IDCRP

Uniformed Services University

INFECTIOUS DISEASE CLINICAL RESEARCH PROGRAM

2021

ANNUAL REPORT

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LETTER *from* IDCRP LEADERSHIP

During the past year, infectious disease clinicians and researchers from the Infectious Disease Clinical Research Program (IDCRP) and its collaborating partners have continued to serve as a central research hub, informing the Department of Defense (DoD) response to the COVID-19 pandemic. Our staff have demonstrated tremendous leadership, diligence, and dedication, working through pandemic challenges and across time-zones to coordinate across the large network of contributing clinical sites and laboratory partners. Through these efforts, we have bolstered our core mission to support military readiness and to counter operational infectious disease threats.

In particular, the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) protocol has substantially added to the SARS-CoV-2 evidence base, informing the development of diagnostic, preventive, and treatment approaches utilized within the Military Health System (MHS). Characterization of clinical outcomes, including "Long COVID" is the focus of multiple analyses underway. A new protocol, the Military COVID-19 Registry Analysis Project (M-RAP), was recently activated and is collecting data from the extensive Joint Trauma System COVID-19 Registry to assess the SARS-CoV-2 burden on active-duty personnel, as well as offering real-time examination of the effectiveness of vaccine products and treatment approaches.

As a testament to the IDCRP's dedication and flexibility, the five non-COVID-19 research areas remained highly productive, including resuming activity of protocols that were paused in 2020 due to the pandemic. For example, the Acute Respiratory Infections Research Area's Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) was extended for another year to strengthen power to achieve its primary objectives. Additionally, a new clinical trial was initiated by the Sexually-Transmitted Infections Research Area, the Meningococcal (Bexsero®) Vaccine for Gonococcal Infection (MAGI) trial, at Walter Reed National Military Medical Center and partner sites to assess effectiveness for preventing gonococcal infection, which could have substantial impact on Force Health Protection in military populations. Further details on the IDCRP research area activities and accomplishments are included in the following report.

The enduring success of the IDCRP is through our unique clinical research network partnerships with the National Institute of Allergy and Infectious Diseases (NIAID), DoD Combatant Commands, and clinicians in the MHS, DoD research and development programs, as well as Veterans Affairs Healthcare System, academia, and industry collaborators. Also crucial for the successful execution of our mission is the strong support we receive from USU leadership, our Operational and Executive Steering Committees, and The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). The IDCRP has been further supported by funding and cooperative partnership with 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 (AFHSD) and Immunization Healthcare Division (IHD) of the Defense Health Agency.

As always, we deeply commend and thank our clinical research and support staff, as well as our many active-duty and civilian investigator partners for their dedication to the IDCRP. We also are sincerely grateful to the military service members and beneficiaries who volunteer their time to participate in our studies. It is an honor and privilege to work with such a remarkable team.

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

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

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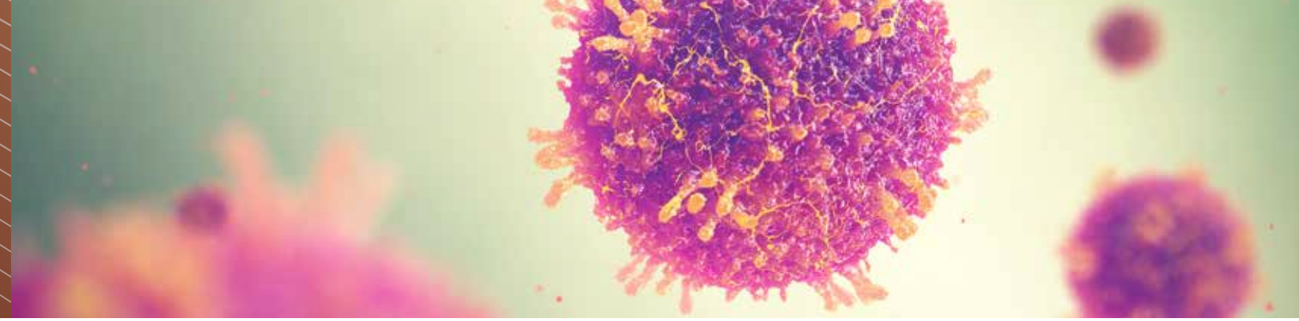
ABOUT IDCRP



The Infectious Disease Clinical Research Program (IDCRP) was founded in 2005 under an interagency agreement between the Uniformed Services University of the Health Sciences (USU) and the National Institute of Allergy and Infectious Diseases (NIAID) 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 affects force readiness by advancing clinical practice and informing health policy for military personnel.

In collaboration with partners from the Department of Defense (DoD), academia, government, and industry, IDCRP supports a broad clinical research portfolio within the Military Health System. From observational, longitudinal cohort studies to field-based interventional trials to 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, Uniformed Services University of the Health Sciences (USU)
Dean, School of Medicine, USU
Chief, Division of Clinical Research (DCR), National Institute of Allergy and Infectious Diseases (NIAID)
Director, Research, Development and Acquisition, Defense Health Agency (DHA)

Operational Steering Committee

Surgeons General Infectious Disease Consultants—Army, Navy, Air Force
Director, Armed Forces Health Surveillance Division
Director, Military Infectious Diseases Research Program, MRDC
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
- Chief, Quality Management
- Clinical Research Managers

NIAID Liaison
Chair, Scientific Review Board

Deputy Program Director
Research Administration Staff
Regulatory Affairs Staff
Chief, Program Operations and Finance
Program Management and Finance Staff

Data Coordination Center (DCC)
Chief, DCC
Data Configuration, Management, and Programming Staff

Partner Organizations
Military Hospitals
Military Research and Development Commands
Military Public Health Commands
Non-DoD Partners

VISION

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

MISSION

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

IDCRP RESEARCH AREAS

- **COVID-19—**Strategic aims focus on improving the speed and accuracy of diagnostics to include the diagnosis of infectious hosts, epidemiology and transmission dynamics, characterization of acute-to-chronic phenotype and immunopathological correlates of SARS-CoV-2 infection, risk prediction, and treatment and preventive approaches.

- **Acute Respiratory Infections—**Strategic aims focus on diagnostics, prevention (influenza vaccine), epidemiology (respiratory threats in training settings), and treatment (severe influenza) of acute respiratory infections among U.S. military personnel and their beneficiaries.

- **Deployment and Travel-Related Infections—**Strategic aims focus on epidemiology of deployment and travel-related infectious threats for military personnel, pre-travel health care and mitigation strategies, novel methodologies for identifying pathogens associated with febrile and diarrheal disease, and improved treatment approaches during deployment.

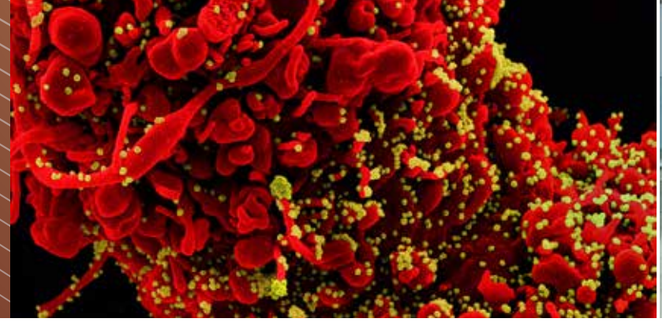
- **Human Immunodeficiency Virus Infections—**Strategic aims include mitigating specific complications of the virus among military HIV-infected patients; identifying, treating, and preventing HIV-associated neurocognitive disorders; developing and employing predictive models to optimize individual management of HIV; and improving therapeutic outcomes with the ultimate goal of functional cure of infection.

- **Sexually-Transmitted Infections—**Strategic aims focus on development of improved means to diagnose, prevent, and treat sexually-transmitted infections, with particular emphasis on emergent drug-resistant gonorrhea, among active-duty members and their beneficiaries.

- **Wound Infections—**Strategic aims focus on addressing knowledge gaps in infection prevention, clinical management, and treatment outcomes in battlefield trauma to inform DoD Joint Trauma System clinical practice; development of effective strategies for the prevention and control of skin and soft-tissue infections, particularly *Staphylococcus aureus*-related, among congregate military personnel in deployment and training settings; and improved understanding of wound microbiology impact on clinical outcomes related to high-threat virulent and antimicrobial-resistant pathogens.

Each area's 2021 accomplishments are presented in the following pages, along with information and projections for 2022.

SARS-COV-2 AND COVID-19



Colorized scanning electron micrograph of a cell (red) infected with SARS-CoV-2 (yellow) showing morphological signs of apoptosis [image credit: NIAID]

(from left) Raquel Resendez, Jose Montes, Javier Mejia, and Priscilla Sandoval of the William Beaumont Army Medical Center EPICC and STORMCHASER teams

The ongoing COVID-19 global pandemic not only poses a serious risk to the health of U.S. service members and Military Health System (MHS) beneficiaries, but also has a substantial impact on military readiness. Although a vast amount of research has been published over the past year, there are still limitations and knowledge gaps related to diagnostic assays, treatment, prophylactic measures, predictors of severe disease, "Long COVID", vaccine effectiveness, and the durability of vaccine and post-infection immunity.

Simon Pollett, MBBS, IDCRP Associate Science Director and COVID-19 Research Area Director

During the past year, COVID-19 research has swiftly evolved with the emergence of new research questions relevant to Force Health Protection (FHP) and clinical practice in MHS beneficiaries, such as those related to chronic sequelae following infections with the novel SARS-CoV-2 pathogen in active-duty personnel. In line with the overall goal to improve the detection, prediction, treatment, prevention, and functional outcomes of COVID-19, the interdisciplinary COVID-19 Research Area has adapted its clinical research portfolio **(Table)** to address these new questions, as well as a rapidly changing countermeasure landscape.

Priority aims of the COVID-19 Research Area include characterization of the epidemiology, phenotype, and immunopathological correlates of SARS-CoV-2 infection, as well as the prediction of infection risk and complications. Led by Dr. Simon Pollett and Dr. Brian Agan, and sponsored through the Defense Health Program, the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) protocol is a prospective, longitudinal observational cohort study of SARS-CoV-2 infections in active-duty service members and MHS beneficiaries. Findings from EPICC are utilized to address critical knowledge gaps and inform and support the development of SARS-CoV-2 diagnostic, treatment, and preventive approaches. The EPICC study includes patients with confirmed SARS-CoV-2 diagnoses or COVID-like illness who are hospitalized or treated as outpatients, asymptomatic individuals with a high risk of exposure, and recipients of a U.S. Food and Drug Administration (FDA) authorized SARS-CoV-2 vaccine. Active at ten military treatment facilities (MTFs) with an online enrollment module, >6,000 individuals have enrolled in EPICC with ~65% being active-duty personnel.

Data collected through EPICC have allowed for characterization of clinical outcomes following SARS-CoV-2 infections, including acute and long-term complications and severity. Risk factors related to severe outcomes following SARS-CoV-2 infections were identified and predictors of complications (e.g., thrombosis), as well as pathological mechanisms correlated to severity (e.g., obesity) also were evaluated. Analyses to examine predictors for "Long COVID", including biomarkers (e.g., inflammation and gut integrity) and host and acute illness characteristics, are underway.

