IDCRP

Uniformed Services University

INFECTIOUS DISEASE CLINICAL RESEARCH PROGRAM

2022

ANNUAL REPORT

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LETTER FROM IDCRP LEADERSHIP

The Infectious Disease Clinical Research Program (IDCRP), of the Uniformed Services University of the Health Sciences (USU), continues to serve as an innovative leader with regard to militarily-relevant, clinical infectious disease research with the primary goal of improving the health of service members and beneficiaries of the Military Health System. The successful execution of the vast clinical research portfolio of the IDCRP can be attributed to the dedication of our staff and the effectiveness of our relationships established with clinical sites, laboratory partners, academia, collaborators, and stakeholders. During the past year, the directorship of the IDCRP transferred from CAPT (Ret.) Timothy Burgess to COL Robert O'Connell who joined the IDCRP following 16 years at The Walter Reed Army Institute of Research, where he served in many roles, including as Director of the Armed Forces Research Institute of Medical Sciences in Bangkok, and most recently as Deputy Commander. We would like to thank CAPT (Ret.) Burgess for his dedication over the years, and particularly commend his tremendous leadership of the Program during the COVID-19 pandemic. Now a member of the USU faculty, CAPT (Ret.) Burgess will continue to serve as a Principal Investigator on many IDCRP protocols. We also wish to thank CDR Mark Simons for his stewardship over the Program during the leadership transition period.

With regard to our measures of success, the Program has continued to inform military health policy with findings from our research analyses supporting more than 30 DoD and non-DoD clinical practice guidelines and policies during the past five years. Findings from HIV-related studies have directly contributed to changes in DoD policy related to active-duty status and commissions for HIV+ service members. Two clinical trials related to the prevention and treatment of travelers' diarrhea were also initiated in 2022 and their findings will help inform operational policy. During the past year, the Program continued to effectively disseminate findings from our clinical studies with >40 publications (11 articles in Tier 1 high-impact journals) and >70 presentations at local and national conferences. Multiple analyses examined longer term conditions after SARS-CoV-2 infections ('Long COVID') to improve the understanding of pathogenesis, treatment, and prevention. This includes the examination of post-SARS-CoV-2 infection outcomes using data collected from surveys and electronic medical records and characterization of clinical phenotypes using machine learning. In addition, new comprehensive surveys were implemented to assess neurocognitive symptoms following SARS-CoV-2 infections (e.g., cognitive impairment, sleep disorders, and mental health sequelae) with the findings being built into an app-based cognitive assessment tool to detect subtle cognitive defects.

For our capability to respond to emergent infection threats and/or high priority initiatives, we have expanded the diversity of individuals involved in our Scientific Review Board to increase the breadth of expertise, allowing us to expedite reviews of new protocols more effectively. For key stakeholder satisfaction, multiple new funding applications were submitted and awarded in 2022. Fostering the next generation of clinical researcher trainees is an important goal of the Program and 48 trainees were involved with IDCRP clinical research studies over the past year with many of the mentored analyses reaching completion and manuscripts being published. Another goal of the Program is to support improvements in antimicrobial stewardship and a newly developed Wound Infections Research Area protocol is focused on the evaluation of DoD antimicrobial stewardship programs. Future success will continue to rely on partnerships, both existing and through new relationships forming through The USU School of Medicine Military Infectious Disease Innovation Hub. Further details on the IDCRP research area activities and accomplishments are included in the following report.

A critical component for the successful execution of the IDCRP mission is the robust support received from USU leadership, our Operational and Executive Steering Committees, and The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. Funding and cooperative partnerships for IDCRP clinical research have also been received from the Defense Health Program, U.S. Army Medical Materiel Development Activity, the Military Infectious Diseases Research Program, the Navy Bureau of Medicine and Surgery, and the Armed Forces Health Surveillance Division and Immunization Healthcare Division of the Defense Health Agency.

We sincerely thank our clinical research and support staff, as well as our many active-duty and civilian investigator partners for their commitment to ensuring the success of the IDCRP. We also thank the military service members and beneficiaries who volunteer to participate in our studies. It is an honor and privilege to work with such an outstanding team.

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

Success Is Defined By: 1) Informing military health policy and practice through translation of research findings; 2) Publications and presentations within impactful and relevant peer-reviewed journals/forums; 3) Capability to respond to emergent infection threats and/or high-priority research initiatives; and 4) Key stakeholder satisfaction, including fostering the education of U.S. Armed Forces clinical infectious disease researchers

Robert O'Connell, MD
Colonel, Medical Corps,
U.S. Army
Director, IDCRP

Mark P. Simons, PhD, MSPH
Commander, Medical Service Corps, U.S. Navy
Deputy Director, IDCRP

David R. Tribble, MD, DrPH
Science Director, IDCRP

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), Department of Preventive Medicine and Biostatistics, and the National Institute of Allergy and Infectious Diseases (NIAID) and through a cooperative agreement with The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). The Program's work is executed through a unique, adaptive and collaborative, international clinical research network. This network directly benefits 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 the 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

Vice President for Research, School of Medicine, USU (Chair)
Dean, School of Medicine, USU
Chief, Division of Clinical Research (DCR), NIAID
Director, Research, Development and Acquisition, Defense Health Agency (DHA)

Operational Steering Committee

Surgeons General Infectious Disease Consultants—Army, Navy, Air Force
Director, Global Emerging Infections Surveillance, Armed Forces Health Surveillance Division
Director, Military Infectious Diseases Research Program, JPC-2
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
Associate Science Director
Research Area Directors

NIAID Liaison
Chair, Scientific Review Board

Deputy Program Director
Director, Center Operations
Chief, Data Operations
Head, Regulatory Affairs and Quality Management
Head, Clinical Research Management
Head, Site Operations
Team Lead, Program Management
Research Administration 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 (ARI)**— Strategic aims focus on high-priority respiratory pathogens with regard to enhancing detection in military populations, characterizing epidemiology and acute-to-chronic outcomes, predicting risk of severe outcomes and complications, and improving treatment and prevention strategies to reduce morbidity, mortality, and operational readiness loss.

- **Deployment and Travel-Related Infections**—Strategic aims focus on the evaluation of risk and operational impact of deployment and travel-related infectious threats for military personnel, effectiveness of current mitigation strategies, evaluation of knowledge of infectious disease threats and prevention methods, assessment of diagnostic test platforms and patient-reported outcomes, evaluation of novel preventive and treatment strategies for travelers' diarrhea, and assessment of the impact of emerging infectious diseases on U.S. military readiness.

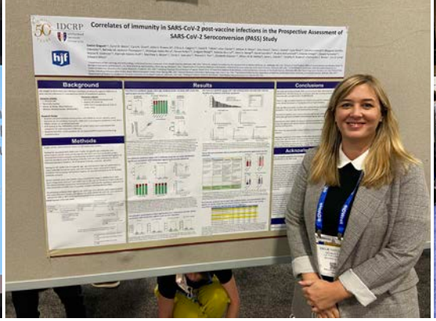
- **Human Immunodeficiency Virus (HIV) and Sexually-Transmitted Infections (STI)**— Strategic aims focus on characterizing the epidemiology and chronic clinical outcomes of priority STIs in U.S. military personnel and beneficiaries, developing and evaluating mitigation strategies related to STI clinical outcomes, supporting development of biomedical countermeasures against STIs in military populations, evaluating care practices and costs related to priority STIs to identify gaps, and assessing novel treatment and prevention strategies for STIs (including HIV) in military populations to inform military policy and practice.

- **Wound Infections**—Strategic aims focus on addressing knowledge gaps in infection prevention, clinical management, microbiologic factors, and treatment outcomes in battlefield trauma infections and community-acquired skin and soft-tissue infections, particularly *Staphylococcus aureus*-related, to inform effective treatment strategies and preventive countermeasures, as well as the evaluation of Military Health System antibiotic stewardship programs to support process improvements.

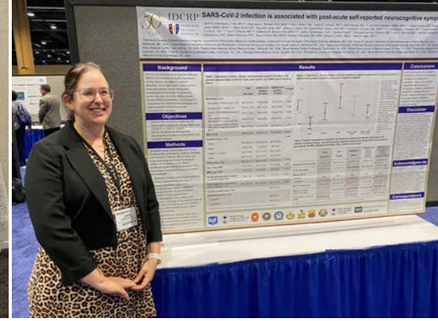
Each area's 2022 accomplishments are presented in the following pages, along with information and projections for 2023.

ACUTE RESPIRATORY INFECTIONS (ARI)

Dr. Simon Pollett presenting at the 2022 Military Health System Research Symposium (MHSRS)



Dr. Emilie Goguet presenting at the 2022 IDSA IDWeek



Dr. Liana Andronescu presenting at the 2022 MHSRS

With the recent SARS-CoV-2 pandemic, along with a resurgent risk of outbreaks of adenovirus, influenza, and other medically important respiratory pathogens, acute respiratory infections (ARIs) remain a substantial threat to the health of military personnel and their beneficiaries. These infections also impose a considerable burden on operational readiness through loss of duty days and interruptions in training cycles.

Simon Pollett, MBBS, IDCRP Associate Science Director and ARI Research Area Director

Rhonda Colombo, MD, MHS, ARI Research Area Deputy Director

During the past year, the ARI and COVID-19 Research Areas merged to form an all-encompassing ARI Research Area. The overall mission of this adaptive, interdisciplinary research program is to improve the detection, prediction, treatment, and prevention of emerging and re-emerging respiratory infection threats with primary relevance to Force Health Protection and mission readiness. With a focus on higher-priority respiratory pathogens (e.g., SARS-CoV-2 variants, influenza, adenovirus, and emerging respiratory threats), the aims of the ARI Research Area include advancing diagnostic/detection approaches, characterizing epidemiology and clinical outcomes (acute and chronic), predicting risk of severe outcomes, and improving prevention and treatment strategies.

Launched in response to the COVID-19 pandemic and now led by Dr. Simon Pollett, a central protocol of the research area is the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC), which is a prospective, longitudinal observational cohort study of SARS-CoV-2 infections in active-duty service members and Military Health System (MHS) beneficiaries. During the past year, analyses of data collected through EPICC have resulted in greater insight into acute clinical outcomes, such as respiratory failure, coronary arteriopathy, and multisystem inflammation, as well as risk factors for severe and contagious vaccine breakthrough infections. Clinical characteristics and symptom profiling of infections caused by the Omicron variant versus prior variants were also evaluated. Moreover, use of machine learning identified how acute symptom clusters associated with SARS-CoV-2 infections correlated with risk of hospitalization and certain inflammatory profiles. Furthermore, EPICC team members also contributed to the evaluation and validation of SARS-CoV-2 diagnostic approaches.

