

IDCRP



INFECTIOUS DISEASE CLINICAL RESEARCH PROGRAM



2018

ANNUAL REPORT

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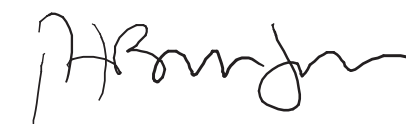
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LETTER *from* the IDCRP DIRECTOR

Twelve years on since its inception, the Infectious Disease Clinical Research Program (IDCRP) remains an innovative leader in multi-site, militarily-relevant, clinical infectious disease research with a broad research portfolio to inform and improve the health and care of service members and beneficiaries. The lasting success of the IDCRP is a direct result of the clinical research network partnerships the Uniformed Services University of the Health Sciences (USU) has established with the National Institute of Allergy and Infectious Diseases (NIAID), Commands and clinicians in the Department of Defense (DoD) Military Health System (MHS) and biomedical research and development enterprise, and collaborators from the Veterans Affairs Healthcare System. Over the past year, the Program has continued to evolve with the initiation of new protocols, including a *Staphylococcus aureus* vaccine trial, evaluation of influenza vaccine effectiveness, and an investigation of longitudinal consequences of infection due to Shiga toxin-producing *Escherichia coli*. Overall, each of the seven research areas had substantial progress and accomplishments, which are outlined in the following report.

The achievements of the IDCRP would not be possible without the indispensable support of USU leadership, our Operational and Executive Steering Committees, NIAID, and cooperative execution through the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. I wish to recognize and thank our DoD funding partners in the Defense Health Program, the Military Infectious Diseases Research Program, the Navy Bureau of Medicine and Surgery, and the Armed Forces Health Surveillance Branch for their continued support and valued partnerships.

It is only through the dedication of our clinical research staff and support personnel and collaboration of active-duty and civilian investigators, that the IDCRP has become the exemplar of a military clinical research network. Last, but not least, I wish to thank the military service members and beneficiaries who graciously volunteer their time to participate as research subjects in our studies. It continues to be a privilege to serve with such an exceptional team.



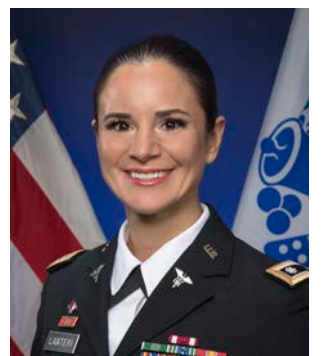
Timothy H. Burgess, MD, MPH
Captain, Medical Corps, U.S. Navy
Director, IDCRP

Core values: Collaboration, Innovation, Quality, Adaptability, Dedication

Success is Defined By: Informing military health policy and practice through translation of research findings; Publications and presentations within impactful and relevant peer-reviewed journals/forums; Capability to respond to emergent infection threats and/or high-priority research initiatives; and Key stakeholder satisfaction



Timothy H. Burgess, MD, MPH
Captain, Medical Corps, U.S. Navy
Director, IDCRP



Charlotte Lanteri, PhD
Lieutenant Colonel, U.S. Army
Deputy Director, IDCRP
EIDAR Director

ABOUT IDCRP

The Infectious Disease Clinical Research Program (IDCRP) was founded in 2005 under an interagency agreement between the Uniformed Services University of the Health Sciences (USU) and the National Institute of Allergy and Infectious Diseases (NIAID). The program's work is executed through a unique, adaptive and collaborative, international clinical research network. This network directly affects force readiness by advancing clinical practice and informing health policy for military personnel.

In collaboration with partners from the Department of Defense (DoD), academia, government, and industry, IDCRP supports a broad clinical research portfolio within the Military Health System. From observational, longitudinal cohort studies to field-based interventional trials to evaluation of long-term health outcomes, IDCRP conducts protocols that address critical knowledge gaps in the control and prevention of infectious disease in the military. Study outcomes have far-reaching implications for public health and disease prevention beyond military communities.

PROGRAM ORGANIZATION

Executive Steering Committee

Dean, School of Medicine, Uniformed Services University of the Health Sciences (USU),
Chief, Division of Clinical Research (DCR), National Institute of Allergy and Infectious Diseases (NIAID)
Director, Research, Development and Acquisition, Defense Health Agency (DHA)

Operational Steering Committee

Surgeons General Infectious Disease
Consultants—Army, Navy, Air Force

Director, Armed Forces Health
Surveillance Branch

Director, Military Infectious Diseases
Research Program, MRMC

Chief, Collaborative Clinical Research
Branch, DCR, NIAID

Chair, Department of Preventive
Medicine and Biostatistics, USU

Veterans Affairs Representative (non-voting)
HJF Representative (non-voting)

Program Coordination Center

Program Director

Science Directorate

Science Director

Deputy Science Director
Research Area Directors
Clinical Research Managers

NIAID Liaison

Chair, Scientific Review Board

Deputy Program Director

Research Administration Staff

Regulatory Affairs Staff

Chief, Program Operations and Finance
Program Management and Finance Staff

Data Coordination Center

Chief, DCC

Data configuration, management,
and programming staff

Partner Organizations

Military Hospitals

Military Research and Development Commands

Military Public Health Commands

Non-DoD Partners

VISION

To substantially reduce the impact of infectious diseases in the military population through collaborative clinical research.

MISSION

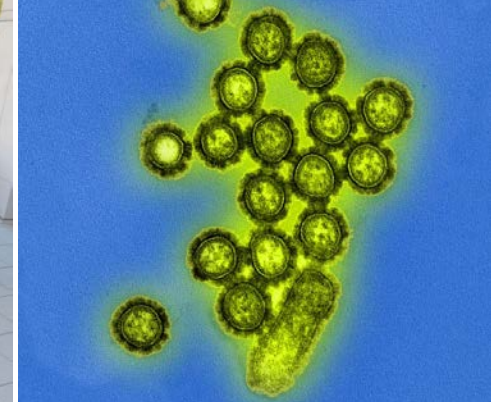
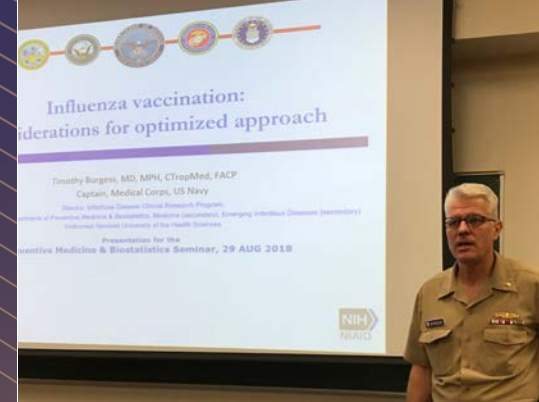
To conduct multicenter infectious diseases clinical research, focusing on high-impact cohort and interventional trials, to inform and improve care of the Warfighter.

IDCRP RESEARCH AREAS

- **Acute Respiratory Infections**—Strategic aims focus on diagnostics, prevention (influenza vaccine), epidemiology (recruit ARI threats), and treatment (severe influenza) of acute respiratory infections among U.S. military personnel and their beneficiaries.
- **Deployment and Travel-Related Infections**—Strategic aims focus on epidemiology of deployment and travel-related infectious threats for military personnel, pre-travel health care and mitigation strategies, novel methodologies for identifying pathogens associated with febrile and diarrheal disease, and improved treatment approaches during deployment.
- **Emerging Infectious Diseases and Antimicrobial Resistance**—Strategic aims focus on emerging infection threat epidemiology along with optimal diagnostic approaches, prevention, and therapeutic interventions.
- **Human Immunodeficiency Virus Infections**—Strategic aims include mitigating specific complications of the virus among military HIV-infected patients; identifying, treating, and preventing HIV-associated neurocognitive disorders; developing and employing predictive models to optimize individual management of HIV; and improving therapeutic outcomes with the ultimate goal of functional cure of infection.
- **Skin and Soft-Tissue Infections**—Strategic aims focus on development of effective strategies for the prevention and control of SSTIs, particularly *Staphylococcus aureus*-related, including vaccine-based interventions, among congregate military personnel in deployment and training settings.
- **Sexually-Transmitted Infections**—Strategic aims focus on development of improved means to diagnose, prevent, and treat sexually-transmitted infections, with particular focus on emergent drug-resistant gonorrhea, among active-duty members and their beneficiaries.
- **Trauma-Related Infections**—Strategic aims focus on addressing knowledge gaps in infection prevention, clinical management, and treatment outcomes in battlefield trauma to inform DoD Joint Trauma System clinical practice, as well as improved understanding of wound microbiology impact on clinical outcomes related to high-threat virulent and antimicrobial-resistant pathogens.

Each area's 2018 accomplishments are presented in the following pages, along with information and projections for 2019.

ACUTE RESPIRATORY INFECTIONS (ARI)



Seasonal outbreaks of acute respiratory infections (ARI) represent a considerable threat to both the health of military personnel and operational readiness during deployment. Among active-duty service members, 30% of infectious disease hospitalizations are the result of ARIs, highlighting the burden of these infections on the Military Health System (MHS).



Christian Coles, PhD,
ARI Research Area
Director



As a result of living in close quarters during training and deployment, along with stressful working conditions in disease endemic regions, military personnel are at increased risk for ARIs. Timely data are needed to accurately describe and monitor the ARI burden in the U.S. military, improve clinical management of influenza-like illness (ILI), and develop and evaluate the impact of ARI control measures.

Led by Dr. Chris Coles and CAPT Timothy Burgess, the cornerstone of the research area is the multi-site, longitudinal ARI Consortium Natural History Study (ARIC NHS), which collects data on the etiology, epidemiology, and immunology of ILI and severe ARI (SARI) in the military. Since initiation of the study in 2009, ARIC NHS has enrolled over 1,910 and 175 cases of ILI and SARI, respectively. Monthly surveillance reports on enrollment, along with ARI etiology and burden data, were provided to the Armed Forces Health Surveillance Branch (AFHSB) Global Emerging Infections Surveillance (GEIS) program and Naval Health Research Center.

Despite wide influenza vaccine coverage in the MHS, effectiveness has been sub-optimal (~19% in Armed Forces personnel and ~51% in

military beneficiaries); however, reasons for the disparities are unknown. As a result, a new protocol, the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED), was developed to assess if differences in vaccine formulations accounted for the variation in effectiveness. The two-year study led by CAPT Burgess began enrolling subjects at five military hospitals in October. Another novel protocol, the Impact of Influenza Vaccine Experience on Effectiveness, will examine the effect of repeated immunizations on influenza acquisition and severity in DoD populations.

