems aim to protect humans, animals, or the environment from an accidental exposure or release from a laboratory. Biosecurity risk mitigation systems seek to protect assets from intentional theft, diversion, or release by malicious individuals inside or outside of the laboratory. The safety and security control approaches are often complementary and should be used in combination to accomplish appropriate risk reduction, but there are advantages and disadvantages to each. Mitigation control options for laboratory biosafety and laboratory biosecurity are categorized by: a) elimination or substitution; b) engineering controls; c) administrative controls: d) operational controls; e) and personal protective equipment [14].

Elimination or Substitution

Mitigation of both laboratory biosafety and biosecurity risks can be done by eliminating the biological agent or toxin altogether, or substituting it with a less hazardous pathogen. Elimination removes all risk of accidental exposure and theft and provides the highest degree of risk reduction. Substitution of an agent with a less virulent pathogen with similar biological characteristics allows the researcher to carry out the necessary research at an inherently lower risk of safety and security concerns. Both of these approaches are favored control strategies to reduce risk, and they also are likely to be less expensive and require less maintenance [15]

If elimination or substitution of the risk is not possible, additional control strategies such administrative, operational, engineering, and personal protective equipment (PPE) controls (described below) are used to minimize safety concerns associated with accidental release and security concerns associated with intentional release.

Engineering Controls

Engineering controls are physical changes to work stations; use of specialized equipment, materials, or production facilities; or any other relevant aspect of the work environment that reduces the risk of accidental or intentional release. Primary containment refers to engineering controls to increase safety of the research personnel and reduce the risks of intentional removal of biological material from the laboratory; secondary containment refers to engineering controls that reduces the risk of release to the environment or surrounding community outside of the facility.

Engineering controls are an effective, yet often misused, strategy to reduce biorisks. Laboratories are often designed around engineering controls, which can provide a false sense of safety and security. Cost, available resources, existing infrastructure, and availability of trained personnel must be considered when choosing these controls.

Engineering controls alone are not sufficient to ensure safety and security in a laboratory; they are only one component of a comprehensive biorisk management program, and should be selected in coordination with other desired controls. Engineering controls generally protect staff as well as the environment and community, but require resources, applicability, and maintenance to effectively reduce risks.

Examples of engineered biosafety controls include biosafety cabinets, chemical fume hoods, changes to the physical features of the facility that allow for better ventilation and air-flow, barrier walls and shields, and separation of incompatible activities; equipment and equipment maintenance, calibration and certification. Likewise, engineered biosecurity controls to reduce the risks of theft or access to biological material or other assets, include access controls (e.g. access restrictions such as keys, locks, badge readers, PIN readers), alarms and/or other detectors, and perimeter fences and gates.

Administrative Controls

Administrative controls are policies, procedures, standards, and guidelines used to control biorisks. This may include health monitoring programs, inventory systems, and training programs.

Worker health programs can support biosafety by protecting workers through prophylactic vaccinations and/or health care monitoring to rapidly identify personnel that may be infected, ill, or susceptible to future infections. Hiring qualified staff, implementing emergency response and contingency plans, posting signage, and documentation in the form of biosafety plans or manuals, and standard operating procedures (SOPs) are other forms of biosafety administrative controls.

Biological sample inventory and life cycle management are vital components of administrative mitigation controls which benefit both biosafety and biosecurity. Other examples include the development and maintenance of current biological agents and toxin inventory and inventory management requirements including access, storage, transfer (shipping , receiving, and sample transport), destruction, and audit (also referred to as material control and accountability); waste management policies; and documentation regarding security policies including facility security, visitor access, personnel management, access to biological agents and toxins (also referred to as personnel security); and information security.

Training is another type of administrative control that is important for mitigating safety and security risks. A biorisk management training program is only effective at reducing risk when a training needs assessment is conducted and a training program is executed based on well-established training models, such as the ADDIE model (Analysis, Design, Development, Implementation, Evaluation) [16]. The entire workforce, including management, laboratorians, custodial staff, maintenance personnel, and security forces, must be included in the training program to ensure all employees are cognizant of the laboratory's policies and the biorisk management system, commensurate with their individual roles and responsibilities.