"Long COVID" (i.e., longer term conditions occurring after COVID-19) was the focus of multiple analyses. Post-SARS-CoV-2 infection outcomes were examined using data collected from surveys and electronic medical records, and COVID-19 post-acute sequelae were characterized using machine learning, to improve the understanding of the pathogenesis, treatment, and prevention of Long COVID. In addition, new comprehensive surveys were implemented to assess neurocognitive symptoms following SARS-CoV-2 infections, such as cognitive impairment, sleep disorders, and mental health sequelae; the findings led to a follow-on study using an app-based cognitive assessment tool to detect subtle cognitive defects. Cardiorespiratory outcomes have also been assessed using the EPICC COVID-19 Chronic Impairment with Pulmonary Symptoms (ChIPS) module. The approach used by the EPICC team in their assessment of Long COVID was noted in the 2022 Health and Human Services National Long COVID Research Strategy.

Led by Dr. David Tribble, the Military COVID-19 Registry Analysis Project (M-RAP) utilizes MHS data on SARS-CoV-2 infections collected through the Joint Trauma System COVID-19 Registry. Through M-RAP, real-world evidence on the post-licensure effectiveness of SARS-CoV-2 vaccines and therapeutics are being amassed to inform future management strategies. The association of boosting with protection against incident SARS-CoV-2 infections in military personnel is also being assessed.

SARS-CoV-2 was also the focus of The Observational Seroepidemiologic Study of COVID-19 at the United States Naval Academy (TOSCANA) and the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS) studies. Through TOSCANA, self-collected saliva was utilized to determine the sero-exposure to SARS-CoV-2 infection among individuals who were vaccinated compared to those who were not, further validating use of saliva immunoassays. The PASS study also provided additional evidence on use of salivary assays for the detection of SARS-CoV-2 exposures and examined vaccine immune correlates of protection against the Omicron variant.

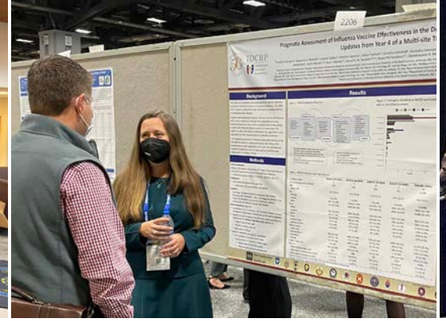
As outbreaks of influenza are common among military populations, another key protocol in the ARI Research Area is the multi-year, open-label, randomized Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) clinical trial. Led by CAPT (Ret.) Timothy Burgess (protocol chair is Dr. Rhonda Colombo), PAIVED is comparing the effectiveness and immunogenicity of three licensed inactivated influenza vaccine formulations (i.e., egg-based, cell-culture-based, and recombinant) in adult MHS beneficiaries. Enrollment in PAIVED closed in January 2022 with approximately 15,500 individuals enrolled over the four influenza seasons being studied. During the past year, PAIVED was expanded at the U.S. Naval Academy (PAIVED@USNA) to evaluate the correlation between salivary and serum SARS-CoV-2 antibodies for assessment of serostatus, which also allowed for the assessment of the programmable salivary immunoassays for influenza immunity.

For 2023, the EPICC team will continue to examine predictors associated with Long COVID, including patient characteristics, acute symptom clusters, and biomarkers. Household transmission of SARS-CoV-2 will continue to be assessed using viral genomics to better understand how household age structure and member vaccination status influences the dynamics of transmission. The potential of linking data from the DoD Serum Repository with the M-RAP study is also being explored. Follow-up visits for the Phase III randomized, double-blind, placebo-controlled multicenter study to determine the safety, efficacy, and immunogenicity of the COVID-19 ChAdOx1 vector vaccine will be completed. For PAIVED, analysis of the epidemiological and laboratory data collected from enrollees with examination of the primary endpoint will be a priority. Led by Dr. Colombo, a new protocol related to the surveillance of ARI at the U.S. Naval Academy (ARIA) will be initiated in the coming year. Furthermore, a new consolidated ARI specimen and data repository protocol will be developed in 2023 to pool clinical data and specimens from all the ARI Research Area protocols. This protocol will allow for meta-cohort analyses, along with being an on-demand repository to permit rapid assay development and provide comparator study populations as new ARI pathogens emerge.

MILITARY IMPACT

Since recognition of the COVID-19 pandemic, findings from interventional trials conducted or supported by the ARI Research Area have bolstered the evidence base for Emergency Use Authorizations and new drug applications for antivirals, immunomodulators, vaccines, and prophylactic/therapeutic monoclonal antibodies; these products have benefitted many, including active-duty service members and MHS beneficiaries. Findings from the analyses related to SARS-CoV-2 were utilized to brief senior DoD leadership, particularly with regard to Long COVID and vaccine effectiveness in the MHS. SARS-CoV-2 genotype data were reported to the DoD Global Emerging Infections Surveillance program of the Armed Forces Health Surveillance Division to support Force Health Protection. Findings from EPICC, PASS, and M-RAP continue to provide effective insights into the detection, prediction, treatment, prevention, and functional illness outcomes of SARS-CoV-2. In addition, data collected through PASS have furthered the evidence base on the durability of SARS-CoV-2 immunity in vaccinated active-duty service members, including those who have been boosted. Immunological analyses from PASS were utilized in the briefing materials provided to the U.S. Food and Drug Administration, Vaccines and Related Biological Products Advisory Committee for review when making decisions related to COVID-19 vaccine boosting.

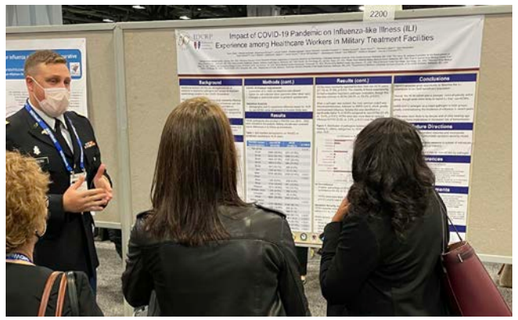
The ARIA investigative team at the U.S. Naval Academy



Dr. Rhonda Colombo presenting at the 2022 IDSA IDWeek

Dr. Stephanie Richard presenting at the 2022 MHSRS

Data collected through PAIVED have significantly contributed to the characterization of ARI epidemiology in U.S. military personnel and MHS beneficiaries and have the potential to inform future influenza vaccine policies for the military. The findings from the PAIVED immunogenicity sub-study may also support the progression toward a universal influenza vaccine. The ARIA study will examine the emergence of militarily-relevant respiratory viruses in a congregate training population and assess how they epidemiologically interact with SARS-CoV-2. Lastly, the planned repository protocol to pool ARI clinical data and specimens will provide a platform to efficiently address questions regarding emerging respiratory threats relevant to the MHS.



CPT Ryan Liberg presenting at the 2022 IDSA IDWeek

HIGHLIGHTS/KEY FINDINGS

- **The IDCRP supported the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored randomized, double-blind, placebo-controlled trial (ACTT-4) by enrolling subjects at military treatment facilities. The trial evaluated use of baricitinib plus remdesivir versus dexamethasone plus remdesivir in adult patients with SARS-CoV-2 infections to prevent a progression of illness requiring use of mechanical ventilation or death. There was no significant difference in the occurrence of survival without use of a ventilator between the groups; however, use of dexamethasone plus remdesivir resulted in a greater frequency of adverse effects, including severe or life-threatening events (36% versus 28% with baricitinib plus remdesivir; risk difference of 7.7%; p=0.012).**
- **During the PAIVED study, >4,200 influenza-like illnesses (ILI) were reported; while the rate in 2020-21 was low (9%) due to preventive efforts related to COVID-19 (e.g., social distancing), a resurgence of ILIs occurred in 2021-22 (27.5%) with SARS-CoV-2 being the most frequently identified pathogen.**
- **Patient-reported outcomes among 764 EPICC enrollees with SARS-CoV-2 infections were characterized using the inFLUenza Patient-Reported Outcomes (FLU-PRO) Plus score, which is an instrument that allows patients to rate the intensity and/or frequency of symptoms. Daily scores were collected for up to 14 days after enrollment. Fully vaccinated enrollees were more likely to return to usual activities after 14 days compared to those who were not fully vaccinated (hazard ratio: 1.24; 95% confidence interval: 1.04-1.48).**
- **Breath biomarkers were assessed for 237 ILI episodes among 235 subjects enrolled in the ARI Consortium Natural History Study (2017-2019) with influenza detected in 13.5% of episodes and human rhinovirus/enterovirus detected in 16% of episodes. Twenty breath volatile organic compound biomarkers distinguishing between positive and negative influenza cases were identified and a predictive algorithm using four candidate biomarkers had an accuracy of 78%.**

DEPLOYMENT AND TRAVEL-RELATED INFECTIONS

Among U.S. service members deployed worldwide for combat operations, humanitarian service, and overseas training exercises, infectious diseases impose a considerable health threat, as well as directly impacting operational readiness. Infectious diseases in the military training environment within the United States are also common, resulting in an additional burden on the Military Health System.

The overall goal of the Deployment and Travel-Related Infections Research Area is to enhance infectious disease preparedness and Force Health Protection of U.S. Armed Forces prior to and during deployment. Primary objectives of the research area include the evaluation of the risk and operational impacts of priority infectious disease threats (including emerging/re-emerging diseases and multidrug-resistant pathogens), effectiveness of current mitigation strategies, knowledge of infectious disease threats and prevention methods among providers, utility of diagnostic test platforms and patient-reported outcome measures for travelers' diarrhea (TD), and the safety and effectiveness of novel preventive and treatment strategies for TD.

Led by Dr. Tahaniyat Lalani, one of the central protocols of the Deployment and Travel-Related Infections Research Area is the Deployment and Travel-Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies among DoD Beneficiaries (TravMil) cohort study. Through this protocol, multiple analyses evaluating the impact of high-priority infectious diseases on military operations in regions where the diseases are endemic or emerging have been completed. In addition, data from TravMil were also used to assess risk factors for non-compliance with malaria prophylaxis recommendations, as well as the epidemiology of febrile illness in deployed military personnel and other DoD travelers. Furthermore, an association between pathogen detection with polymerase chain reaction (PCR)-based assays and occurrence of TD was determined by comparing stool smears obtained from TravMil enrollees with diarrheal episodes with those collected from asymptomatic travelers.

Central to the research area are clinical trials evaluating preventive and treatment strategies for TD, of which all are collaborative efforts with the United Kingdom Ministry of Defence. During the past year, enrollment began in the P2 clinical trial (led by Dr. David Tribble), which is a randomized, double-blind, placebo-controlled trial evaluating the efficacy of enterotoxigenic *Escherichia coli* passive immunoprophylaxis (Travelan®) for maintenance of gut health during a 10 to 20-day period of travel. In addition, as a follow-on to the successful Trial Evaluating Ambulatory Therapy of TD (TrEAT TD) clinical trial, which demonstrated that a single high dose of rifaximin (1,650 mg) with adjunct loperamide was effective at treating acute watery diarrhea, the TrEAT TD 2.0 clinical trial began enrolling in 2022. Also led by Dr. Tribble, the TrEAT TD 2.0 trial is evaluating the efficacy of a single low dose of rifaximin (550 mg) versus azithromycin (500 mg), both with adjunct loperamide use, for the treatment of moderate or severe acute watery diarrhea.

