Chapter 16

VETERINARY BIOMEDICAL SCIENCE

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INTRODUCTION

The US Army Medical Department (AMEDD) workforce is composed of medical and support professionals from several different employment categories to include civilian, contractors, and uniformed military. The AMEDD officers have been organized into six corps: (1) Dental Corps, (2) Medical Corps, (3) Medical Service Corps, (4) Medical Specialist Corps, (5) Nurse Corps, and (6) Veterinary Corps. The AMEDD further divides these corps into subspecialties called areas of concentration (AOC), which correspond with divergent medical missions, all supporting the US Army. Three AOCs within the Veterinary Officer Corps produce the majority of the corps' medical research: (1) veterinary laboratory animal medicine (64C), (2) veterinary pathology (64D), and (3) veterinary biomedical science (64E). This chapter describes the unique roles the veterinary biomedical scientist (VBS) plays in the Department of Defense (DoD). The 64E is both an experienced doctor of veterinary medicine (DVM) and doctor of philosophy (PhD) in a medical research discipline. The VBSs work to solve some of the most challenging scientific and medical problems threatening the nation's security. (See also Chapter 14, Laboratory Animal Medicine, and Chapter 15, Veterinary Pathology, for more information about the other two prominent medical research AOCs within the Veterinary Corps and about the various DoD research facilities where military medical studies are conducted.)

VETERINARY BIOMEDICAL SCIENTISTS: AN OVERVIEW

Unique Skill Set

As veterinarians, VBS officers are educated in the fundamental disciplines of biology, chemistry, pathology, pharmacology, physiology, and toxicology. They possess practical problem-solving skills gained through clinical experience. This educational and practical background, combined with a firm knowledge of research methodology, makes VBSs well prepared to conduct DoD research. In particular, their comprehensive knowledge of the diverse set of animal pathogens as well as the means to prevent and treat them are the key skills that enhance the VBSs' capabilities for conducting research on DoD's challenging medical threats.

Of the 40 pathogens listed in the Federal Select Agents that pose a severe threat to humans, 12 are animal pathogens or animals are a reservoir, and 11 are animal pathogens that pose a severe threat to animals.[1] Zoonotic pathogens with a primary animal host constitute the major offensive bioweapons for two likely reasons. First, modern animal pathogens' interactions with the environment and potential human hosts are dynamic. Over time, as humans moved to cities, contact with animals decreased, leading to humans gradually being exposed to fewer and fewer animal pathogens, thus increasing the susceptibility of humans to those same pathogens. The complexity of these interactions have also increased because of advances in travel, increased urbanization, and encroachment into wildlife areas.[2,3] Bioterrorists and other bad actors can take advantage of an immunologically naïve target population to enhance the effectiveness of a bioweapon.

Second, animal pathogens that can be processed for purposeful, malicious intentions with relatively unsophisticated means are readily available globally and relatively easy to store. Sometimes, a reservoir of agents and their processing facilities are cloaked under the guise of agricultural production or other dual-use technology. VBSs' expertise in veterinary and zoonotic pathogens enables them to effectively conduct, manage, and lead research for bioweapons medical countermeasures.

VBSs are also uniquely qualified to support DoD chemical weapons defense missions. Veterinarians routinely educate clients on ways to prevent exposure to agricultural and household chemicals because—whether in agricultural or companion animal settings—humans unintentionally expose animals to chemicals that have similar properties to those used in warfare. Clinically managing an inadvertent intoxication is similar to treating exposure to a chemical threat agent of a similar class.

In clinical poisonings, veterinarians first recognize symptoms to identify the class of poison. Next, they deduce the likely causative agent. They then select the proper treatment or antidote, titrating that regimen to effect. Although not all poisons have an antidote, most chemicals have some regimen that can ameliorate the adverse effects or be supportive to the animal. Proper case management and preventive measures result from a thorough understanding of the exposure route, the mechanism of toxicity, and the pharmacodynamics of the therapy regimen. This knowledge and experience base prepares VBSs extremely well to conduct and support chemical weapons medical countermeasures research.

In addition to utilizing unique veterinary skills, as PhD graduates, VBS officers provide in-depth, specialized input based on their individual career paths that support DoD's research needs. Traditionally,

the VBS officers' PhD studies focused on the shared fundamentals between animal and human medicine (quite often, the process and conditions of a specific disease behave similarly in several species). The study of these similarities and differences among and between species using basic and clinical sciences is commonly known as "comparative veterinary medicine." In keeping with the prevailing designation, the US Army Medical Command (USAMEDCOM) originally titled the 64E AOC "veterinary comparative medicine officer." However, by 2011, the specialty had evolved to include more sophisticated means to study many disease processes. These *in vitro* systems look at effects at the molecular, cellular, and tissue levels, devoid of animal models and less comparative in nature. USAMEDCOM then retitled the 64E AOC "veterinary biomedical scientist."[4]

The AMEDD builds the VBS AOC in one of two ways: (1) a civilian veterinarian with a PhD in a medical discipline of interest to the DoD enters directly into military service as a VBS or (2) a relatively seasoned Veterinary Corps Officer (VCO) competes for the opportunity to obtain a PhD in a basic scientific discipline through Long-Term Health and Education Training and subsequently attends a medical, veterinary, or university graduate school PhD program. These routes bring diversely experienced individuals to meet DoD's challenging medical threats. The scope of duties and assignments for these officers is also diverse.

Scope of Duties

The 64Es execute an array of duties at a number of positions across the DoD. Although most work in the US Army Medical Research and Materiel Command (USAMRMC) laboratories within the USAMEDCOM conducting research, some operate at other USAMEDCOM subordinate commands such as the Regional Health Commands (Provisional) and the Office of The Surgeon General, US Army. Key VBS billets also exist at US Navy laboratories within the Naval Medical Research Center (NMRC). Other DoD agencies and activities have billets for more senior VBSs such as the Uniformed Services University of Health Sciences (USUHS), the Defense Threat Reduction Agency (DTRA), and Health Affairs.

Those VBSs holding research and development positions throughout the DoD search for new products to battle numerous health threats to service members. A number of the adverse health effects studied by the DoD come from infectious disease; threat agents of chemical, biological, radiological, or nuclear (CBRN) origin; injurious environmental hazards; or toxic chemicals.