Operational Controls

Operational controls are mitigation controls that employ standard operating procedures (SOPs) and internationally accepted practices to improve biorisk management. They are designed to guide personnel with precise instructions to carry out tasks consistently and efficiently, and should be routinely observed, evaluated, and validated with staff to maximize comprehension. The written documentation is an administrative control, but the process of performing procedures as specified must be continuously evaluated. The procedure requires evaluation for document relevance, necessary training, and effectiveness of safety and security measures.

SOPs can be developed for a variety of practices and procedures for both laboratory biosafety and biosecurity. Depending on the work performed in a given laboratory, biosafety SOPs may target pathogen handling, sample analysis, waste disinfection and decontamination, and safety emergency incident response events, among others. Examples of biosecurity SOP objectives may include, sample transport, pathogen storage, operation of physical security systems, emergency incident response events, identification badge usage, visitor control, personnel management procedures, security force procedures, and security incident response plans.

Personal Protective Equipment

When used correctly, PPE is a biosafety mitigation control that provides protection to individual workers from the most hazardous pathogens and chemicals. PPE selection is based on the work conducted and the pathogens handled, thus, it is dependent upon the risk assessment. A variety of PPE is commercially available to prevent serious safety injuries including, laboratory coats, safety glasses, face shields, N95 and N100 respirators, and gloves.

These are devices worn by workers to protect them against chemicals, toxins, and pathogenic hazards in the laboratory. PPE is considered the least effective control strategy, as it protects only the person wearing it.

The effectiveness of PPE to reduce risk also relies on administrative and operational controls regarding the purchase, storage, use, donning and doffing, and waste disposal procedures. The performance of PPE use and appropriate procedures must also be monitored to ensure effective risk management.

Risk Communication

Biorisk communication is the interactive transmission and exchange of information and opinions throughout the risk analysis process about risk, risk related factors, and risk perceptions among risk managers, risk communicators, the general public, and other impacted parties [2]. Because laboratories handling animal and zoonotic pathogens are an essential piece of a country's veterinary infrastructure, it is important that the laboratory's benefits, risks, and biological risk mitigation plans are transparent and clearly communicated to all relevant stakeholders [17]. Laboratory staff, the surrounding community, livestock owners, policy makers, and government authorities are all pertinent stakeholders, and the information shared with each should be tailored to the specific audience to address their individual concerns and level of technical need-to-know. This will help prevent misinterpretations and miscommunications.

Effective biorisk communication ensures transparency to minimize fear and apprehension that might be expressed over possible exposures, and conveys laboratory risks. Messages, language, and literature should be tailored to provide clear and understandable information concerning the work being conducted.

Verification with Continual Improvement

Biological risks in the laboratory are dependent on the work performed, and must therefore be reassessed each time a practice or procedure changes or is implemented. The laboratory facility, management practices, and procedures should also be regularly evaluated to ensure that changes have not altered previously established risks. Effective performance measurements can call attention to practices that are no longer adequate or that are failing over time.

Burnett and Olinger in *Laboratory Biorisk Management*, propose a more thorough measure of performance to replace conventional audits and surveys that establishes performance indicators during system development and includes: 1) establishing priorities where risk is greatest; 2) defining the indicators and metrics of success for a given outcome; 3) defining the indicators and metrics of success for a given activity; 4) collecting data and report results; 5) responding to findings, and; 6) improving performance indicators [18]. This system provides the end-user with a more standardized method of evaluation that incorporates laboratory staff into the evaluation process. Continuous performance evaluation provides the staff and stakeholders with confidence in the system, and also helps lend sustainability to the practices and procedures [2].

Responsible Capacity Building

Strengthening capacity in a laboratory is essential to successfully detect, assess, respond, and monitor disease events within a country. Developing such capacity requires both commitment and resources within a laboratory network. Generally speaking, laboratory capacity is well developed in industrialized countries and weak in most low and limited-resource countries, many of which are home to dangerous endemic human and animal pathogens, devastating infectious disease outbreaks, and adversarial threats [19]. Consequently, various international, governmental and non-governmental organizations attempt to boost laboratory capacity in many of these countries through the purchase of laboratory equipment and/or technical training of laboratory personnel in hopes of improving national biosurveillance and reducing the threat of biological acquisition.