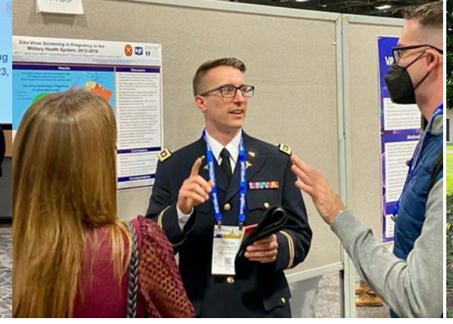
Another recently completed trial is the Trial Evaluating Regimens for Chemoprophylaxis Against TD (Prevent TD), which is a randomized, placebo-controlled, double-blind trial evaluating two doses of rifaximin (550 mg daily or 550 mg twice daily) for the prevention of TD. Post-hoc analyses of the gut microbiome and resistome from military personnel enrolled in Prevent TD, as well as from enrollees in the original TrEAT TD

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

CDR Mark Simons, Dr. Tahaniyat Lalani, and Andrea Fuentes at a site visit at Tripler Army Medical Center

The P2 Study Team at Tripler Army Medical Center with Dr. Tribble and Dr. Lalani

The TrEAT TD 2.0 Kick-Off Meeting Group



Maj Trevor Wellington presenting at the 2022 IDSA IDWeek.
[Photo credit: Army.mil; Cpl Steven Bell]. The appearance of U.S. DoD visual information does not imply or constitute DOD endorsement.

LCDR Danielle Pannebaker of NAMRU-6, TrEAT TD 2.0 site Principal Investigator at Joint Task Force Bravo, Soto Cano Air Base

Dr. Simon Pollett presenting at the 2022 American Society of Tropical Medicine and Hygiene meeting

clinical trial, demonstrated a decrease in the gut microbiome richness associated with occurrence of TD and international travel. It was also found that rifaximin prophylaxis during deployment increased the acquisition of antibiotic resistance genes. Based on these findings, the storage and testing standard operating procedures being used in the P2 and TrEAT TD 2.0 clinical trials were modified to improve pathogen detection and expand the evidence base on the impact of enteropathogens on the gut microbiome and resistome.

Led by Dr. Tribble, a new protocol of the research area is the Deployment Infection Threat Assessment and Outcomes Survey among U.S. Marines (MARSID) study. The primary objective of MARSID is to estimate the infectious disease incidence, trends, and operational impact on U.S. Marines deployed to developing regions using a post-deployment survey. Infectious diseases being examined include diarrhea, acute respiratory infections, febrile illness, skin and soft-tissue infections, and sexually-transmitted infections. Findings from the survey will support Force Health Protection infectious disease threat assessment and provide valuable syndromic incidence estimates. During the past year, the study was initiated with U.S. Marines returning from military exercises in the U.S. Indo-Pacific Combatant Command region being enrolled.

Data collected from the Knowledge, Attitudes, Practice and Outcomes Study (KAPOS), led by COL Patrick Hickey, were previously utilized to complete a U.S. Food and Drug Administration post-licensure analysis of Tafenoquine, which was approved for use in the Military Health System for malaria prophylaxis and radical cure of *Plasmodium vivax*. However, as the study coincided with the COVID-19 pandemic, there was a low number of prescriptions during the study period, so the analysis will be repeated in 2023.

During the past year, a number of surveillance studies funded by the DoD Global Emerging Infections Surveillance (GEIS) program were also completed or are nearing completion. This includes the evaluation of the seroincidence and risk of Coccidioides infections among active-duty personnel stationed at Naval Air Station Lemoore, California, as well as the serosurveillance of arbovirus infections among service members deployed to Puerto Rico and the Southern Combatant Command region during peak periods of Chikungunya and Zika virus transmission and a serosurvey of emerging *Borrelia* species among personnel stationed in at-risk regions in the United States. Post-infectious sequelae following an outbreak of Shiga toxin-producing *E. coli* (STEC) infections among personnel at the Marine Corps Recruit Depot San Diego and Edson Range in California were also examined.

For 2023, a focus of the Deployment and Travel-Related Infections Research Area will be on the completion of enrollment and follow-up for the P2 and TrEAT TD 2.0 clinical trials. Enrollment in a new study designed to assess the risk of leptospirosis with jungle warfare/operations training is expected to begin in the coming year, as well as the initiation of a new study examining the association of the gut microbiome with Guillain-Barré Syndrome. Existing partnerships with academic institutions and DoD laboratories will continue to be leveraged to identify new opportunities for clinical trials and surveillance efforts focused on pathogens deemed high-priority to the Military Health System.

MILITARY IMPACT

Findings from analyses executed through the Deployment and Travel-Related Infections Research Area have improved the understanding of the operational impact of highly prevalent and priority infections and risk of re-emerging infectious disease threats, as well as expanding the evidence base on the effectiveness of preventive and treatment approaches to inform clinical practice guidelines and develop new investigational therapies. In particular, findings from the ongoing P2 clinical trial will be used to create a knowledge product for the DoD related to use of nutraceuticals to maintain gut health during deployment or travel. Moreover, the results of the TrEAT TD 2.0 clinical trial could inform recommendations regarding use of a lower dose of rifaximin for the treatment of acute watery diarrhea, which would address the current concerns of high cost, potential side-effects, and antibiotic resistance with use of the higher rifaximin doses. Evaluations of the occurrence of relevant infectious diseases in regions prioritized for surveillance by Combatant Commands and DoD GEIS were completed with the finding being reported to GEIS. This included an examination of post-infectious sequelae following a STEC outbreak in a military training environment. Dr. Lalani and other investigators of the research area also serve on the GEIS Steering Committee and provide input on the GEIS Enterics Roadmap. While clinical trials focused on the mitigation of diarrheal disease are a centerpiece of the research area, another key aim is to evaluate provider-knowledge and prescription practices relevant to deployment health with a goal of improving the use and effectiveness of existing mitigation strategies. Lastly, translational research efforts focus on refining culture-independent methods for enhanced pathogen detection on diarrheal stool smears in austere environments.

HIGHLIGHTS/KEY FINDINGS

- **A retrospective assessment of serum specimens stored in the DoD Serum Repository collected from 2,000 military personnel who served at Naval Air Station Lemoore (San Joaquin Valley) between 2011-2017 was conducted. The population included personnel who had a sample collected before and after transition to the site. The annual incidence of coccidioidomycosis ranged from 0 to 1.32 cases/100 person-years with the overall seroconversion incidence being 0.5 cases/100 person-years.**
- **In an analysis through KAPOS, the TD prescription patterns of 80,214 adult service members and beneficiaries were assessed, and TD self-treatment prescriptions with service members were low and equally prescribed from both military and civilian clinical sites. However, TD self-treatment prescriptions were more likely to be prescribed to beneficiaries from providers at military clinical sites compared to civilian sites (odds ratio: 2.8; 95% confidence interval: 2.6-3.0).**
- **Assessment of 291 malarial prophylaxis (i.e., chloroquine) prescriptions through KAPOS identified that 10% of patients received inappropriate prescriptions with the majority being prescribed by non-travel medicine specialists. The primary reason the prescriptions were inappropriate was due to the occurrence of chloroquine resistance at the travel destination.**
- **Using signs and symptoms data collected through the TrEAT TD clinical trial, a TD severity score was established for application as a secondary outcome in future field studies. Malaise (odds ratio: 5.9-44.3) and nausea (odds ratio: 2.8-37.1) were most strongly associated with impaired function. A TD severity score that incorporated diarrhea frequency plus several signs and symptoms was identified as a better predictor of negative impact on function compared to a score that incorporated any single sign or symptom.**

HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND SEXUALLY-TRANSMITTED INFECTIONS (STI)

Adriana Le Van of the USU Jerse Lab

The Madigan Army Medical Center HIV Natural History Study research team receiving IDCRP Appreciation Awards for their outstanding contributions to the study.

Col Jason Okulicz, HIV NHS Principal Investigator (seated), moderating a HIV session at the 2022 IDSA IDWeek.

Active-duty service members with HIV are diagnosed early after infection and achieve viral suppression rapidly as the result of the effective Military Health System (MHS) HIV screening and cascade of care framework, including timely initiation of combination antiretroviral therapy. Despite this ideal care, non-AIDS complications, such as cardiovascular disease, cancer, and neurocognitive impairment still impact the health of these active-duty military personnel and MHS beneficiaries more frequently than in individuals of the same age without HIV. In addition, the rates of sexually-transmitted infections (STIs) in military personnel, both with and without HIV, remain higher compared to civilian populations of similar demographics, which is further complicated by the emergence of antimicrobial-resistant pathogens.

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

Recognizing shared research capabilities, aims, and methods, as well as overlapping populations of interest, the HIV and STI Research Areas were merged into one HIV/STI Research Area in 2022. With the overall goal of the newly combined HIV/STI Research Area being the elimination of new STIs and prevention of adverse impacts of existing infections among active-duty service members and MHS beneficiaries, the primary objectives include the characterization of epidemiology and clinical outcomes of high-priority STIs, development and evaluation of strategies to mitigate adverse clinical outcomes, supporting development of STI biomedical countermeasures, evaluation of care practices and costs related to priority STIs to inform practice recommendations, and assessment of STI treatment and prevention strategies to inform military policy and practice.

One of the central protocols of the HIV/STI Research Area is the U.S. Military HIV Natural History Study (NHS). Led by Dr. Brian Agan, the HIV NHS has enrolled more than 6,400 HIV+ active-duty service members and MHS beneficiaries since 1986, resulting in a massive repository of clinical data and blood specimens. Using data collected through the HIV NHS, investigators have assessed acute and chronic non-AIDS complications, occurrence of co-infections and STIs, mental health outcomes, and STI risk-related behavior practices. In response to the COVID-19 pandemic, the HIV NHS was modified to reduce follow-up visits to be once yearly and also allow remote/virtual visits. During the past year, the burden of *Neisseria gonorrhoeae* (gonococcus, GC) infections in the HIV NHS population was examined. Furthermore, in an analysis funded by the USU Health Services Research Program (renamed the Center for Health Services Research), the quality of HIV care, cost, and healthcare delivery were also assessed in the military population using the HIV Virtual Cohort Study, also led by Dr. Agan.

With the goal of supporting the health, function, and readiness of HIV+ military personnel and MHS beneficiaries, the HIV-Associated Neurocognitive Disorders (ALLHANDS) study is examining functional consequences of HIV-associated neurocognitive disorder (HAND) in a high-demand military setting. Led by Dr. Agan, ALLHANDS is also evaluating potential HAND biomarkers with possible use in diagnostic platforms. Recent analyses include the assessment of an abbreviated screening battery to identify neurocognitive impairment among HIV+ individuals and an examination of neurocognitive dysfunction among individuals on long-term antiretroviral therapy (>10 years). The association of non-AIDS complications with HIV serostatus is also being analyzed through the DoD HIV Virtual Cohort Study, which is examining clinical data from HIV+ individuals and matched HIV-negative controls obtained from the MHS Data Repository.