In addition to discovery research, VBSs also manage the development of research products starting from initial requirements generation and product inception. During early development, Army VBSs team with other professionals to determine a product's proof of concept or proof of principle. The VBS role continues through advanced development, carrying the product through the regulatory process towards the final stage, US Food and Drug Administration (FDA) approval. The DoD and its partners fully evaluate candidate products; only those medical products approved by the FDA will be used by the DoD. Since these products fill unique needs in the DoD pharmacological armamentarium, policies must be in place prior to their clinical use. The VBSs and others promulgate these DoD policies at senior levels.

Mission Process

The 64E's main mission is conducting scholarly research towards the development of medical defense products that have clinical and practical application to protect DoD personnel (and potentially others) from health threats, particularly those threats that are specific to the DoD. As noted in the previous section, this mission is guided by a process that starts with requirements, leads to discovery research and then development processes, and ends with deployment of the knowledge gained or a medical product. Gaining FDA approval, securing funding, and developing product policy are integral parts of this deployment. VBSs are among the few AOCs with the requisite skill sets to work the full spectrum of product development from product inception to developing policy on drugs, biologicals, and devices, because, as PhD researchers, they engage at the early stages of discovery and proof of concept studies. Nearly a quarter of the 64E population work products through the developmental stages. with the most senior VBSs managing product policy. Both roles take advantage of their DVM clinical skills (Colonel [Retired] James Boles, chapter author and The Army Surgeon General's 64E consultant 2011–2015, personal knowledge).

As with all DoD research, requirements drive the medical research the VBSs conduct. The requirements strategy starts with an assessment of doctrine, organization, training, materiel, leadership and education, personnel, or facilities (DOTML-PF) identified through the Joint Capabilities Integration Development System (JCIDS). If the process determines that a material solution fills the gap, subject matter experts review preexisting materials for appropriateness. If no product exists, which is usually the case for military unique requirements, discovering and then developing a new

product is often the means of closing the gap. Medical products designed to mitigate the adverse effects of CBRN agents and foreign infectious diseases often fall into the military unique category.

The medical materiel solutions approach employed by the DoD in the requirements stage always involves closing the capability gap to address threats that are military relevant. Military relevant drugs, biologicals, and devices, collectively known as medical countermeasures (MCMs), play a huge role in the prevention and treatment of disease and comprise a large segment of the 64E's mission.

VBSs and others design, develop, and test proposed medical solutions. Unfortunately, the discovery of an MCM does not always proceed as desired. The DoD expects VBSs' ideas and inquiries to evolve into experimentation and, eventually, a discovery or device to prevent or treat medical threats. However, in reality, VBSs' experimental findings may only inform future studies, with the hope that further experimentation will finally lead to material solutions or changes in the way DoD operates to avoid the hazard. In other words, knowledge gained through 64E experimentation may alter the way the DoD uses existing personal or collective protective, detection, or diagnostic devices; tactics, techniques, and procedures; or even medical interventions. Other times, the experimentation has to cease and restart in another direction using the knowledge gained to define identified problems (eg, implementation) to determine the limits of a potential investigational drug or biologic.

As with discovery, development of MCMs is not necessarily step-by-step or linear either. Modern drug and biologic development is a complex process for several reasons, including the relatively high failure rate of new drugs and biologics. This forces developers to analyze cost-benefits in second generation or new prototype MCMs and plan accordingly to gain FDA approval. VBSs not only play a key role in product development, but also in gaining FDA approval, advancing only those products with the greatest chance for approval. An additional regulatory challenge stems from the ethical restriction of developing MCMs for threats that cannot be tested directly in humans. The "Animal Rule"[5] was established by the FDA to specifically address this dilemma, but it has been challenging to meet the human safety considerations with adequate pivotal animal study data. The specialized skills that enable VBSs to compare animal and human responses with study criteria are critical to the success of DoD MCM development.

In addition to navigating FDA approval, when possible, 64Es collaborate with industry to share costs and risks or gain a capability. For example, when working to find medical materiel solutions to military relevant threats that have broader societal implications, VBSs often partner with non-DoD commercial enterprises to help offset the additional costs in time and dollars required for broadening the labeling. As the end user for private companies is not limited to the typical DoD end user (ie, a healthy, 20- to 40-year-old service member), extra research must be conducted to ensure the materiel solution benefits the larger target group. By sharing the cost of expanding the label with non-DoD companies, the US government's cost to develop the new solution may be less than if developed solely for service members.

In contrast, the limited ability to partner with others in the development of MCM for military unique threats may create funding challenges. For example, prior to the 2001 anthrax letter mailings, there was little interest in public or private investments in anthrax vaccine or antibiotics to thwart anthrax because the deliberate use of anthrax as a weapon was largely perceived as a military unique threat. However, after the general public learned about the tainted letters sent to civilian recipients, vaccine and antibiotic development against anthrax was energized (Colonel [Retired] James Boles, chapter author, personal knowledge).

Medical materiel solutions also may act as a deterrent to CBRN threats. If adversaries believe that US forces are well prepared to meet CBRN challenges, these enemies may be less willing to deploy CBRN agents. This deterrence is a multiplier when used in combination with the other elements of DOTML-PF geared toward avoiding or mitigating CBRN threats. Together, nonmedical DOTML-PF and medical materiel solutions make US warfighters a more difficult target for adversaries. This concept was made clear in the 2011 Deputy Surgeon Generals' briefing on the small pox vaccine when two deputy surgeon generals commented that a vaccinated force is a positive medical readiness issue and a perceived deterrent (Colonel [Retired] James Boles, chapter author and The Army Surgeon General's 64E consultant 2011–2015, personal knowledge). Thus, 64Es contribute to the complete development life cycle (from requirements through implementation policy) of DoD's medical threats countermeasures.

One of the last tasks VBSs complete in the continuum of MCM product development is promulgating policy for warfighter use of developed products. In helping to develop preventive or therapeutic solutions and applicable use policies, 64Es support the AMEDD's motto of "To Conserve Fighting Strength."[6] These solutions should provide DoD service members not only the confidence that they can survive, but also that they can continue conducting the mission in environmentally hostile settings.

Although the concepts of conserving the fighting strength and deterrence each play a role in DoD policy decisions about the use of MCM, FDA labeling guides broader medical usage policy. FDA labeling includes specific information about a drug or biological such as its medical use, intent, and limitation information (the extent of its safe use in populations as a whole). DoD policies are linked to the broader FDA guidance and mandate MCM use on certain populations based on their risk of exposure to infectious or CBRN agents. For example, a number of DoD policies dictate mandatory use of antimalarials or vaccines and prophylactic drugs against CBRN agents (ie, antimalarials are required during operations within malaria-prevalent areas, while anthrax and small pox vaccines must be administered to personnel in high-threat areas). VBSs help create these policies to protect service members from harm in unique operational settings. No matter the population or operational setting, VBSs promulgate DoD policies according to FDA label instructions while addressing any special needs to better safeguard individuals at risk and the population as a whole.

