

## Emerging Infectious Diseases and Antimicrobial Resistance (EIDAR)

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**ABSTRACT** Introduction: The Infectious Disease Clinical Research Program's (IDCRP) Emerging Infectious Diseases and Antimicrobial Resistance (EIDAR) Research Area is a Department of Defense (DoD) clinical research capability that is responsive and adaptive to emerging infectious disease (EID) threats to US military readiness. Among active-duty and other Military Health System (MHS) beneficiaries, EIDAR research is largely focused on evaluating the incidence, risk factors, and acute- and long-term health effects of military-relevant EIDs, especially those caused by high-consequence pathogens or are responsible for outbreaks among US military populations. The EIDAR efforts also address Force Health Protection concerns associated with antimicrobial resistance and antimicrobial stewardship practices within the MHS. Methods: The EIDAR studies utilize the approach of: (1) Preparing for emergent conditions to systematically collect clinical specimens and data and conduct clinical trials to assist the military with a scientifically appropriate response; and (2) Evaluating burden of emergent military-relevant infectious diseases and assessing risks for exposure and development of post-infectious complications and overall impact on military readiness. Results: In response to the Ebola virus epidemic in West Africa, the IDCRP partnered with the National Institutes of Health in developing a multicenter, randomized safety and efficacy study of investigational therapeutics in Ebola patients. Subsequently, the EIDAR team developed a protocol to serve as a contingency plan (EpICC-EID) to allow clinical research activities to occur during future outbreaks of viral hemorrhagic fever and severe acute respiratory infections among MHS patients. The EIDAR portfolio recently expanded to include studies to understand exposure risks and impact on military readiness for a diversity of EIDs, such as seroincidence of non-Lyme disease borreliosis and *Coccidioides* fungal infections among high-risk military populations. The team also launched a new prospective study in response to the recent Zika epidemic to conduct surveillance for Zika and other related viruses among MHS beneficiaries in Puerto Rico. Another new study will prospectively follow U.S. Marines via an online health assessment survey to assess long-term health effects following the largest DoD Shiga Toxin-Producing *Escherichia coli* outbreak at the U.S. Marine Corps Recruit Depot-San Diego. In cooperation with the Trauma-Related Infections Research Area, the EIDAR Research Area is also involved with the Multidrug-Resistant and Virulent Organisms Trauma Infections Initiative, which is a collaborative effort across DoD laboratories to characterize bacterial and fungal isolates infecting combat-related extremity wounds and link lab findings to clinical outcomes. Furthermore, the EIDAR team has developed an Antimicrobial Resistance and Stewardship Collaborative Clinical Research Consortium, comprised of Infectious Disease and Pharmacy specialists. Conclusions: The EIDAR Research Area is responsive to military-relevant infectious disease threats that are also frequently global public health concerns. Several new EIDAR efforts are underway that will provide Combatant Command Surgeons, Infectious Diseases Service Chiefs, and other Force Health Protection stakeholders with epidemiological information to mitigate the impact of EIDs and antimicrobial resistance on the health of U.S. military service members and their dependents.

### BACKGROUND

In 1992, the Institute of Medicine published a landmark report, *Emerging Infections: Microbial Threats to Health in the United States* that raised the awareness of the medical communities about the threat of new and emerging infections. Since then, myriad new or re-emerging infectious diseases have challenged the medical community, including West Nile virus, severe acute respiratory syndrome, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), pandemic influenza, Ebola virus, and Zika virus (ZIKV).<sup>1,2</sup>

The US military has significant laboratory-based assets to study countermeasures for emerging infections and potential biological weapons threats at the Walter Reed Army Institute of Research (WRAIR), Naval Medical Research Center (NMRC),

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and the U.S. Army Medical Research Institute of Infectious Diseases. In addition, Department of Defense (DoD) overseas labs can leverage opportunities to conduct surveillance for emerging threats, as well as conduct large scale vaccine or therapeutic trials. One significant gap; however, was having a clinical platform in DoD medical facilities to conduct multi-center clinical research on potential emerging threats and biodefense.