Led by Dr. Coles, the Study to Address Threats of ARI in Congregate Military Populations (ATARI) focuses on the assessment of ILI transmission, etiology, and epidemiology among U.S. Army recruits at Fort Benning (GA). In the early weeks of training, symptomatic ILI was associated with coronavirus, rhinovirus, enterovirus, and influenza. Based on self-reporting, 33% of the enrolled trainees had an ILI episode with the majority not seeking healthcare. These findings demonstrate that attack rates based on clinic attendance largely underestimates the ILI burden.

Enrollment at five ARIC NHS sites (led by CDR Janine Danko) as part of the collaborative, multi-site National Institutes of Allergy and Infectious

CAPT Burgess presenting at a USU
Department of Preventive Medicine
and Biostatistics seminar

Diseases (NIAID)-sponsored FluPlasma 2 trial designed to examine the efficacy of hyperimmune anti-influenza plasma for treatment of severe influenza closed in 2018 and data analysis is underway. In the coming year, the IDCRP will continue to partner with GEIS to conduct ILI surveillance in the high-risk trainee population at Fort Sam Houston (TX), as well as contribute samples to the GEIS Bioinformatics Consortium for advanced etiology characterization.

In 2019, the ARI Research Area will build on its collaborative network, along with investigator expertise and experience in conducting interventional studies, with particular emphasis on influenza vaccine effectiveness. Furthermore, opportunities to examine ILI in deployed settings, such as shipboard populations, will be investigated.

MILITARY IMPACT

The goal of the ARI Research Area is to support the development of effective ARI control strategies for the U.S. military to limit the impact of ARI on the health, performance, and mission-readiness of active-duty personnel. Since 2009, our findings have advanced understanding of the changing distribution and determinants of ARI in this population, as well as its control. This is achieved through continued military hospital-based ARI surveillance to provide epidemiology, clinical severity, and burden of disease estimates in relevant groups; surveillance for viral respiratory pathogens with pandemic potential and “routine” respiratory pathogens that might impact operational readiness; characterization of temporal and regional changes in circulating influenza virus subtypes and genotype strains; contributing healthcare utilization and operational burden data to allow comparison of the cost-effectiveness of different control measures designed to enhance force health protection; and providing performance data on detection tools needed to assess impact on routine surveillance for pathogen-specific respiratory infections.

HIGHLIGHTS/KEY FINDINGS

- The Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) is a novel protocol that is designed to determine whether there are clinically meaningful differences in the effectiveness and immunogenicity between egg-derived, cell-culture-derived, and recombinant licensed influenza vaccines.
- In an ARIC NHS study, 12% of 902 subjects were positive for coronavirus with HCoV-OC43 contributing the greatest proportion. Except for greater gastrointestinal symptoms with HCoV-HKU1 species, there were no species-specific differences in clinical characteristics.
- In an ARIC NHS study, 12% of 902 subjects were positive for coronavirus with HCoV-OC43 contributing the greatest proportion. Except for greater gastrointestinal symptoms with HCoV-HKU1 species, there were no species-specific differences in clinical characteristics.
- Assessment of the standardized FLU-PRO questionnaire by hospitalized and non-hospitalized patients with ILI found the scores to be reliable, reproducible, and responsive to change in patients testing negative for influenza, suggesting that it can be used in studies of confirmed influenza and ILI.
- Influenza contributed the greatest burden to SARI cases (detected in 43% of patients), while rhinovirus/enterovirus had the highest proportion in ILI cases (17% of patients) followed by influenza (12% of patients).

DEPLOYMENT AND TRAVEL-RELATED INFECTIONS



TravMil enrollment at Schofield Barracks, Hawaii



Deployment Travel Meeting April 30, 2018



Dr. Lalani presenting at the 2018 Military Health System Research Symposium

Deployment and travel-related infections are a considerable source of morbidity among military personnel and substantially impact military operational readiness.



Tahaniyat Lalani, MBBS, MHS, Deployment and Travel-Related Infections Research Area Director



Service members are at risk for various infectious disease threats during deployment, with the most common being travelers' diarrhea (TD), but also includes vector-borne illnesses (e.g., malaria, dengue, and Zika virus) and respiratory pathogens. These infections directly and adversely affect the readiness of military operations. The primary goals of the Deployment and Travel-Related Infections Research Area are to 1) assess epidemiologic threats and clinical and operational outcomes, 2) develop rapid diagnostic platforms for pathogen-specific diagnoses in the deployed setting, and 3) perform clinical trials and effectiveness studies to improve prevention and treatment recommendations.

The central protocol of the research area is the Deployment and Travel-Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies among DoD Beneficiaries (TravMil) cohort study, led by Dr. Tahaniyat Lalani. During 2018, TravMil continued to enroll subjects with a focus on deployers/travelers going to regions with risk of TD or vector-borne pathogens. Over the last few years, the TravMil study has also expanded from being at select military travel clinics to recruiting, enrolling, and following up with large groups at deployment locations, such as Soldier Readiness Processing sites. This change has allowed for increased engagement with Combatant Commands (COCOM), Force Health Protection offices, and deploying units.

The prevention and treatment of TD remains a high priority to COCOMs. During the past year, enrollment in the Trial Evaluating Regimens of Rifaximin for Chemoprophylaxis against Travelers' Diarrhea (Prevent TD), led by CAPT Ramiro Gutierrez at the Naval Medical Research Center, continued at two U.S. sites. To date, 196 subjects have been enrolled, including 101 service members participating in the Pacific Pathways exercise in 2018. Enrollment is expected to be completed in 2019 and will include British military personnel participating in a training exercise in Kenya through a partnership with the United Kingdom Ministry of Defence.

As part of the Trial Evaluating Treatment of Ambulatory Travelers' Diarrhea (TrEAT TD) protocol, and in collaboration with the University of Virginia, the IDCRP sponsored development of a customized TaqMan® PCR assay for detection of pathogens associated with TD. Assessment of the performance characteristics of the TaqMan assay in the deployed setting was completed and a manuscript was published in PLOS One. Owing to its high sensitivity and specificity, widespread use of the assay is now occurring within several national and international surveillance and research settings. In addition, laboratory testing for studies related to characterizing the immune responses of patients with enterotoxigenic *Escherichia coli* and enteroaggregative *E. coli*-associated watery diarrhea, as well as the antibody response to *Shigella* proteins and/or lipopolysaccharides in the sera of patients with acute *Shigella*-associated disease was completed. Analysis of the data is forthcoming for 2019.

During 2018, the Diarrhea Case-Cohort study, a new protocol led by Dr. David Tribble and supported by Global Emerging Infections Surveillance (GEIS), was initiated to provide pathogen-specific diarrhea incidence information for DoD beneficiaries stationed on Oahu. The study will assess region-specific disease risk based on travel history and findings will further the understanding of clinical, microbiological, and immunological outcomes.

Another protocol is the Knowledge, Attitudes, Practice, and Outcomes Study (KAPOS), which is led by COL Patrick Hickey at USU. The focus of the study is to evaluate Military Health System providers' breadth of knowledge and practice patterns related to the prevention of infectious diseases in the pre-travel and pre-deployment settings, which are critical issues for mitigating infectious disease threats and optimizing force health protection in the expeditionary military. Presently, data collection and analysis is underway with the focus on developing a traveler cohort and examining prescription patterns within travel medicine specialists and non-specialists.

MILITARY IMPACT

The Deployment and Travel-Related Infection Research Area focuses on disease surveillance and randomized trials and has provided an evidence base to develop deployment-related clinical practice guidelines for management of acute watery diarrhea. This achievement addressed an important goal for the research area, which is to inform practice guidelines based on evidence accrued from clinical trials, and laid the groundwork for future implementation science initiatives. In addition, several protocols in the research area (TrEAT TD, TravMil, Prevent TD and the Stool Card Validation study) evaluate the use of field expedient diagnostics for determining the pathogen-specific epidemiology of illnesses, which will inform the development of effective preventive and treatment measures. Looking forward, the research area will focus on collaborative efforts with GEIS and the USU Center for Global Health Engagement to best address COCOM-specific priority surveillance efforts, as well as using data-driven guidelines to improve the practice of deployment and travel medicine through our knowledge, attitudes, and practices initiatives.

HIGHLIGHTS/KEY FINDINGS

- Nearly 200 subjects have enrolled in Prevent TD and approximately 90% have been randomized and received the study drug with deployments either completed or underway.
- Sensitivity and specificity of TaqMan® Array PCR on frozen stool using Whatman FTA Elute cards was 73% and 98%, respectively. These findings support use of FTA cards in combination with the TaqMan assay for detection of TD enteropathogens in the field setting.
- Susceptibility to *Campylobacter* infection is likely high with only small doses required for colonization. In *Campylobacter* outbreaks, illness occurs at lower doses, while high doses are required for challenge studies and is potentially the result of selection bias.
- In a TravMil laboratory study, *in vitro* assessment of sera from two subjects with Zika infection suggest that high levels of dengue virus cross-neutralizing antibodies could potentially prevent enhancement of dengue infection in individuals with prior Zika exposure. *In vivo* studies are needed to further examine the cross-reactivity.

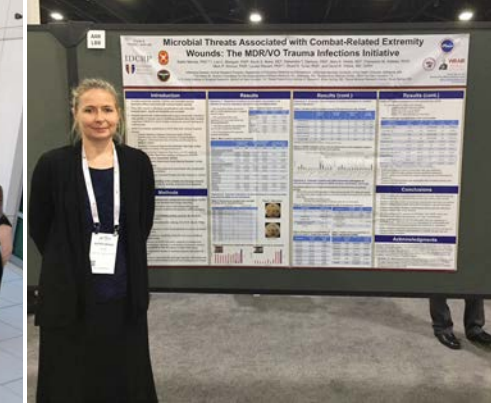
EMERGING INFECTIOUS DISEASES AND ANTIMICROBIAL RESISTANCE (EIDAR)



LTC Lanteri receiving a tour of the Jungle Warfare Training Center (Okinawa, Japan) from the company commander



Emerging Infectious Diseases & Antimicrobial Resistance (EIDAR)



Dr. Katrin Mende presenting a poster at 2018 ASM Microbe

New or re-emerging infectious diseases constitute a considerable threat to force health protection and operational readiness for military personnel deployed to disease-endemic regions. Multidrug-resistant infections, which are associated with substantial morbidity, represent another threat to deployed personnel as the incidence of these infections are increasing worldwide.