Yet *responsible* and *sustainable* laboratory capacity building requires more than supplying a laboratory with sophisticated equipment and advanced personnel training. Any laboratory capacity building efforts with the aim of reducing the spread of infectious diseases is obligated to include an awareness of, and require a long-term commitment to, recognizing and mitigating a laboratory's biosafety and biosecurity risks.

It is imperative that efforts to improve laboratory capacity do not inadvertently or unnecessarily increase the risk of biological acquisition and/or the risk of accidental exposure. These risks are inherently present when obtaining, isolating, manipulating, and storing dangerous, and most importantly, unnecessary, animal or zoonotic material at a laboratory. Capacities that affect both biosafety and biosecurity would include the acquisition of laboratory equipment and/or reagents that enhance the capacity to culture, propagate, and/or store dangerous pathogens. Specific biosecurity risks may include equipment that could be considered dual-use including biosafety cabinets and personal protective equipment. Once acquired by nefarious individuals, some laboratory equipment and personal protective equipment may allow for proliferation practices that were once previously too dangerous to practice. It is also important to be aware that even personnel educational training that increases a laboratory's technical capacity could be misused to proliferate and disseminate dangerous biological pathogens. Specific capacities that affect biosafety would include the acquisition of any piece of equipment or the application of any procedure that may actually increase the potential for release, exposure, and infection. This would include, for example, research procedures that involve increased handling of dangerous animal and zoonotic agents and/or equipment that creates aerosols or the potential for spilling.

Rather, efforts should focus on implementing responsible laboratory capacity that improves a laboratory's ability to detect disease, but at the same time complements laboratory's biosafety and biosecurity profile. This can be accomplished by reducing the amount of unnecessary biological material and dual-use equipment stored and handled at the facility, as well as implementing protocols and procedures that would reduce the reliance on equipment or material. For any essential biological material or equipment that must be retained for mission critical laboratory purposes, a complete and robust biosafety and biosecurity risk assessment should be executed and any identified risks mitigated appropriately. Any personnel training that divulge technical capabilities that may pose a proliferation risk should be evaluated critically for absolute necessity, and all technical training should include an awareness of dual-use issues associated with biological work. Lastly, capacities should also contribute to providing additional risk mitigation by provisions for personal protective equipment against exposure and infection for the laboratory staff during routine research.

Challenges and Sustainability

The design and implementation of a large-scale biorisk management system may be overwhelming unless a standardized risk-based approach is used. Identifying and assessing hazards helps laboratory managers prioritize resources to mitigate the greatest risks. In most cases, risks can be controlled using elimination and substitution, targeted engineering controls, administrative controls, operational controls, and PPE. Using a standard approach to biorisk management, that includes the laboratory staff, and measures laboratory performance, helps to build a sustainable and effective system. Moreover, it creates a culture of biorisk management in the laboratory.

Little published data is available on the sustainability or effectiveness of laboratory biosafety and biosecurity systems globally. However, sustaining biorisk management systems is complex and dependent on a mixture of factors including; inherent risks, available resources, regulatory requirements, effective laboratory policies, management commitment and determination, and the laboratory culture [20]. In most laboratories, laboratory biosafety is fundamentally appreciated and practiced. Most laboratory personnel and researchers intrinsically appreciate the need to protect themselves and their communities from accidental exposures. However, the concept of laboratory biosecurity is newer, and consequently, the value of such programs may be overlooked.

Thus it is essential to cultivate a culture biorisk management that encompasses both safety and security into a laboratory's daily routine. The collection, transport, isolation, and storage of such agents pose inherent risks that must be managed to support the efficient and timely control of dangerous outbreak of infectious diseases and well as improve the quality of work done in the laboratory. The recent outbreaks of dangerous human and animal outbreaks and lessons learned from these outbreaks, underscores the importance of robust biorisk management systems and their sustainability.

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