Therefore, in 2011, the Infectious Disease Clinical Research Program (IDCRP) leadership decided to add a research area related to Biodefense and Emerging Infectious Diseases (BD/EID). This nascent program has evolved, perhaps more significantly than any other research area since its establishment. In addition to the aforementioned gap in the DoD clinical centers, the decision to add this new research area was based on other strategic needs. The military's focus on agents that threaten national security or military personnel on the battlefield may be different than civilian preparedness response efforts for bioterrorism or pandemics. This research area helped align the program with key DoD and non-DoD stakeholders to enhance the IDCRP's ability to respond to new or re-emerging threats and support military clinical capabilities to study biodefense countermeasures.

### VIRAL HEMORRHAGIC FEVERS

Agents causing viral hemorrhagic fevers, including Ebola and Marburg viruses, have been targets of vaccine and therapeutics development in the DoD. Viral hemorrhagic fevers have threatened combat, peacekeeping, and training operations for decades in areas such as the Balkans (Dobrava virus), Korea (Hantaan virus) and the South Pacific (dengue virus) and, as a result, have motivated the development of preventive measures. Consequently, the first study in the BD/EID Program area was a collaboration between the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center and military investigators on the safety and immunogenicity of Ebola and Marburg DNA vaccines, assessed at a WRAIR collaborative field site at Makerere University in Kampala, Uganda. The results showed that, given separately or together, both investigational DNA vaccines, one encoding Ebola virus Zaire and Sudan glycoproteins and one encoding Marburg virus glycoprotein, were well-tolerated and elicited antigen-specific humoral and cellular immune responses.<sup>3</sup> These findings contributed to the accelerated development of more potent Ebola virus vaccines that encode the same wild-type glycoprotein antigens that were tested during the 2013–16 Ebola virus disease outbreak in West Africa.<sup>4,5</sup>

In 2014, the largest-ever Ebola virus outbreak was recognized in the West African countries of Guinea, Liberia, and Sierra Leone. The DoD responded with providing military members to build Ebola treatment units, provide logistics

support, and diagnostics teams and assays in-country under Operation United Assistance.<sup>6</sup> Multiple different investigational countermeasures were employed during the outbreak and NIAID led a multi-center group to prioritize the potential countermeasures and develop a randomized controlled trial to study the most promising options. IDCRP investigators participated in the prioritization effort and the IDCRP's team at the Walter Reed National Military Medical Center served as the only DoD site participating in the protocol: a randomized controlled trial of the monoclonal antibody ZMapp for treatment of Ebola virus disease. The study enrolled 72 patients and demonstrated improved outcomes from Ebola virus disease in those receiving ZMapp, although the results did not meet pre-specified criteria for statistical significance.<sup>7</sup>

### VACCINIA VIRUS VACCINATION

As a naturally occurring infection, smallpox was the target of a successful global eradication campaign in the 1950s and vaccination of civilian populations ceased in the 1970s. Nevertheless, because of ongoing concerns of bioterrorism, the U.S. military continues to vaccinate at-risk operational forces, some healthcare workers, and service members in Korea.<sup>8</sup> During the last decade, over one million individuals received the vaccine, which is made from the Vaccinia virus. In addition to conferring protection against smallpox, the Vaccinia virus demonstrated promise as a vaccine-delivery system, inducing immunity to pathogens such as HIV. As a result, another early study assessed host immune factors that might attenuate the response to vaccinations. Because of its potential use in HIV candidate vaccines, investigators at the IDCRP and the Military HIV Research Program, with support from the U.S. Military Vaccine Agency, evaluated the potential impact of pre-existing immunity to Vaccinia with the use of Vaccinia-vectored vaccines in a cell-based infection model. Using longitudinal sera from military personnel who had been vaccinated, the investigators found that serum antibody responses to smallpox vaccination did not persist over extended periods of time (e.g., 5 years post-vaccination), suggesting that prior vaccination for smallpox might not interfere with the effectiveness of novel vaccines using Vaccinia virus as a vector.<sup>9</sup>