The Emerging Infectious Diseases and Antimicrobial Resistance (EIDAR) Research Area conducts clinical studies to assess emerging global infectious disease threats to military operations (e.g., multidrug-resistant organism [MDRO] trauma-related infections and vector-borne pathogens) in terms of epidemiology, etiology, patient outcomes, and the consequent impact on the health and readiness of U.S. military service members. With the goal of answering the requirements of the Global Health Security Agenda and the National Security Strategy for preparedness and response related to infectious disease outbreaks, the EIDAR research portfolio focuses on two critical elements: 1) preparing for emergent conditions to systematically collect clinical specimens and data and conduct clinical trials that can assist the military with a scientifically appropriate response; and 2) evaluating burden of militarily-relevant infectious diseases and assessing risks for exposure and development of post-infectious complications and overall impact on military readiness. To that end, EIDAR has continued to develop strategic partnerships with the Armed Forces Health Surveillance Branch section on Global Emerging Infections Surveillance (GEIS), as well as the USU Center for Global Health Engagement (CGHE) in order to support force health protection directives. A cornerstone of EIDAR is the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EpiCC-EID) contingency protocol, which is designed to activate when patients are diagnosed with high-consequence infections at military treatment facilities. When activated, EpiCC-EID provides a unique capability by allowing the DoD to address

clinical questions in parallel with a public health response through the collection and analysis of specimens, clinical outcomes, and epidemiologic data crucial to informing effective patient management. Another function of EpiCC-EID is that it provides the groundwork for conducting interventional trials with collaborative research partners, as well as evaluating new diagnostic assays, drugs, or vaccines in patients throughout the Military Health System (MHS).

A significant accomplishment of 2018 was the development of a new EIDAR protocol in response to the largest outbreak of Shiga toxin-producing *Escherichia coli* (STEC) within the U.S. military. This prospective cohort study will examine the long-term health impacts of STEC infections through a 5-year follow-up online survey related to clinical outcomes. This study aims to identify risk factors for chronic post-infectious health issues that can be applied to improving outcomes during potential future infectious diarrhea outbreaks, which is a serious threat among U.S. military trainees. The EIDAR research portfolio further expanded as three new protocols (all supported by GEIS) that leverage the DoD Serum Repository received USU Institutional Review Board approval in 2018, allowing data collection to commence. One of the studies focuses on active-duty personnel stationed at a high-risk disease endemic military installation (i.e., Pacific Naval Air Station Lemoore) to examine the seroincidence and risk of *Coccidioides* infection, which is a fungal infection characterized by substantial morbidity and mortality. A second study will examine the risk for infection with *Borrelia* bacteria (responsible for Lyme disease and related syndromes) and clinical outcomes

among personnel at U.S. military training facilities in endemic regions of the United States. This study is in collaboration with the USU Department of Pathology who will conduct serological testing. The final study, in collaboration with the Walter Reed Army Institute of Research Viral Diseases Branch, will assess the burden and impact of Zika-like illness on the fitness for duty of military service members at Rodriguez Army Health Clinic in Puerto Rico.

Over the past year, the EIDAR team continued to investigate clinical questions related to militarily-relevant MDRO issues. In particular, through collaboration with the Trauma-Related Infections Research Area, multiple analyses under the Multidrug-Resistant and other Virulent Organisms (TIDOS MDR/VO) Trauma Infections Initiative (led by Dr. Katrin Mende, EIDAR Deputy Director) assessing wound microbiology and interaction of wound pathogens are underway. Moreover, through collaboration with the Deployment and Travel-Related Infections Research Area, data analysis on the TravMil MDRO colonization study is nearing completion.

In support of DoD Combating Antibiotic-Resistant Bacteria (CARB) Initiative, the Antimicrobial Resistance/Antimicrobial Stewardship (ASP) Clinical Research Consortium established by EIDAR in 2017 performed a landscape review of ASP efforts

within the MHS and identified clinical evidence gaps to be addressed by multi-site studies. The Consortium is developing a Knowledge, Attitudes, and Practices survey to identify trends and practices driving antimicrobial prescribing patterns among MHS healthcare providers.

MILITARY IMPACT

The EIDAR Research Area remains responsive to both persistent and ever-evolving infectious disease threats impacting the health and operational readiness of the U.S. military. The EIDAR research portfolio includes studies that address clinical knowledge gaps on identifying and characterizing emerging infectious disease threats with the overall goal of providing actionable information to inform force health protection guidance. The EIDAR team is also conducting microbiological investigations to support development of improved clinical practices to prevent emergence and transmission of virulent, difficult-to-treat, multidrug-resistant bacterial, and fungal wound infections. Lastly, EIDAR functions as the central coordinator of multi-site studies assessing key clinical knowledge gaps crucial for promoting ASP practices to avert the emergence and spread of antimicrobial resistance within the MHS.

HIGHLIGHTS/KEY FINDINGS

- EIDAR will lead the first study examining long-term consequences of STEC infections among a U.S. military population in response to the U.S. Marine Corps Recruit Depot-San Diego outbreak (largest within the U.S. military). This study will assess incidence of functional bowel disorders, osteoarticular symptoms, and quality of life issues.
- A new collaboration with investigators at the U.S. Army Medical Research Institute of Infectious Diseases will expedite molecular and immunological testing of clinical specimens, particularly those requiring high-level (i.e., Biosafety Level-4) capabilities, to assist in evaluating high-consequence pathogens among MHS patients.
- EIDAR is conducting the first study within the U.S. military to assess the seroincidence of a newly identified *Borrelia* species recently recovered near Fort McCoy (Wisconsin).
- A study is underway evaluating ~7,500 cases of antibiotic-resistant bloodstream infections within the MHS to identify risk factors and evaluate outcomes.

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

More than 10,000 active-duty service members have been infected with HIV and there are still approximately 300 new HIV diagnoses per year over the past decade. As a result of early diagnosis and the mounting success of antiretroviral therapy, the number of HIV+ service members who are able to remain on active duty has risen; however, non-AIDS complications, such as neurocognitive impairment, are being increasingly recognized at a younger age and constitute a threat to long-term health.



Brian Agan, MD,
Deputy Science Director
and HIV Research Area
Director



Since clinical research related to HIV in the Military Health System was first initiated, understanding of the disease has significantly improved; however, data gaps are still being identified. Further research is needed to determine best methods to ensure long-term survival, minimize the occurrence of non-AIDS complications, maximize fitness for duty for HIV+ service members, examine the ‘cascade of care’ among newly diagnosed service members, and improve HIV and sexually-transmitted infection (STI) prevention programs. These vital issues represent the core strategic aims of the HIV Research Area, with the central goal of ensuring and restoring the long-term health and function of HIV+ military personnel and beneficiaries.

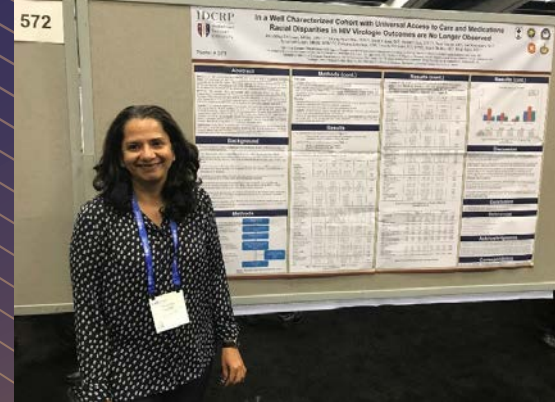
The cornerstone of the HIV Research Area is the U.S. Military HIV Natural History Study (NHS), which is led by Dr. Brian Agan and provides research and specimen collection essential to further understand the impact of HIV in the military setting. Presently, the NHS has enrolled over 6,100 HIV+ active-duty service members and beneficiaries and collected an extensive amount of data and specimens for analysis.

During 2018, investigators from the University of Duisburg-Essen requested assistance from NHS investigators to confirm a finding from their cohort that suggested that use of integrase strand transfer inhibitor (INSTI) antiretroviral therapy (ART) resulted in loss of CD4 cells after approximately three years of treatment. Using NHS long-term follow-up data, a similar observation was noted. As

INSTIs are recommended first-line HIV therapy in multiple regions of the world, including the United States and Europe, these findings may prompt further evaluation, if they are replicated. Follow-on laboratory analyses have suggested a potential mechanism of action and additional study is underway.

Among a portion of individuals who adhere to ART regimens, there is insufficient increase in CD4 levels, and this immune non-response (INR) has been associated with adverse outcomes. As part of a collaboration with the U.S. Military HIV Research Program (MHRP), low CD4 levels and a longer time of HIV infection prior to ART initiation were identified as INR risk factors. Presently, an investigation using a systems biology approach in collaboration with Case Western Reserve University to further examine INR risk factors is underway. In collaboration with the Atlanta Veterans Affairs Health Care System, Emory University, and the Medical College of Wisconsin, a standardized definition of INR to increase comparability of findings across studies and support identification of INR predictors is being developed.

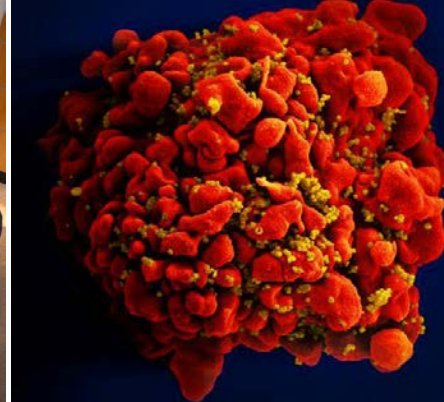
Although it is becoming increasingly recognized that non-AIDs comorbidities are more common in people with HIV, including military personnel, the amount of the burden attributable to HIV and which risk reduction treatments are effective is uncertain. One comorbidity, HIV-associated neurocognitive disorder (HAND), is the chief reason that HIV+ service members are assigned limited duty status. Evaluation of the functional consequences of HAND in a high demand setting and developing methods to enable easier



Dr. Anuradha Ganesan presenting at the
2018 IDSA IDWeek



IDCRP
Uniformed
Services
University
2018 IDCRP HIV Research Area Annual Meeting



identification of the disorder are crucial areas of research with potential military policy implications that may allow active-duty members with HIV to expand job functions and increase rank. During 2018, the HIV Associated Neurocognitive Disorders (ALLHANDS) protocol completed enrollment of HIV+ and HIV- subjects and longitudinal follow-up visits are underway. Four presentations with findings from ALLHANDS were presented at the annual National Institutes of Health (NIH) NeuroHIV workshop, which is attended by experts from multiple NIH Institutes and the academic community.

This past year also saw progress with other HIV Research Area protocols. The HIV Virtual Cohort Study (VCS) continues to move forward and initial abstraction of data through the Military Health System Data Repository is beginning. For the Rifaximin study, led by Dr. Anuradha Ganesan, data analysis for the randomized controlled trial was completed. Primary analysis of data collected from sites in the United States, Kenya, and Thailand was completed as part of Immune Reconstitution Inflammatory Syndrome (IRIS) protocol (led by Dr. Irini Sereti of NIAID and Dr. Jintanat Ananworanich of MHRP). The Strategic Timing of Anti-Retroviral Therapy (START) protocol was successfully transitioned to long-term follow-up with simplified visits. Lastly, long-term cellular and viral reservoir data collected for the CD4 Zeta protocol, led by COL (Ret.) Naomi Aronson, to examine the HIV reservoir and persistence of the gene therapy modified cells is underway.

