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Editorial

Special Issue: Infectious Disease Research: Animal Models and Risk Management

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The success of an animal care and use program depends on various factors, including a work environment in which laboratory animal care and research personnel can perform their work without risking their health and safety. Personnel are exposed to various hazards in performing veterinary care, husbandry care, and research experiments. Therefore, it is imperative that institutions maintain a robust and comprehensive occupational health and safety program (OHSP) that can effectively assess and mitigate risks and address exposures. Examples of hazards include chemicals used for sanitation (for example, disinfectants and descaling acids), inhalant anesthetics, compounds or toxins used to create animal models, some therapeutic or experimental drugs and interventions (for example, carcinogenic or chemotherapeutic agents), infectious organisms and potentially infected materials, radiation, ergonomic hazards, noise, and allergens.

According to the *Guide for the Care and Use of Animals*, the OHSP must be consistent with federal, state, and local regulations.[9] The federal law *Occupational Safety and Health (OSH) Act (29 CFR 15) applies to* most private sector employers and their workers and some public sector employers and their workers in the U.S. Compliance with regulations and standards under this law can be enforced either directly through the OSH Administration (OSHA) or through an OSHA-approved state plan.[13] Other documents also contribute to the OHSP regulatory framework of an animal care and use program. Foremost of these is the *Occupational Health and Safety in the Care and Use of Research Animals*, created by the Committee on Occupational Safety and Health in Research Animal Facilities, Institute of Laboratory Animal Resources.[11] Published in 1997, this remains to be the authoritative guidance on the occupational health and safety of personnel in the animal care and use program. Other pertinent regulatory documents are the *Biosafety in Microbiological and Biomedical Laboratories* and *NIH Guidelines for Research involving Recombinant or Synthetic Nucleic Acid Molecules*. An effective OHSP generally requires the combined responsibility and cooperative interactions of several groups within an institution (Figure 1).[9] A systematic and recurring review of the OHSP is essential to assessing its effectiveness and formulating action plans to correct shortcomings. OHSP evaluations by external experts (for example, those performed by AAALAC International during accreditation site visits) can also provide an institution with valuable feedback on whether its program meets or exceeds applicable standards. In fact, OHSP deficiencies have consistently ranked in the top 3 AAALAC mandatory findings for correction.[12]

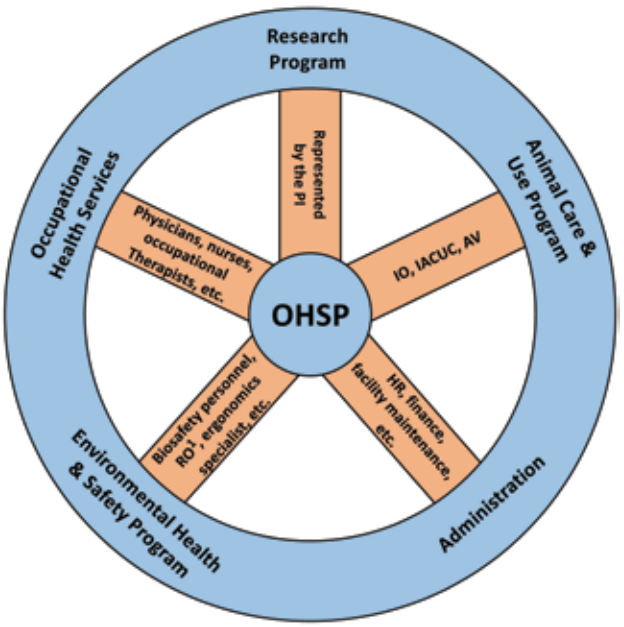

Figure 1. According to the *Guide for the Care and Use of Animals*,[9] coordination among the 5 groups in the institution is needed for an effective OHSP.1RO = Responsible Official. This is the individual at the entity who is accountable for entity compliance with the Select Agent Regulations.[8]

The past few decades have seen tremendous advances in how animals are used in research. But despite this progress there remains to be the people who feed the animals, clean their dirty cages and provide them clean ones, ensure their health and treat them if necessary, and use them for training and education, or experiments. In association with an institution's responsibility for the well being of its animal subjects, an institution is also responsible for the well being of the people who work with these animals. In addition to recognizing the importance of compliance with regulatory requirements, the institution must view ensuring personnel health and safety as one of its ethical obligations.

Use of laboratory animals runs the gamut from simple classroom instructional courses to the use of sophisticated methods of creating and studying an animal model. As such, a comprehensive OHSP is expected to cover anyone who has indirect or direct exposure to animals and their byproducts. A robust OHSP

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Figure 2. World map showing vector-borne and zoonotic diseases. Adopted with permission from One Health Initiative.[14]

is particularly crucial when infectious agents or potentially infected materials are used. Such experimentation has the potential to compromise not only the health and safety of the individual worker but also that of the general public.