Role in Program and Product Management

Program and product management is a required skill for all VBS officers. VBSs manage well-funded, large basic research programs in infectious disease, combat casualty care, military operational medicine, and congressional special interests. However, the ultimate goal of product and program management is to turn the research products of knowledge and materials into clinical drugs, biologics, devices, and diagnostics that protect service members against CBRN and other medical threats.

All VBS research programs depend on reliable funding, and the development of MCMs against the medical effects of weapons of mass destruction is no exception. The USAMRMC CBRN Defense Coordinating Office helps align MRMC CBRN-related research. This office, headed by a VBS, facilitates communications and interactions between the medical research community and the major funding agency, the Joint Science and Technology Office at DTRA. VBSs also provide crucial input on building the Program Objective Memorandum, which presents the planned allocation of available resources toward needed medical research over a 5-year period.[7]

Role in Department of Defense Policy

Currently, senior VBSs are positioned within the Office of the Assistant Secretary of Defense for Health Affairs and DTRA, where their experience in the community is leveraged to socialize and promulgate policy that can affect the DoD and interagency communities. VBSs are responsible for assisting a staff of physicians, nurses, scientists, and administrators and must understand MCM medical implications, the science behind their action, and potential adverse events. VBSs lead reviews on available FDA-approved products, those in early phases of study and those in advanced development. The VBS and staff are also responsible for promulgating policy regarding the use of MCMs in operational settings. Oftentimes, these policies direct select populations to follow product label instructions that are augmented with special instructions according to operational situations, including geographical settings or subpopulations at great risk.

VBSs serve a unique role in the development of CBRN MCMs and the science and technology (S&T) mission of DTRA. VBSs' contributions include project management for a portfolio of chemical biological research studies; advising Regional Contingency Teams on medical issues such as recent Ebola outbreaks; strategic input to CBDP issues such as infrastructure support for the DoD laboratories that conduct chemical biological research; program-wide engagement seeking MCM development of cost and schedule improvement; representing the CBDP medical S&T in DoD medical research forums; and liaison with all the DoD laboratories partnered with the Joint S&T Office.

Special Missions

The 64Es also have opportunities to apply their unique skill sets during specific special missions. For example, in recent historical events such as the collapse of the former Soviet Union, VBSs utilized their specialized research skills and knowledge to strengthen vulnerabilities found in the scientific infrastructure security of biological agents. During the dissolution process, VBSs provided vital expertise and consultation to program leaders regarding the potential for collaborative efforts between the United States and former Soviet states for nonmilitary purposes (Colonel [Retired] James Boles, chapter author, personal knowledge).

During the Persian Gulf postwar period, several VBSs provided boots-on-the-ground expertise to United Nations Special Commission missions to Iraq and gave advice on potential biological threats. VBSs also were essential team members when making critical distinctions between the peaceful, and potentially nefarious, uses of scientific apparatus. Similarly, VBSs offered crucial skills and expertise during the 2001 anthrax letter mailings, supporting MRMC and MEDCOM missions via Operation Noble Eagle. Most recently, VBSs provided insight on the appropriate use of radiobiological MCM

Figure 16-1. Veterinary Bioscience Officer Deborah Whitmer, chapter author, served as a theater veterinarian and assisted an Agriculture Development Team's veterinary capacity-building mission in Nangarhar Province, Afghanistan, during Operation Enduring Freedom. Whitmer, a lieutenant colonel during this mission, instructed fifth-year Afghan veterinary students on physical examination, necropsy, and pathology specimen collection methods.
Photograph courtesy of Colonel Deborah Whitmer.

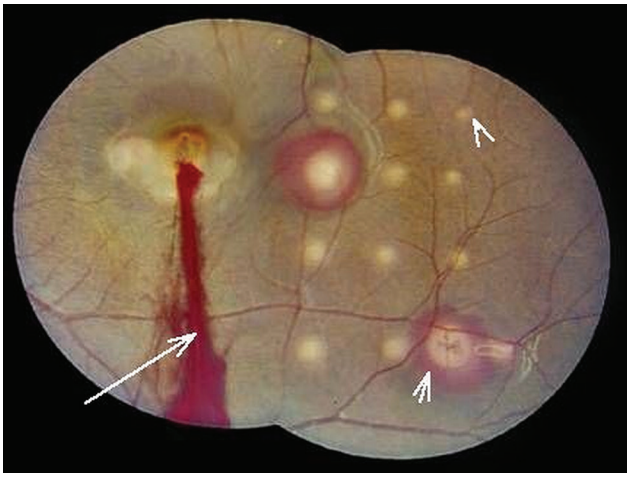


Figure 16-2. Fundus photograph of multiple experimentally induced laser retinal lesions demonstrating variable visible injury. Left to right: Significant foveal lesion with overt hemorrhage into the vitreous; middle lesion with red rim and white center is indicative of retinal hemorrhage; upper right circular white lesion indicative of a minimal visible lesion. Injury variability is a function of the exposure dose and its location on retina, as well as the variables of the laser, including wavelength, pulse duration, retinal irradiance diameter, and pulse repetition frequency.
Reproduced from Whitmer DL, Stuck BE. Directed energy (laser) induced retinal injury: current status of safety, triage, and treatment research. *US Army Medical Department Journal*. January–March 2009:52.

(ie, potassium iodide) during the 2011 tsunami and subsequent release of radiation from the Fukushima nuclear reactor (Colonel [Retired] James Boles, chapter author and The Army Surgeon General's 64E consultant 2011–2015, personal knowledge).

VBSs can also deploy to assignments outside of their primary AOC. Assignment opportunities such as theater veterinarian provide myriad experiences, some that directly support operations and others that utilize the diversity of the 64E's education and skills. For example, during deployments, VBSs have assisted host nations build veterinary capacity and capabilities and have facilitated training, including disease and injury prevention guidance (Figure 16-1 and Figure 16-2). Many times, the human and veterinary healthcare and issues encountered during deployments are closely related because the locations troops are sent to are often agrarian-based communities (Colonel Deborah Whitmer, chapter author, unpublished briefings on veterinary health sector development at International Security Assistance Force Health Sector Development Conference with Government of Afghanistan Ministry of Agriculture, 2010).