### EMERGING INFECTIONS

Within the IDCRP, there is a broad intersection of emerging infections across multiple other IDCRP research areas, such as the Skin and Soft-tissue Infections and Trauma-Related Infections.<sup>10,11</sup> In particular, research has focused on the epidemiology, risk factors, and prevention of community-associated methicillin-resistant *Staphylococcus aureus* skin and soft-tissue infections in military personnel,<sup>10</sup> as well as emergent trauma-related infections, such as invasive fungal wound infections.<sup>11</sup> In line with the President's 2014 Executive Order for Combating Antibiotic-Resistant Bacteria,<sup>12</sup> IDCRP also led

the way to identify and assess the public health impact of multidrug-resistant gonococci.<sup>13</sup> Other early investigations into EID threats assessed a range of disease agents, such as *Rickettsia parkeri* in the Tidewater region of Virginia shortly after it was identified as an endemic disease in that region.<sup>14</sup> As the BD/EID program continued to evolve, it was renamed as the Emerging Infectious Disease & Antimicrobial Resistance (EIDAR) Research Area in 2014 and continues to grow to encompass a broad clinical research portfolio, covering a diversity of military-relevant EIDs.

Infectious disease threats to military forces remain high due to deployment worldwide, frequently to areas with limited medical and public health infrastructure. Novel respiratory pathogens, such as MERS-CoV and avian influenza strains, pose significant risk to military populations.<sup>15</sup> The 2013–16 Ebola outbreak in West Africa exposed vulnerabilities and delays in responding to research opportunities, and led to the recognition that the U.S. needs the capability to study infectious disease outbreaks in real time, as well as being included in routine public health response planning.<sup>16</sup>

#### **A MILITARY TREATMENT FACILITY (MTF)-BASED CONTINGENCY PROTOCOL TO FACILITATE CLINICAL RESEARCH DURING OUTBREAKS**

The rapid deployment of large numbers of military personnel into disease endemic areas heightens their risk for acquiring infectious diseases. In these settings, the conditions and circumstances (i.e., crowding and inadequate access to hygiene) facilitate potential for disease transmission to other susceptible individuals. The return of military forces from disease-endemic areas also imposes a significant disease risk to other military personnel, military dependents, as well as the general public, by creating an avenue for the importation of novel pathogens into the United States and increasing the risk of localized outbreaks and major epidemics. The impact of monitoring for and describing the epidemiology and clinical characteristics of novel respiratory pathogens with pandemic potential among military personnel is necessary to ensure a timely, comprehensive epidemiologic, immunologic, virologic, and clinical characterization of the initial cases of an EID in what may be a mounting epidemic or pandemic.

The IDCRP has prided itself on responding rapidly to new research opportunities; however, the time it takes to draft and receive regulatory approval for new protocols may lead to missed opportunities during an outbreak, especially for short-lived events. With this in mind, in 2015, the IDCRP established the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EpiCC-EID) protocol, which was designed to fill critical needs by providing military hospitals with a plan to respond rapidly to public health crises/outbreaks of diseases with severe outcomes with potential to spread to the civilian populations in the United States and abroad. The objectives of this protocol are to characterize the epidemiologic, laboratory, immunologic, and clinical

characteristics of infections caused by high-consequence pathogens, such as severe acute respiratory infections or viral hemorrhagic fevers, among individuals presenting for care at MTFs to inform effective patient care. This protocol is intended to reduce the response time to facilitate collaborative research partnerships for interventional therapeutic trials, vaccines, or new diagnostic assays for a novel respiratory pathogen or viral hemorrhagic fever as part of a whole of government approach.