Findings from EPICC have also been used to validate patient-reported outcome measurement tools through correlation with the host immune response, host genomic markers, and virological data. Humoral and cell-mediated immune responses to SARS-CoV-2 infections, including those with emergent variants (e.g., Delta variant), have been estimated out to 12 months post-infection and compared with vaccine-induced immunity. Furthermore, biomarkers of clinical outcomes (e.g., viral genotype, viral load, host genomic variants, soluble cytokines, and interferon autoantibodies) have also been assessed. More recently, Emergency Use Authorization (EUA) vaccine effectiveness in the MHS has been estimated in the EPICC study with endpoints including hospitalization, symptoms, viral load, and biomarkers. Comparisons of vaccine and post-infection immunity, which include host correlates of vaccine immunogenicity and comparison of vaccine products, are being extended to examine boosting.

Another observational protocol is the Prospective Assessment of COVID-19 Seroconversion and Shedding (PASS) study. Led by Dr. Edward Mitre, PASS examined the ratio of symptomatic/asymptomatic infections in a high-exposure population (e.g., healthcare workers), as well as how immunity to seasonal coronaviruses and prior SARS-CoV-2 infections correlate with infection risk. The PASS study characterized the durability and breadth of EUA vaccine immunity, including against Delta variants, and the frequency of subclinical and clinical infections after vaccination over time. In addition, The Observational Seroepidemiologic Study of COVID-19 at the U.S. Naval Academy (TOSCANA), initiated by Dr. Eugene Millar and Dr. Christian Coles, has completed enrollment and is analyzing specimens collected from midshipmen for SARS-CoV-2 antibodies. Seroprevalence findings from this study provided estimates on the SARS-CoV-2 infection rates in this congregate setting. TOSCANA is also examining the validity of serosurvey through salivary assays, and evaluating mucosal immunity to both SARS-CoV-2 infection and vaccination. The Prospective Investigation of SARS-CoV-2/COVID-19 Epidemiology and Serology (PISCES) study, led by COL Eric Garges, is analyzing the spread of SARS-CoV-2 and other respiratory viruses in households of USU affiliates, and providing further important data on the validity of saliva-based serosurvey results.

A new protocol, the Military COVID-19 Registry Analysis Project (M-RAP), was initiated toward the end of 2021. The COVID-19 Registry was established by the Joint Trauma System in 2020 to collect data related to SARS-CoV-2 across MTFs. Led by Dr. David Tribble, M-RAP is utilizing data collected through the registry to characterize the morbidity and mortality burden associated with acute SARS-CoV-2 infections with a focus on active-duty service members. Post-infection sequelae will be assessed in comparison to matched individuals without SARS-CoV-2 infections to examine a range of persistent and emergent conditions to identify attributions, time course, risk factors, diagnostic capabilities, impact of interventions, and healthcare cost/utilization. Furthermore, the effectiveness of vaccines (by vaccine type/product) on SARS-CoV-2 incidence and outcomes will also be evaluated.

Another high-priority aim of the research area is to improve the speed and accuracy of SARS-CoV-2 detection for active-duty personnel and MHS beneficiaries. Through EPICC, and in collaboration with one of the 15 virological and immunological laboratories engaged in this study, subgenomic polymerase chain reaction-based assays were compared against the gold standard of culture positivity. Predictors of viral genome sequence recovery were identified, which will inform large-scale genomic epidemiology efforts. Gastrointestinal specimens collected from individuals enrolled in EPICC are also being examined to improve sewerage sequencing methods for public health surveillance. Furthermore, EPICC findings have validated a high-throughput serodiagnosis platform to include examination of the platform's accuracy with identifying breakthrough infections in vaccinated individuals. The platform has subsequently been refined to include identification of several variants of concern.

Christopher Diaz collecting blood at Brooke Army Medical Center

Improving the prevention and treatment of SARS-CoV-2 infections in the MHS are also priorities for the research area. Led by CAPT Timothy Burgess, IDCRP collaborated with the National Institute of Allergy of Infectious Diseases (NIAID), Division of Microbiology and Infectious Diseases, on the international multi-center Adaptive COVID-19 Treatment Trials (ACTT). Findings from ACTT-1 and ACTT-2 on the evaluation of antiviral and immunomodulatory agents (i.e., remdesivir and baricitinib) supported regulatory approvals. During the past year, the ACTT series concluded with ACTT-4, which examined the combination of baricitinib and remdesivir compared to dexamethasone and remdesivir. Adult active-duty service members and MHS beneficiaries hospitalized at seven

Table. IDCRP COVID-19 Research Portfolio

PROTOCOL	STUDY TYPE	SITES
EPICC: Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential	Observational (data collection and analysis)	Brooke Army Medical Center (BAMC); Carl R. Darnall Army Medical Center; Fort Belvoir Community Hospital (FBCH); Landstuhl Regional Medical Center (LRMC); Madigan Army Medical Center (MAMC); Naval Medical Center Portsmouth (NMCP); Naval Medical Center San Diego (NMCSD); Tripler Army Medical Center (TAMC); Walter Reed National Military Medical Center (WRNMMC); William Beaumont Army Medical Center (WBAMC); Womack Army Medical Center (WAMC)
ACTT: A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults	Interventional (ACTT-1, ACTT-2, ACTT-3, ACTT-4 completed)	BAMC; MAMC; NMCP; NMCSD; TAMC; WRNMMC; WAMC
CAMP-NY: COVID-19 Antibody Prevalence in Military Personnel Deployed to New York	Observational (completed)	Javits Center (New York)
COMFORT: Prevalence of novel coronavirus by PCR and antibodies among personnel deployed on the USNS COMFORT during the COVID 19 pandemic	Observational (completed)	USNS Comfort; NMCP
PASS: Prospective Assessment of COVID-19 Seroconversion and Shedding	Observational (data collection, analysis)	WRNMMC; Naval Medical Research Center (collaboration)
PISCES: Prospective Investigation of SARS-CoV-2/ COVID-19 Epidemiology and Serology	Observational (data analysis)	Uniformed Services University of the Health Sciences (USU)
TOSCANA: The Observational Seroepidemiologic Study of COVID-19 at the United States Naval Academy	Observational (data analysis)	U.S. Naval Academy
STORMCHASER: A Phase III Randomized, Double-blind, Placebo-controlled, Multi-center Study in Adults to Determine the Safety and Efficacy of AZD7442, a Combination Product of Two Monoclonal Antibodies, for Post-exposure Prophylaxis of COVID-19	Interventional (data collection, analysis)	MAMC; NMCP; USU; WBAMC
A Phase III Randomized, Double-blind, Placebo-controlled Multicenter Study in Adults to Determine the Safety, Efficacy, and Immunogenicity of AZD1222, a Non-replicating ChAdOx1 Vector Vaccine, for the Prevention of COVID-19	Interventional (data collection, analysis)	BAMC; FBCH; NMCSD; Wilford Hall Ambulatory Surgical Center; WRNMMC
M-RAP: COVID-19 Military Registry Analysis Project	Observational (analysis)	Registry-based data collection from MHS hospitals

MTFs were enrolled in ACTT-4. To further analyze the real-world effectiveness of COVID-19 treatments (e.g., steroids and monoclonal antibodies), data collected through the EPICC and M-RAP studies are being assessed. Potential treatment approaches are also being informed through pre-clinical mechanistic and prognostic studies (e.g., interferon auto-immunity) using EPICC specimens and data in a bedside-to-the-bench framework.

Led by Dr. Simon Pollett, safety and post-hoc data analysis are underway for the Phase III clinical trial evaluating the safety and efficacy of a combination product of two monoclonal antibodies for post-exposure prophylaxis of COVID-19 (STORMCHASER). Research area investigators and site staff also continue to support the ongoing AstraZeneca Phase III vaccine trial. Furthermore, specimens collected through PASS and TOSCANA are being utilized to examine vaccine-induced immunity. In particular, data on vaccine boosting from the PASS study were used to brief the National Institutes of Health Office of the Director.

In the coming year, research efforts will focus on the comprehensive characterization of "Long COVID" outcomes, particularly brain health, and examination of the effectiveness of COVID-19 treatments, as well as post-licensure safety assessment of products. The development of a longer-term COVID-19 cohort at the U.S Naval Academy to address the epidemiology and prevention of SARS-CoV-2 in the context of other acute respiratory infections is also planned. Mechanistic studies in collaboration with laboratory partners will be conducted to further the understanding of the pathogenicity and prevention of SARS-CoV-2.

EPICC enrollment at North Island Naval Air Station, San Diego, CA

Janell Cain working in the laboratory at Madigan Army Medical Center

Umair Jarral and Andrea Silva of the EPICC team at Fort Belvoir Community Hospital; also supported the AstraZeneca vaccine trial

MILITARY IMPACT

The ongoing COVID-19 pandemic, with emergence of new variants of concern, remains a considerable threat to the health of active-duty service members and MHS beneficiaries. Results from interventional trials supported by the COVID-19 Research Area have strengthened the evidence base for EUA applications for remdesivir (also subsequent FDA approval), baricitinib, vaccines, and prophylactic monoclonal antibodies. In addition, findings from observational studies have been utilized to brief DoD senior leadership on high-priority topics, such as "Long COVID". Genotype data collected through the PASS and EPICC protocols are provided to the Armed Forces Health Surveillance Division, Global Emerging Infectious Surveillance program to support FHP. As data continue to be collected through EPICC, PASS, and M-RAP, these studies will further the understanding of SARS-CoV-2 detection, risk prediction, prevention, treatment, and functional illness outcomes, as well as providing real-world evidence and safety data related to countermeasures utilized in the MHS.

HIGHLIGHTS/KEY FINDINGS

- **In support of the NIAID-sponsored randomized, double-blind, placebo-controlled trial evaluating baricitinib plus remdesivir in adult COVID-19 hospitalized patients (ACTT-2), subjects were enrolled at five MTFs. Patients receiving baricitinib had a reduced time to recovery (median: 7 days; 95% confidence interval [CI]: 6-8 days vs 8 days; 95% CI: 7-9 days with the control group), and had a lower frequency of serious adverse events (16% vs 21%) and new infections (6% vs 11%). These findings supported the EUA approval for use of baricitinib in hospitalized patients who require supplemental oxygen therapy.**
- **24 EPICC enrollees with vaccine breakthrough infections (≥14 days after the final SARS-CoV-2 vaccine dose) were characterized. Patients were largely active-duty personnel (79%) with no comorbidities (67%). Illness onset was a median of 50.5 days (interquartile range: 31.5-73.5 days). While 14% reported severe symptoms and the duration of illness lasted up to 2 weeks, no patients were hospitalized.**
- **The performance of prognostic scores (National Early Warning Score and Modified Early Warning Score) collected/ calculated during the ACTT-1 trial was assessed. The scores were weakly to moderately predictive regarding mortality, deterioration, and recovery with significant improvements noted when age was applied to the scores. Overall, the scores were not sufficiently predictive to replace clinical judgment.**
- **Analysis of 511 COVID-19 patients (24% obese, 14% severely obese) identified obesity as being independently associated with severe disease requiring hospitalization and supplemental oxygen therapy. When assessed using body mass index categories, risk increased in a dose-response manner with severe obesity having the highest risk.**

ACUTE RESPIRATORY INFECTIONS (ARI)

The PAIVED study team at Brooke Army Medical Center

PAIVED enrollment at Madigan Army Medical Center

The global H1N1 influenza and SARS-CoV-2 pandemics occurring nearly 100 years apart, coupled with periodic outbreaks of adenovirus, influenza, and other respiratory viruses, highlight the significant threat acute respiratory infections (ARIs) pose to the health of active-duty personnel, military trainees, and Military Health System (MHS) beneficiaries. Along with imposing a considerable health burden, ARIs also substantially impact operational readiness through interruptions in training cycles and loss of duty days.