VETERINARY BIOMEDICAL SCIENTISTS: ANIMAL MODELERS

As noted earlier in this chapter, the VBS's knowledge of interspecies differences facilitates a deeper understanding of unique host responses and disease processes. Scientists such as immunologists, physiologists, and microbiologists correlate endpoints or markers of protection in animals with those thought to be protective in humans. Protective drug studies also usually involve pharmacologists and toxicologists and, quite often, VBSs. Many times, the VBS handles the overall study design and is the subject matter expert for some aspect of the challenge agent, vaccine, or drug being tested.

As noted earlier in this chapter, VBSs often use a comparative medicine approach to extrapolate known and experimental findings in one species and apply them to another species of interest for the purposes of discovery. Using the comparative medicine approach to bridge the similarities and differences between species has dominated the VBS profession for years, especially when conducting efficacy testing of biologics and drugs. The observed differences sometimes lead VBSs to new hypotheses as to why the species behaved differently. Often, the differences have manifested as

varying sensitivities to specific disease-causing agents, which leads to the discovery of new ways to disrupt a disease agent's deleterious effects (eg, clinical signs and symptoms). In other instances, analysis of the observed differences resulted in a better understanding of an agent's mechanisms of entry and action. The 64E's analysis of the comparative host species' defense mechanisms is instrumental when developing medical interventions designed to interrupt key events in a particular agent's pathogenesis.

Another aspect of comparative medicine studies is predictive modeling, which utilizes interspecies differences to plan, affect, and interpret the testing of hypotheses using animals as models. In this construct, VBSs conduct detailed studies in a test species, draw conclusions from the data, and then extrapolate the animal findings to human medicine. Although VBSs seek a simple, well-designed study that extrapolates easily to humans, in reality, there are no perfect animal models and sometimes no single model that extrapolates well. Interspecies differences create limits in the modeling of human disease in animals, and 64Es must know the limits of any given animal model to best match it to the study's intent and experimental conditions. Often the limit is caused by the way and degree to which etiological agents gain entry into different species and eventually affect their molecules, cells, tissues, organs, and organ systems. Since biological systems are prone to variation, often 64Es must use multiple animal models to support complex studies to produce improved predictive data on the efficacy of drugs and vaccines in humans.

VETERINARY BIOMEDICAL SCIENTISTS: "BENCH" RESEARCHERS

VBSs recently graduated from their PhD programs apply their academic experience with new technologies at the laboratory "bench" in the Army's laboratories. These VBSs' knowledge of improvements in experimental design as well as diagnostic and imaging technologies allow them (with other scientific officers) to start answering questions that were impossible to respond to only a few years ago.

Today's more sensitive technologies have helped scientists uncover previously unidentified factors in cellular life processes that lead to cell or organ death. In addition, developments in molecular biology are applied by VBSs through relevant modeled *in vivo* studies to explain the roles certain genes play in response to simulating medical threat stimuli or events. For example, an environmental contaminant may elicit a specific response in a normal mouse. However, differences may occur in responses to that same environmental contaminant in mice that lack a gene of interest or in transgenic mice with multiple copies of the same gene. Changes in response between these study groups can be attributed to the targeted gene; these response findings would have seemed unfathomable before this type of genome manipulation became possible.

DEPARTMENT OF DEFENSE MEDICAL RESEARCH LABORATORIES: A GLOBAL VIEW OF DIVERSE VETERINARY BIOMEDICAL MISSIONS

US Army VBSs work in DoD laboratories scattered throughout the globe, from relatively remote sites in the field or in OCONUS (outside the continental United States) laboratories to state-of-the-art facilities in the national capital region. The MRMC- and NMRC-based laboratories and their subordinate CONUS (Continental United States) laboratories are the services' laboratories to conduct research and testing in infectious diseases, CBRN defense, environmental stressors, surgery, and material toxicity.

Among the MRMC CONUS laboratories, USAMEDCOM assigns VBSs to the Walter Reed Army Institute of Research (WRAIR), the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the US Army Medical Research Institute of Chemical Defense (USAMRICD), the US Army Research Institute of Environmental Medicine (USARIEM), and the US Army Institute of Surgical Research. The OCONUS laboratories with VBS assignments are the Armed Forces Research Institute of Medical Science in Bangkok, Thailand (a subordinate directorate of WRAIR), the Naval Medical Research Command (NMRC) Naval Medical Research Unit 3 (NAMRU-3) in Cairo, Egypt, and NAMRU-2 in Phnom Penh, Cambodia. (See Figure 14-1 in Chapter 14, Laboratory Animal Medicine, for a more comprehensive listing of laboratory site locations, CONUS and OCONUS.)

The OCONUS laboratories provide access to endemic infectious disease agents not found elsewhere, as well as the vectors and human populations naturally exposed to them. These laboratories also provide a staging platform to conduct studies in even more remote locations harboring infectious disease agents and vectors (eg, jungle rainforests only accessible by boat or foot). When study requirements exceed the local capacity of the OCONUS laboratory, VBS personnel are able to contact their peers at the MRMC and NMRC laboratories for support.

In addition to the MRMC and NMRC laboratories, VBSs have been routinely stationed at the Army Public Health Center (APHC). APHC supports the Army's only Good Laboratory Practices toxicology laboratory, which investigates the toxicity of material with potential health hazards or effects on the Army's operational environment.

In most duty assignment locations, the VBS works with other military research professionals to produce scientific products. One exception to the VBS being stationed in laboratories or in product-oriented institutes is the VBS who has been assigned to an academic position at the USUHS. The VBS's mission in this academic setting has been to support and further the myriad research endeavors at the USUHS, not produce medical products per se.

Military Medical Research in Infectious Disease

The WRAIR is the Army's flagship organization for infectious disease research. VBSs at WRAIR conduct research projects in a variety of scientific disciplines (eg, bacteriology, parasitology, and virology), performing bench work; serve in research management positions, leading and managing the projects; and even have served as the institute's commanding officer.