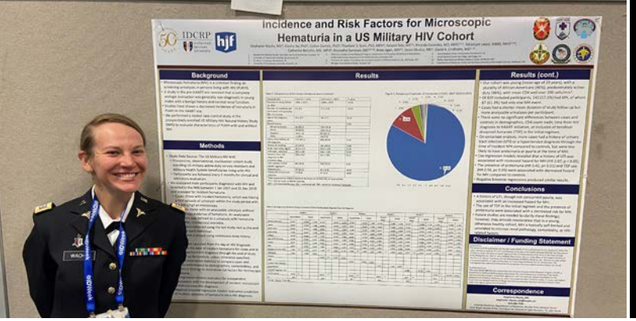
In collaboration with the University of Alabama at Birmingham and GlaxoSmithKline plc, a Phase II randomized, placebo-controlled, observer-blinded clinical trial of the group B Meningococcal (Bexerso®) Vaccine for Gonococcal Infection (MAGI Trial) is currently underway. Led by COL Eric Garges, the primary outcome of the trial is to assess the efficacy of the Bexsero® vaccine as a potential interim prevention strategy against GC in high-risk populations and the resulting findings will help inform DoD clinical practice. Over the past year, enrollment continued at Walter Reed National Military Medical Center, as well as at two DoD-associated sites in Thailand; however, there were delays in reaching enrollment targets due to the Mpox (monkeypox) pandemic and vaccine response impacting the at-risk population targeted for the MAGI Trial. Nevertheless, it is expected that all targets will be reached to complete the trial. Funded through the Defense Health Agency Immunization Healthcare Division, the immune response to GC was also assessed *in vitro* using archived specimens from service members who received the meningitis B vaccine (Bexerso®).

Another protocol is the GC Resistance Study, led by COL Garges, which is undergoing revisions to expand surveillance efforts and evaluation of clinical outcomes to include *Chlamydia trachomatis* and *Mycoplasma genitalium*, as well as to examine antimicrobial resistance and the impact of high-priority STIs on operational readiness. Increased capture of data and isolates from STI-related cases identified at U.S. sites is also planned. In the past year, deployment-relevant surveillance GC isolates were received from the Republic of Georgia and are being assessed by the USU GC Reference Laboratory and Repository, which is led by Dr Ann Jerse (USU), coordinated by IDCRP, and funded by the DoD Global Emerging Infections Surveillance (GEIS) program. Isolates are expected to be received from sites in Kenya and Thailand in 2023 as part of the evaluation of antimicrobial resistance among military-related populations.

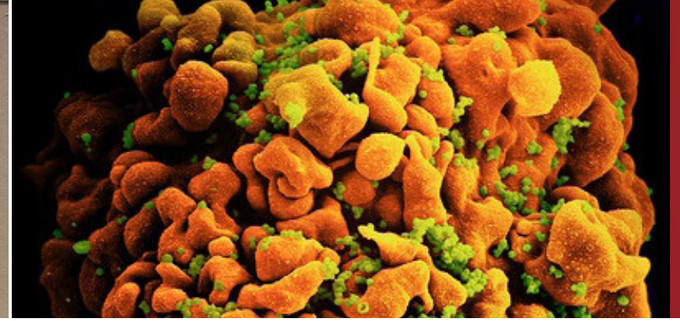
In the coming year, a new HIV repository protocol will be developed to pool the data collected through the HIV NHS and other studies for comprehensive analysis and to streamline collaborative efforts. Discussions are underway to expand analyses for the HIV NHS, as well as the GC Resistance Study, to examine the incidence of high-priority STIs, including syphilis infections as an increase in the incidence of syphilis in the United States has been observed in recent years. Another new protocol being developed is the DoD-Veterans Affairs (VA) Overlap Cohort Study, which will be a collaborative effort between the HIV NHS and the Veterans Aging Cohort Study (VACS, a similar HIV cohort study in the VA). The goal of this new protocol will be to examine the incidence, predictors, and impact of long-term and chronic HIV-related outcomes. A new initiative being planned will also provide important information regarding the optimization of vaccine protection among active-duty service members, including HIV+ personnel. A protocol to examine the impact of the Mpox pandemic on military populations is being discussed.

MILITARY IMPACT

The aims and objectives of the newly merged HIV/STI Research Area were developed to be responsive to clinical HIV and STI-related research requirements with a focus on the evaluation of high-impact and high-prevalence STIs as detailed by the Defense Health Agency, including GEIS, the Tri-Service HIV Working Group, and the Military Infectious Diseases Research Program. In response to the National Defense Authorization Act of 2017 and supported through the USU Center for Health Services Research, the HIV/STI Research Area has evaluated aspects of HIV care within the MHS with regard to DoD policy and practice, including the quality of HIV care, impact of Service-specific policies on the frequency of HIV+ active-duty service member medical evaluations, and examination of in-person versus remote care visits of HIV+ personnel. The research area has also conducted analyses to directly address objectives of the National HIV/AIDS Strategy and Federal Implementation Plan related to the prevention of new HIV infections, improving HIV-



CPT Stephanie Wachs presenting at the 2022 IDSA IDWeek



Scanning electron micrograph of an HIV-infected H9 T cell [photo credit: NIAID]

related outcomes among HIV+ individuals, and reducing HIV-related disparities and health inequities. Other efforts include the identification and prediction of complications relevant to active-duty service members, such as HAND, and the conduct of a collaborative, multisite, interventional trial to evaluate the Bexsero® vaccine for use in mitigating the impact of GC on Force Health Protection. Findings from the GC Resistance Study and the GC Repository on the geographic distribution and susceptibility patterns of isolates are provided to GEIS to inform operational planning. A member of the investigative team also serves on the GEIS Antimicrobial Resistance Working Group. Active engagement with partner militaries provides valuable information on GC surveillance that is used to support improvements in the technical capabilities and laboratory methods for host nation partners.

HIGHLIGHTS/KEY FINDINGS

- **Enrollment in the Phase II randomized, placebo-controlled, observer-blinded MAGI clinical trial designed to evaluate the efficacy of the Bexsero® meningococcal vaccine for protection against gonorrhea infection was initiated and will continue through 2023 with a follow-up period of 15 months. Presently, the DoD sites have enrolled 535 participants, which is 75% of the total enrollees in this pivotal trial. If effective, this vaccine will protect against gonorrhea, a common STI among service members, helping to improve Force Health Protection and military readiness.**
- **Findings from IDCRP HIV-related analyses informed a recent revision to the DoD Instruction 6485.01 entitled 'Human Immunodeficiency Virus (HIV) in Military Service Members' and the related Defense Health Agency Procedural Instruction and 6 June 2022 Assistant Secretary of Defense Memorandum. This included an important update to DoD HIV policy to remove restrictions on deployments or commissions for HIV+ service members who are asymptomatic and have a clinically confirmed undetectable viral load.**
- **Data collected from the HIV NHS were assessed with regard to appropriate use of statins per guidelines from the American College of Cardiology/American Heart Association. Among 486 HIV+ enrollees who met ≥1 criterion for statin use, 62% received statin therapy. Individuals who were of African American race or Hispanic ethnicity were significantly less likely to receive statin prescriptions compared to non-Hispanic white individuals. Individuals who had a higher CD4 count (odds ratio [OR]: 1.12, 95% confidence interval [CI]: 1.05–1.20 per 100 cells/μL) or received tenofovir disoproxil fumarate at antiretroviral therapy initiation (OR: 1.66, 95% CI: 1.01–2.74) were significantly more likely to receive a statin prescription.**
- **In a case-control analysis using data collected through the HIV NHS, the utility of immune system T cell markers to identify risk for cancer in virally suppressed HIV+ individuals was examined. Cases and controls were matched on CD4+ count, duration of HIV infection, and viral suppression. The cases showed increased presence of dysfunctional peripheral T cells 12 months before cancer diagnosis, which may serve as a biomarker for increased cancer risk among HIV+ individuals.**
- **Using data from the HIV NHS and the WRAIR Military HIV Research Program African Cohort Study (AFRICOS), the clinical relevance of immune non-response (INR) with regard to its relationship with serious non-AIDS events was examined. Prevalence of INR was 11% in the HIV NHS and 26% in the AFRICOS population. INR was significantly associated with a 61% increase in relative risk of having a serious non-AIDS event.**

WOUND INFECTIONS

Battlefield wound infections have significant impacts on both the short- and long-term health of wounded warriors. There is also considerable morbidity associated with skin and soft-tissue infections (SSTIs) acquired in community settings, such as training facilities and deployments. Adding to the challenge of preventing and managing wound infections is the increasing prevalence of multidrug-resistant (MDR) pathogens, as well as the emergence of novel microbial threats. Overall, battlefield wound infections and community-acquired SSTIs impose a substantial health burden on the service member, and also operational and financial burdens on the Military Health System (MHS).

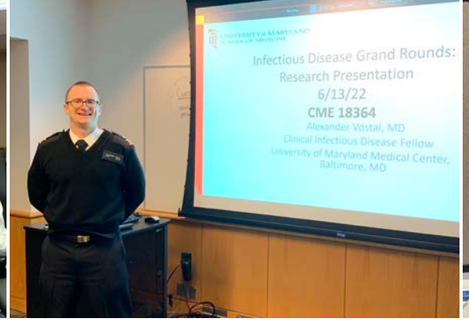
The goal of the Wound Infections Research Area is to reduce the impact of combat trauma-related infections and community-acquired SSTIs among military personnel through improved evidence-based clinical practice guidance and the determination of effective prevention and treatment strategies. During the past year, the strategic aims of the research area were revised to continue to be responsive to the changing infectious disease priorities of the MHS.

With regard to battlefield-related trauma, the central protocol is the Trauma Infectious Disease Outcomes Study (TIDOS), which assesses short- and long-term infection outcomes among wounded warriors. Led by Dr. David Tribble, TIDOS systematically collected detailed data on trauma and clinical characteristics, medical and surgical management, infection diagnoses, and microbiology from military personnel wounded during deployment over a 5.5-year period (2009-2014) through the Joint Trauma System (JTS) Department of Defense Trauma Registry (DoDTR) and the TIDOS Infectious Disease Module of the DoDTR. Data on trauma-related infections that developed after the initial period of hospitalization were also collected from subjects enrolled in the TIDOS longitudinal follow-up cohort through DoD and Veterans Affairs (VA) sources. During 2022, a supplement of *Military Medicine* was published, which provides an overview of major initiatives of TIDOS and discusses the clinical relevance of findings. Another accomplishment over the past year is the completion of the evaluation of healthcare resource utilization and costs associated with infections (including MDR Gram-negative infections) complicating combat-related trauma. Additional TIDOS analyses completed during the past year include the assessment of burn infections, seasonality of combat-related wound and wound infection microbiology, and occurrence of sepsis with regard to timing of diagnosis and use of newer sepsis definitions (i.e., Adult Sepsis Event and Bacteremia/Fungemia Shock Event) of the Centers for Disease Control and Prevention (CDC). Analysis of the infectious complications of penetrating central nervous system injuries is nearing completion.