We anticipate the coming year to be successful in our expanding areas of HIV research. Non-AIDS outcomes, including the study of HAND, remain a priority. With the possibility of a functional cure, we are also working with MHRP to consider a trial of a therapeutic HIV vaccine.

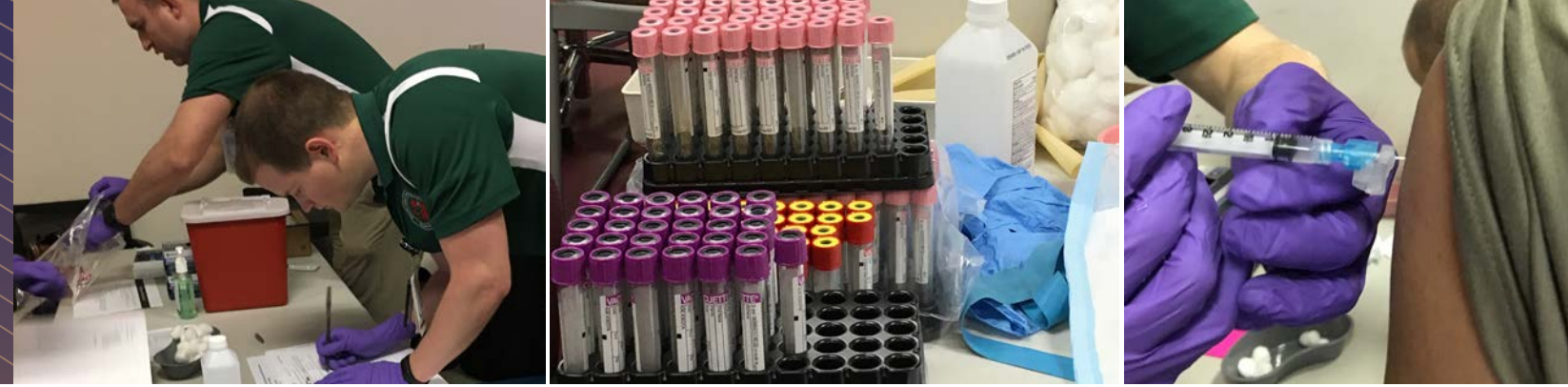
MILITARY IMPACT

The HIV Research Area portfolio supports the Military Health System by evaluating clinical care and serious outcomes among people diagnosed with HIV. The HIV VCS seeks identifiable or modifiable risk factors for adverse effects of HIV that may enable early diagnosis, treatment, or prevention. Our current work to evaluate the ‘cascade of care’ among active-duty found to be newly HIV+ to identify potential areas for military care improvement is nearly complete among NHS subjects and will be expanded into the HIV VCS. Recently, we convened a DoD HIV Quality of Care Interest Group comprised of Service Leaders for HIV and IDCRP investigators, along with representative from Defense Health Agency (DHA), MHRP, and USU Health Services Research Program. Lastly, our assessment of STIs among HIV+ subjects continues to generate data that may inform policy to improve diagnosis and treatment of these infections, as well as enhance understanding of transmission to support preventive efforts in the military.

HIGHLIGHTS/KEY FINDINGS

- Immune non-response was observed in 11% of NHS subjects and 26% of MHRP African Cohort subjects. A CD4 slope <100 cells/uL/year over first 1-2 years of therapy was reproducible and the best predictor of clinical outcomes.
- Examination of the NHS participant survey showed a high level of willingness to participate in interventional HIV studies. This is evidenced by a high rate of enrollment in ALLHANDS for optional lumbar puncture and MRI scans.
- NHS investigators provided subject-matter expertise to DHA as they respond to the National Defense Authorization Act of 2017 to evaluate HIV viral suppression rates among HIV+ receiving care in the military, which includes assisting with case definitions, evaluating findings, and advising on additional quality care metrics.

SKIN AND SOFT-TISSUE INFECTIONS (SSTI)



Staphylococcus aureus vaccine trial at Fort Benning, GA, in January 2018

Military personnel, particularly trainees and deployed service members, are at increased risk for developing skin and soft-tissue infections (SSTIs), which are most frequently caused by Staphylococcus aureus. As these infections impose a substantial operational and healthcare utilization burden, SSTIs are a top concern of the Military Health System.



Eugene Millar, PhD,
SSTI Research Area
Director

Due to the high infectious disease burden associated with SSTIs, the overall objective of the research area is to determine effective strategies related to the prevention and control of SSTIs in military populations. Among congregate populations, such as military trainees, SSTIs are largely caused by *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), and, as such, IDCRP prevention strategies and associated epidemiologic studies primarily focus on this pathogen.

In January 2018, we initiated a Phase 2 trial of a *S. aureus* vaccine candidate (NDV-3A; NovaDigm Therapeutics, LLC), led by LTC Jason Bennett (USU), among U.S. Army Infantry trainees at Fort Benning, GA, to evaluate the safety, immunogenicity, and efficacy of vaccination against nasal acquisition of *S. aureus*. Funded through the U.S. Army Medical Materiel Development Activity, this study is a significant achievement as it is the first *S. aureus* vaccine

trial to be conducted in a high-risk population of military trainees. Use of a vaccine to inhibit *S. aureus* colonization would be momentous in furthering the development of strategies related to the prevention of SSTIs in military populations.

In addition to the vaccine trial, the SSTI Research Area, led by Dr. Eugene Millar, has a broad portfolio of observational research studies (led by LTC Bennett and Dr. Millar), which strengthen the evidence base of SSTI and *S. aureus* epidemiology, risk factors, clinical characteristics, immunology, and microbial genomics. In 2018, data analysis was completed for the Submarine MRSA Study, which found a moderate level of *S. aureus* colonization among U.S. Navy submariners at Kings Bay, GA; however, the prevalence of MRSA was low and no cases of SSTIs occurred during the deployment period. This negative study was important to allay Command concerns regarding this pathogen.

The genomic characterization of *S. aureus* infection and colonization isolates is also a focus of multiple studies. As part of the SSTI Cohort Study at Fort Benning, longitudinal data on the transmission, acquisition, and natural history of SSTIs, including MRSA SSTIs, were collected from military trainees. Presently, molecular characterization of *S. aureus* isolates is nearing completion. In addition, through a collaboration with the Harvard School of Public Health, the dynamics of MRSA transmission are being examined using whole genome sequencing. Genomic methods are also being applied in the analysis of specimens from the Epidemiology, Etiology, and Immunology of SSTI study. In particular, MRSA colonization isolates were assessed in collaboration with the Naval Medical Research Center (NMRC) Biological Defense Research Directorate and methicillin-susceptible *S. aureus* infection isolates are being examined by Walter Reed Army Institute of Research (WRAIR) Multidrug-Resistant Organism Repository and Surveillance Network (MRSN). Furthermore, through a new collaboration with the Johns Hopkins Applied Physics Laboratory, whole genome sequencing of *S. aureus* isolates from individuals with recurrent *S. aureus* SSTIs was recently completed, using specimens from the SSTI Epidemiology study and the SSTI Prevention Trial. Finally, investigators in the Department of Microbiology and Immunology at USU are examining characteristics of the host microbiome, namely longitudinal changes in microbiome and its association with infection risk.

In 2019, enrollment and follow-up activities for the Phase 2 *S. aureus* vaccine trial at Fort Benning are expected to be completed with results by 2020. The processing of immunology and microbiome specimens collected from the prior cohort studies is nearing completion and analyses are planned for the upcoming year. New initiatives related to the genomic and proteomic characterization of *S. aureus* clinical and colonizing isolates are also underway.

MILITARY IMPACT

Substantial operational, healthcare, and economic costs are associated with the burden of SSTIs, particularly MRSA-associated SSTIs, in military populations. Efforts under the SSTI Research Area support the development of preventive strategies by (1) generating epidemiological, clinical, immunological, microbiological, and genomic data related to SSTIs among high-risk military trainees; (2) detailing the epidemiological and economic burden of SSTIs in military training setting; (3) assessing the effectiveness of personal hygiene-based efforts on other common communicable diseases, such as acute respiratory infections; (4) examining transmission dynamics of MRSA in SSTI clusters among trainees via whole genome sequencing; and (5) conducting a Phase 2 *S. aureus* vaccine trial among military trainees to evaluate effectiveness in the prevention of nasal acquisition. Together, these initiatives will provide a strong evidence base to combat the threat of SSTIs among military populations.

HIGHLIGHTS/KEY FINDINGS

- Following initiation of the Phase 2 *S. aureus* vaccine trial at Fort Benning, GA, more than 50% of the target population of U.S. Army Infantry trainees have been enrolled with the completion of the trial expected to occur in mid-2019. Future interventional trials in the high-risk military training population will benefit from the successful execution of this current trial.
- Among U.S. Navy submariners, 25% were nasally colonized with *S. aureus* prior to deployment and 13% were colonized at a post-deployment visit. Prevalence of MRSA was <1% and no SSTIs were identified.
- Molecular genomics studies found that intrahost reservoirs are common among individuals with recurrent *S. aureus* SSTIs, which indicate that host decolonization strategies after the initial infection may be necessary to reduce the risk of recurrence.
- Methicillin-susceptible *S. aureus* (MSSA) contributes ~40% of *S. aureus*-associated SSTIs and the majority of colonizing isolates. Genomic characterization of MSSA isolates will advance our understanding of the epidemiology and pathogenesis of these infections.