Bacteriology

VBSs are an integral part of the burgeoning antimicrobial-resistance and wound-infection research effort at WRAIR. This effort was initiated in 2009 in response to an increase in antibiotic-resistant nosocomial pathogens infecting trauma wound patients from Operations Iraqi Freedom and Enduring Freedom.[8,9] Isolate collection procedures were established in theater and throughout military health systems to capture ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species) from affected patients. These multidrug-resistant isolates were phenotypically and genetically characterized and catalogued for follow-on use in drug discovery research.[10]

The WRAIR's multidisciplinary antimicrobial-resistance team consists of infectious disease physicians, microbiologists, biochemists, and VBSs. The VBS's initial research role was to develop foundational animal models that were capable of establishing infection in wounded tissue using the military-relevant multidrug-resistant ESKAPE isolates and measuring treatment effects of novel topical and systemic antimicrobial treatments. The team created mouse, rat, and pig models of wound infection. The mouse model is now well established and is utilized by DoD, academic, and industry researchers as a key preclinical assessment of the efficacy of candidate antibacterial compounds.[11,12]

VBSs also are applying the same molecular and epidemiological methods used in human studies to characterize the spread of multidrug-resistant bacterial pathogens in military working dog (MWD) populations, partnering with the DoD Food Analysis and Diagnostics Laboratory and the DoD MWD Veterinary Service to complete these animal studies.[13] The human and animal population goals are the same: identify best practices to prevent pathogen dissemination and create effective therapeutics to treat the infections that occur.

Parasitology

Parasitic diseases such as malaria continue to plague humanity and are a medical threat to DoD personnel deployed to areas where the organism and the vector are endemic. Malaria has the highest global mortality of all parasitic diseases, killing as many as 450,000 people each year, primarily children in Africa.[14,15] VBSs play a critical role in the basic science of determining targets for interrupting the life cycle of malaria parasites. Although disease prevention is the preferred approach to countering malaria, effective treatment of this debilitating and lethal disease is also necessary. VBSs elucidate immunological targets for vaccines and discover prophylactic drugs, as well as drugs designed to safely rid the host of the parasite.

Along with laboratory animal medicine veterinarians, VBSs also actively develop animal models for testing vaccines and therapeutics.[16] The importance of animal models in malaria testing of vaccines and therapeutics is twofold: (1) the complex genome of the malaria parasite makes external gene manipulation difficult and (2) the host-parasite relationship necessary to sustain a viable parasite complicates *in vitro* testing. Animal models play a pivotal role in addressing these issues in both research and efficacy testing.[17] VBSs also assist in human studies that determine safety and efficacy of next generation antimalarials by conducting bench analysis of samples and managing animal models used prior to human trials, as well as managing the DoD research programs and laboratories that conduct these studies.

Virology

VBSs take part in the disease surveillance and diagnosis of viral illness in overseas DoD and Department of State personnel, leading to a greater understanding of the epidemiology and importance of a number of

viruses. VBSs have studied the isolates from viral surveillance programs to determine mechanisms of pathogenicity for zoonotic pathogens such as West Nile virus and avian influenza. These studies have increased the proficiency and accuracy of viral identification, including novel pathogens, utilizing next generation sequencing.[18,19]

Military Medical Research for the Defense against Chemical Warfare Agents and Toxins

VBSs at the USAMRICD contribute to the development of MCMs that protect personnel against the medical effects of chemical warfare agents, toxins of biological origin, and toxic industrial chemicals. USAMRICD research supports both US warfighters through DoD-funded research as well as US civilians via National Institutes of Health-funded projects. VBSs serve as co- or principal investigators on research projects addressing relevant exposure routes (ie, inhalation and percutaneous) of traditional nerve agents, vesicant (blister) agents, and toxic industrial products such as cyanide and phosgene, and nontraditional chemical agents.[20,21]

VBSs support research projects at USAMRICD by implementing innovative research tools and models that contribute to the three R's that commonly guide animal use in DoD research: (1) reduction, (2) refinement, and (3) replacement.[22] (See Chapter 14, Laboratory Animal Medicine, for more information about legislation and regulations regarding animal use in DoD research.) The 64E surgical support to implant improved telemetry instrumentation with multiple specialized and sophisticated physiological monitoring leads is an example of one such VBS innovation. This telemetry allows the collection of vast amounts of data in group-housed, instrumented animals. These data are not compromised by the frequent manipulation of the animals by handlers. This results in fewer variables affecting the physiological responses to chemical agent exposure and detection of MCM therapeutic effects. VBSs' expertise also introduced another alternative research approach: expanding animal models to include zebrafish (Colonel Deborah Whitmer, chapter author, personal knowledge).

Additionally, VBSs have served in multiple leadership roles at the USAMRICD, from the branch and division chiefs and the commander's planning staff to deputy commander and commander levels. Frequently, they hold these leadership and resource management positions while concurrently being actively and directly engaged in research. VBS officers' contributions to USAMRICD's chemical agent and biotoxin MCM research programs have directly contributed to the development of a novel therapeutic product—human serum butyrylcholinesterase—advancing this prophylaxis to the development stage of the DoD medical product acquisition process.[23]

Military Medical Research for the Defense Against Biological Warfare Agents

VBSs are involved in vaccine development as MCMs at many levels within DoD research. One vaccine development example at the USAMRIID involved the nonclinical evaluation of a DNA-based vaccine against lethal hantaviruses delivered via an FDA-cleared, handheld, needle-free jet-injection device (PharmaJet Stratis Needle-Free Injector; PharmaJet, Inc, Golden, Colorado). The study demonstrated that delivery of these vaccines via the handheld device induced binding and neutralizing antibodies in the serum in rabbits and nonhuman primates.[24] Previously, these DNA vaccines were shown to be protective against viral challenge but historically had required more complex techniques such as formulation with gold-beads and gene-gun injection or delivery via electroporation.[25] Unlike gene-guns or electroporators, the PharmaJet Stratis Needle Free Injector does not require any power source or compressed gases.

Typically, DNA vaccines are rapidly scalable, have specific targets, and have less stringent refrigeration needs. These aspects, coupled with the stand-alone PharmaJet device, offer much potential as a deployable MCM for the DoD. This combination of a DNA vaccine and needle-free delivery device, if effective in humans, will offer MCM protection that US forces could quickly field and rapidly scale for large-volume production in emergent situations.

VBSs at the USAMRIID also have been instrumental in describing the efficacy of the current anthrax vaccine (Biothrax, Anthrax Vaccine Adsorbed, or AVA; Emergent Biosolutions, Rockville, Maryland) and managing its development. VBSs were principal investigators for studies describing the effects of anthrax (*Bacillus anthracis*), staph enterotoxin B (*Staphylococcus aureus* enterotoxin B), botulinum neurotoxins (*Clostridium botulinum* toxins), and other biological agents in a number of animal species for the purpose of developing MCMs.[26–28] These studies led to more definitive animal models that will lay the groundwork to support efficacy testing of future vaccines, treatments, and diagnostics.