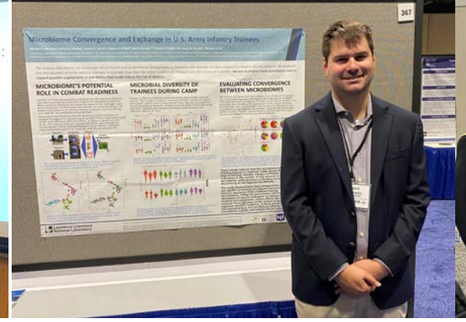
As part of the examination of the long-term outcomes of battlefield trauma and associated infections, enrollees in the TIDOS cohort were asked to provide responses to the SF-8 Health Survey at the time of their discharge from the hospital, as well as at follow-up intervals. In collaboration with Dr. Jay McDonald of the VA St. Louis Health Care System, a longitudinal evaluation of physical, mental, and social health factors determined through the survey responses was completed. In addition, social and mental health information (e.g., opioid and alcohol use, depression, and post-traumatic stress disorder) were collected from TIDOS cohort enrollees who left active-duty

Katrin Mende, PhD, Wound Infections Research Area Director

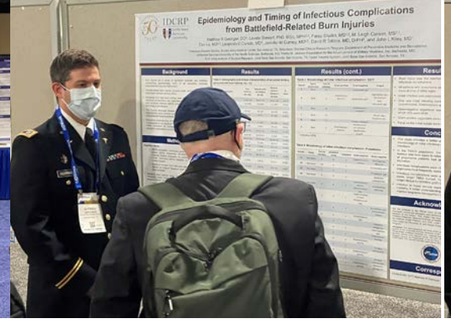
Dr. David Tribble, Maj John Kiley, and MAJ Joseph Yabes meeting with Col Stacy Shackelford and COL Jennifer Gurney of the Joint Trauma System



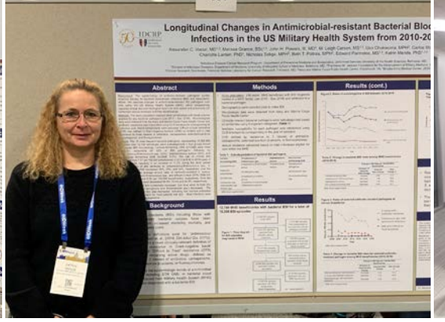
Dr. Alexander Vostal presenting at the University of Maryland Medical Center Grand Rounds



Dr. Michael Morrison presenting at the 2022 Military Health System Research Symposium



CPT Matthew Geringer presenting at the 2022 IDSA IDWeek



Dr. Katrin Mende presenting at the 2022 IDSA IDWeek

The Wound Infections Research Area team at the IDCRP Program Coordination Center

status and received VA healthcare. Analysis of these data, in collaboration with Dr. McDonald, is planned for the coming year.

It is recognized that blast casualties with severe polytrauma are at risk of developing high-consequence infections, including sepsis and invasive fungal wound infections (IFIs), which are associated with substantial morbidity and mortality. A new TIDOS initiative, in collaboration with the U.S. Army Institute of Surgical Research (USAISR) and the U.S. Army Telemedicine and Advanced Technology Research Center (TATRC) and funded by the USU Transforming Technology for the Warfighter Program, will conduct analyses to identify early infection predictors and the resulting findings will be used with machine learning to develop a clinical decision support tool for infection risk stratification in the prehospital setting, particularly when prolonged field care is likely, to aid clinicians with regard to triage, resuscitative care, and prioritization for medical evacuation. The tool may also be used after hospital admission to provide diagnostic support with greater precision as more data (e.g., laboratory values) become available.

As early diagnosis and timely initiation of medical and surgical treatment are critical for the successful management of IFIs, use of polymerase chain reaction (PCR)-based assays to aid in the diagnosis of IFIs have been examined by Dr. Anuradha Ganesan and the TIDOS team with the objective of identifying the best diagnostic methods for use in future conflicts. During 2022, analyses of the performance characteristics of a real-time Mucorales PCR (MucorGenius®) assay and semi-nested assays targeted to clinically-relevant filamentous fungi (i.e., order Mucorales, *Aspergillus* spp., and *Fusarium* spp.) using fixed surgical pathology specimens were completed.

The TIDOS MDR and Virulent Organisms (MDR/VO) Trauma Infections Initiative, led by Dr. Katrin Mende, is a collaborative effort with multiple DoD laboratories to analyze specimens and associated clinical data to further the understanding of the complex microbiology of battlefield wounds and wound infections. During the past year, the comprehensive characterization of *Enterobacter cloacae* clinical isolates, including resistance patterns, obtained from combat casualties was completed. In collaboration with Dr. Kristi Frank of USU, evaluation of the activity of lysozymes against biofilms of *Enterococcus faecalis* isolates was initiated in 2022.

With the high frequency of community-acquired SSTIs, largely attributed to *Staphylococcus aureus*, developing among military trainees, numerous epidemiological and microbiological studies of SSTIs were conducted among U.S. Army Infantry trainees at Fort Benning, GA, over a 10-year period, resulting in a massive amount of collected specimens and associated clinical data. During the past year, the longitudinal humoral immune response to both methicillin-resistant and methicillin-susceptible *S. aureus* (MRSA and MSSA, respectively) colonization and infection was evaluated in collaboration with J&J/Janssen using specimens collected from the SSTI Cohort Study. Cultures collected from the trainees have also been utilized to examine changes in the microbiome during the training cycle. During 2022, a new SSTI Repository Protocol was developed to pool data from four SSTI Fort Benning studies with prior IDCRP SSTI studies conducted among Marine recruits at Quantico, as well as deployed personnel on a U.S. Navy submarine and an assault ship. This protocol will serve as the foundation to conduct analyses related to priority research questions to further expand the knowledge base, particularly with the objective of informing SSTI prevention strategies.

Another protocol of the Wound Infections Research Area is the Antibiotic-Resistant Bloodstream Infections (BSI) protocol, which collected data from the MHS Data Repository on MHS beneficiaries with a BSI diagnosis between January 2010 and December 2019. Microbiological data were also obtained from the Navy and Marine Corps Public Health Center. During the past year, data on recurrent BSI episodes and longitudinal trends in antimicrobial resistance of common, clinically-relevant bacterial pathogens were examined.

For 2023, TIDOS investigations will continue to focus on blast-related wounds and clinical outcomes, emphasizing wound-specific outcomes to assess and support refinement of optimal prevention and management strategies. A new TIDOS collaboration with the University of Minnesota is being developed to conduct analyses to further the evidence base related to the prevention and management of battlefield-related infections to support the refinement of existing and development of new JTS clinical practice guidelines (CPGs). Merging data from subjects with extremity injuries in TIDOS with data from the Trauma-Associated Osteomyelitis Study to create a military extremity injury resource is also being discussed. For the new SSTI Repository Protocol, 2023 will focus on creating the merged dataset. The Evaluation of DoD Antimicrobial Stewardship Programs is another new protocol developed for the Wound Infections Research Area with the objective of assessing DoD antimicrobial stewardship programs in relation to the CDC's Core Elements for Hospital and Outpatient Antibiotic Stewardship.

MILITARY IMPACT

The five aims of the Wound Infections Research Area remain responsive to priorities of the Military Infectious Diseases Research Program, the DoD JTS, and the MHS. New initiatives through TIDOS will directly support the JTS, addressing gaps related to combat casualty care and resulting in process improvements. In particular, the planned collaboration with the University of Minnesota will result in the refinement of existing JTS CPGs and the development of the first JTS CPG for the management of battlefield-related infections, while the collaboration with USAISR and TATRC will create a clinical decision support tool to aid triage, en-route care, and prioritization of medical evacuation. The TIDOS team is also discussing a collaboration with the JTS to develop the next-generation of the DoDTR and the framework for a contingency protocol for use during future conflicts. For community-acquired SSTIs, the new SSTI Repository Protocol will serve as the centerpiece protocol to conduct analyses to address priority research questions to support preventive and management strategies for use in military training and deployed settings, with the goal of reducing the impact of SSTIs on the health of military personnel, as well as on decreasing the operational burden associated with this disease. Overall, the Wound Infections Research Area continues to maintain a robust research platform, which supports evidence-based CPGs for management of militarily-relevant wound infections.