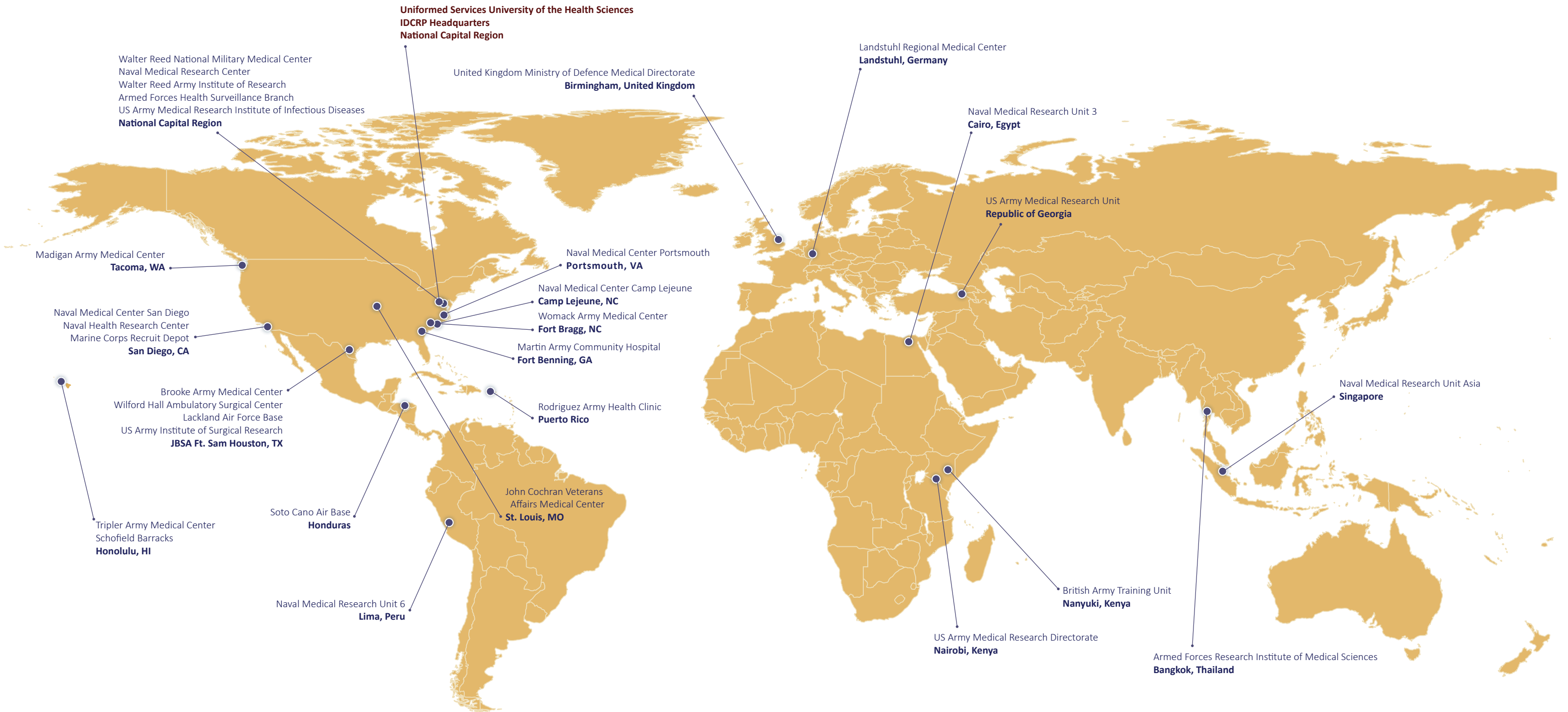
2018 SSTI Research Area
Investigator Meeting

IDCRP PARTNER NETWORK

31
PARTNER SITES

120+
EMPLOYEES

71
ACTIVE PROTOCOLS



SEXUALLY-TRANSMITTED INFECTIONS (STIs)



2018 STI Annual Investigators Meeting

LTC Garges presenting at the 2018 STI Investigator Meeting

Sexually-transmitted infections (STIs) are widespread in the Military Health System (MHS), constituting a threat to force health protection and medical readiness. In addition, ongoing prevention and treatment efforts are essential, as highly mobile militaries and defense forces can play a role in the global distribution of emerging and resistant STIs.



LTC Eric Garges, MD,
STI Research Area
Director

Despite having similar demographics, military service members have high rates of STIs compared to their civilian counterparts. In general, the risk of STIs among military populations has not changed considerably over the last few years, with STIs remaining among the most common reportable infections among military active-duty and a substantial threat to force health protection. While surveillance data are available, few systematic studies have been conducted to examine and better understand these trends.

The cornerstone of the STI Research Area remains the *Neisseria gonorrhoea* (GC) Resistance Study and Repository, which is led by LTC Eric Garges and Dr. Ann Jerse. Over the past year, the domestic GC epidemiologic study has continued at Brooke Army Medical Center, Madigan Army Medical Center, Naval Medical Center Portsmouth, and Naval Medical Center San Diego with Naval Medical Center Camp Lejeune being included as a new site. Presently, over 700 individuals have been enrolled in the study, providing valuable information on infection risk for gonorrhea and chlamydia within the MHS. The data on antimicrobial resistance collected from the sites has largely confirmed that patterns of antimicrobial-resistant GC isolates in service members are similar to those seen in their local communities.

Another protocol in the STI Research Area portfolio, led by Dr. Anuradha Ganesan, is the 3 Anatomic Site GC/CT Testing Among HIV+ DoD Beneficiaries study, which is focused on the prevalence of and risk factors for gonorrhea and

chlamydia. The study has provided important data on use of self-collected swab testing for STIs, as well as the incidence of extragenital disease in high-risk groups within the MHS. The antimicrobial resistance of GC isolates was also assessed. In 2019, the extragenital disease burden in a high-risk HIV-negative population within the MHS will be evaluated. A planned sub-study will characterize the molecular epidemiology of chlamydia infections in the same high-risk HIV-negative population, allowing for more precise identification of sexual networks.

A companion protocol was the 3 Site GC/CT Testing Among Well-Women study (led by Dr. Robert Deiss and CAPT Mary Bavaro), which focused on the scientific relevance of 3-anatomic site screening in well-women seeking care who were not identified as high-risk for STIs. As early findings suggested that increased screening in well-women of average risk did not indicate a hidden reservoir of disease, the study was closed early and data analysis completed.

After a strong showing in the pilot study at Naval Medical Center Portsmouth, the Social Networks Study to better understand military STI transmission pathways, led by LTC Garges, was initiated this past year. Presently, one-third of the target population has been enrolled. Data analysis is expected to be completed in 2019.

In the upcoming year, new studies will evaluate the burden of STIs over time and examine populations at high risk for STI-related sequelae. Analyses to describe provider practices and

adherence to treatment guidelines to better inform future interventions are also being developed. Furthermore, cost-effectiveness studies are needed to better understand the impact of STIs and related-conditions on MHS spending, which would inform decision-making related to allocation of resources. An additional focus of the research area will be on implementation science and systems approaches to STI prevention, diagnosis, and therapy.

MILITARY IMPACT

The overall goal of the STI Research Area is to support the prevention, diagnosis, and treatment of STIs to reduce risk and decrease disease among active-duty members and beneficiaries. Results from the GC resistance studies have provided contemporary data on antibiotic susceptibility patterns, as well as valuable information on the potential geographic origins of each isolate, supporting DoD operational planning and providing critical data related to the global distribution of antimicrobial-resistant GC. In our role as the coordinating center for the DoD GC Resistance Laboratory and

Repository, we provide standardized culture, susceptibility testing, and advanced molecular characterization of isolates submitted across the U.S. and overseas sites. Additionally, we serve as a reference lab and technical resource for the Global Emerging Infections Surveillance (GEIS)-funded partners with GC surveillance efforts taking place at the DoD overseas labs. The GEIS Data-to-Decision Initiative highlights the military value of our research area efforts, as timely epidemiologic data are provided directly back to Combatant Command Force Health Protection Officers for situational awareness and response, as needed. Looking forward, we intend to develop academic collaborations and other partnerships to evaluate biomedical countermeasures with direct military implications related to the management of STIs to have the greatest impact on operational readiness.

HIGHLIGHTS/KEY FINDINGS

- A GC isolate exhibiting resistance to cefixime was identified for the first time from the Republic of Georgia through a collaborative effort with GEIS.
- Increased exposure to antimicrobial-resistant STIs during deployment and travel has been a concern; however, findings indicate a lower level of resistance to commonly used antibiotics in deployed military personnel compared to the corresponding region.
- Studies to evaluate the Food and Drug Administration-approved 4cMenB (Bexsero®) vaccine for use in GC risk reduction are underway. If shown to be effective, this vaccine may serve a dual purpose in reducing the risk of both meningitis serogroup B and gonorrhea among service members.
- New collaborations with the Division of Microbiology and Infectious Diseases at the National Institutes of Allergy and Infectious Diseases are being established to evaluate potential forward-deployed diagnostic methods and to examine new therapeutics.

TRAUMA-RELATED INFECTIONS

Improving the prevention and clinical management of infections complicating battlefield trauma, particularly blast trauma, remains one of the highest priorities of the DoD. A further challenge in the care of patients with complex wounds and polytrauma is the occurrence of virulent and multidrug-resistant pathogens.



David Tribble, MD, DrPH, Science Director and Trauma-Related Infections Research Area Director



The primary aims of the Trauma-Related Infections Research Area are strategically focused to address knowledge gaps in the prevention and clinical management of combat-related infections. Specifically, research priorities include blast injuries, multidrug-resistant bacterial infections, long-term outcomes and quality of life, Joint Trauma System (JTS) clinical practice guidelines, and antibiotic stewardship. Since inception of the research area, the centerpiece protocol remains the Trauma Infectious Disease Outcomes Study (TIDOS), which is led by Dr. David Tribble. In brief, TIDOS systematically collected information on the medical management, microbiology, and infectious outcomes from military personnel wounded during deployment from June 2009 through December 2014. Infection-related follow-up data after hospital discharge continues to be captured from cohort enrollees through the Military Health System Data Repository. Data are also collected for enrollees who have entered Veterans Affairs (VA) health care through collaboration with the VA St. Louis Health Care System under the leadership of Dr. Jay McDonald.



The 3rd Japan-US Forum on Blast Injury (JUFBI 2018) May 9-11, 2018, Tokyo, Japan

In 2018, the 3rd Japan-US Technical Information Exchange Forum on Blast Injury brought together experts to share both knowledge and experiences related to blast trauma from across the globe. TIDOS investigators attended the meeting and presented information on blast wound infection epidemiology and microbiology. Findings from TIDOS analyses were also presented at the 2018 Military Health System Research Symposium session on minimizing the impact of wound infections following blast-related injuries.

Among combat casualties, extremity wounds are not only the most common type of injury, but are frequently complicated by infections. During 2018, an analysis to examine the effectiveness of specific antimicrobial regimens related to the treatment of deep soft-tissue infections was completed. While less common, non-extremity wound infections are also a focus of TIDOS analyses. One recently completed analysis on genitourinary injuries and urinary tract infections was conducted in collaboration with the VA St. Louis Health Care System. Presently, examination of the risk factors for intra-abdominal infections is underway.

As invasive fungal wounds infections (IFIs) are associated with substantial morbidity among blast



CPT Mary Ford (Internal Medicine Resident) presenting at San Antonio Uniformed Services Health Education Consortium Research Day



Trauma-Related Infections Research Area 9th Annual Investigators Meeting, 14-16 March 2018



Spot plating evaluating antagonistic activity of *Enterococcus* spp. against *Acinetobacter baumannii*

casualties, early diagnosis is critical for effective management and improved outcomes. The IFI Molecular Diagnostics Protocol, led by Dr. Anuradha Ganesan and funded under the Defense Medical Research and Development Program, assesses molecular diagnostics methods to support earlier diagnoses with increased accuracy. Following a comprehensive review by subject-matter experts, a technical report presenting findings of the assessment of a polymerase chain reaction (PCR)-based assay was presented to the JTS for consideration in review of JTS IFI practice guidelines. Additional evaluation of formalin-fixed surgical pathology tissue specimens from IFI patients diagnosed based on culture findings and not histopathology is underway to further assess the utility of the PCR-based assay.