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

With the goal of reducing the burden of ARIs in the MHS, the primary aims of the ARI Research Area include: evaluation of strategies for the prevention of influenza and other ARIs in military populations; reduction of ARI-related morbidity impacting Force Health Protection through innovative diagnostic and treatment approaches; mitigation of ARI transmission in congregate and deployed settings; and assessment of severe, epidemic, or emerging ARIs encountered in military populations to inform the development of effective countermeasures. ***Please see pages 4-7 (COVID-19 Research Area) for information on SARS-CoV-2 research.***

As vaccination is a critical component of influenza prevention, and thus key to improving operational readiness, the Pragmatic Assessment of Influenza Vaccine Effectiveness in the DoD (PAIVED) clinical trial is currently the cornerstone of the ARI Research Area portfolio. Led by CAPT Timothy Burgess and Dr. Rhonda Colombo, PAIVED is a multi-year, open-label, randomized clinical trial designed to compare the effectiveness and immunogenicity of three licensed inactivated influenza vaccine formulations (i.e., egg-based, cell-culture-based, and recombinant) in adult MHS beneficiaries. Initiated in 2018, PAIVED has enrolled more than 10,700 participants in the intervening three influenza seasons. In addition, approximately 900 PAIVED participants have enrolled in the immunogenicity substudy. Serology specimens collected during the first year of PAIVED were used to compare influenza subtype A/H3N2 neutralizing antibody responses elicited by the three different inactivated influenza vaccine formulations. The immunogenicity data collected across multiple influenza seasons are expected to inform vaccine development.

During the 2020/2021 influenza season, self-collected nasal swabs were utilized when mitigation measures implemented for the COVID-19 pandemic limited in-person visits for influenza-like illness (ILI). This protocol modification allowed continued ascertainment of influenza using a polymerase chain reaction (PCR)-based assay. Nevertheless, lower than expected cases of influenza during the 2020/2021 season necessitated extending PAIVED for another year with an expanded enrollment target of 18,000.

The Impact of Influenza Vaccine Experience on Effectiveness (Flu VE) protocol is assessing the question of whether repeat seasonal influenza immunizations may contribute to suboptimal vaccine effectiveness in active-duty service members. Data related to vaccinations, acquisition of influenza, and severity of illness were collected from the MHS Data Repository, and analysis is nearing completion.

Another core protocol of the research area is the multisite, longitudinal ARI Consortium Natural History Study (ARIC NHS), led by CAPT Burgess. Data collection for ARIC NHS was halted in 2019 when personnel and resources were prioritized to support PAIVED. During the past year, repository serum samples from ARIC NHS enrolled subjects with confirmed seasonal coronavirus infections were provided to laboratory partners to support the development of a diagnostic assay for SARS-CoV-2.

It is recognized that military personnel living in crowded, congregate settings (e.g., training settings) are at an increased risk of ARIs. As such, the transmission, etiology, and epidemiology of ILIs among U.S. Army trainees at Fort Benning, GA, were examined through the Study to Address Threats of ARI in Congregate Military Populations (ATARI). Specimens collected from enrollees are undergoing minor variant genomic analysis to provide further information on ILI transmission in military training settings.

In 2022, data collection and analysis for the PAIVED clinical trial will remain the top priority of the ARI Research Area. During the past year, PAIVED collected data on SARS-CoV-2 as a cause of ILI in the military; further exploration of the relationship between influenza, influenza vaccination, and SARS-CoV-2 is planned. In addition, partnerships between the ARI and COVID-19 Research Areas will be leveraged to advance research priorities and goals for both programs.

MILITARY IMPACT

Influenza and other ARIs continue to be a substantial source of morbidity among military service members and MHS beneficiaries. To improve Force Health Protection and operational readiness, the ARI Research Area has focused on furthering the understanding of ARI pathogens and providing support for the development and optimization of effective preventive approaches. Findings from the ARIC NHS, ATARI, and the Anonymous Survey Among Trainees studies have provided valuable information on epidemiology, etiology, transmission patterns, risk factors, immunology, and healthcare-seeking behavior related to influenza, ILIs, and severe ARIs in the MHS. Specimens from ARIC NHS also supported the swift development of a multiplex microsphere immunoassay for SARS-CoV-2 detection. In addition, the Flu Breath Study examined the utility of breath testing as part of an influenza diagnostics strategy, and if deployable to the field, the toolkit would be highly relevant for military medicine. Findings from PAIVED, as well as Flu VE, will help to inform future influenza vaccine policy and practice in the MHS and directly support Force Health Protection. Data collected through the PAIVED immunogenicity substudy also have the potential to influence progress toward a universal influenza vaccine.

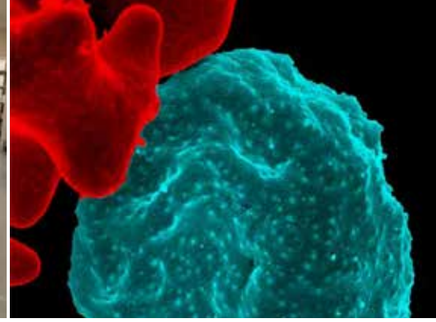
HIGHLIGHTS/KEY FINDINGS

- **Men with well-controlled HIV who enrolled in the ARIC NHS with an ILI reported a higher frequency of gastrointestinal symptoms and fatigue compared with men who were HIV-negative; however, other measures of ILI symptom severity were similar. Men with HIV were more likely to receive antiviral treatment for ILI despite similar illness severity, suggesting a tendency toward more cautious treatment of ILI in patients with HIV.**
- **The third year of PAIVED (October 2020 – January 2021) enrolled 3,269 subjects with approximately 10% reporting at least one ILI. No pathogen was identified in the majority of samples; SARS-CoV-2 and rhinovirus were each identified in 12% of specimens. The mean duration of ILI events was 9.6 days with a mean of 3 days of limited activity and 1.6 days of missed work.**
- **Examination of data from the first three years of PAIVED identified the 2019/2020 influenza season as having the highest proportion of ILI (28%), and 2020/2021 with the lowest (9.6%). Consistent with national influenza surveillance reports, influenza activity dropped precipitously in March 2020 and no influenza, respiratory syncytial virus, or metapneumovirus were isolated in 2020/2021, suggesting that mitigation measures enacted to limit transmission of SARS-CoV-2 also reduced the spread of other key respiratory viruses.**
- **During the 2019/2020 influenza season, compliance was greater with healthcare-collected nasal swabs compared to self-collected swabs; however, self-collected swabs had a higher pathogen detection rate, likely resulting from a shorter interval between symptom-onset and swab collection.**

DEPLOYMENT AND TRAVEL-RELATED INFECTIONS

3D computer-generated image of a cluster of drug-resistant, curly-cue shaped, Campylobacter spp. bacteria based upon scanning electron microscopic (SEM) imagery [image credit: Alissa Eckert, CDC]

Michele Tisdale, IDCRP research associate, working in the lab at Naval Medical Center Portsmouth



Colorized SEM of a red blood cell infected with malaria parasites (colorized in blue) [image credit: NIAID, NIH]

Infectious diseases continue to be a serious threat to the health of service members, as well as substantially impacting operational readiness, during overseas deployment for combat operations, humanitarian missions, training exercises, or other military-related travel.

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

One of the primary aims of the Deployment and Travel-Related Infections Research Area is to evaluate the risk and operational impact of infectious disease threats among high-risk populations in the United States (e.g., military trainees) and during deployment. Understanding the differential risk of these infectious diseases (e.g., vector-borne infections, travelers' diarrhea [TD], and respiratory diseases) in deployed and training populations provides the foundation for high-quality interventional and translational research efforts to mitigate the burden on the Military Health System (MHS).

The Deployment and Travel-Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies among DoD Beneficiaries (TravMil) cohort study, led by Dr. Tahaniyat Lalani, provides valuable surveillance data to Combatant Commands and the DoD Global Emerging Infections Surveillance (GEIS) program. Although enrollment was suspended in 2020 due to the COVID-19 pandemic, multiple analyses were completed, including an assessment of the incidence and operational impact of TD, influenza-like illness, and febrile illness in active-duty personnel traveling overseas on deployment, temporary duty assignments, or participation in military exercises in regions prioritized by GEIS and Combatant Commands.

Due to the high incidence of TD among deployed personnel, clinical trials focused on the safety and effectiveness of preventive and therapeutic measures are an important strategic aim. Led by CAPT Ramiro Gutierrez, and in collaboration with the United Kingdom Ministry of Defence (U.K. MOD), analysis of the data from the Trial Evaluating Regimens of Rifaximin for Chemoprophylaxis Against TD (Prevent TD) was completed. This randomized, double-blind, placebo-controlled trial assessed the efficacy of two different dose regimens of rifaximin (550 mg daily or twice-daily) for TD prevention in 449 military personnel, traveling for up to 42 days. The trial did not demonstrate a significant difference in TD prevention between the rifaximin and placebo groups, likely due to the low incidence of TD. Two additional clinical trials in partnership with the U.K. MOD, will begin enrollment in 2022. One of the clinical trials is a follow-on to the Trial Evaluating Ambulatory Therapy of TD (TrEAT TD) study, which demonstrated that a single high dose of rifaximin (1,650 mg) with adjunct loperamide was effective in treating acute watery diarrhea. Funded by the Military Infectious Diseases Research Program, TrEAT TD 2.0 will assess the efficacy of a lower dose of rifaximin (550 mg) versus azithromycin (500 mg); both with adjunct loperamide therapy for treatment of acute watery diarrhea. Enrollment will target personnel deployed to the British Army Training Unit in Kenya and U.S. personnel serving at the Soto Cano Air Base in Honduras.

The second clinical trial, funded by the Defense Health Program and also in collaboration with the New York Center for Travel and Tropical Medicine, will assess the clinical efficacy of nutraceutical products for the maintenance of gut health during deployment and travel. Originally designed to examine a probiotic, prebiotic, and passive immunoprophylaxis, an agreement could not be reached with the manufacturer of the prebiotic, so the revised P3 study will focus on evaluation of Florastor® and Travelan®, each versus placebo.

Recently, Tafenoquine was approved for use in the MHS as malaria prophylaxis and radical cure of *Plasmodium vivax*. Funded by the U.S. Army Medical Materiel Development Activity, data collected through the Knowledge, Attitudes, Practice and Outcomes Study (KAPOS), led by COL Patrick Hickey, were utilized to complete a U.S. Food and Drug Administration-required post-licensure safety surveillance study of Tafenoquine. The frequency of Tafenoquine prescriptions was low, so a repeat analysis is planned for 2022.

Moving forward, we will examine how our existing partnerships with academic institutions and DoD laboratories can be leveraged to support additional clinical trials and surveillance studies focused on high-priority pathogens. Observational studies that were delayed due to the COVID-19 pandemic will be assessed for re-engagement in the coming year.