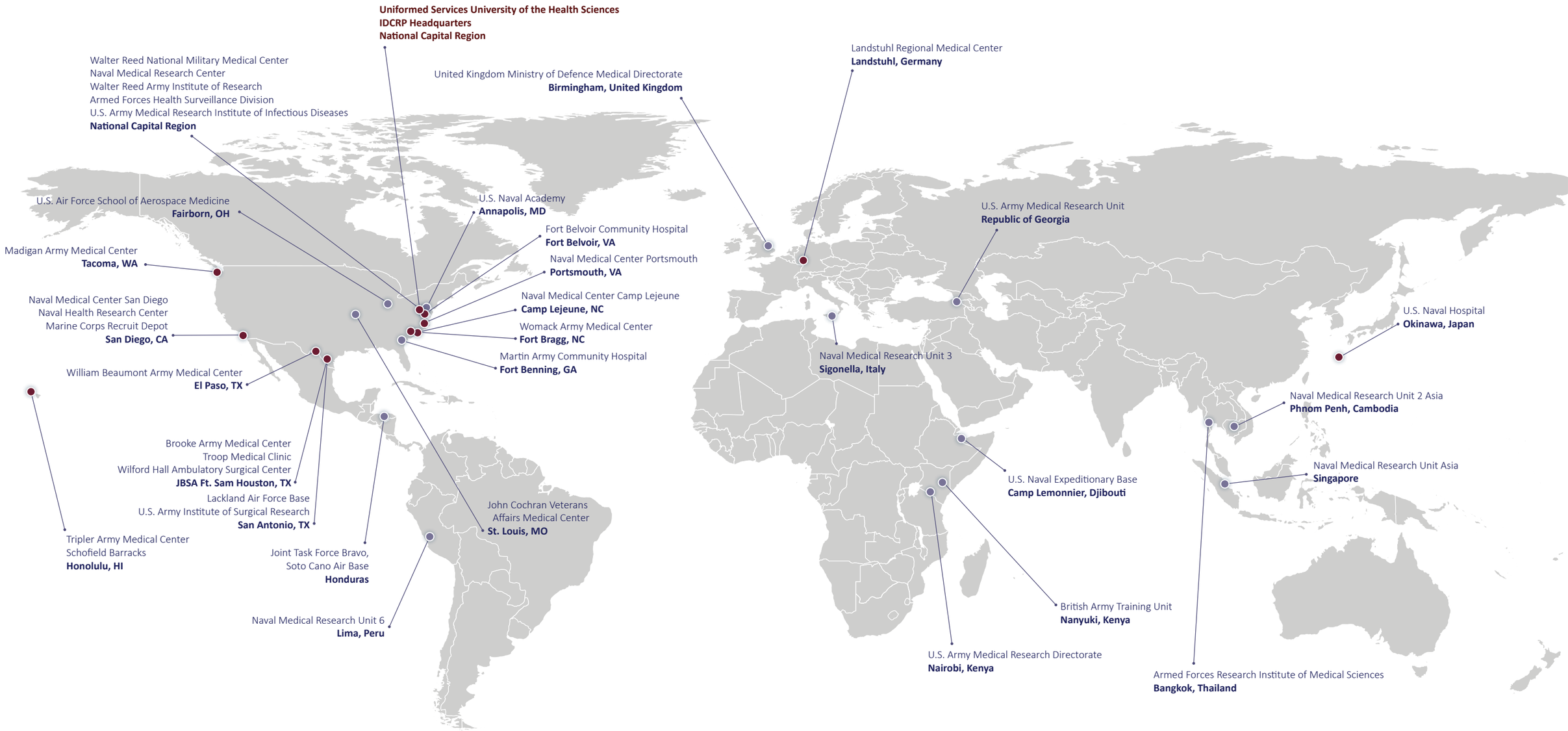
HIGHLIGHTS/KEY FINDINGS

- **A 2022 supplement of *Military Medicine* reported over a decade of impactful IDCRP combat trauma-related research, highlighting the history and clinical relevance of TIDOS and DoD JTS CPG development support, as well as clinical findings from research on extremity wound infections, IFIs, wound microbiology, and long-term outcomes.**
- **The proportion of recurrent BSIs in the MHS attributed to 1 of 15 common pathogens over a 10-year period was lower than what has been reported in civilian literature with the majority of patients having substantial comorbidities.**
- **Assessment of admission Sequential Organ Failure Assessment (SOFA) scores collected from 882 critically-ill combat casualties determined that for every 1 point increase in the SOFA score collected at Landstuhl admission, the odds of developing an infection increased by 20%.**
- **A new SSTI Repository Protocol, pooling clinical data, research specimens, and bacterial isolates from seven IDCRP SSTI protocols, has been developed to provide a robust platform to advance analyses on gaps in knowledge in SSTI epidemiology, clinical outcomes, and immunology to support future research on prevention strategies.**

IDCRP PARTNER NETWORK

38 PARTNER SITES

70+ ACTIVE PROTOCOLS



CENTER OPERATIONS

The successful execution of the diverse clinical research portfolio of the Program is dependent on an efficient, robust, and well-integrated operational structure.

Matthew Pearl, MS
Director, Center Operations

Todd Stroberg, RN, BSN
Head, Clinical Research Management

Mark Fritschlanski
Head, Regulatory Affairs and Quality Management

During the past year, the IDCRP reviewed and restructured the divisions central to Program operations with the objective of creating a fully integrated unit and improving efficiency of all related operations. Led by Mr. Matthew Pearl (Director, Center Operations), the newly formed Center Operations is responsible for the oversight, planning, and coordination of the central functions of the Program. Five new Heads or leads were also established in the areas of Clinical Research Management, Regulatory Affairs and Quality Management, Site Operations, Program Management, and Data Operations ***(See Page 20)*** to effectively support the IDCRP research areas.

The primary goals for Center Operations are to improve standardization across the IDCRP clinical research portfolio with regard to the development and execution of research protocols and the production of high-value knowledge products. In addition, an aim of Center Operations is to assist the Program Management team with the development of budgets to appropriately meet the research needs for the investigative teams and to ensure retention of personnel in a highly competitive job market.

Led by Mr. Todd Stroberg, the Clinical Research Management team includes USU-based IDCRP Clinical Research Managers (CRM) and Research Area Coordinators. The Clinical Research Management team is vital to the successful execution of the IDCRP clinical research portfolio by supporting investigative teams and Data Operations with regard to protocol development, operations, and management. During the past year, an improved and expanded CRM communication plan, group collaboration, enhanced information sharing tools, trainings, and rapid response problem solving approach were implemented.

The Regulatory Affairs and Quality Management teams, led by Mr. Mark Fritschlanski, supports the development and implementation of IDCRP clinical research protocols by ensuring regulatory compliance and ethical conduct. The Regulatory Affairs team also acts as the liaison between the Program and regulatory officials at USU, the Defense Health Agency, DoD partners, and the National Institute of Allergy and Infectious Diseases. During 2022, the Regulatory Affairs team supported the investigative teams by providing regulatory consultations on protocol design and documentation, preparing and assessing regulatory documents, and reviewing 144 protocols and other protocol-related materials prior to submission to the USU Institutional Review Board. The primary goal of the Quality Management team is to facilitate excellence across all IDCRP participating sites, implement best practices, and verify the quality of work being performed. During the past year, new quality management plans and associated standard operating procedures (SOPs) focused on risk-based monitoring principles were developed and implemented for six protocols.

With the emergence of new infectious disease threats, such as SARS-CoV-2, the Program expanded to new partner sites and engaged new military populations. As such, the Site Operations team, led by Ms. Susan Chambers, was established to provide centralized oversight to ensure standardization, efficiency, and quality across the broad IDCRP Partner Network with regard to research training, competency, conduct, and resource utilization. Goals of the Site Operations team include the establishment of site-specific SOPs and comprehensive site assessments to inform site selection for the clinical research studies and optimize assets of the Partner Network. Since Site Operations was established in August, operational practices have been assessed and evaluated to inform the approach and prioritization of standardization efforts. Specifically, the standardization of operational practice reviews and approvals was established, and site management leaders are being engaged in new initiatives to improve communication, training, resource utilization, and performance tracking.

A robust operational and financial foundation is critical for the successful execution of the Program's clinical research portfolio. The Program Management team, led by Ms. Victoria Barron, effectively oversees financial aspects of the Program. During the past year, the Program Management team has increased efficiency by more accurately predicting costs across the various protocols, as well as improving standardization and communication with the other divisions of Center Operations. In addition, the Program Management team established a new dashboard to provide real-time tracking and updating of the various agreements that are required for the Program's collaborations with government, civilian, and academic institutions and coordinated the development of a new method for providing payments to study participants.

For the coming year, a goal of the Clinical Research Management team is to improve the efficiency and regulatory compliance of protocol development and subsequent operations through the development and implementation of SOPs, templates, guidelines, and checklists. Improved systems to track and manage protocols will also be established to improve workflow for protocol development, execution, oversight, and communication. Plans for the Regulatory Affairs and Quality Management teams include the implementation of the Florence electronic Trial Master File (eTMF) system and continued development and refinement of SOPs and policies to improve efficiency and regulatory compliance. In 2023, the Site Operations team will work to enhance and expand the operational capabilities of the IDCRP Partner Network, establish and evaluate competency standards and training tools for research roles, provide and maintain assessments of IDCRP sites and resources, and expand network operational efficiencies and capabilities to meet the milestones set by the clinical research portfolio. In addition, a goal of the Program Management team for the coming year is to develop a budget tracking tool to further improve efficiency and standardization.

Susan Chambers, RN, BSN, CCRC
Head, Site Operations

Victoria Barron, MPA
Team Lead, Program Management

HIGHLIGHTS

- **The Florence eTMF system, which is an application utilized to support the development and tracking of essential clinical research study documents, will be implemented by the IDCRP Regulatory Affairs team in cooperation with the Regulatory Affairs team at HJF. This effort has included the development of a new SOP and policy documents, as well as the training of 11 IDCRP staff members on the new eTMF system.**
- **The Clinical Research Management team, with the support of the Research Support Group, successfully initiated two new clinical trials, the P2 trial and the TrEAT TD 2.0 trial under the Deployment and Travel-Related Infections Research Area, at multiple sites within the IDCRP Partner Networks.**

DATA OPERATIONS

The Data Coordination Center (DCC) serves as the foundation for the high-quality, high-value clinical research executed by the Program.

Edward Parmelee, MSc
Chief, Data Coordination Center

Central to the effectiveness of the IDCRP clinical research portfolio, the DCC is comprised of highly experienced data managers/developers and SAS/Oracle programmers. Led by Mr. Edward Parmelee (DCC Chief), DCC team members provide their expertise to IDCRP investigators with regard to conceptualization, design, collection, management, cleaning, and analysis of data, as well as publication of the resulting findings.

The resources of the DCC are used for all IDCRP protocols where the Program is the primary data collector or functions as the central data repository. As part of the restructure of the IDCRP during the past year, the DCC has been included in the Center Operations group (***see Pages 18-19***) to improve the functionality of the team by fully integrating the DCC with other operational aspects of the IDCRP. The overall goal of the DCC is to ensure high-quality data collection, management, processing, and access for the IDCRP clinical research portfolio.

During 2022, the DCC provided support services for 43 IDCRP research studies, including 4 studies that are entirely virtual (i.e., all data collected from the Military Health System [MHS] Data Repository). Protocol support efforts included the creation or modification of data collection workflows and the acquisition of data from MHS Data Repository. The DCC team has also continued to effectively utilize the REDCap system, which is a browser-based electronic data capture system and workflow methodology used in the design and execution of clinical research databases. In particular, DCC team members have become experts in modifying and supplementing the capacities of REDCap in novel ways, which allows the DCC to remain on the cutting edge of data collection.

In support of COVID-19 clinical research, the DCC team developed and deployed a neurocognitive assessment module that enrollees in the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) protocol could complete on their smartphone or tablet. Furthermore, the DCC is collaborating with the Joint Trauma System staff on data processes related to abstraction, in-processing, transformation, and upload to the IDCRP Oracle server for the COVID-19 Military Registry Analysis Project (M-RAP).

For 2023, the DCC will continue to focus on improving the efficiency and efficacy of data operations through the review, update, and creation of standard operating procedures, along with assessing processes with regard to primary objectives and ensuring appropriate training for all team members. Another new initiative, a specimen tracking system, will also be implemented in the coming year, using one protocol as the initial test. Furthermore, in support of the Acute Respiratory Infections at the Academy (ARIA) protocol, which will be examining data from students and staff at the U.S. Naval Academy in 2023 to guide health policy and situational response, the DCC is preparing to provide near real-time cleaning of data elements critical for decision-making.

HIGHLIGHTS

- **Research repository protocols are planned for all IDCRP research areas to allow continued use of study data for purposes other than original study goals. This will be a large effort for the DCC as it will involve pooling data from multiple protocol sources.**
- **Final migration of data from the HIV Natural History Study and the HIV-Associated Neurocognitive Disorders (ALLHANDS) protocols from legacy electronic data capture systems (e.g., ClinPlus and Mi-Forms) into REDCap workflows was completed, enabling new data collection functionality for site teams.**

SCIENTIFIC REVIEW BOARD

The IDCRP Scientific Review Board (SRB) is responsible for performing independent, comprehensive scientific reviews of clinical research protocols and protocol amendments prior to their submission to the USU Institutional Review Board (IRB).