Another serious complication of trauma is osteomyelitis, which is generally characterized by multiple surgeries, extended use of antibiotics, and lengthy hospitalizations and ambulatory care. The Trauma-Associated Osteomyelitis protocol, led by Dr. Tribble, evaluated risk factors for the development of osteomyelitis among combat casualties with open fractures of the tibia, femur, and arm long bones. Published analyses provide risk factors for initial and recurrent tibial osteomyelitis. Collaboration with the VA St. Louis Health Care System is also investigating long-term outcomes in these patients.

During 2018, numerous analyses were also completed under the TIDOS Multidrug-Resistant and Virulent Organisms (MDR/VO) Trauma Infections initiative, which is funded through the Military Infectious Diseases Research Program and led by Dr. Katrin Mende. The Initiative involves a collaborative effort across multiple DoD laboratories (Walter Reed Army Institute of Research, Naval Medical Research Center, U.S. Army Institute of Surgical Research, and Brooke Army Medical Center) with the goal of maximizing the understanding of complex polymicrobial wounds through use of clinical data connected to the TIDOS Microbiology Repository. Analyses being planned will further examine the interaction of common wound bacteria (e.g., ESKAPE pathogens), as well as assess clinical outcomes in relation to wound microbiology and biofilm formation.

MILITARY IMPACT

The research area's aims and objectives continue to be responsive to priorities of the DoD JTS and provide important information during inter-war periods by improving the understanding and best practices of infection-related issues following battlefield injury. The strengths and opportunities presented by this research area present a robust platform to support development and refinement of evidence-based clinical practice guidelines for the management of combat trauma-related infections during future conflicts.

HIGHLIGHTS/KEY FINDINGS

- Among patient with blast trauma, approximately one-fourth develop at least one trauma-related infection, with extremity wound infections being the most frequent.
- In a MDR/VO Trauma Infections Initiative analysis, 237 *Klebsiella pneumoniae* isolates were examined and multidrug resistance was associated with prior use of fluoroquinolones and anti-pseudomonal penicillin.
- Among 89 TIDOS-VA cohort enrollees with genitourinary trauma, 21% developed at least one urinary tract infection.
- Patients with open femur fractures characterized by substantial loss of muscle or dead muscle have high risk of developing osteomyelitis.
- IFI Molecular Diagnostics PCR-based assay had high specificity (99%) and sensitivity (83%) in tissues with documented angioinvasion when compared to histopathology as the reference standard.

THE IDCRP STAFF

The success of the IDCRP stems from its employees, who are highly skilled individuals with tremendous dedication to clinical infectious disease research and improving the health of military service members.

In 2018, the IDCRP employed an average of 120 research and program-support personnel who have demonstrated the exceptional capability of rising to the challenge of servicing a diverse portfolio of infectious disease research and a multifaceted workload within the program.

As the organization is focused on research, more than half of the staff are professionals who directly interact with both patients and research study subjects at the clinical sites. Detailed in the figure below, the majority of these research professionals are clinical research coordinators. The remaining members of the staff are comprised of investigators based at military clinical sites and USU and protocol-support personnel, such as clinical research and data managers, laboratory staff, and biostatisticians.

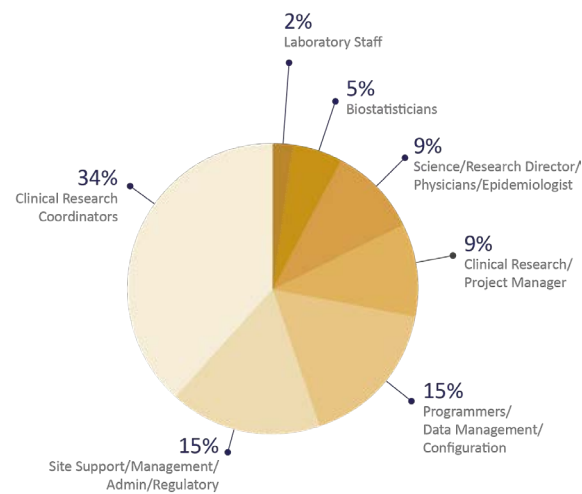
Among the diverse individuals comprising the IDCRP staff, expertise includes infectious diseases, preventive medicine, public health, epidemiology, microbiology, data programming, statistical analysis, and program management. Over half of the IDCRP staff members hold at least two degrees and all possess a wealth of knowledge and experience.

The staff of the IDCRP are highly integrated within DoD medical treatment facilities, USU, and operational clinics both within the United States and in overseas locations.

We wish to thank our employees for their continued excellence, diligence, and substantial contributions to the program.



The IDCRP Team at the 2018 IDCRP Leaders Meeting



IDCRP Personnel Distribution by Occupation, 2018

DATA COORDINATION CENTER

The Data Coordination Center (DCC) serves as a critical element of the IDCRP's research efforts by providing high-quality data collection, management, processing, and access.

The DCC team is comprised of data system designers, data managers, data entry staff, and SAS / Oracle programmers (led by Edward Parmelee, Chief) who support IDCRP research investigations by providing expertise related to the conceptualization, design, collection, management and cleaning, analysis, and publication of study data. The essential resources provided by the DCC are utilized for all IDCRP research studies where the Program is the primary source of data as either the collector or repository. During the past year, the data configuration programming and SAS programming groups were combined with the goal of improving productivity and effectiveness. Overall, 31 IDCRP studies were supported by the DCC in 2018, including 4 studies that were entirely Military Health System (MHS) Data Repository-based.

A considerable effort in 2018 was related to expanding the use of the MHS Data Repository as a data source for IDCRP studies. The IDCRP was first granted permission to access this valuable resource several years ago in order to supplement the data utilized in studies from the Trauma-Related Infections and HIV Research Areas. During the past year, the DCC began acquiring data for other virtual (i.e., relying solely on MHS Data Repository). Access to the MHS Data Repository is restricted and the DCC presently is working to increase the number of staff with appropriate clearance to be allowed to abstract data, which is expected to be completed in 2019.

Another accomplishment in 2018 was the implementation of REDCap, which is a fully-functional electronic data collection system and workflow approach widely used by academic organizations, as well as the DoD for designing and entering clinical data into study databases. The system provides participant interaction features not previously available, such as text messages. Using REDCap, the DCC completed setup of data collection systems for two protocols that required rapid development due to time constraints, something we had not been able to do with our legacy data systems. The protocols were the Shiga Toxin-producing *Escherichia coli* (STEC) Outbreak Investigation in the EIDAR Research Area and the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) trial as part of the ARI Research Area.

In 2019, the primary goals of the DCC are to continue implementation of REDCap and transfer current studies that use the older electronic data captures systems into a new data workflow in REDCap. In addition, REDCap will be validated as 21CFR11 compliant in order to use it to conduct intervention-based clinical trials. Furthermore, the IDCRP hosts a registry to store certain protected health information and personally identifiable information about subjects enrolled in our studies. As with the current electronic data capture systems, the registry system no longer meets the changing needs of the IDCRP, and a new registry will be implemented in the coming year.



*Edward Parmelee, MS
Chief, Data Coordination Center*

HIGHLIGHTS

- Acquired data from the MHS Data Repository for four studies and completed approval process necessary to acquire data for two additional studies.
- On-boarded and implemented use of REDCap with setup of electronic data collection systems for two new high priority protocols. Data collection systems were designed, programmed, and put into production within approximately two months.
- Implemented the National Institutes of Health Toolkit for cognitive assessment for the HIV Research Area ALLHANDS protocol.

PROGRAM OPERATIONS AND FINANCE

Program operations and finance is a critical component of the IDCRP, with staff members providing support to both the Program leadership and Research Area teams in order to accomplish program and research goals.



Samuel Davis, PhD, Chief, Research Support and Operations

Providing administrative support to the IDCRP, the Research Support Group (RSG) is led by LTC Charlotte Lanteri, IDCRP Deputy Director and EIDAR Research Area Director. Over the past year, the RSG has continued to be an essential element of the program, effectively coordinating travel requests for multiple protocols, organizing annual investigator meetings, tracking clearance requests for deliverables, and offering general support as needed.

The Program Management and Finance Team (PM/F) is led by Dr. Samuel Davis, the Chief of Program Operations and Finance. The PM/F team has diligently worked to improve the overall efficiency of the IDCRP by managing the ever growing portfolios of the seven research areas, as well as overseeing funding and delivering an array of process solutions and financial analyses to enhance resource management.

In 2018, a Clinical Trial Management System (CTMS) was developed as part of an initiative to promote standardization related to budget and expense reporting. The integration of existing financial files into the newly developed CTMS was an arduous task, but worthwhile, as the end product will result in streamlined and meaningful financial reports and analysis. The CTMS financial module is expected to be fully operational in 2019.



The IDCRP Program Management and Finance Team

Another accomplishment over the past year was the creation of the Master External Funds Report, which provides information on the status of funding requests and timelines of when funding awards are expected to be received by USU. Monthly meetings with USU and HJF finance and program representatives were also initiated to discuss the reports in an effort to improve transparency and increase communication among stakeholders.

The consistent high-quality work of both the RSG and PM/F teams, as well as recent innovations such as the CTMS, support the ongoing success of the IDCRP.



LTC Charlotte Lanteri and the IDCRP Research Support Group

CLINICAL RESEARCH OPERATIONS

The Clinical Research Operations group coordinates and manages the everyday operations for every research protocol within the IDCRP.

The IDCRP team of clinical research managers (CRMs) are integral to the success of the IDCRP research portfolio by providing support to Principal Investigators, the Data Coordination Center, Site Managers and protocol teams regarding the development of protocols and conduct of research studies. In 2018, the CRMs managed a portfolio of 71 protocols at various stages of the research lifecycle, including 14 protocols that are actively enrolling subjects. An additional three protocols are in development.

During 2018, a significant accomplishment for the IDCRP was the initiation of a Phase 2 trial of a *Staphylococcus aureus* vaccine candidate at Fort Benning, GA, under the Skin and Soft-tissue Infections Research Area. The CRMs involved in the trial have been instrumental in ensuring its successful execution with minimal disruption to the training schedules of those enrolled in the study.

The input of CRMs was also invaluable in supporting the rapid development of the Acute Respiratory Infections Research Area PAIVED randomized control trial protocol, which will compare the effectiveness of available influenza vaccine formulations.