Relevant animal models to support biodefense MCM development are essential, and VBSs draw on integration of their clinical and scientific expertise to develop sound and valid research models. As clinical efficacy trials are not possible with the majority of these pathogens, FDA licensure via animal efficacy studies

is the critical path for most biodefense MCMs. VBSs study clinical parameters that can be extrapolated from animals to humans to support such critical paths. For example, a VBS study of nonhuman primates infected with Venezuelan equine encephalitis virus using cDNA microarrays and real-time PCR resulted in identification of molecular markers of early and late viral infection.[29] The study further characterized how host genes are altered in response to Venezuelan equine encephalitis virus, which could serve as clinical parameter endpoints or drug or vaccine development animal studies or clinical trials. (For more information about the treatment for this virus and other infectious agents and the control of zoonotic diseases that affect military personnel and public health, see Chapter 11, Zoonotic and Animal Diseases of Military Importance, and Chapter 13, Global Zoonotic Surveillance and Control.)

VBS scientific and military relevant contributions are also evident in development of assays used in biodefense. Early VBS-initiated work led to the development and implementation of a high-throughput assay to measure neutralizing antibodies against lethal viruses such as Sin Nombre virus and Andes virus.[24,30] This assay was subsequently used in animal studies and clinical trials evaluating Ebola vaccines in response to the 2014 outbreak in West Africa.[31,32] Collaborative work among the VBSs, Medical Service Corps officers, and civilian scientists at USAMRIID, USAMMDA, and the Joint Program Manager-Medical Countermeasure Systems (Diagnostics) resulted in the DoD deploying the first diagnostic test for Ebola virus infection under the FDA-issued Emergency Use Authorization process. This process enables clinical use of an investigational assay; this rapidly developed accurate diagnostic assay was deployed throughout the United States and to DoD overseas clinical laboratories in response to the 2014 Ebola outbreak in West Africa.[33] (More detailed information on the US Army veterinary response to Ebola and other disease prevention and public health missions can be found in Chapter 1, Military Veterinary Support Before and After 1916.)

VBS perform a vital role in coordinating critical and complex antibiotic resistance determination and testing of antibiotic MCM to treat diseases such as anthrax, glanders, meliodiosis, plague, and tularemia, all of which pose a significant risk to the warfighter.[1] Several cooperative research and development agreements with various pharmaceutical companies and universities led to the testing of nearly 200 unique compounds. VBS-supported research at USAMRIID also identified antibiotics to treat battlefield-related infections caused by multidrug-resistant microorganisms. VBSs' efforts determined susceptibilities to 45 antibiotics for 30 genetically and geographically diverse strains of *Yersinia pestis*. These findings provide reference information for assessing new antibiotic agents and a baseline to monitor the emergence of resistance.[34] Other VBSs' efforts identified novel compounds effective against tularemia and anthrax.[35]

Sometimes original solutions to complex problems come from unexpected sources, and VBS creativity often bridges these resource gaps. For example, how can a healthcare provider properly diagnose ill patients in developing countries or in theater when traditional tests require refrigerated storage? Often these fragile items sit in delivery trucks, on airport tarmacs, or in holding facilities at ambient temperatures, arriving nonfunctional at the point-of-use.

To address this challenge, VBSs sought a solution, and they discovered that cartilaginous fish and camelids produce a unique form of antibody, termed sdAbs, that retains functionality independent of storage temperatures.[36] Diagnostic tests based upon sdAbs are not constrained to narrow storage criteria; in fact, these diagnostic assays remain functional after exposure to near boiling temperatures, harsh chemicals, or contact with enzymatic digestion.[37] Both sharks and alpacas were vaccinated with BSL-4 hemorrhagic viral antigens, their sdAbs were collected, and inclusion of these antibodies in diagnostic assays yielded comparable data to traditional platforms.[38]

Military Medical Research in Physiology

VBSs at the USARIEM are recognized for their contributions to environmental extremes research such as the effects of heat, cold, and terrestrial altitude on human performance, health, effectiveness, and nutritional needs. USARIEM VBSs have served in key support and staff roles (ie, attending veterinarian and executive officer) as well as in the vital leadership role of USARIEM commander. VBSs at USARIEM have contributed to and produced performance optimizing and preventive medicine doctrine, health hazard assessments, and predictive algorithms for operational decision aids.[39] They have also provided clinical support of the research animal colony, conducted research as co-principal investigators, or supported projects through direct veterinary clinical skills on research protocols.

VBS leadership and collaboration was instrumental in USARIEM meeting a challenging new human performance mission in support of the Training and Doctrine Command. USARIEM conducted the physical demands study component of Training and Doctrine Command's requirement to determine the physical standards for combat military occupational specialties opened to female soldiers. The impact of USARIEM's study will have a lasting effect on US Army policy and

manpower utilization based on rigorous evidence-based research (Colonel Deborah Whitmer, chapter author, personal knowledge).

However, USARIEM environmental research is not limited to just humans. Recently, the Army extended a study on the impact of environmental factors on mission capability to canine performance. VBSs have assisted in evaluating CBRN protective shelters for MWDs to combat negative physiological effects such as overheating. In this study, VBSs are using remote sensing to determine the effects of heat on MWD performance. (Remote monitoring of physiological parameters during military operations may serve as an early indication of physiological stress leading to performance degradation.) Although this ongoing study is focused on MWDs, the results may have applicability to humans as well. Eventually, leaders may use remotely monitored physiological parameters to determine that a mission or training event should be modified or terminated (Colonel Deborah Whitmer, chapter author, unpublished data, 2012).

Military Directed Energy Medical Research

VBSs have worked as collaborative members of Tri-Service and Army research teams to address directed energy (DE) medical threats. VBSs at the US Army Institute of Surgical Research have served as principal investigators using animal and nonanimal (cell-based) models for development of protective eyewear and treatment options for DE (laser) ocular injuries.[40] VBSs have also actively participated in team assessments and analysis of the conditions and clinical evaluation of suspected ocular injuries secondary to laser exposure in human patients (Colonel Deborah Whitmer, chapter author, personal knowledge).