MILITARY IMPACT

Surveillance of high-priority, militarily-relevant infectious disease threats and clinical trials evaluating TD therapeutic and preventive approaches inform deployment-related clinical practice guidelines and mitigation efforts. Data on TD medical management collected through TravMil were reported back to enrolled units and guidance was provided to medics regarding the optimal use of mitigation strategies. Ongoing clinical trials will examine low-dose rifaximin for TD treatment (TrEAT TD 2.0) and the efficacy of multiple nutraceutical products in a single study (P3). A lower effective dose of rifaxmin for treatment of acute watery diarrhea would be more cost-effective and potentially have fewer side effects and impact on antibiotic resistance compared to antibiotics used currently. The findings from the P3 clinical trial will be used to create a knowledge product for the DoD regarding use of nutraceuticals to maintain gut health during deployment or travel. With regard to diagnostics, results from TravMil demonstrate that stool smears collected by participants during travel and tested by a polymerase chain reaction (PCR)-based assay (TaqMan® Array Card) are an effective alternative or supplement to conventional methods for diarrheal specimen collection in austere environments with limited storage and testing capabilities. The research area has greatly benefited from partnerships with DoD research laboratories (within the United States and overseas) and with the U.K. MOD for the execution of clinical trials and translational research efforts. As the research area moves forward, we will continue to leverage these relationships to conduct high-priority surveillance efforts and high-quality clinical trials to inform and improve deployment and travel medicine within the MHS.

HIGHLIGHTS/KEY FINDINGS

- **Examination of fecal specimens collected from U.S. and U.K. military service members enrolled in the TrEAT TD clinical trial suggest that single-dose antibiotic treatment for acute watery diarrhea had minimal impact on the functional composition of the fecal microbiome and antibiotic resistance acquisition.**
- **Using archived stool specimens from the Stool Card Validation study, the pathogen detection rate using the quantitative TaqMan® Array Card PCR-based assay was lower than expected. This finding suggests that significant genomic degradation occurred with samples archived for >5 years.**
- **In an assessment of 99 enrollees in TravMil, there was an incident multidrug-resistant organism colonization rate of 3.5 per 1,000 travel days with a higher incidence of extended spectrum-β-lactamase-producing *Escherichia coli* associated with travel to Asia.**
- **Examination of data from the MHS Data Repository identified 34,425 validated helminth infection diagnoses over a 6-year period with ~4,000 cases being infections other than enterobiasis.**

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Early diagnosis and timely initiation of combination antiretroviral therapy (cART) have resulted in the majority of HIV+ service members achieving viral suppression with resulting lifespans expected to be similar to those of individuals who are uninfected. While recent advances have led to more HIV+ service members remaining on active duty, they are still at risk for developing non-AIDS complications.

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

The HIV Research Area strives to improve the understanding of clinical outcomes impacting HIV+ service members (e.g., HIV-associated neurocognitive disorder [HAND], diabetes, ophthalmologic disease, cardiovascular disease, cancer, and liver disease) with the goal of advancing HIV care and treatment to maintain the health, function, and readiness of HIV+ active-duty service members and beneficiaries of the Military Health System (MHS). The core protocol of the HIV Research Area is the U.S. Military HIV Natural History Study (NHS), which is led by Dr. Brian Agan. Since initiation in 1986, the NHS has enrolled >6,400 HIV+ active-duty service members and MHS beneficiaries, and the data and blood specimens collected through the study have allowed for comprehensive examination of non-AIDS complications, occurrence of co-infections, sexually-transmitted infection (STI) risk-related behavior, and mental health outcomes. While enrollment and follow-up visits for the NHS were suspended at the beginning of the COVID-19 pandemic, study visits resumed in the latter half of 2021 at all participating sites. The NHS team is now adapting the protocol to enable remote subject participation to reduce travel-associated burdens, expand access to research visits, and maximize safety.

In collaboration with the Defense Health Agency (DHA) Triservice HIV Working Group, data collected through the NHS were utilized to evaluate performance using the cascade of care framework (i.e., HIV diagnosis, linkage to care, cART prescription, and viral suppression) in the MHS, as well as quality life among HIV+ active-duty service members. Follow-on analyses funded by the USU, Health Services Research Program are examining aspects of HIV clinical healthcare utilization and cost, including quality, impact of remote stationing, and the cost of military-, civilian-, and mixed-care models.

Neurocognitive impairment is estimated to affect 20-50% of people living with HIV on cART with a lower incidence occurring in those who are diagnosed and treated early. Among HIV+ service members, HAND is a key concern that may result in duty restrictions. Led by Dr. Agan, the functional consequences of HAND in high-demand military settings and potential biomarkers to support diagnostic tools are being examined through the HIV-Associated Neurocognitive Disorders (ALLHANDS) protocol. As screening batteries for HAND are time- and resource-intensive, the performance of an abbreviated screening battery was evaluated in collaboration with investigators from the National Institute of Mental Health and National Institute of Neurological Disorders and Stroke. After being halted for most of 2020 and 2021 due to the COVID-19 pandemic, study visits for ALLHANDS are now being resumed.

Through the DoD HIV Virtual Cohort Study, data were collected from the MHS Data Repository

Dr. Anuradha Ganesan of the HIV NHS investigative team

Dr. Senay Topal of the HIV NHS investigative team

Susan Banks of the Naval Medical Center Portsmouth HIV NHS study team

from HIV+ individuals and matched HIV-negative controls to assess the association between HIV serostatus and non-AIDS complications. These data obtained from racially diverse, healthy, and relatively young individuals with open access to healthcare, routine HIV screening, and cART present a unique study population with the potential of identifying early, modifiable predictors of non-AIDS complications. For the CD4 Zeta protocol, led by COL (ret.) Naomi Aronson, follow-up visits were completed and analysis to examine the HIV reservoir and persistence of gene therapy modified cells is continuing.

For the upcoming year, postponed discussions are resuming regarding a DoD-VA Overlap Cohort Study in collaboration with the Veterans Aging Cohort Study, with the goal of evaluating predictors of long-term HIV-related outcomes. In addition, led by Dr. Anuradha Ganesan, a randomized-controlled trial to assess the safety and immunogenicity of the Shingrix® vaccine in both young HIV-negative and older HIV+ individuals is being evaluated. Furthermore, a new collaboration was established with the University of California at San Francisco to study the genetics of interleukin-1β and the impact of its varying levels on the pathogenesis of cardiovascular disease in the setting of HIV.

MILITARY IMPACT

The overarching goal of the HIV Research Area is to inform military HIV policy and clinical practice guidelines and improve the long-term health, function, and readiness of HIV+ active-duty service members, benefiting not only MHS beneficiaries, but also civilian populations. Through the protocols enacted in the HIV Research Area, the cascade of HIV care framework in the MHS has been assessed and demonstrated that the DoD is exceeding targets related to diagnosis, cART initiation, and viral suppression advocated from the top levels of U.S. government to end the U.S. HIV epidemic. As a follow-on to the successful cascade-of-care studies completed, the quality and cost of HIV-related healthcare among active-duty service members are being evaluated. The DHA Triservice HIV Working Group is the Advisory Committee for this healthcare utilization study and will be able to communicate the findings to the DHA for use in supporting the standardization of DoD HIV policy and practices. Analysis is underway on the effect of HIV on neurocognitive functional performance, which may inform HIV-related policies regarding duty status. Furthermore, findings from analyses on STI acquisition among HIV+ service members may support improvements in STI prevention, diagnosis, and treatment in people living with HIV.

HIGHLIGHTS/KEY FINDINGS

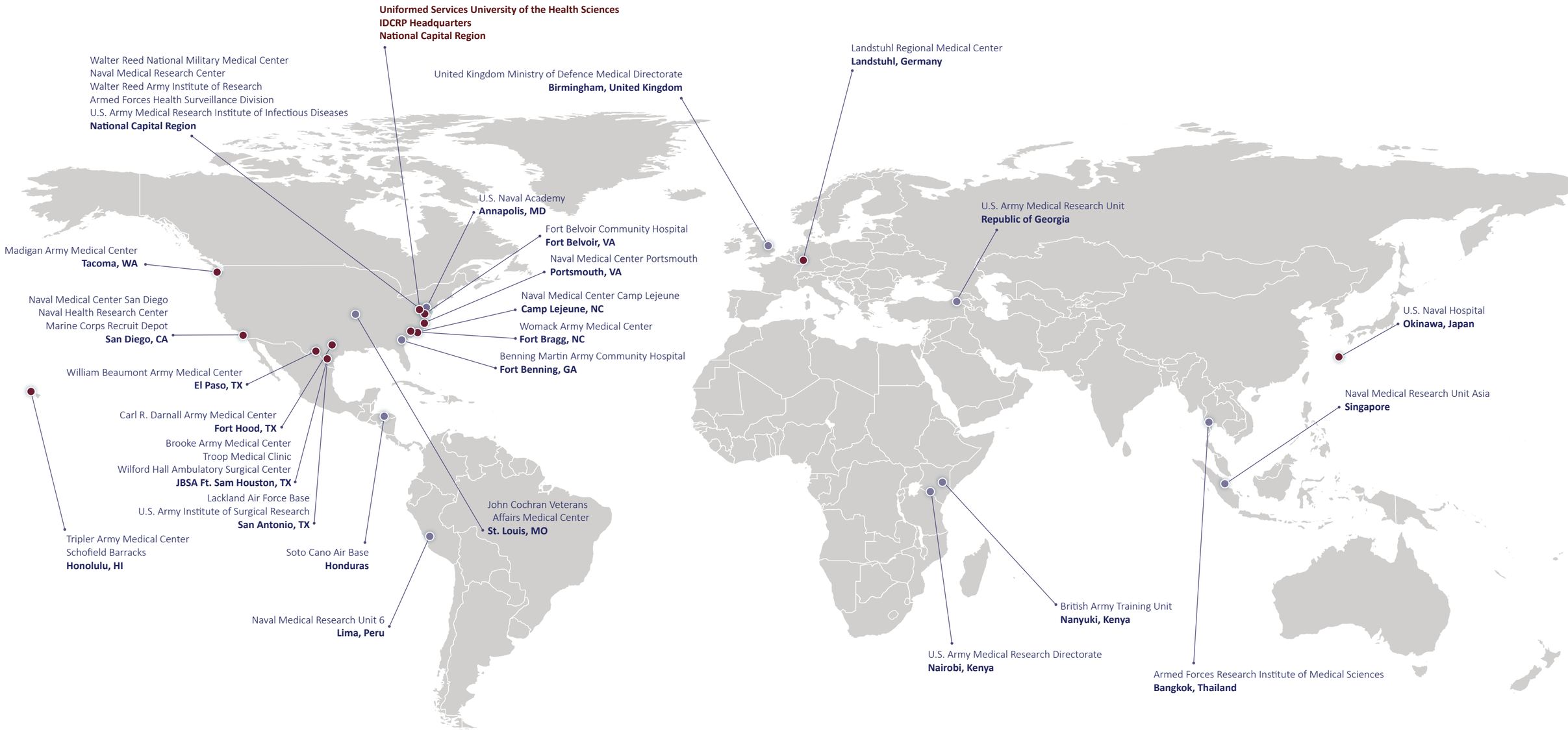
- **An abbreviated screening battery to identify neurocognitive impairment among people living with HIV was assessed in 169 NHS enrollees. While the abbreviated battery had moderate specificity (79.9%) compared to the full screening battery, the low sensitivity (50.0%) indicated that improvement is needed.**
- **Weight gain was associated with use of all ART classes in individuals with a body mass index (BMI) <25 kg/m², while it was only associated with use of integrase strand transfer inhibitor (INSTI) and protease inhibitor-based regimens in those with a BMI ≥25 kg/m². African Americans with a BMI ≥25 kg/m² on INSTI-based regimens had the greatest weight gains.**
- **In an examination of 2,779 NHS enrollees, chronic liver enzyme elevation was associated with Hispanic/other ethnicity race, non-nucleoside reverse transcriptase inhibitor-based cART, and being cART naïve. Not having interruptions in cART, African American race, and use of INSTI-based regimens were determined to be protective.**
- **Comparison of brain MRI scans between people living with HIV and matched controls without HIV identified that increased brain white matter hyperintensities (WMH) was associated with HIV serostatus. Among people living with HIV, age, male sex, hypertension, tobacco use, hepatitis C co-infection, and occurrence of measurable tumor necrosis factor α in cerebrospinal fluid were associated with increased brain WMH.**