The IDCRP SRB conducts scientific reviews to assess the feasibility and scientific validity of protocols and protocol amendment submissions with regard to research questions, hypotheses, aims/objectives, and methods to ensure the quality of scientific content prior to IRB submission. Chaired by Dr. John Powers (National Institute of Allergy and Infectious Diseases liaison) and supported by Vice Chair CDR Mark Simons (IDCRP Deputy Director), all new IDCRP protocols, as well as protocol amendments resulting in substantial changes to the associated protocol, are reviewed by the SRB.

Subject-matter experts are selected for each SRB review panel based on the respective research questions described in the submitted protocol or protocol amendment and include biomedical scientists, statisticians, and other scientific review panel members affiliated with the IDCRP Partner Network. The SRB Chair (or Vice Chair when the Chair is recused or unavailable) conducts a precursor evaluation of each submission to assign it to one of the three potential review pathways that is determined to be the most appropriate and efficient pathway for the submission. The Chair Review is the most rapid pathway with completion occurring within 14 days of submission. The next pathway is the Low Resource Review, which is completed within 28 days of submission. The final pathway is the Standard Review, which is completed within 35-45 days of submission.

During the past year, the SRB reviewed four new protocols and six protocol amendments; two submissions are currently undergoing Chair Review. To improve the productivity and timely responses of the review pathways, Principal Investigators and the SRB Chair had discussions related to the study design prior to finalizing the protocol and submitting it. A limiting factor in expediting the review pathways is that SRB reviews may not be initiated until the panels are fully staffed. In an effort to avoid unnecessary delays, investigators were asked to suggest the names of potential reviewers prior to submission, which allowed for their availability and willingness to participate on the panels to be confirmed prior to the material being submitted.

In 2023, the SRB Chair will continue to address challenges that occur in the review process to further improve efficiency of the Standard Review pathway and reduce the time required to complete the reviews, while still maintaining scientific rigor. To support being able to effectively staff the SRB panels, investigators will be required to provide a tentative timeline of steps leading to the SRB submission upon approval of the original concept. An additional process improvement strategy is to provide training and mentorship to the junior investigators with regard to developing a protocol and how to link research question(s) to the study design and statistical analysis.

John Powers, MD, Chair, Scientific Review Board

SRB Reviews and Approvals	Numbers
Submission to the SRB	**10**
New protocols	4
Protocol amendments	6
SRB disposition	
Approved	8
Under Review	3*

**One submission from the prior year is under revision by the investigative team.*

EDUCATION/MENTORSHIP

A key objective of the IDCRP is supporting the continuing educational growth of the next generation of clinical infectious disease (ID) researchers in the United States Armed Services through mentored research projects and research engagement.

Dr. Nusrat Epsi presenting at 2022 USU Research Day

Drs. Nusrat Epsi and Liana Andronescu with their mentor, Dr. Stephanie Richard (middle)

Capt Matthew Soderstrom receiving 1st place in the Resident Poster Competition at the 2022 SAUSHEC Research Day

As part of the IDCRP mission to foster educational growth and opportunities, residents, ID fellows, and medical/graduate students in the U.S. Armed Services are provided options to conduct mentored research projects developed with and supervised by IDCRP investigators and to participate in ongoing research led by investigators. These opportunities are available at USU and military treatment facilities within the IDCRP Partner Network, including Brooke Army Medical Center, Madigan Army Medical Center, Naval Medical Center Portsmouth, Naval Medical Center San Diego, and Walter Reed National Military Medical Center (WRNMMC). In addition, trainees from the National Institute of Health (NIH), University of Maryland, George Washington University, and San Diego University are also participating in IDCRP research projects. Participating in mentored research projects provides trainees with real-world, hands-on experience, which improves their understanding of the conduct of research studies including design, data collection and analysis, and publication/presentation of findings. Furthermore, the clinical ID research capstone curriculum for USU medical students, as well as continuing GME activities at WRNMMC and the Armed Forces Infectious Disease Society are supported by the Program.

During 2022, 43 residents (across multiple specialties, including Internal Medicine, Preventive Medicine, Psychology, Health Economics, and Neurosurgical), medical/graduate students, ID Fellows, and MPH students, as well as 5 post-doctoral trainees, either began or completed IDCRP-mentored research projects. One trainee from NIH National Institute of Neurological Disorders and Stroke utilized data from the HIV Natural History Study neurocognitive sub-study to assess neurocognitive dysfunction with neuronal injury in HIV+ individuals. In addition, data from the Acute Respiratory Infections (ARI) Research Area EPICC protocol are being utilized to support one epidemiologic PhD dissertation and one lab-based dissertation. A post-doctoral fellow is also completing a mentored research project using data from the ARI Research Area PASS study.

Twenty-five oral and poster presentations involving trainees were presented at local and national conferences during the past year. Moreover, 20 manuscripts co-authored by trainees were published or accepted for publication. Trainees who participated in IDCRP-mentored research projects also received award recognition in 2022 *(see IDCRP Awards and Honors, page 28)*.

Research engagement is an integral component for the success of the IDCRP's education mission. As such, IDCRP investigators attended public health student practicum and project fairs in 2022, discussed research opportunities with medical students and ID Fellows at USU and participating military treatment facilities, and informed medical training program Directors about available IDCRP-mentored opportunities. Medical school graduates, USU faculty, and ID consultants were also asked to discuss with trainees the impact of clinical research in their respective paths to further increase awareness of the importance of ID research and spark interest in participating in research opportunities.

Overall, the IDCRP continues to be successful in meeting the objectives of the Program's education mission to strengthen high-quality clinical ID research in the Military Health System through effectively mentoring the growth of active-duty researchers.

SELECTED IDCRP TRAINEE EDUCATION PUBLICATIONS AND PRESENTATIONS

PUBLICATIONS

Ford MB, Mende K, Kaiser SJ, Beckius ML, Lu D, Stam J, Li P, Stewart L, Tribble DR, Blyth DM. Clinical Characteristics and Resistance Patterns of *Pseudomonas aeruginosa* Isolated from Combat Casualties. *Military Medicine*. 2022; 187(3-4): 426-434.

McCarthy SL, Stewart L, Shaikh F, Murray CK, Tribble DR, Blyth DM. Prognostic Value of Sequential Organ Failure Assessment (SOFA) Score in Critically-Ill Combat-Injured Patients. *Journal of Intensive Care Medicine*. 2022; 37(11):1426-1434.

Walker PF, Bozzay JD, Schechtman DW, Shaikh F, Stewart L, Carson ML, Tribble DR, Rodriguez CJ, Bradley MJ. Anastomotic Outcomes in Military Exploratory Laparotomies in the Modern Combat Era. *American Surgeon*. 2022; 884(4):710-715.

Epsi N, Richard SA, Lindholm DA, Mende K, Ganesan A, Huprikar N, Lalani T, Fries AC, Maves RC, Colombo RE, Larson DT, Smith A, Chi SW, Maldonado CJ, Ewers EC, Jones MU, Berjohn CM, Libraty DH, Sanchez Edwards M, English C, Rozman JS, Mody RM, Colombo CJ, Samuels EC, Nwachukwu P, Tso MS, Scher AI, Byrne C, Rusiecki J, Simons MP, Tribble D, Broder CC, Agan BK, Burgess TH, Laing ED, Pollett SP. Understanding 'Hybrid Immunity': Comparison and Predictors of Humoral Immune Responses to SARS-CoV-2 Infection and COVID-19 Vaccines. *Clinical Infectious Diseases*. 2022; May 24; ciac392.

Helfrich AM, Fraser J, Hickey P. Destination Based Errors in Chloroquine Malaria Chemoprophylaxis Vary Based on Provider Specialty and Credentials. *Travel Medicine and Infectious Diseases*. 2022; 102310.

Ellis GC, Lanteri CA, Hsieh HC, Graf PCF, Pineda G, Crum-Cianflone NF, Berjohn CM, Sanders T, Maves RC, Deiss R. Coccidioidomycosis Seroincidence and Risk among Military Personnel, Naval Air Station Lemoore, San Joaquin Valley, California, USA. *Emerging Infectious Diseases*. 2022; 28(9): 1842-1846.

Noiman A, Esber A, Wang X, Bahemana E, Adamu Y, Iroezindu M, Kiweewa F, Maswai J, Owuoth J, Maganga L, Ganesan A, Maves RC, Lalani T, Colombo RE, Okulicz JF, Polyak C, Crowell TA, Ake JA, Agan BK. Clinical Factors and Outcomes Associated with Immune Non-response among Virally Suppressed Adults with HIV from Africa and the United States. *Scientific Reports*. 2022; 12(1): 1196.

Celone M, Pecor D, Potter A, Richardson A, Dunford J, Pollett S. An Ecological Niche Model to Predict the Geographic Distribution of the Yellow Fever and Mayaro Virus Vector, *Haemagogus janthinomys*, in South America. *PLoS Neglected Tropical Diseases*. 2022; 16(7): e001056.

PRESENTATIONS

2022 Conference on Retroviruses and Opportunistic Infections (CROI), 13-16 February 2022, Denver, CO.

Ham L, Hsieh HC, Kelly E, Chu X, Ganesan A, Utz G, Maves R, Silverman I, Tramont E, Rapoport SI, Nath A, Agan B, Snow J, Smith B, Kapetanovic S, for the NIH-DoD NeuroHIV Consortium. Childhood Trauma Modifies Brain Morphology and Cognition in People with HIV.

2022 National American College of Physicians Meeting, 28-30 April 2022, Chicago, IL

Fleit M, Fraser J, Hickey PW, Mitre E, Hartzell J. Diagnosis and Management of Enterobiasis in Military Treatment Facilities.

2022 Military Health System Research Symposium, 12-15 September 2022, Kissimmee, FL.

Soderstrom MA, Blyth DM, Carson ML, Campbell WR, Yabes JM, Shaikh F, Stewart L, Tribble DR, Murray CK, Kiley JL. Seasonality of Microbiology of Combat-related Wound Infections in Afghanistan.

Andronescu LR, Richard SA, Scher AI, Lindholm DA, Mende K, Ganesan A, Huprikar N, Lalani T, Smith A, Mody R, Jones MU, Bazan SE, Colombo RE, Colombo CJ, Ewers E, Larson DT, Maves RC, Berjohn CM, Maldonado CJ, English C, Sanchez Edwards M, Rozman JS, Rusiecki J, Byrne C, Pollett S. SARS-CoV-2 Infection is Associated with Post-Acute Self-Reported Cognitive and Mental Health Symptoms.