Communicable diseases have recently sparked renewed interest from both the research community and the general public. Factors leading to this interest include identification of outbreaks of emerging and reemerging diseases (Figure 2), increased surveillance, technological advances that facilitate news reporting and sharing, and globalization. A case demonstrating the interplay of these factors is the 2013–2016 Ebola virus outbreak in West Africa.[7] The majority of cases in this outbreak were localized to 3 countries with intense transmission (Sierra Leone, Liberia, and Guinea) while 7 other countries including the United States had minor outbreaks with a nonsustained transmission or isolated cases, all with origins attributable to West Africa.[7]

Other diseases such as H5N1 influenza infection and severe acute respiratory syndrome (SARS) have highlighted the importance of a "one-health" approach to disease detection and prevention.[4] This concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals, and the environment.10 This initiative is especially important because 6 out of every 10 infectious diseases in humans are spread from animals.[4] Certainly, the economic impact of infectious diseases is significant. A survey referenced recently by the CDC revealed that during 2013 in the United States alone 19.3 million physician visits were due to infectious and parasitic diseases.3 Research using animal models continues to advance both the prevention of known infectious diseases and the recognition and control of rare and emerging infectious threats.

This issue of *Comparative Medicine* addresses the basic tenets and principles of an OHSP, with a strong focus on the use of biohazards and infectious disease research. The issue begins with a review article by Melissa Dyson[8] and colleagues on the institutional oversight for occupational health and safety for use of biohazards. This article provides an overview of the regulatory framework that forms the backbone of responsible use of biohazards in research.[8] Programmatic components like exposure control, disaster plans, health surveillance, training and education, and information management are discussed.8 The article concludes by summarizing key items in fulfilling the ethical and regulatory responsibilities of an effective OHSP. One aspect of an OHSP is the provision of personal protective equipment (PPE), which is the subject of the second article written by Jason Villano, yours truly, in collaboration with colleagues. The article aims to give readers a knowledge base for evaluating the adequacy and effectiveness of institutional PPE requirements by providing a comprehensive review of risk assessment, common PPE used in laboratory animal research, and PPE standards and regulations.[17]

Dalis Collins and colleagues wrote the third article, which focuses on viral vector biosafety. The use of viral vectors has become an increasingly popular methodology in laboratory animal research by facilitating targeted approaches to disease treatment and animal model development. The article focuses on literature review and industry practices, including animal containment housing, to mitigate risks associated with viral vector use. Subsections of the article describe the 4 most commonly used viral vector systems (adenoviruses, adeno-associated viruses, herpsevirsues, and lentiviruses), and findings and recommendations for their use.[6]

The next 2 articles are overviews of 2 general topics on the use of animals in infectious disease research. The first, written by Lesly Colby, Lauriane Quenee, and Lois Zitzow, presents general considerations on the use of animals in research. It begins by addressing 1 of the 3 guiding principles of animal research: replacement (as part of the 3Rs). Once an animal model is deemed appropriate, the experimental design considerations should be evaluated. The authors categorized these into 3: 1) scientific, including intrinsic animal characteristics like animal size and anatomical limitations; 2) welfare, including medical management and humane endpoints; and 3) regulatory.5 The article emphasizes that infectious disease studies using animal models are best done as a collaborative effort. The other article, authored by Erin Reynolds and colleagues, reviews animal models of arthropod-borne viral (arboviruses) infections, with the discussion on those vectored by mosquitoes, ticks, and midges, and for which vaccines and therapeutics are not readily available. Examples include dengue, Chikungunya, Zika, flaviviruses, African swine fever, and bluetongue. The authors underscore the value of such animal models, indicating that there is no substitute for using them if we are to understand in detail the interactions between the virus, vector, and host, or the interactions between the host cells and tissues involved in the response to an arbovirus.[15]

Finally, animal models of 2 emerging diseases are discussed in separate articles. These 2 were primarily chosen out of the many communicable diseases because of their involvement in the most recent disease outbreaks that shook the world. These outbreaks tested science and medicine and global preparedness for a possible pandemic. They highlighted, among other things, the fact that their threats were real because man's knowledge and understanding of these rare and highly dangerous diseases are lacking and that globalization poses a confounding factor in outbreak management plans. Authored by Marisa St. Claire and colleagues, the first article details various animal models of Ebola virus infection. The discussion compares rodent models to nonhuman primate models, concluding that macaques serve as the model of choice.[16] The other article discusses animal models of Zika virus infection and was written by Michael Bradley and Claude Nagamine. Simi-

larly, this article is divided into small and large animal models used to uncover the pathogenesis of this emerging disease and to develop a vaccine and therapeutic strategies.[1]The authors also indicate considerations in animal model development.

This special topic issue was made possible by the tremendous contributions of the authors who willingly took on the task of writing and showed tenacity in doing so; the colleague-reviewers whose great feedback strengthened the scientific merit of the articles; and the Comparative Medicine editorial and production staff, whose guidance helped steer this forward. We hope that this issue shows that the OHSP is integral to the overall animal care and use program and that infectious disease and biohazard research using animal models constitute a fundamental approach in understanding the disease and developing prevention strategies and treatment regimens.

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