IDCRP PARTNER NETWORK

35
PARTNER SITES

150+
EMPLOYEES

50+
ACTIVE PROTOCOLS



SEXUALLY-TRANSMITTED INFECTIONS (STI)

The MAGI study team at Walter Reed National Military Medical Center

Mr. Reuel Sandy, a Research Associate with the Jerse Lab, conducting confirmatory analysis of frozen gonococcal specimens

Among active-duty service members, the rates of select sexually-transmitted infections (STIs) are higher compared to civilian populations of similar age, race, and geographic locations. The emergence of multidrug-resistant Neisseria gonorrhoeae, as well as increased antimicrobial resistance of Mycoplasma genitalium, highlights the ongoing public health threat of these infections, including in the Military Health System. Effective STI countermeasures are critical to reduce the substantial burden on Force Health Protection.

COL Eric Garges, MD, STI Research Area Director

With the overall goal of eliminating the transmission of STIs in the Military Health System and improving both Force Health Protection and medical readiness, the primary aims of the STI Research Area are the evaluation of high-risk sexually-transmitted pathogens, development of STI biomedical countermeasures for use in military populations, and examination of novel treatment strategies among active-duty personnel to support public health policy decisions and improved practice patterns.

Although enrollment in the longstanding STI Antimicrobial Resistance Study (previously the Gonococcus Resistance Study), led by COL Eric Garges, was halted during most of the past year due to the ongoing COVID-19 pandemic, there was still activity related to the protocol. Specifically, data collected from the 700 subjects enrolled in the study were analyzed with regard to differential risk behaviors for genital gonorrhea and chlamydia infection, risk of infection on military deployment, and comparison with STI data from high-risk civilian populations. In addition, the protocol was refined with new scientific objectives to include surveillance of additional high-impact and high-prevalence pathogens beyond *Neisseria gonorrhoeae* (gonococcus, GC), such as *Mycoplasma genitalium*, along with assessing the functional impact of these infections on Force Health Protection and patient-reported outcomes. Enrollment in this revised version of the study began in late 2021. Furthermore, after a laboratory shutdown caused by the COVID-19 pandemic, activity was reinitiated in 2021 for the USU GC Reference Laboratory and Repository (coordinated by IDCRP and led by Dr. Ann Jerse, USU), which is funded by the DoD Global Emerging Infections Surveillance (GEIS) program. Isolates were recently received from the Republic of Georgia and isolate collection is also expected from sites in Kenya and Thailand.

The Bexsero® Serostudy, led by COL Garges and funded through the Defense Health Agency Immunization Healthcare Division (DHA IHD), utilized specimens from service members who received the OMV meningitis B vaccine (Bexsero®) and were archived in the DoD Serum Repository to comprehensively assess the immune response to GC *in vitro*. Laboratory testing was completed during the past year and data analysis for the primary endpoint has been completed with additional analyses underway. These findings are being used to support the Phase II randomized, placebo-controlled, observer-blinded clinical trial designed to evaluate the efficacy of the Meningococcal (Bexsero®) Vaccine For Gonococcal Infection (MAGI Trial). Sponsored by the National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases, the trial is a collaborative effort with the University of Alabama at Birmingham and GlaxoSmithKline plc. Enrollment in the MAGI Trial has been initiated at the two DoD-associated sites in Thailand, as well as at Walter Reed National Military Medical Center. Enrollment is planned to continue through 2022 with a follow-up period of 15 months. Overall, it is expected that the DoD sites will provide >50% of enrollees in this pivotal trial.

Enrollment in the Survey of Social Networks and STI Risk Study closed during the past year and multiple analyses of the data are underway or near completion. The comprehensive evaluation of partnership formation and behaviors, including assessment of risk factors, provides valuable behavioral data needed to understand the high rates of bacterial STIs reported in active-duty service members and support the development of mitigation strategies.

During the past year, a new collaborative effort coordinated through the USU Department of Microbiology was initiated to support the pre-clinical evaluation of a combined GC/chlamydia vaccine. In the coming years, the STI Research Area is expected to play an integral role in the development and potential translation of this pre-clinical product. The STI Research Area will also continue to act as the DoD GEIS coordinating partner in GC antimicrobial resistance surveillance efforts, and we are working closely with GEIS leadership to improve the efficiency of the GEIS GC surveillance plan and increase surveillance in U.S. military populations deployed to high-risk settings.

MILITARY IMPACT

The overall goal of the STI Research Area is to support the prevention, diagnosis, and treatment of STIs to eliminate STI transmission among active-duty members and beneficiaries and improve Force Health Protection. Findings from the STI Antimicrobial Resistance Study provide up-to-date information on the geographic distribution of isolates connected to antimicrobial susceptibility patterns, which are used for operational planning by the DoD. Susceptibility testing and advanced molecular characterization of isolates collected from the United States and overseas are assessed through the DoD GC Resistance Laboratory and Repository. Epidemiologic data on increasing azithromycin resistance among GC isolates in the Western United States is provided to Combatant Commands through the GEIS Data to Decision Initiative for situational awareness and response, as needed. Engagement with partner militaries for GC surveillance remains active in Ghana, Thailand, Peru, and the Republic of Georgia, providing valuable local Force Health Protection data and supporting improvements in the technical capability and laboratory methods for host nation partners.

HIGHLIGHTS/KEY FINDINGS

- **The DHA IHD-funded Bexsero® serostudy demonstrated that a modified version of the OMV meningitis B vaccine (Bexsero®) was able to increase GC clearance in a mouse infection model. These findings provide direct evidence of cross-species protection and demonstrate the potential use of several GC outer membrane proteins as vaccine targets.**
- **Examination of data for 1,416 sexual partnerships found that while recent occurrence of STIs was not associated with disassortative mixing on age group or military status, it was associated with disassortative mixing on race/ethnicity.**
- **Novel sequencing of data from the USU GC Reference Laboratory and Repository has demonstrated a high frequency of GC strains with an increased risk of disseminated infection in select overseas locations.**

WOUND INFECTIONS

Whether as the result of battlefield trauma during wartime or through the development of community-associated skin and soft-tissue infections (SSTIs) during peacetime operations (e.g., military training), wound infections impose significant health, operational, and financial burdens on the Military Health System (MHS). An added challenge in the prevention and management of wound infections is the rising prevalence of multidrug-resistant (MDR) pathogens and emergence of novel microbial threats.

Katrin Mende, PhD,
Wound Infections
Research Area Director

The overall goal of the Wound Infections Research Area is to reduce the short- and long-term impact of wound infections among military personnel through improved evidence-based clinical practice guidance and determination of effective strategies for prevention and treatment.

Analyses examining infectious outcomes of battlefield trauma are largely conducted through the Trauma Infectious Disease Outcomes Study (TIDOS), which is led by Dr. David Tribble. Since being initiated in 2009, detailed data on trauma and clinical characteristics, medical and surgical management, infections, and microbiology were systematically collected from military personnel wounded during deployment over a 5.5-year period. Further, information on the occurrence of trauma-related infections that developed after the initial hospitalization period was obtained from subjects enrolled in the TIDOS longitudinal follow-up cohort through both DoD and Veterans Affairs (VA) sources. During 2021, data were obtained from the MHS Data Repository and comprehensive assessment of the healthcare cost and resource utilization associated with combat-related trauma and subsequent MDR Gram-negative infections is underway. As part of the follow-up assessment of TIDOS cohort enrollees, and in collaboration with Dr. Jay McDonald of the VA St. Louis Health Care System, longitudinal analysis of physical, mental, and social health factors determined through SF-8 Survey responses is nearing completion.

Assessment of short- and long-term outcomes of blast trauma continues to be a priority of the research area. With the goal of improving the categorization of polytrauma, particularly with extremity wounds, an injury profile has been developed and is nearing finalization. It is recognized that blast casualties with severe polytrauma are at risk of developing high-consequence infections associated with substantial morbidity and mortality, including invasive fungal wound infections (IFIs). Early diagnosis and timely initiation of medical and surgical treatment are critical for the successful management of IFIs. As such, the TIDOS team, led by Dr. Anuradha Ganesan, is assessing use of polymerase chain reaction (PCR)-based assays to aid in the diagnosis of IFIs and identify the best diagnostic methods for use in future conflicts. During 2021, the performance of semi-nested PCR-based assays targeted toward clinically relevant fungi were evaluated using specimens from patients with negative histopathology and positive fungal cultures.

Non-extremity combat-related wound infections are also the focus of multiple ongoing TIDOS analyses. During the past year, analyses were initiated to comprehensively examine infectious complications of penetrating central nervous system injuries and burns. In addition, sepsis among combat casualties is being evaluated, utilizing detailed information on the timing of diagnosis, occurrence of other infections, and microbiology. Lastly, the seasonality of combat-related infections and associated microbiology is also being assessed.

(from left) Dr. Katrin Mende, MAJ John Kiley, and Maj Joseph Yabes of the TIDOS team at Brooke Army Medical Center

Dr. Mende conducting laboratory work at Brooke Army Medical Center

Led by Dr. Katrin Mende, the TIDOS MDR and Virulent Organisms (MDR/VO) Trauma Infections Initiative 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. At present, comprehensive characterization of *Enterobacter cloacae* clinical isolates obtained from combat casualties is nearing completion.

In congregate populations, such as deployed personnel and military trainees, community-associated SSTIs impose considerable healthcare and operational burdens (e.g., loss of training days). Led by Dr. Eugene Millar and COL Jason Bennett, numerous epidemiological and microbiological studies of SSTIs, largely attributed to *Staphylococcus aureus*, were conducted at Fort Benning, GA, over a 10-year period. These protocols resulted in a massive repository of specimens accumulated from U.S. Army Infantry trainees linked to clinical data, resulting in a greater understanding of the genomic characterization and transmission dynamics of methicillin-resistant (MRSA) and methicillin-susceptible *S. aureus* (MSSA) colonization and infection in military training settings.