#### **EFFORTS FACILITATING PREPAREDNESS AND RESPONSIVENESS WITHIN THE MILITARY HEALTH SYSTEM (MHS) IN CONDUCTING CLINICAL RESEARCH TO ADDRESS INFECTIOUS DISEASE OUTBREAKS**

The EIDAR Research Area directs studies in response to the Global Health Security Agenda and the National Security Strategy requirements for preparedness and response to infectious disease outbreaks. As discussed above, the EpiCC-EID protocol provides the MHS with a unique capacity for preparedness in facilitating systematic collection of clinical specimens and data at MTFs to support the military with a scientifically appropriate response. In addition, EIDAR supports studies investigating the disease burden, risk factors, and clinical outcomes associated with emerging and/or re-emerging pathogens responsible for causing outbreaks of disease affecting U.S. military populations.

Recently, ZIKV emerged as a major public health crisis, with the World Health Organization in February 2016 declaring ZIKV-related congenital abnormalities a Public Health Emergency of International Concern.<sup>17</sup> The U.S. military service members deploying to disease endemic areas where the outbreak was occurring (primarily in South America) or stationed in Puerto Rico were also at risk for ZIKV exposure. Given limitations on the availability of laboratory testing, U.S. (and DoD) policy precludes testing of asymptomatic men for diagnosis of ZIKV infection. To date, there have been 175 confirmed ZIKV cases in the MHS, primarily in deployers and travelers to Puerto Rico and South America.<sup>18</sup> Following the ZIKV outbreaks, there was a recognized need for establishing means for conducting active surveillance of ZIKV (and related arboviruses, such as dengue and chikungunya) among MHS beneficiaries in a disease-endemic location to better prepare for any subsequent re-emergence of these diseases. To this end, the EIDAR team, in collaboration with the WRAIR Viral Diseases Branch, developed a prospective protocol to conduct surveillance of ZIKV and related arboviral infections among active-duty service members and their dependents presenting with symptoms at the Rodriguez Army Health Clinic in Puerto Rico. This study will allow early detection of outbreaks among MHS beneficiaries on the island, assessment of impact on military readiness, and ready reporting to Force Health Protection officials.

Chikungunya virus is another mosquito-borne infectious disease threat to deployed U.S. military service members

that is caused by an RNA virus related to dengue and ZIKV, and sometimes is misdiagnosed since these viruses share similar clinical signs and common geographic distribution.<sup>19</sup> Chikungunya infection causes febrile illness, often characterized by debilitating joint pain and, in some cases, progresses to severe rheumatic disease. While the majority of patients recover fully, some cases are associated with chronic issues of joint pain; eye, neurological and heart complications; and gastrointestinal complaints.<sup>20</sup> An EIDAR virtual cohort study is underway, involving analysis of data extracted from the Disease Reporting System Internet by collaborators at the Navy Marine Corps Public Health Center EpiData Center and the MHS Data Repository, to evaluate short- and long-term health outcomes, disability, and healthcare utilization attributable to chikungunya infection in MHS beneficiaries.

In addition to vector-borne tropical infectious diseases, diarrheal disease is another major threat to U.S. military operations worldwide; however, further investigation is merited to determine the potential long-term health consequences of severe gastrointestinal infections. The impact on military medical readiness of diarrheal illness (travelers' diarrhea) encountered during overseas deployments is a well-characterized Force Health Protection issue and is a major focus for prevention and treatment research within the IDCRP Deployment and Travel-Related Infection Research Area.<sup>21-23</sup> In contrast, less is known about the deleterious health consequences associated with outbreaks of enteric diseases among military populations at installations within the continental United States. Moreover, mounting evidence reported in the literature, primarily from epidemiological studies among civilian populations impacted by diarrheal disease outbreaks, suggests post-infectious sequelae (medical complications observed following infection) is a growing concern.<sup>24-26</sup> Shiga Toxin-Producing *Escherichia coli* (STEC) infection, a major cause of foodborne illness in the United States and associated with consuming undercooked beef, is linked to life-threatening complications manifesting in the acute phase of infection as severe hemorrhagic colitis and hemolytic uremic syndrome, as well as lesser known sequelae emerging months to years later.<sup>27</sup>