Military uses of DE sources include lasers and high-powered microwave generators. The military application and numbers of DE devices on the battlefield is increasing dramatically. Examples of common military applications include target designators, live-fire training devices, illuminators and dazzlers, and range finders. The potential for ocular injury from the high-powered yet hand-held devices commonly used are significant (Figure 16-3a–d). This dynamic research area is linked to a preventive care force protection mission as well as establishing DE-safe ocular exposure thresholds.[41]

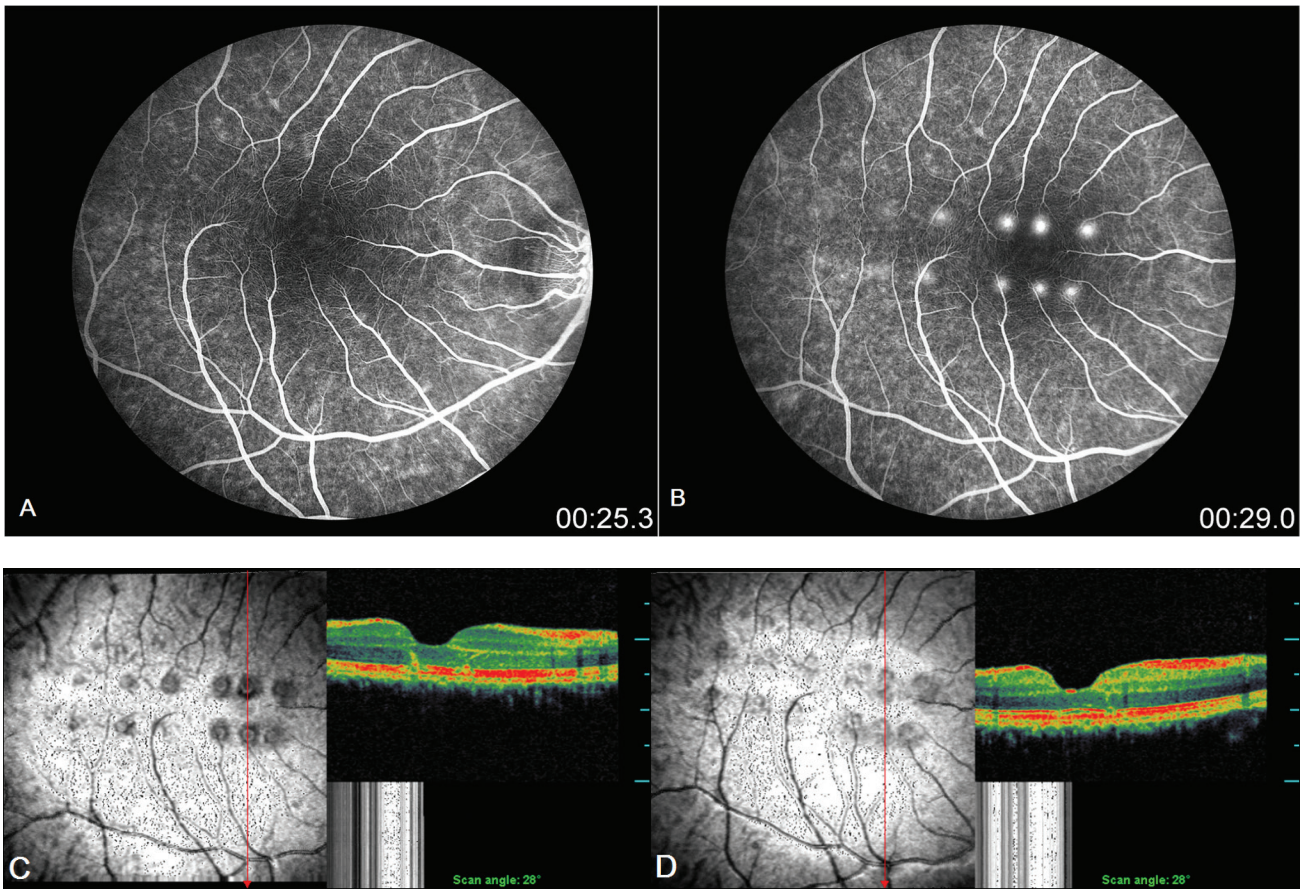
Collaborative Medical Research in the Field

VBSs support and conduct DoD research in numerous OCONUS laboratories in collaboration and coordination with the host nation's government and medical and scientific staffs. Host nations may not favor multinational studies, especially when their local governments perceive few benefits or feel exploited. However, the presence of DoD OCONUS laboratories has, and continues to signal, a long-term commitment by the United States to fund and conduct regionally relevant disease research.

A symbiotic relationship can be created when the host nation facilitates the research and the DoD provides technical and financial support: in the end, both parties benefit from the training provided and the medical knowledge derived. While collaborative disease outbreak investigation under field conditions is not necessarily a fundamental or an exclusive role of the overseas laboratories, OCONUS laboratories are uniquely positioned and staffed for this type of mission. NAMRU-2, NAMRU-3, and the Armed Forces Research Institute of Medical Sciences all maintain VBSs on their manning documents.

The American Veterinary Medical Association defines "One Health" as the collaborative effort of multiple disciplines—working locally, nationally, and globally—to attain optimal health for people, animals, and the environment. As the concept of "One Health" becomes more firmly established within the public health community, VBSs assigned to overseas laboratories may play even more prominent roles in zoonotic infectious disease research, continuing to focus on serious force health protection threats such as anthrax, brucellosis, Q fever, plague, Rift Valley fever, and influenza. (See Chapter 13, Global Zoonotic Surveillance and Control, for more information about the "One Health" concept.)

In 2006, such an opportunity occurred when H5N1 avian influenza spread throughout Asia. Veterinary officers assigned to NAMRU-3 responded to disease outbreaks in Turkey, Iraq, and Afghanistan. These officers translated the outbreak response into immediate molecular epidemiology research efforts that contributed to global H5N1 genetic research and later established longer-term collaborative research efforts. Veterinarians assigned to the overseas laboratories have also worked through host country governments to develop or enhance avian, pandemic, and seasonal influenza preparedness and diagnostics in Afghanistan, Armenia, Azerbaijan, Bulgaria, Egypt, Iraq, Jordan, Kazakhstan, Kyrgyzstan, Macedonia, Nepal, Oman, Pakistan, the Republic of Georgia, Sudan, Tajikistan, Thailand, Turkmenistan, Ukraine, and Uzbekistan (Colonel [Retired] James Boles, chapter author, personal knowledge).