During 2021, a pilot study examining microbiome convergence among U.S. Army Infantry trainees at Fort Benning was completed by Dr. Nicholas Be at the Lawrence Livermore National Laboratory. Based on the results of the pilot study, and with the support of IDCRP investigators, Dr. Be has received external funding for a larger microbiome assessment, which will include specimens from the SSTI Cohort Study. A new collaboration with J&J/Janssen was also initiated to examine the humoral immune response to MRSA and MSSA colonization and infection over time using SSTI Cohort Study specimens. Further, a collaboration with Antigen Discovery, Inc. is utilizing an MRSA proteome array with saliva and serum samples to identify novel antigens associated with incident MRSA and MSSA colonization.

In 2022, TIDOS investigations will continue to primarily focus on blast-related wounds and clinical outcomes, emphasizing wound-specific outcomes to assess and support refinement of optimal prevention and management strategies. Moreover, a subset of the TIDOS population that is most severely injured and incurs the greatest morbidity will be comprehensively evaluated. Moving forward, a SSTI repository analysis protocol is being developed to support streamlined execution of high-impact, scientifically- and military-relevant clinical SSTI research using the amassed data and specimens from the Fort Benning protocols.

MILITARY IMPACT

The five aims of the Wound Infections Research Area remain responsive to priorities of the DoD Joint Trauma System and MHS. The TIDOS analyses of battlefield-related wound infections offer crucial data to improve the understanding and support best practices for infection prevention and management needed in future conflicts. Detailed evaluation of the epidemiology, microbiology, and preventive strategies of community-associated SSTIs (MRSA and MSSA) in high-risk military populations (e.g., trainees) have reduced the healthcare burden on the MHS and improved operational readiness. Overall, leveraging the strengths and opportunities of the Wound Infections Research Area has resulted in a robust research platform that supports the development and ongoing refinement of evidence-based clinical practice guidelines for management of militarily-relevant wound infections.

HIGHLIGHTS/KEY FINDINGS

- **Risk factors for abdominal surgical site infections following combat-related exploratory laparotomy include sustaining colorectal or duodenum injuries and being diagnosed with a prior non-intraabdominal infection.**
- **There were significant differences in exposure to specific AmpC-inducing antibiotics and AmpC induction levels prior to isolation between patients with recovery of a single *Enterobacter cloacae* infecting isolate versus serial recovery.**
- **Assessment of *Klebsiella pneumoniae* isolates for misclassification identified 4% as *Klebsiella variicola*, and those isolates were more likely to be associated with bacteremia and less likely to be MDR.**
- **Through the Antibiotic-Resistant Bloodstream Infections (BSI) protocol, BSIs in the MHS were identified over a 9-year period with β-hemolytic streptococci contributing the highest percentage to recurrent episodes.**

THE IDCRP STAFF

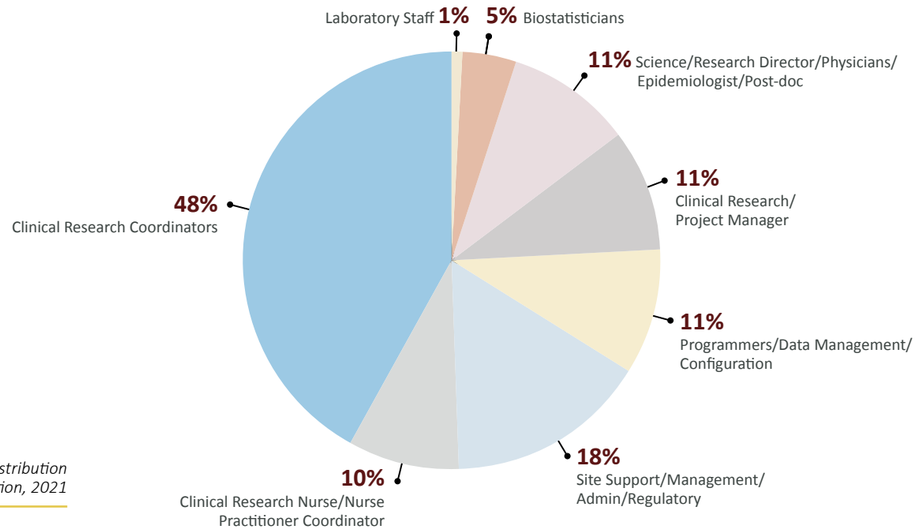
It is through the expertise, diligence, and commitment of our employees, that the IDCRP continues to be a successful, central hub of military clinical infectious disease research, benefiting not only military personnel, but also beneficiaries of the Military Health System.

During the past year, more than 150 research and program-support personnel were employed by the IDCRP to support its clinical research portfolio, which ranges from retrospective observational studies to interventional clinical trials. Despite the diversity of the studies, our remarkable staff members effectively surmount the challenges inherent with conducting clinical research, both expected and unexpected. In particular, our personnel persevered against obstacles that developed in response to the ongoing COVID-19 pandemic, pivoting and modifying protocols to include virtual aspects and specimen self-collection.

Over half of our staff members have direct interaction with study subjects enrolled in our research protocols at clinical sites within the IDCRP military hospital/clinic network. Specifically, clinical research coordinators and clinical research nurse (or nurse practitioner) coordinators represent a high percentage of these professionals (see figure). Staff members also include clinical investigators and laboratory staff based at our partner military clinical sites and USU, as well as protocol-support personnel (e.g., clinical research and site managers), regulatory affairs specialists, program and data managers, data programmers, and biostatisticians. While the bulk of our personnel are located at our headquarters in Bethesda, MD, IDCRP has staff members at DoD military treatment facilities, USU, and operational clinics within the United States and at overseas locations.

More than half of our personnel have received at least two degrees with expertise in infectious diseases, public health, preventive medicine, epidemiology, microbiology, data management/programming, statistical analysis, program management, and regulatory affairs. The extensive experience and wide-ranging knowledge of our staff members are directly responsible for the continued success of the Program.

We wish to thank our staff members for their ongoing excellence in supporting IDCRP clinical research, particularly with the challenges imposed by the COVID-19 pandemic.



IDCRP Personnel Distribution by Occupation, 2021

DATA OPERATIONS

The Data Coordination Center (DCC) is a critical component for the successful execution of high-valued, quality research conducted by the Program.

Led by Mr. Edward Parmelee (DCC Chief), the DCC team includes individuals with expertise in data system design, data management, data entry, and SAS / Oracle programming, allowing them to deliver vital support to the IDCRP's investigative teams with regard to data conceptualization, design, collection, management, cleaning, analysis, and publication.

During 2021, the DCC provided data support services for 41 IDCRP studies, including 4 studies that are entirely virtual (e.g., all data abstracted from the Military Health System [MHS] Data Repository). With the ongoing COVID-19 pandemic, DCC resources were largely directed to support data operations for COVID-19 Research Area protocols. In particular, the Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) protocol required near constant data collection modifications as SARS-CoV-2 research continued to evolve with the emergence of new outcomes and endpoints of interest. These changes required the development and revision of case report forms, programming and testing of electronic data collections workflows, deployment of project updates to participating sites, and approval of Data Sharing Agreements. The DCC also supported the acquisition of laboratory data for the COVID-19 Research Area protocols from the Specimen Processing Laboratory.

Although protocols within the COVID-19 Research Area were prioritized, the DCC continued to effectively support protocol data operations for the other IDCRP research areas. Case report forms were created or modified for four protocols, while the programming and testing of electronic data capture systems were completed for five studies. In addition, data from the MHS Data Repository were acquired for seven studies.

Over the years, the DCC has continued to advance their expertise with 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. The REDCap system has been used to create data workflows for recently developed protocols, while the systems of older, ongoing protocols continue to be migrated into REDCap. During the past year, the first upgrade to the REDCap system was completed to allow the IDCRP use of new functionality features that recently became available in the current version.

Edward Parmelee, MSc
Chief, Data Coordination Center

In 2022, the DCC plans to update relevant Standard Operating Procedures and formalize study support products/activities that were successful with the EPICC protocol (e.g., curated core datasets) for use in future studies. The DCC also expects to design, create, and implement the migration of at least two more of the ongoing IDCRP studies from their current legacy data management systems into REDCap. In addition, the subject registry system for the HIV Natural History Study will be improved to allow site personnel direct interaction with the registry. Furthermore, a research data repository will be constructed for the HIV Natural History Study as the Mi-Forms Data Collection platform is retired and the data collection instruments are migrated into REDCap.

HIGHLIGHTS

- **In response to new requirements for Data Sharing Agreement applications related to the safeguard of DoD health data on non-federal systems, the DCC worked with the HJF IT department to create documents to provide detailed descriptions of the data management systems.**
- **Data collection workflows for the HIV Associated Neurocognitive Disorders (ALLHANDS) study using IDCRP's legacy data collection systems that are being retired (e.g., ClinPlus, Mi-Forms, and Qualtrics) were successfully migrated into REDCap.**

PROGRAM OPERATIONS & FINANCE

Integral to the successful execution of the high-quality, high-impact clinical research conducted through the IDCRP is a well-organized, robust operational and financial foundation.

Samuel Davis, PhD, Chief, Program Operations and Finance

Led by Dr. Samuel Davis (Chief of Program Operations and Finance), the Program Management and Finance (PM&F) team continued to maintain a high level of readiness in response to the demanding research environment of operating during the ongoing COVID-19 pandemic. In particular, the COVID-19 Research Area, managed by Ms. Tigiste Girma (Program Manager Team Lead), required substantial support to process funding awards from the Defense Health Program, develop cooperative agreements, and maintain clinical studies being conducted at multiple military treatment facilities within the IDCRP Partner Network through the procurement of resources and personnel.

The PM&F team also meticulously supported the five other research areas within the IDCRP, including processing funding awards, conducting multifaceted financial analyses, and assisting with the development of grant proposals, subcontracts, and cooperative agreements. Multiple studies that were delayed or paused because of barriers imposed by the COVID-19 pandemic resumed enrollment and follow-up in late 2021, requiring the reallocation of resources and personnel to support these studies at partner sites. During the past year, the PM&F team also streamlined the resource management approach utilized by the Program, improving efficiency and financial planning.

Communication remains a crucial component of effectual program operations. As such, monthly meetings between the PM&F team and representatives from the USU and HJF financial and program management teams continued during the past year. Central to these discussions is the Master External Funds Report, which provides up-to-date information on incoming funding awards, including the expected timing of award receipt at USU.

In addition to the PM&F team, the Research Support Group (RSG) is also vital to the success of the Program by providing administrative support for IDCRP senior leadership, clinical research managers, and other team members. During 2021, the RSG team evolved the approach used for tracking the clearance status of deliverables, oversaw the implementation of various virtual platforms for meetings, managed supply orders for clinical sites, and ensured the proper disposal of archived files.

The further advancement of efficiency and resource management in support of IDCRP remains the overall goal for the PM&F and RSG teams in the upcoming year. Development of new financial planning and resource-management tools to enhance budget building, management, and analysis will also be assessed.