In response to the U.S. military's largest outbreak of STEC (nearly 300 cases) which occurred at the U.S. Marine Corps Recruit Depot-San Diego in the Fall of 2017, a new EIDAR protocol was developed to investigate long-term health impact of STEC infection through a 5-year follow-up online survey-based study assessing clinical outcomes. The overall objective is to determine the incidence of post-infectious sequelae, including functional bowel disorders (irritable bowel syndrome, dyspepsia, constipation), osteoarticular symptoms (reactive arthritis and avascular necrosis), and renovascular disease (hypertension and chronic kidney disease) in Marines identified as STEC cases during the outbreak relative to non-ill matched controls. A series of analytic modeling approaches will be used to develop a risk model health outcomes risk score to determine how comorbidities, demographics, and

other factors affect risk for developing post-infectious sequelae. This health outcomes risk score could be a Force Health Protection tool for identifying individuals at greatest risk for long-term complications in military populations affected by future diarrheal illness outbreaks.

The EIDAR portfolio also supports studies among U.S. military populations to identify the exposure risk to pathogens encountered within the continental United States. Specifically, there are two ongoing retrospective studies involve laboratory analyses of DoD Serum Repository specimens from service members to evaluate the burden of military-relevant infectious diseases: newly emergent non-*Borrelia burgdorferi* tick-borne *Borrelia* bacterial infections causing Lyme disease and related syndromes at U.S. military training installations and *Coccidioides* fungal infection at the high-risk disease endemic Naval Air Station Lemoore. Findings from these studies will inform if future investigations into protective measures, novel therapeutics, or improved diagnostics are warranted to protect service members from these pathogens.

The EIDAR Research Area aims to be increasingly responsive to addressing clinical research gaps informative to shaping Force Health Protection policy. Recent strategic partnerships with the Armed Forces Health Surveillance Branch Global Emerging Infections Surveillance Section and the Uniformed Services University of the Health Sciences (USU) Center for Global Health Engagement have been critical to aligning EIDAR research efforts with Geographic Combatant Command Surgeons' requirements for addressing the threat of regional infectious diseases affecting military operations. These and other partnerships with key DoD stakeholders will continue to advance the operational relevance of EIDAR work.

## ANTIMICROBIAL RESISTANCE ACTIVITIES

Antimicrobial resistance is a serious health threat worldwide. New forms of antibiotic resistance have emerged over the past decades and can spread rapidly with some pathogens becoming resistant to multiple types and classes of antimicrobials.<sup>28-32</sup> Colonization with and infections caused by multidrug-resistant organisms (MDROs) appear common and have a significant impact on military populations.<sup>33-37</sup> In addition, MDRO infections further complicate the care of wounded warriors, are associated with high morbidity and mortality, and add substantial and avoidable costs to the healthcare system due to prolonged and costlier treatments, longer hospital stays, and additional patient visits.

The IDCRP has had a long interest in studying antimicrobial resistance in several of its research areas. As a result, EIDAR research on MDROs and infections caused by these organisms overlap with several other IDCRP research areas, including Trauma-Related Infections, Deployment and Travel-Related Infections, and Sexually Transmitted Infections Research Areas.<sup>11,13,23</sup>