Over the past year, the workload of the Clinical Research Operations team was evaluated and multiple innovations to enhance efficiency were either implemented or are being considered for use in the coming year. In addition, there was an increase in collaborative meetings with the USU Human Research Protections Program Office, which has improved communications and reduced timelines for straightforward submissions (e.g., protocol amendments). For 2019, quality management-related standard operating procedures and protocol quality management plans will be reviewed and updated, as needed.



The IDCRP Clinical Research Operations team

HIGHLIGHTS

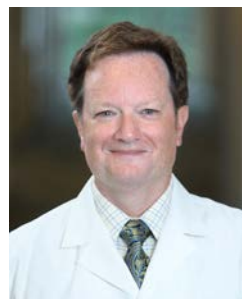
- The newly created CTMS will provide financial reports for each research area with detailed information on funding awards, projects, expenses, and protocols that is both comprehensive and yet easy to understand.
- The process for submitting and obtaining clearance for deliverables (e.g., manuscripts and presentations) through USU was consolidated into one pathway overseen by RSG, greatly improving efficiency.
- The Master External Funds Report provides information on the status of funding requests in terms of when the funding is expected, en route, and has facilitated communication with USU and HJF.

HIGHLIGHTS

- A cloud-based project management system, Smartsheet, was implemented, allowing the Research Area Directors, Principal Investigators, and other IDCRP team members to have real-time collaboration and reporting across various sites.
- A new electronic regulatory binder system, TransPerfect, is being evaluated for use, which will increase availability of documents and enhance readiness for external regulatory audits.
- Visits to IDCRP sites to evaluate quality management procedures are planned for 2019. Presently, visits to Walter Reed National Military Medical Center and Fort Benning have occurred, resulting in improved quality management practices and communication with the sites.

SCIENTIFIC REVIEW BOARD

The IDCRP Scientific Review Board (SRB) is structured to execute independent, thorough, and efficient scientific reviews of clinical research protocols and related protocol amendments prior to submission to the USU Institutional Review Board (IRB).



John Powers, MD, Chair, Scientific Review Board

The overarching purpose of the SRB (chaired by National Institute of Allergy and Infectious Diseases [NIAID] Liaison, Dr. John Powers, and Vice Chair LTC Charlotte Lanteri) is to comprehensively review submissions to ascertain if the research questions, hypotheses, aims and objectives, and methods described in the protocol are scientifically valid and meaningful, as well as being feasible to accomplish. Prior to the SRB review, a research concept is evaluated by the Concept Scoring Panel, Senior Science Group, and Operational Steering Committee, who discuss programmatic and military relevance and uniqueness, as well as the scientific validity of the concept and make recommendations regarding whether it should move forward with protocol development. The SRB reviews all new protocol submissions, including retrospective and prospective studies that involve participants who are already enrolled in approved protocols. This formative review is intended to enhance the scientific quality of new IDCRP protocol submissions prior to review by the USU IRB.

The SRB process includes three separate review pathways, with the level required for each submission determined by the SRB Chair (or the Vice Chair when the Chair is recused or unavailable).

Review Pathway	Estimated Timeline
Standard Review	35-45 days
Low Resource Review	28 days
Chair Review	14 days

Review panels for SRB submissions are identified based on the focus of the specific protocol or amendment under review with the panel generally including subject-matter experts, biomedical scientists, and statisticians, along with additional scientific review panel members affiliated with IDCRP research networks (as appropriate).

During 2018, the SRB continued to be productive with approval of 8 new protocols and 6 protocol amendments; however, one of the new protocols was withdrawn following SRB review. There are also three new protocols that will be submitted for review in the coming months. During the past year, the efficiency of SRB reviews was improved through discussions with the Principal Investigators related to study design prior to protocol development. The suggestion of potential reviewers early on in the development stage also aided in expediting the review process by allowing the SRB Chair to determine reviewer availability in advance of the submission.

For 2019, efforts will continue to streamline the review process by encouraging communication with Principal Investigators, providing new reviewers with training to improve the quality of reviews, and standardizing the timeline for SRB submissions. In addition, review of protocols by the SRB Chair or Vice Chair prior to SRB submission will be conducted to ensure the scientific quality of submissions. These efforts will increase the productivity of the SRB, as well as upholding the high standard of quality reviews.

REGULATORY AFFAIRS

The IDCRP Regulatory Affairs team supports investigators in the preparation of new research protocols and assists with execution of existing protocols by ensuring ethical and regulatory compliance. The Regulatory Affairs team also serves as an effective liaison between the IDCRP and USU, DoD partners, National Institute of Allergy and Infectious Diseases (NIAID), collaborators, and other regulatory agencies.

At present, the IDCRP has 71 active protocols, of which 56 are nonexempt studies and 15 are exempt studies. Over the past year, Ms. Luca Illinik, the IDCRP Regulatory Affairs Specialist, supported many of the IDCRP submissions, including 39 protocol amendments, 9 continuing reviews, 5 initial reviews, and 7 miscellaneous protocol actions to the USU Institutional Review Board (IRB). In particular, six new protocols were successfully routed to the USU IRB in 2018. With the forthcoming revision to the Federal Policy for the Protection of Human Subjects ('the Common Rule'), Ms. Illinik prepared and conducted highly informative webinar training sessions on the proposed changes.

A great deal of the success of the IDCRP is owed to its partnerships and collaborations with various military, government, and civilian research laboratories and institutions. With each of these relationships, different official agreements and documentation (e.g., Cooperative Research and Development Agreements, Data Use Agreements, and Memorandum of Understanding) are required before the collaboration can move

forward. During the past year, Ms. Stephanie Cammarata, Agreements Officer, successfully submitted 26 agreements for review as either a new collaboration or a renewal of an existing agreement.

While use of the Electronic IRB (eIRB) system has resulted in improvements, such as standardization of processes across the Military Health System and elimination of protocol and amendment submission redundancies, there are still challenges related to frequent changes in the submission forms and a non-intuitive document management interface. Ms. Illinik is an eIRB superuser, which allows her to bridge technical gaps that may arise between IDCRP clinical research managers and USU IRB analysts, facilitating successful submissions and protocol action processing. A substantial accomplishment over the last year has been the implementation of the eIRB multi-site functionality at participating military installations for all USU IDCRP multi-site studies.



Luca Illinik, BS, CIP, CCRP, Regulatory Affairs Specialist

HIGHLIGHTS

- IDCRP worked closely with the Defense Health Agency (DHA) Privacy Board to ensure that Health Insurance Portability and Accountability Act (HIPAA) Authorizations and Informed Consent Documentation were revised to comply with DHA specific requirements.
- Requests for Regulatory Affairs team support are now managed through a cloud-based project management platform.
- Update of Institutional Agreement for IRB Review for each IDCRP partner site completed as required due to merger of two USU IRB panels into a single unified board.

EDUCATION / MENTORSHIP

The IDCRP is committed to fostering the training and development of future infectious disease clinical researchers in the United States military.

The IDCRP utilizes three strategies in support of furthering the education and research experiences of trainees: mentored research, didactic learning, and research engagement.

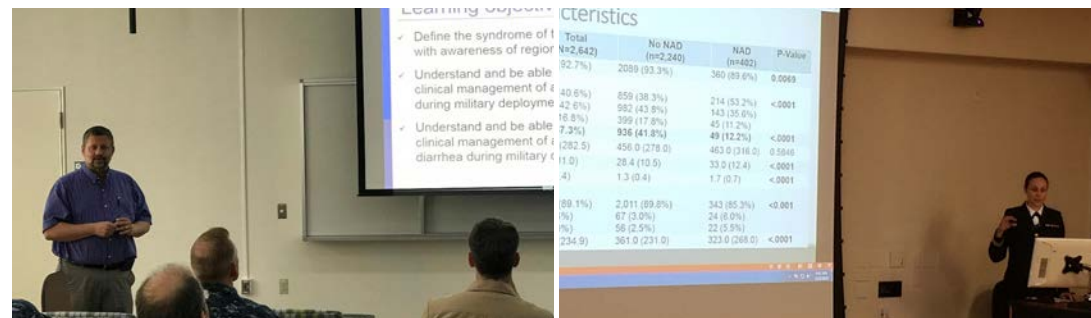
As part of mentored research, medical and public health students, residents, and infectious disease (ID) fellows in the armed forces are provided opportunities to participate in IDCRP-led projects at USU, as well as military hospitals, such as Brooke Army Medical Center, Walter Reed National Military Medical Center (WRNMMC), Naval Medical Center San Diego, and Madigan Army Military Center. Furthermore, the clinical ID research capstone curriculum for USU medical students is also supported by IDCRP investigators. In brief, mentored research opportunities are intended to provide trainees with hands-on experience related to designing research studies, collection of data, and statistical analysis and interpretation. During the past year, approximately 25 trainees conducted research with IDCRP mentors and these efforts resulted in 20 oral and poster presentations at local and national infectious diseases conferences with many of the trainees being recognized with awards for their research. Furthermore, one DrPH candidate (USU) is conducting an IDCRP analysis in support of her degree and another individual was awarded a Master's degree (Naval Postgraduate School) based on his IDCRP analysis. Multiple manuscripts with the findings are in preparation or have been submitted for journal consideration. The

IDCRP also supports the Armed Forces Infectious Disease Society (AFIDS) annual Spring meeting and continuing graduate medical education efforts at WRNMMC.

For didactic learning, IDCRP investigators initiated a course at WRNMMC more than a decade ago to teach ID fellows about the fundamentals of conducting clinical research by providing background knowledge on how to formulate clinical research questions, as well as common study methods and designs. Due to a favorable response, recording the lecture series to make it available online to military medical trainees at other sites is being considered.

Over the past several years, IDCRP investigators, mentored trainees, and USU faculty have diligently worked to raise awareness about ID clinical research in the armed services. In addition to publishing and presenting clinical research findings, IDCRP investigators attend public health student practicum and project fairs, meet with ID fellows and medical residents to discuss training opportunities, and correspond with medical training Program Directors regarding IDCRP mentored research opportunities.

The ongoing success of the IDCRP education mission supports the growth of active-duty ID clinical researchers in the U.S. Armed Services.



(Left) Dr. David Tribble presenting grand rounds at Naval Hospital Okinawa, Japan
(Right) LT Christie Joya presenting at 2018 AFIDS

SELECT IDCRP TRAINEE EDUCATION PRESENTATIONS

Conference on Retroviruses and Opportunistic Infections (CROI), 4-7 March 2018

Carney BW, White J, Xu X, Sunil T, Daniels C, Byrne M, Ganesan A, Deiss R, Macalino GE, Agan BK, Okulicz J. Relationship Between Depression and Risk Behaviors in a US Military HIV Cohort.

Larson DT, Won SH, Ganesan A, Maves R, Okulicz J, Kronmann K, Chu X, Schofield C, O'Bryan T, Agan BK, Deiss R. Statin Use and Cardiovascular Disease Mitigation among Persons Living with HIV.