HIGHLIGHTS

- **Linking of the master budgets for the 2021, 2022, and 2023 fiscal years allowed program managers to provide more accurate predictions of IDCRP personnel and non-personnel costs across multiple years.**
- **The PM&F team improved the sub-contracting capabilities related to servicing logistical needs for the procurement of Mitra® blood specimen collection kits for the Acute Respiratory Infections Research Area PAIVED clinical trial.**
- **With the high number of deliverables generated by the Program in 2021, largely through the COVID-19 Research Area, RSG became the central hub for clearance tracking and improved transparency of deliverables with sites within the IDCRP Partner Network.**

QUALITY MANAGEMENT & CLINICAL RESEARCH OPERATIONS

Critical to the successful execution of the wide-ranging studies comprising the IDCRP clinical research portfolio is centralized quality assurance and quality management oversight.

Since the IDCRP was first established, the Program has grown more diverse and complex with regard to its research protocols, of which the vast majority are multi-site studies with locations both within the United States and overseas. The mission of the Quality Management Program, led by Ms. Christina Fox (Chief), is to ensure regulatory compliance, data quality, and consistency by providing guidance to investigators and study team members on quality management measures and improving the standardization of practices and reporting across clinical sites.

During 2021, a Quality Assurance Assessment of the IDCRP was conducted, resulting in improved efficiencies across protocols, enhanced staffing plans, and a greater understanding of best practices. Newly developed quality control checklists were also utilized by members of the Clinical Research Operations team and Regulatory Affairs coordinators for study enrollment and follow-up to ensure activities (e.g., informed consent, eligibility, specimen collection, and study payment) were completed in compliance with the respective protocols. Formal quality management training sessions were provided to study teams involved in high-impact COVID-19 Research Area protocols (i.e., EPICC and STORMCHASER).

New guidance documents (e.g., regulatory requirements for site-specific processes, study record maintenance, and electronic consent processes) were also developed and disseminated during the past year. In addition, multiple COVID-19 Research Area study playbooks were created to provide standardized steps and checklists regarding regulatory requirements and submissions. Furthermore, the Quality Management Program team continues to assist with study audits conducted by the USU Human Research Protections Program to ensure regulatory compliance and develop best practices across partner sites.

The USU-based IDCRP team of Clinical Research Managers, military treatment facility (MTF)-based Site Managers, and MTF lead Clinical Research Coordinators who directly support Principal Investigators, the Data Coordination Center, and protocol teams are crucial for the effective execution of the IDCRP clinical research portfolio. During the past year, these team members supported enrollment and follow-up for the Acute Respiratory Infections Research Area PAIVED trial, as well as multiple protocols from the COVID-19 Research Area. A new clinical trial through the Sexually-Transmitted Infections Research Area was also initiated.

For 2022, the knowledge gained from the Quality Assurance Program Assessment will be utilized to further refine and improve the quality and efficiency of IDCRP clinical research protocols. Goals include the establishment of an IDCRP-wide Quality Management Program, development of a Quality Assurance Manual, standardization of metrics across the IDCRP, and training team members on Standard Operating Procedures.

Christina Fox, CCRC, CCRP, Chief, Quality Management

HIGHLIGHTS

- **Quality management plans and corresponding checklists were developed for six protocols, including four clinical trials, that enrolled participants in 2021 (or will enroll in 2022). Study team members underwent training sessions to ensure compliance.**
- **A Program-wide Quality Assurance Assessment heavily focused on the COVID-19 Research Area EPICC study was completed, resulting in the development of a process improvement strategy, which highlighted best practices to disseminate throughout the IDCRP Partner Network, identified key gaps, and established a process to standardize site buildings.**

SCIENTIFIC REVIEW BOARD

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

John Powers, MD, Chair, Scientific Review Board

Scientific reviews are performed by the IDCRP SRB to assess the feasibility and scientific validity of protocols and protocol amendments with regard to research questions, hypotheses, aims/objectives, and methods with the goal of ensuring the quality of scientific content prior to IRB submission. Chaired by Dr. John Powers (National Institute of Allergy and Infectious Diseases liaison) and Vice Chair CDR Mark Simons (IDCRP Deputy Director), all new protocols and amendments resulting in significant changes to the associated protocol submitted by IDCRP investigators are reviewed by the SRB.

Individuals are selected for the SRB panels based on the research questions described in the protocol or protocol amendment to be reviewed and include subject-matter experts, biomedical scientists, statisticians, and other scientific review panel members affiliated with IDCRP research networks. The SRB Chair (or Vice Chair when the Chair is recused or unavailable) evaluates each submission and assigns it to one of three potential review pathways (i.e., Standard Review, Low Resource Review, and Chair Review) with the goal of optimizing efficiency. Among the review pathways, the Chair Review is the most rapid with completion occurring within 14 days, while the Low Resource Review and Standard Review are generally completed within 28 days and 35-45 days, respectively. An Expedited Review pathway (14-day timeline) was established to review all protocols and protocol amendments submitted through the COVID-19 Research Area in response to the public health urgency associated with the ongoing pandemic.

During the past year, the SRB reviewed 6 new protocols and 13 protocol amendments. Among these submissions, 1 of the protocols and 6 of the protocol amendments were related to COVID-19 research and assigned to the Expedited Review pathway. In response to the accelerated timeline, reviewers identified for the Expedited Review pathway completed their preparatory work for the reviews within 3-5 days. To enhance the efficiency of this pathway, there were discussions between the Principal Investigators and SRB Chair regarding study design prior to protocol development. Reviews through the SRB may not commence until the panels are fully formed, so potential reviewers were also suggested by the Principal Investigators prior to submission, which allowed the SRB to be able to confirm availability and willingness to serve on the panels and improve the timeliness of the review initiation.

For the coming year, the SRB Chair will further streamline the Standard Review pathway to improve efficiency and reduce the time required to complete the reviews, while maintaining scientific rigor. Process improvements include encouraging Principal Investigators to suggest names of potential reviewers at least one month prior to submission, standardizing SRB submission timelines, providing new reviewers with training to improve quality of reviews, and educating junior investigators on protocol development with regard to research questions and study design.

SRB Reviews and Approvals	Numbers
Submission to the SRB	**19**
New protocols	6
Protocol amendments	13
SRB disposition	
Approved	16
Under Review	3

REGULATORY AFFAIRS

With the goal of ensuring ethical conduct and regulatory compliance, the Regulatory Affairs team utilizes their expertise to support the development of new research protocols, oversee ongoing protocols, provide Program-wide regulatory training, prepare for regulatory monitoring, and develop agreements necessary for execution of protocols.

In addition to ensuring regulatory compliance of the IDCRP portfolio, the Regulatory Affairs team (led by Dr. Lev Nevo and Ms. Elisa Chapo, Program Regulatory Affairs Specialists) also functions as the liaison between the IDCRP and regulatory officials at USU, the Defense Health Agency, DoD partners, and the National Institute of Allergy and Infectious Diseases.

While COVID-19 clinical research studies remained a priority during the past year, DoD Clinical Investigation Departments resumed processing of non-essential study submissions, allowing for the reengagement of many of the Program's non-COVID-19 research protocols that were paused in response to the pandemic. In addition, new studies and clinical trials were initiated in 2021, including the Sexually-Transmitted Infections Research Area Meningococcal (Bexsero®) Vaccine Against Gonorrhea Infection (MAGI Trial). This protocol reengagement / activation resulted in an increased number of requests for pre-Institutional Review Board (IRB) reviews and regulatory guidance.

Weekly meetings with the USU Human Research Protection Office and training on post-IRB approved tasks also resumed in 2021. Furthermore, working with Ms. Christina Fox (Chief, Quality Management Program), the Regulatory Affairs team was instrumental in the successful completion of COVID-19 Research Area EPICC study audits at Carl R. Darnall Army Medical Center and Tripler Army Medical Center. Specifically, the Regulatory Affairs team ensured that all regulatory questions that arose during the audits were appropriately addressed, and all corrective actions were completed.

With the large number of multi-site studies included in the IDCRP clinical research portfolio, as well as collaborations and partnerships with military, government, civilian, and academic research institutions and laboratories, agreements are vital for the successful execution of these studies. During 2021, Ms. Stephanie Cammarata, IDCRP Agreements Officer, managed a portfolio of more than 180 active agreements with 76 agreements submitted for review as either a new collaboration, renewal, or modification of an existing agreement. Thirty-one of the new agreements were related to COVID-19 research efforts.

For 2022, goals include the development of a Program-wide Regulatory Affairs Handbook, as well as improving the efficiency of the Regulatory Smartsheet Dashboard and continuing to provide training sessions to staff members. Ms. Cammarata will also implement process improvement plans for the management of agreements, educate new hires, and conduct annual training of the Agreements Standard Operating Procedure. Moreover, the Regulatory Affairs team will focus on developing templates and tools to reduce the number of stipulations received per eIRB submission and assist the Quality Management Chief with developing the Program-wide Quality Management Program.

Lev Nevo, MD, Program Regulatory Affairs Specialist

Elisa Chapo, BS, Program Regulatory Affairs Specialist

HIGHLIGHTS

- **IDCRP Regulatory Affairs team successfully conducted 157 pre-IRB reviews (68 and 89 for non-COVID-19 and COVID-19 research studies, respectively) of documents, including initial protocol submissions, site-specific protocol templates, protocol modifications, reportable events, and closures.**
- **Average turnaround time for pre-IRB reviews was 1.16 days per non-COVID-19 research submissions and 0.89 days per COVID-19 research submissions.**

EDUCATION / MENTORSHIP

The IDCRP is highly committed to fostering the growth of the next generation of clinical infectious disease (ID) researchers in the United States Armed Services.

Capt Ryan Collier, recipient of the Jay Sanford Award for the Best Research Presentation by a Fellow

Dr. Alexander Vostal, recipient of the IDSA IDWeek Trainee Award

To support its education mission, the IDCRP utilizes mentored trainee research projects, as well as participation in ongoing research. Residents, ID fellows, and medical/graduate students in the U.S. Armed Services are provided opportunities to conduct mentored research projects developed with and overseen by IDCRP 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).

Through these mentored research projects, trainees receive real-world, hands on experience, resulting in a greater understanding of aspects of study design, data collection and analysis, and publication/presentation of findings.

The clinical ID research capstone curriculum for medical students available through USU training program, continuing GME activities at WRNMMC, and the Armed Forces Infectious Disease Society are also supported by IDCRP investigators. During the past year, studies conducted through the COVID-19 Research Area (i.e., EPICC, PASS, PISCES, and STORMCHASER) also were presented at Accreditation Council for Graduate Medical Education-accredited CME seminars.

During 2021, 53 residents (across multiple specialties, including Internal Medicine, Neurosurgical, Ophthalmology, and Surgical), medical/graduate students, ID Fellows, and post-doctoral trainees either began or completed their IDCRP-mentored research projects. In particular, one doctoral candidate is utilizing data from the Sexually-Transmitted Infection Antimicrobial Resistance Study in support of her dissertation and data from the EPICC study are being used to support two PhD dissertations and an MPH practicum in public health. Furthermore, through the HIV Research Area, an independent project and separate practicum in collaboration with the Defense Health Agency Triservice HIV Working Group resulted in a USU trainee receiving her MPH.

During the past year, 32 oral and poster presentations involving trainees were presented at local and national conferences. In addition, 21 manuscripts co-authored by trainees were published or accepted for publication. Trainees who participated in IDCRP-mentored research projects also received award recognition in 2021 (see IDCRP Awards and Honors, page 28).