In alignment with the President's launch of the 2014 Executive Order for Combating Antibiotic-Resistant Bacteria, EIDAR efforts address Force Health Protection concerns associated with antimicrobial resistance (AMR) and filling clinical knowledge gaps related to best practices for antimicrobial stewardship programs (ASPs) within the MHS. One such major effort is the Trauma Infectious Disease Outcomes Study (TIDOS) Multidrug-Resistant and other Virulent Organisms (MDR/VO) Trauma Infections Initiative, which is a collaborative effort across DoD laboratories with expertise in wound microbiology and infections (including USU, Brooke Army Medical Center, U.S. Army Institute of Surgical Research, WRAIR, and NMRC).<sup>11</sup> The MDR/VO Trauma Infections Initiative was established to investigate the combat trauma wound microbiology and infections linked to well-characterized clinical data and outcomes to expand our understanding of the complex microbiology inherent within combat wounds. Through the TIDOS MDR/VO Initiative, several analyses have been performed to examine microorganisms collected from combat casualties from Iraq and Afghanistan, assess antimicrobial resistance, and evaluate associations with clinical outcomes.<sup>11</sup>

Patients colonized or infected with pathogens having *in vitro* resistance are reported to have more co-morbidities, longer hospital stays prior to infection, and increased exposure to antibiotics.<sup>38</sup> Each of these factors can independently influence clinical outcomes regardless of *in vitro* susceptibilities. Therefore, understanding patient comorbidities is important when assessing the impact of *in vitro* resistance on outcomes, along with the development and prevention of infection. Comorbidities may differ in a military population compared to the general public, especially in combat-related trauma patients and, thus, may affect outcomes differently in this population.<sup>39</sup> The impact of *in vitro* resistance in a military population has not been evaluated. To address this clinical knowledge gap, an EIDAR retrospective study is investigating association between phenotypic *in vitro* bacterial resistance, patient comorbidities and outcomes in antimicrobial-resistant bloodstream infections (AR-BSIs) in adult DoD beneficiaries, utilizing data extracted from the MHS Data Repository. Analyses are underway of microbiology and clinical data from ~7,500 cases to describe the demographics and risk factors of MHS patients who develop AR-BSIs. Results from this study will help direct MHS resources to more effectively prevent and plan care for these patients.

### ANTIMICROBIAL STEWARDSHIP (ASP) ACTIVITIES

Antibiotic use is a crucial factor leading to antibiotic resistance. Up to half of all antibiotics prescribed are not needed or are not effective as prescribed, increasing the risk of bacteria becoming resistant to those antibiotics.<sup>40,41</sup> Antibiotic misuse also contributes to adverse drug reactions in patients and increased healthcare costs. Thus, there is an urgent need to ascertain further clinical knowledge on optimal and

appropriate antibiotic use to inform policies that form the basis of hospital ASPs.

The EIDAR team leveraged the IDCRP's extensive clinical research network, which includes active-duty investigators located at MTFs worldwide, to develop an AMR/ASP Collaborative Clinical Research Consortium, comprising Infectious Disease and Pharmacy specialists from 10 Army, Navy, and Air Force MTFs. To date, the consortium performed a landscape review of ASP efforts within the MHS and identified clinical evidence gaps to be addressed by the group through multisite studies. One ongoing effort of the consortium is creating a Knowledge, Attitudes, and Practices survey to identify trends and practices driving antimicrobial prescribing patterns among MHS healthcare providers, with the aim of generating findings informative to making recommendations for improving ASP practices and training within the MHS to support optimal practices in managing microbial infections.

### CONCLUSION

The EIDAR Research Area was established to ensure the IDCRP remained nimble and responsive to studying new and emerging disease threats to military populations in a constantly evolving landscape. In addition to the specific efforts within EIDAR, the EIDAR team will continue to partner with other IDCRP research areas, as well as external collaborators, to achieve the goal of mitigating the impact of military-relevant EIDs, especially high-consequence pathogens and MDR infections, on military readiness. Newer efforts such as the EpiCC-EID protocol, STEC- short and long-term health effects, ZIKV epidemiology, and AMR efforts, will continue to advance the IDCRP's military operational relevance.

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