Figures 16-3a–d. Retinal lesions created by Argon lasers (directed energy) (DE) in a nonhuman primate models injury pathology and response to treatment for human DE retinal injuries. The panels shown are from the same right eye over a 30-day period. **(a)** Non-injured baseline retina photograph with fluorescein angiography (FA). **(b)** View of 3 days post-argon laser lesions with topical ocular medications and intravitreal injection treatment photograph FA. **(c)** View of 3 days post-injury with treatment optical computer tomography scan (OCT) demonstrating depth and specific layers of retinal injury. **(d)** View of 30 days post-injury with treatment OCT scan demonstrating progression of retinal tissue repair.
Images and data provided courtesy of an Institute Animal Care and Use Committee (IACUC)-approved protocol and Colonel Deborah Whitmer, chapter author.

Military Medical Research in Toxicology

Evaluating Military Materials

The Army acquisition process requires a health hazard assessment and a toxicity clearance for all new materiel proposed for entry into the Army supply system.[42] The program manager is responsible for selecting the material and ensuring that it is safe prior to use. Material assessments may be conducted on something as simple as a proposed commercial lubricant for weapons cleaning, a change in the formulation of a silicon liner in a facemask, or the potential human health exposures of redesigned munitions.

VBSs contribute to the scientific direction of the Army's testing facility for toxicology of environmental and occupational exposures at the APHC. This laboratory determines hazard levels for military unique substances within the Army's garrison and operational environments. Veterinary toxicologists play a vital role in translating research and environmental data into exposure limits to delineate what constitutes a "safe" level of exposure. The resultant hazard determinations influence the composition and use of weapon systems and equipment.

Additionally, because some materials (munitions, for example) have the potential to concentrate in training ranges over time, the chronic environmental contamination of these materials above "safe" levels of environmental or occupational human exposure levels could eventually limit the continued use of these contaminated training locations. In some cases, the technology is so new or militarily unique that

insufficient information is available regarding the proposed components or the potential levels of soldier exposure. For these substances, VBSs conduct or support studies to provide better estimates of the potential human health impact should exposures occur.[43]

As VBSs develop original studies for material development assessments, several factors must be considered, coordinated, and integrated into the study design. Original studies require a collaborative effort to validate the chemical characteristics of the proposed formulation, physical characteristics in the environment of use, and accidental exposure scenarios that may occur. VBSs must incorporate all this information when making a recommendation of whether to use a major safety component of a weapons system. An example of the necessity and beneficial outcome of VBS-derived material toxicological studies occurred when APHC VBSs, in collaboration with investigators at the Armed Forces Radiobiological Research Institute, demonstrated that the toxicological effects of a promising replacement alloy for depleted uranium was unacceptable because of the high incidence of cancers in rodents.[44] (VBSs managed the Good Laboratory Practices toxicological studies conducted at APHC that led to this determination.)

VBSs also helped make a material decision regarding Army signal devices. Research has shown that repeated exposure to dyes in military training and operational environments could cause adverse health effects.[45–48] Inhalation studies performed at APHC provided data that helped identify safe exposure levels of several proposed alternative colors for use in signal devices.[49] VBSs played a vital role in this testing by developing a viable animal model for inhalation exposure and designing inhalation chambers that would accurately and repeatedly dose test animals.[46]

Other VBS material studies focus on the health risks presented by certain weapons systems' propellants, including perchlorate, cyclotrimethylenetrinitramine (an explosive known as RDX), chromium, lead, and other minor components of munitions.[50,51] Additional potential routes of toxicant exposure from weapons systems include occupational exposure by production workers or ordinance personnel due to direct contact or inhalation following detonation.

As development of signal devices, material, and ordinance evolves, the potential for toxicological effects and inadvertent environmental contamination increases as new propellants are proposed and chemical characteristics of the mixtures change to meet different functional requirements. VBSs will continue to support and manage the research to evaluate these new formulations, with the goal of producing safer operational materials and training environments for US military members.

Evaluating Environmental Exposures

DoD public health leaders consult VBS toxicologists during and after any toxic event affecting the military environment, including the potential contamination of the food supply. The Deepwater Horizon oil spill that occurred in April 2010 in the Gulf of Mexico is one example of such contamination.[52] Of particular concern was whether the dispersants used to capture the ongoing oil spill (or their metabolites) would accumulate in food sources such as shellfish at potentially harmful levels. APHC, working with other DoD and federal agencies, developed a new assay to detect propylene glycol and 2-butoxyacetic acid and ensure seafood safety. APHC Laboratory Sciences personnel also validated the assay for reliability and accuracy to ensure a protocol was available for any subsequent oil spill catastrophes (Lieutenant Colonel Cindy Landgren, chapter author, personal knowledge).

Biomedical Research at the Uniformed Services University of the Health Sciences

At the USUHS Biomedical Instrumentation Center, VBS officers facilitate and coordinate the use of core research facilities in the health professional school of the armed forces. The facility includes microscopic imaging (electron, confocal, and fluorescent); translational imaging (positron emission and magnetic resonance); biochemical characterization (flow cytometry); proteomics and structural biology (mass spectrometry and crystallography); and genomics. The tools provided by the Biomedical Instrumentation Center inform and enable innovative research in a wide variety of disciplines, ranging from anatomy to zoonotic disease. Most notable of late is the application of these tools to investigate the pathogenesis and therapy of traumatic brain injury.[53]

The VBS also provides instruction for medical, nursing, and graduate students; advises the university on the instrumentation aspects of the research portfolio; and serves as a liaison between the academic and the administrative sides of the institution. Thus, the veterinary biomedical science staff plays a key team role at the USUHS in the continuing goal to provide and maintain a state-of-the-art core facility.

SUMMARY

The majority of adverse health effects encountered in the military come from infectious disease, threat agents of CBRN origin, toxic chemicals, and injurious environmental and occupational hazards. VBSs are frequently called upon by DoD leaders to answer critical questions related to these threats based on

their specialized expertise in clinical practice, basic and applied research, product development, project management, and policy development. The VBSs' knowledge on route, mechanism of toxicity, and drug pharmacodynamics is critical to identifying targets of intervention in chemical weapons defense research.

VBSs are also involved in myriad project and product management activities leading to approval and licensure of medical drugs, biologics, devices, and diagnostics to assist military service members and civilian communities worldwide. Veterinary biomedical science research on vaccines, drugs, antidotes, infectious disease, ocular injuries, toxins, and chemicals, together with global biosurveillance and countermeasures, are among their many contributions to military and public well-being.

In addition to being highly specialized officers, like other members of the Veterinary Corps, VBSs have deployed to fulfill missions outside their primary area of expertise while serving in positions that can make optimal use of their leadership qualities. Locally, nationally, and globally, the VBS officer is a key contributor to attaining optimal health for people, animals, and the environment through research.

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