Military Health System Research Symposium, 20-23 August 2018

Ford M, Mende K, Kaiser SJ, Beckius ML, Lu D, Carson ML, Tribble DR, Blyth DM. Clinical Characteristics and Outcomes Associated with *Pseudomonas aeruginosa* Isolated from Operations Enduring Freedom and Iraqi Freedom Trauma Patients Suffering Blast Injuries.

IDSA ID Week, 3-7 October 2018

Buchek GM, Mende K, Telu K, Kaiser SJ, Tribble DR, Fraser J, Mitra I, Lalani T, Yun HC. Travel-associated Multidrug-resistant Organism Acquisition and Risk Factors among US Military Personnel.

Ewers E, Won S, Okulicz J, Ferguson T, Deiss R, Maves R, Kronmann K, Lalani T, Agan B, Whitman TJ, Ganesan A. Changes in Lipid Profiles for Patients to Tenofovir Alafenamide (TAF)-containing Regimens: Perspectives from a Military HIV-positive Cohort.

Ganesan A, Won S, **Joya C**, Deiss R, Maves R, Kronmann K, Lalani T, Schofield C, Whitman TJ, Okulicz J, Agan B. In a Well Characterized Cohort with Universal Access to Care and Medications Racial Disparities in HIV Virologic Outcomes Are No Longer Observed.

Jansen N, Daniels C, Sunil TS, Xu X, Cota JM, Byrne M, Ganesan A, Deiss R, Agan B, Okulicz J. Factors Associated with Erectile Dysfunction Diagnosis in HIV-infected Individuals: A Case-control Study.

Kiley JL, Mende K, Kaiser SJ, Carson ML, Lu D, Whitman TJ, Petfield JL, Tribble DR, Blyth DM. Clinical Characteristics and Outcomes of *Klebsiella pneumoniae* Infection in Service Members Who Sustained Trauma in Iraq and Afghanistan.

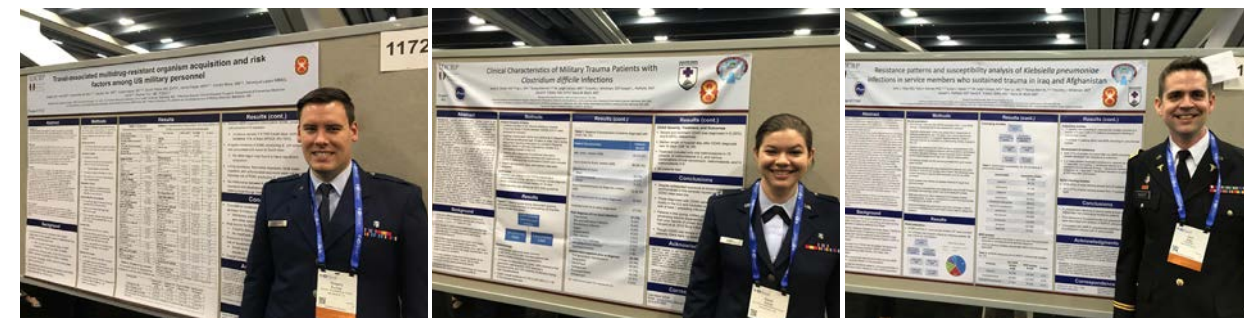
Lago K, Telu K, Tribble DR, Ganesan A, Kunz A, Geist C, Fraser J, Mitra I, Lalani T, Yun H. Impact of Doxycycline as Malaria Prophylaxis on Risk of Travelers' Diarrhea among International Travelers.

Pomerantz HS, Beckius ML, Blyth DM, Akers KS, Tribble DR, Mende K. Antifungal Activity of Cerium Nitrate Against Mold Isolates Associated with Combat-related Injuries Including Burns.

Schall SE, Li P, Merritt T, Carson ML, Whitman TJ, Petfield JL, Tribble DR, Blyth DM. Clinical Characteristics of Military Trauma Patients with *Clostridium difficile* Infections.

Verratti K, Player R, **Wood S**, Schlett C, Ellassal E, Forsyth E, Ellis M, Tribble DR, Millar E, Bennett J. Genomic Characteristics of Recurrent *Staphylococcus aureus* Skin and Soft Tissue Infection among US Army Trainees

Yabes JM, Stewart L, Shaikh F, Lu D, Merritt T, Mende K, Carson ML, Robben PM, Leimbach R, Petfield JL, Ganesan A, Tribble DR, Blyth DM. Risk of Acute Kidney Injury in Combat-injured Patients Associated with Concomitant Vancomycin and Extended-Spectrum β -lactam Antibiotic Use.



Trainee presentations at 2018 IDSA ID Week. From left, Capt Gregory Bucheck, Capt Sarah Schall, and CPT John Kiley

IDCRP AWARDS AND HONORS

IDCRP COLLABORATORS AND PARTNERS

During 2018, multiple Infectious Disease Fellows and Residents received awards or honors for their mentored IDCRP-related graduate medical education research. In addition, LTC Charlotte Lanteri, IDCRP Deputy Director; EIDAR Research Area Director, received one of the USU 2018-19 School of Medicine Impact Awards as recognition for her achievements and contributions over the academic year.

Name	Award/Honor	Awarding Organization
LTC Charlotte Lanteri	2018-19 School of Medicine Impact Award	USU
CPT Mary Ford	1 st Place for Resident Research Podium Competition	San Antonio Uniformed Services Health Education Consortium Research Day
LT Janette Noveras	1 st place for Resident Podium Competition for Research Conducted Outside of Naval Medical Center San Diego (NMCS D)	33 rd Annual Academic Research Competition at NMCS D
LT Christie Joya	1 st Place for Trainee Presentation	Armed Forces Infectious Disease Society
LT Derek Larson	2 nd Place for Trainee presentation	Armed Forces Infectious Disease Society
MAJ Heather Pomerantz	2 nd place for Podium Competition	Texas Infectious Diseases Society

CPT Mary Ford receiving her resident research award

MAJ Heather Pomerantz with podium competition award

LT Janette Noveras with her resident competition award and her mentor, Dr. Robert Deiss

LTC Charlotte Lanteri receiving the USU School of Medicine Impact Award from CAPT Mark Riddle



Department Of Defense Sites

U.S. Military Hospitals and Clinics

Brooke Army Medical Center, JBSA Fort Sam Houston, TX
Landstuhl Regional Medical Center, Germany
Madigan Army Medical Center, Joint Base Lewis McChord, WA
Marine Corps Recruit Depot, San Diego, CA
Martin Army Community Hospital, Ft. Benning, GA
Naval Medical Center Camp Lejeune, Jacksonville, NC
Naval Medical Center Portsmouth, VA
Naval Medical Center San Diego, CA
Rodriguez Army Health Clinic, Puerto Rico
Schofield Barracks Health Clinic, Tripler Army Medical Center, Oahu, HI
Soto Cano Air Base, Honduras
Troop Medical Clinic, Fort Sam Houston, TX
Walter Reed National Military Medical Center, Bethesda, MD
Wilford Hall Ambulatory Surgical Center, JBSA Fort Sam Houston, TX
William Beaumont Army Medical Center, El Paso, TX
Womack Army Medical Center, Ft Bragg, NC

U.S. Military Research Commands

Naval Medical Research Center (NMRC)
• Biodefense Research
• Enteric Disease
• Viral and Rickettsial Diseases
• Wound Infections
NMRC—Subordinate Commands
• Naval Health Research Center, San Diego, CA
• Naval Medical Research Unit No. 6 Lima, Peru
• Naval Medical Research Unit No. 2, Singapore
• Naval Medical Research Unit No. 3, Cairo, Egypt
• Naval Submarine Medical Research Laboratory

U.S. Army Institute of Surgical Research
U.S. Army Medical Research Institute of Infectious Diseases
Walter Reed Army Institute of Research
• Military HIV Research Program
• Multidrug Resistant Organism Repository and Surveillance Network
• Specimen Processing Laboratory
• Wound Infections
• Overseas Research Detachments
– Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand
– U.S. Army Medical Research Directorate, Nairobi, Kenya
– U.S. Army Medical Research Unit, Tbilisi, Georgia
– U.S. Army Medical Materiel Development Activity

Other U.S. Military Commands/Programs

Defense Health Agency
• Armed Forces Health Surveillance Branch (AFHSB)
– Global Emerging Infection Surveillance (GEIS) Program
• Immunization Healthcare Branch,
Bureau of Medicine and Surgery, Department of Navy (BUMED)
Congressional Defense Medical Research Program (CDMRP)
Defense Advanced Research Projects Agency (DARPA)
Military Infectious Diseases Research Program (MIDRP)
Navy Marine Corps Public Health Center (NMCPHC)
San Antonio Uniformed Services Health Education Consortium

United States Government Health Agencies

Centers for Disease Control and Prevention
Food and Drug Administration
National Institutes of Health
• National Institute of Allergy and Infectious Diseases
– Division of AIDS
– Division of Clinical Research

– NIAID Flu Networks
– Vaccine Research Center

- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- National Institute of Health Clinical Center
- U.S. Department of Veterans Affairs
- Atlanta Veterans Affairs Medical Center
- South Texas Veterans Health Care System
- St. Louis Veterans Affairs Medical Center
- Veterans Aging Cohort Study
- Veterans Affairs Connecticut Healthcare System

Foreign Health Agencies and Organizations

Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City
Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City
National Institute for Public Health and the Environment (RIVM), The Netherlands
Thai Red Cross AIDS Research Centre
United Kingdom Ministry of Defence
• Royal Centre for Defense Medicine, Birmingham, UK
• British Army Training Unit, Nanyuki, Kenya
• Defence Medical Directorate, Birmingham, UK
• Defence Statistics (Health) MOD Abbey Wood

Academia

Bryant and Stratton College
Columbia University
Drexel University
Duke University
Emory University
Harvard University School of Public Health
Johns Hopkins University, Bloomberg School of Public Health
New York University
University of California-Los Angeles
University of California-San Diego
University of Maryland-Baltimore
University of Minnesota
University of Nebraska
University of North Carolina
University of Pennsylvania
University of Pittsburgh
University of Texas Health Science Center at San Antonio
University of Texas Medical Branch
University of Texas-San Antonio
University of Toledo College of Medicine and Life Sciences
University of Vermont
University of Virginia
University of Washington
University of Wuerzburg Medical Center, Germany
Vanderbilt University
Yale University

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Leidos Biomedical Research, Inc.
NovaDigm Inc.
Scripps Research Institute



National Institute of Allergy and Infectious Diseases

IDCRP



Infectious Disease Clinical Research Program

Uniformed Services University of the Health Sciences
Department of Preventive Medicine & Biostatistics

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