Coggins S, Goguet E, Pollett S, Samuels E, Lusvarghi S, Davies J, Illinik L, Sanchez-Edwards M, Jackson-Thompson BM, Moser M, Tso M, Hollis-Perry M, Ortega O, Parmelee E, Tribble DR, Olsen CH, Schully KL, Burgess TH, Broder CC, Weiss CD, Laing ED, Mitre E. Antibody Durability, Vaccine-related Symptoms, and Omicron Neutralization after BNT162b2 mRNA COVID-19 Vaccination in the Prospective Assessment of SARS-CoV-2 Seroconversion (PASS).

Goertzen SM, Lindholm D, Walter RJ, Huprikar N, Ganesan A, Mende K, Rozman J, Harrell TE, Peterson P, Simons M, Tribble D, Agan B, Burgess TH, Pollett S, Morris MJ. COVID-19 Chronic Impairment with Pulmonary Symptoms (ChIPS).

2022 IDSA ID Week, 19-23 October 2022, Washington, D.C.

Geringer M, Stewart L, Shaikh F, Carson ML, Lu D, Cancio LC, Gurney JM, Tribble DR, Kiley JL. Epidemiology and Timing of Infectious Complications from Battlefield-Related Burn Injuries.

Soderstrom MA, Blyth DM, Carson ML, Campbell WR, Yabes JM, Shaikh F, Stewart L, Tribble DR, Murray CK, Kiley JL. Seasonality of Microbiology of Combat-related Wound Infections in Afghanistan.

Liberg R, Schofield C, Colombo RE. Impact of COVID-19 Pandemic on Influenza-like Illness (ILI) Experience among Healthcare Workers in Military Treatment Facilities.

Epsi N, Lindholm DA, Ganesan A, Lalani T, Smith A, Mody R, Jones MU, Bazan SE, Colombo RE, Colombo CJ, Ewers EC, Larson DT, Berjohn CM, Maves RC, Fries AC, Scher AI, Byrne C, Rusiecki J, Sanchez Edwards M, Rozman JS, Mende K, Simons MP, Tribble D, Agan BK, Burgess TH, Pollett SD, Richard SA. Precision Phenotyping of "Long COVID" through Machine Learning.

Andronescu LR, Richard SA, Laing ED, Saperstein AK, Modi J, Heaney CD, Fraser JA, Shaikh S, Broder CC, Burgess TH, Pollett SD, Millar EV, Coles CL, Simons MP. Evaluating SARS-CoV-2 Surveillance Strategies at the United States Naval Academy: A Comparison of Saliva and Dried Blood Spot Serosurveillance against Molecular-Confirmed Case Detection.

IDCRP AWARDS AND HONORS

We would like to congratulate the Infectious Disease fellows and trainees who received recognition for their IDCRP-mentored research projects over the past year. In addition, we congratulate Maj David Lindholm for receiving the Scholarship in Action Award for his publication reporting findings from the Acute Respiratory Infections (ARI) Research Area, Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) protocol. COL Eric Garges also received the Defense Meritorious Service Award.

We also wish to congratulate Lt Col Elizabeth Markelz, a member of the ARI Research Area Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) investigative team, who received the 2022 Physician Award by the Society of Federal Health Professionals (AMSUS), which recognizes the accomplishments of a federal physician who had made outstanding contributions as a clinician, researcher, educator, or healthcare executive. Lt Col Markelz was also recognized by the San Antonio Uniformed Services Health Education Consortium with the 2022 Professionalism Award and the Lt. Gen Paul K. Carlton Jr. Graduate Medical Education Faculty Award.

Name	Award/Honor	Awarding Organization
Academic or General Award/Honor		
COL Eric Garges	Defense Meritorious Service Award	Secretary of Defense
Lt Col A. Elizabeth Markelz	2022 Physician Award	Society of Federal Health Professionals (AMSUS)
Lt Col A. Elizabeth Markelz	2022 Professionalism Award	San Antonio Uniformed Services Health Education Consortium
Lt Col A. Elizabeth Markelz	Lt. Gen. Paul K. Carlton Jr. Graduate Medical Education Faculty Award	San Antonio Uniformed Services Health Education Consortium
Research-Related Award for IDCRP-Related Research Study		
Maj David Lindholm	FY22Q1 Scholarship in Action Award	Brooke Army Medical Center
Capt Matthew Soderstrom	1st Place in Resident Poster Competition	San Antonio Uniformed Services Health Education Consortium
Maj Ryan Collier	4th Place in the Commander's Award in the Fellow Clinical Research Category	San Antonio Uniformed Services Health Education Consortium
Dr. Alexander Vostal	2022 IDSA IDWeek Trainee Abstract Travel Award	Infectious Diseases Society of America
LT Michelle Kautz	1st place in Research Conducted Under the Jurisdiction of Another Institution category at the Naval Medical Center Portsmouth Annual Academic Research Conference	Naval Medical Center Portsmouth

Left: Maj Lindholm receiving his Scholarship in Action award from BG Clinton Murray

Middle: Lt Col Markelz receiving the Lt. Gen. Paul K. Carlton Jr. Award from Brig Gen Jeannine Ryder and COL Kimberlie Biever (courtesy of Army.mil)

Right: Maj Collier with his Commander's Award, pictured with his wife.

IDCRP COLLABORATORS & PARTNERS

Department Of Defense Sites

U.S. Military Hospitals and Clinics

- Brooke Army Medical Center, JBSA Fort Sam Houston, TX
- Fort Belvoir Community Hospital, VA
- Joint Task Force Bravo, Soto Cano Air Base, Honduras
- Landstuhl Regional Medical Center, Germany
- Madigan Army Medical Center, Joint Base Lewis McChord, WA
- 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
- Schofield Barracks Health Clinic, Oahu, HI
- Tripler Army Medical Center, Oahu, HI
- Troop Medical Clinic, Fort Sam Houston, TX
- U.S. Air Force School of Aerospace Medicine (USAFSAM)
- U.S. Naval Academy, Annapolis, MD
- U.S. Naval Expeditionary Base, Camp Lemonnier, Djibouti
- U.S. Naval Hospital Okinawa, Japan
- 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)
  - Biological Defense Research Directorate
  - Enteric Disease
  - Viral and Rickettsial Diseases
  - Wound Infections
- NMRC—Subordinate Commands
  - Naval Health Research Center, San Diego, CA
  - Naval Medical Research Unit No. 2 Asia, Phnom Penh, Cambodia
  - Naval Medical Research Unit No. 3, Sigonella, Italy
  - Naval Medical Research Unit No. 6 Lima, Peru
- U.S. Army Institute of Surgical Research
- U.S. Army Medical Research Institute of Infectious Diseases
  - Emerging Infectious Diseases
  - U.S. Military HIV Research Program
  - Viral Diseases Branch
- Walter Reed Army Institute of Research
  - Emerging Infectious Diseases Branch
  - Military HIV Research Program
  - Multidrug Resistant Organism Repository and Surveillance Network
  - Specimen Processing Laboratory
  - Wound Infections
  - Viral Diseases
  - Overseas Research Detachments
    - Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand
    - U.S. Army Medical Research Unit, Tbilisi, Georgia
    - U.S. Army Medical Research Directorate-Kenya, Nairobi, Kenya
    - U.S. Army Medical Materiel Development Activity

Other U.S. Military Commands/Programs

- Defense Health Agency
  - Armed Forces Health Surveillance Division (AFHSD)
    - Global Emerging Infection Surveillance (GEIS) Program
  - Immunization Healthcare Division (IHD)
- Bureau of Medicine and Surgery, Department of Navy (BUMED)
- Congressionally Directed Medical Research Program (CDMRP)
- Defense Advanced Research Projects Agency (DARPA)
- Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense
- Military Infectious Diseases Research Program (MIDRP)
- Navy Marine Corps Public Health Center (NMCPHC)
- San Antonio Uniformed Services Health Education Consortium (SAUSHEC)

United States Government Health Agencies

- Biomedical Advanced Research and Development Authority
- Centers for Disease Control and Prevention
- Food and Drug Administration
- Lawrence Livermore National Laboratory
- National Institutes of Health
  - National Cancer Institute
  - National Institute of Allergy and Infectious Diseases
    - Division of AIDS
    - Division of Clinical Research
    - NIAID Flu Networks
    - Division of Microbiology and Infectious Diseases
    - 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
  - James J. Peters VA Medical Center, Bronx, NY
  - St. Louis Veterans Affairs Medical Center
  - Veterans Aging Cohort Study
  - Veterans Affairs Connecticut Healthcare System
  - Veterans Affairs Sierra Nevada HealthCare System

Foreign Health Agencies and Organizations

- International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b)
- National Institute for Public Health and the Environment (RIVM), The Netherlands
- Royal Thai Army Clinical Research Center
- SEARCH Research Foundation and Innovation (IHRI) clinic
- 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

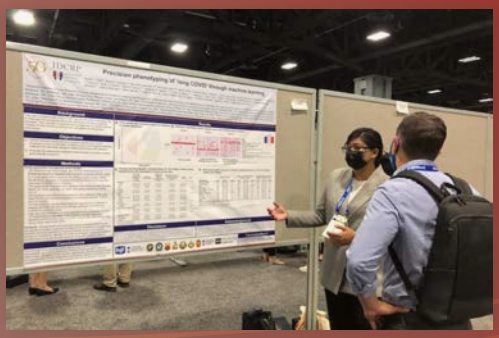
Academia

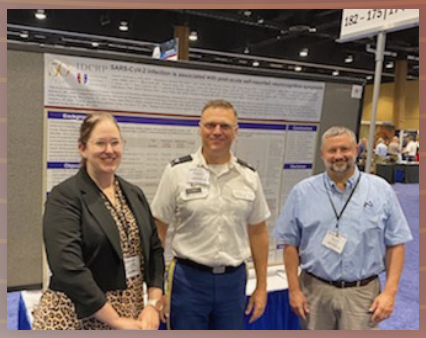
- Emory University
- Harvard T. H. Chan School of Public Health
- Icahn School of Medicine at Mount Sinai
- Johns Hopkins Applied Physics Laboratory
- Johns Hopkins School of Medicine
- Johns Hopkins Bloomberg School of Public Health
- Michigan State University
- University of California-San Diego
- University of California-San Francisco
- University of Georgia, Athens, Georgia
- University of Glasgow, Scotland
- University of Minnesota
- University of Nevada, Reno
- University of Notre Dame
- University of Pennsylvania
- University of Pittsburgh
- University of Texas Health Science Center at San Antonio
- University of Texas-San Antonio
- University of Toledo College of Medicine and Life Sciences
- University of Vermont
- University of Virginia
- University of Washington
- Washington University in St. Louis
- Yale University

Research Organizations and Industry Partners

- AstraZeneca plc
- Antigen Discovery, Inc.
- GlaxoSmithKline plc
- Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.
  - Austere Environments Consortium for Enhanced Sepsis Outcomes (ACESO)
- Integrated Biotherapeutics, Inc.
- Janssen Pharmaceuticals, Inc.
- Leidos Biomedical Research, Inc.
- Menssana Research, Inc.



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