Along with mentored research projects, the success of the IDCRP's education mission is dependent on research engagement. During the past year, IDCRP investigators attended public health student practicum and project fairs, met with medical students and ID Fellows to discuss research opportunities, and kept Directors of medical training programs informed of available IDCRP-mentored opportunities. To further kindle enthusiasm for clinical research and increase awareness of ID opportunities in the U.S. Armed Services, ID consultants and USU faculty, including military graduates, were encouraged to convene with trainees and discuss how research impacts their respective practices.

Overall, the IDCRP education mission remains successful in bolstering high-quality clinical ID research in the Military Health System through supporting the growth of active-duty researchers.

Mentors MAJ John Kiley (left) and Maj Joseph Yabes (right) with ID Fellow, CPT Matthew Geringer (middle)

SELECT IDCRP TRAINEE EDUCATION PUBLICATIONS & 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*. Accepted for publication.

Epsi NJ, Richard SA, Laing ED, Fries AC, Millar E, Simons MP, English C, Colombo CJ, Colombo RE, Lindholm DA, Ganesan A, Maves RC, Huprikar N, Larson D, Mende K, Chi SW, Madar C, Lalani T, Broder CC, Tribble D, Agan BK, Burgess TH, Pollett SD. Clinical, Immunological and Virological SARS-CoV-2 Phenotypes in Obese and Non-obese Military Health System Beneficiaries. *Journal of Infectious Diseases*. 2021; 224(9):1462-1472.

Kiley JL, Mende K, Beckius ML, Kaiser SJ, Carson ML, Lu D, Whitman TJ, Petfield JL, Tribble DR, Blyth DM. Resistance Patterns and Clinical Outcomes of *Klebsiella pneumoniae* and Invasive *Klebsiella variicola* in Trauma Patients. *PLoS One*. 2021; 16(8):e0255636.

Bozzay JD, Walker PF, Schechtman DW, Shaikh F, Stewart L, Carson ML, Tribble DR, Rodriguez CJ, Bradley MJ. Risk Factors for Abdominal Surgical Site Infection after Exploratory Laparotomy among Combat Casualties. *Journal of Trauma and Acute Care Surgery*. 2021; 91(2S): S247-S255.

Yabes JM, Stewart L, Shaikh F, Robben PM, Petfield JL, Ganesan A, Campbell WR, Tribble DR, Blyth DM. Risk of Acute Kidney Injury in Combat-Injured Patients Associated with Concomitant Vancomycin and Extended-spectrum Beta-lactam Antibiotic Use. *Journal of Intensive Care Medicine*. 2021; 36(7): 818-827.

Kline DA, Daniels C, Xu X, Sunil T, Ganesan A, Agan BK, Colombo RE, Kronmann KC, Blaylock JM, Okulicz JF, Markelz AE. Antiretroviral Therapy Anchor-based Trends in Body Mass Index Following Treatment Initiation Among Military Personnel with HIV. *Military Medicine*. 2021; 186(3-4) 279-285.

Buchek G, Mende K, Telu K, Kaiser S, Fraser J, Mitra I, Stam J, Lalani T, Tribble D, Yun HC. Travel-associated Multidrug-resistant Organism Acquisition and Risk Factors among US Military Personnel. *Journal of Travel Medicine*. 2021; 28(3): taab028.

Carney B, Daniels C, Xu X, Sunil T, Ganesan A, Blaylock JM, Kronmann KC, Schofield C, Lalani T, Agan B, Okulicz JF. Association between Depression and HIV Treatment Outcomes in a US Military Population with HIV Infection. *AIDS Research and Therapy*. 2021; 18(1): 29.

PRESENTATIONS

10th Annual Conference of the American Society of Health Economists, 21-23 June 2021

Topal S, Richard P, Young J, Ganesan A, Gleeson T, Blaylock J, Okulicz J, Chu X, Agan B. The Effect of HIV Medical Evaluation Mandates on Healthcare Quality and Expenditure.

Topal S, Richard P, Young J, Ganesan A, Gleeson T, Blaylock J, Okulicz J, Chu X, Agan B. Expenditure, Utilization, and Appropriateness of Healthcare for HIV+ Beneficiaries in a US Single-Payer System.

2021 Southeastern Surgical Congress, 21-24 August 2021, Atlanta, GA.

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.

2021 IDSA ID Week, 29 September – 3 October 2021

Bennett W, Mende K, Beckius M, Rahman A, Tribble DR, Yabes JM. *Enterobacter cloacae* Infection Characteristics and Outcomes in Military Personnel who Sustained Trauma in Iraq and Afghanistan.

Vostal A, Grance M, Chukwuma U, Morales C, Lanteri C, Poitras BT, Parmelee E, Powers JH III, Mende K. Clinical and Microbiological Characteristics of Common Bacterial Bloodstream Infections in the US Military Health System.

Epsi NJ, Powers JH, Lindholm DA, **Helfrich AM**, Huprikar NA, Ganesan A, Lalani T, Mody RM, Madar C, Bazan SE, Colombo RE, Larson DT, Maves RC, Utz GC, Tribble D, Agan BK, Burgess TH, Malloy A, Pollett SD, Richard SA. A Machine Learning Approach Identifies Distinct Early-Symptom Cluster Phenotypes Which Correlate with Severe SARS-CoV-2 Outcomes.

Lu Z, Pena-Damata J, **Pohida K, Lake C, Epsi NJ**, Richard SA, Agan BK, Pollett SD, Simons MP, Dalgard CL, Blair P, Chenoweth J, Snow AL, Burgess TH, Malloy AMW, and the EPICC Study Group. Classical Antigen Presenting Cell Activation Correlates with T cell Immunity and COVID-19 Severity.

Kautz M, Epsi NJ, Richard SA, Colombo RE, Ganesan A, Collins L, Burgess T, Maves R, Markelz AE, Geaney C, Seshadri S, Utz G, Mende K, Hrncir D, Modi JR, Fries A, McClenathan B, Schofield C, Montgomery JR, Skerrett C, Spooner C, Coles CL, Lalani T. Compliance and Performance Characteristics of Subject Collected Versus Health-Care Worker Collected Nasal Swabs for Respiratory Viral Surveillance.

Collier RP, Lalani T, Telu T, Kuo H, Fraser JA, Tilly DH, Ganesan A, Kunz AN, Geist CC, Yun HC, Lindholm D. Malaria Chemoprophylaxis Adherence among U.S. Active Duty Service Members during Deployment to Endemic Regions.

Boatwright MA, Tilley DH, Utz G, Kunz A, Colombo R, Telu K, Fraser J, Kuo H, Tribble D, Lalani T. Operational Impact of Infections Disease Threats During Military Travel.

IDCRP AWARDS & HONORS

We congratulate the Infectious Disease Fellows and residents who received recognition for the IDCRP-mentored research studies at numerous conferences during the past year.

We wish to congratulate Dr. David Tribble (IDCRP Science Director) for receiving the Distinguished Service Award by the 2021 Military Health System Research Symposium (MHSRS) as recognition for his substantial contributions to the success of Military Health System research over the years and demonstration of outstanding leadership in pursuit of excellence. In addition, the IDCRP Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) COVID-19 Cohort Team received the MHSRS Outstanding Research Accomplishment Team award (focused on SARS-CoV-2) for the high-impact research generated by the team over the past year.

In 2021, Dr. Tribble, CAPT Timothy Burgess, and COL Eric Garges received the USU School of Medicine Dean's Impact Awards. Moreover, Dr. Anuradha Ganesan was recognized as the Walter Reed National Military Medical Center Department of Medicine Researcher of the Year. Furthermore, Dr. Rupal Mody was named the William Beaumont Army Medical Center Staff Researcher of the Year. She was also awarded the Civilian Award for Humanitarian Service for her support of DoD COVID-19 operations.

Name	Award/Honor	Awarding Organization
Academic or General Award/Honor		
Dr. David Tribble	Distinguished Service Award	Military Health System Research Symposium
Dr. David Tribble	School of Medicine Dean's Impact Award	USU
CAPT Timothy Burgess	School of Medicine Dean's Impact Award	USU
COL Eric Garges	School of Medicine Dean's Impact Award	USU
Dr. Rupal Mody	Civilian Award for Humanitarian Service	Department of the U.S. Army
Research-Related Award		
Dr. Rupal Mody	Staff Researcher of the Year	William Beaumont Army Medical Center
Dr. Anuradha Ganesan	Department of Medicine Researcher of the Year	Walter Reed National Military Medical Center
Research-Related Award for IDCRP-Related Research Study		
CPT Mary Ford	Jay P. Sanford Travel Grant	USU
Dr. Alexander Vostal	2021 IDSA IDWeek Trainee Award	Infectious Disease Society of America
The EPICC-COVID-19 Cohort Team	Outstanding Research Accomplishment/Team/ SARS-CoV-2	Military Health System Research Symposium
Capt Ryan Collier	Jay Sanford Award for the Best Research Presentation by a Fellow	U.S. Air Force Chapter of the American College of Physicians
CPT Maddi Fleit	Resident Research Podium Winner	U.S. Army Chapter of the American College of Physicians

Left: CAPT Timothy Burgess, Dr. Brian Agan, and COL Kevin Chung accepting the Outstanding Research Team award on behalf of the EPICC COVID-19 Cohort Team

Middle: Dr. David Tribble accepting the Distinguished Service Award

Right: Dr. Rupal Mody with her Civilian Award for Humanitarian Service

IDCRP COLLABORATORS & PARTNERS

Department Of Defense Sites

U.S. Military Hospitals and Clinics

- Benning Martin Army Community Hospital, Ft. Benning, GA
- Brooke Army Medical Center, JBSA Fort Sam Houston, TX
- Carl R. Darnall Army Medical Center, Fort Hood, TX
- Fort Belvoir Community Hospital, VA
- Landstuhl Regional Medical Center, Germany
- Madigan Army Medical Center, Joint Base Lewis McChord, WA
- Naval Medical Center Camp Lejeune, Jacksonville, NC
- Naval Medical Center Portsmouth, VA
- Naval Medical Center San Diego, CA
- Schofield Barracks Health Clinic, Oahu, HI
- Soto Cano Air Base, Honduras
- Tripler Army Medical Center, Oahu, HI
- Troop Medical Clinic, Fort Sam Houston, TX
- U.S. Naval Academy, Annapolis, MD
- 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. 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 Directorate-Kenya, Nairobi, Kenya
    - U.S. Army Medical Materiel Development Activity
    - U.S. Army Medical Research Unit, Tbilisi, Georgia

Other U.S. Military Commands/Programs

- Defense Health Agency
  - Armed Forces Health Surveillance Division (AFHSD)
    - Global Emerging Infection Surveillance (GEIS) Program
  - Immunization Healthcare Division,
- 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

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
- Thai Red Cross AIDS Research Centre
- United Kingdom Ministry of Defence
  - Royal Centre for Defense Medicine, Birmingham, UK
  - British Army Training Unit, Nanyuki, Kenya
  - Defence Medical Directorate, Birmingham, UK
  - Defence Statistics (Health) MOD Abbey Wood

Academia

- 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 & 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.

NIH National Institute of Allergy and Infectious Diseases

IDCRP Uniformed Services University

hjf

Infectious Disease Clinical Research Program

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