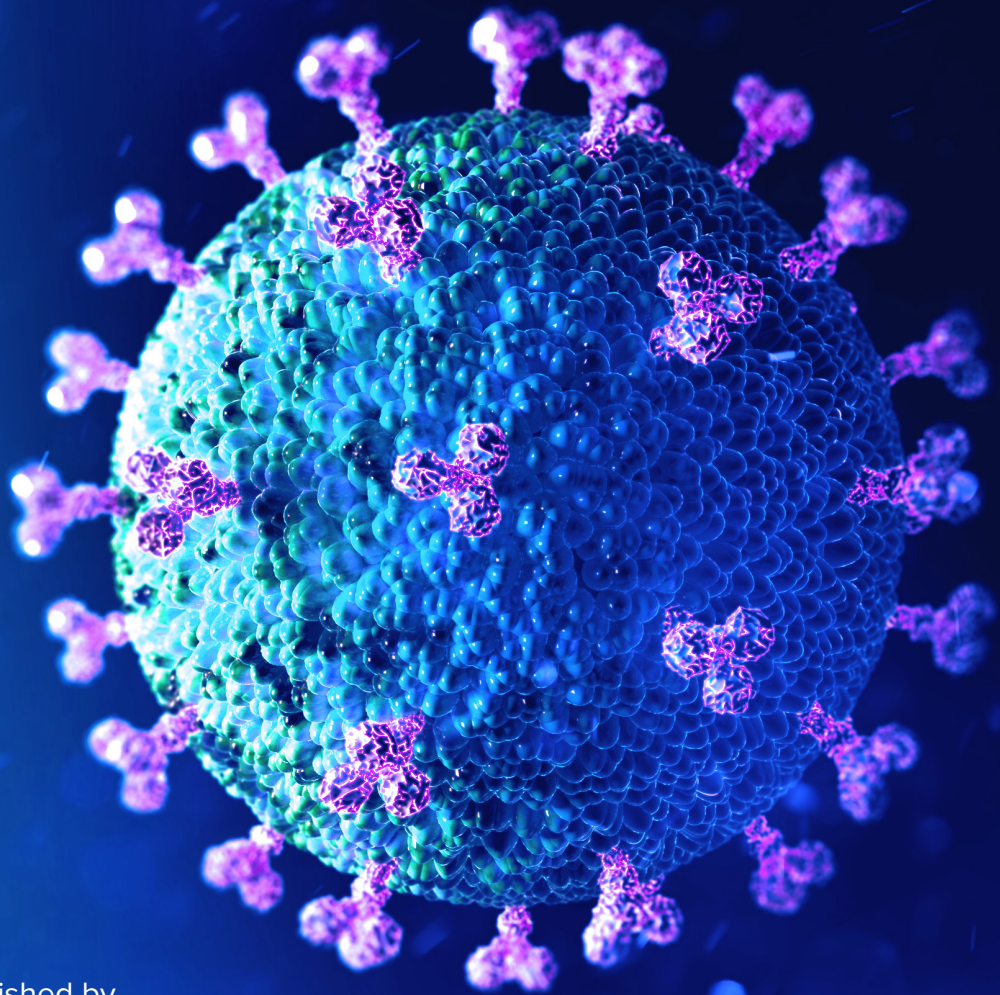


The Impact of Military Medicine: Pandemic Response

AN ANTHOLOGY



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Introduction

In 1983, Congress created The Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) to advance military medicine for the benefit of service members, veterans, family members, and ultimately the general public. To deliver on this promise, HJF works with the dedicated and talented members of the military as well as academic and industry partners to discover, innovate, and share results from research and clinical trials. Areas of focus include such topics as critical care, traumatic brain injury, human performance, cancer treatments, and most relevantly for this anthology of military medicine impact stories, infectious disease.

Gifted yet humble medical experts and other federal agency staff brainstormed ideas, pivoted focus, called on collaborators, and explored new ways to make meaningful impact during the COVID-19 pandemic response, but those stories are not well known outside of military medicine. Amidst more sensational stories and breaking news, military medical investigators, logisticians, and solutions experts made discoveries, streamlined processes, and partnered across industry and academia: it's time for those stories to be told more widely.

Learning from the COVID-19 pandemic, especially from those dedicated individuals who did not make the nightly news, helps the Nation prepare for future health care emergencies. Drawing on the concepts of collaboration, agility, speed, focus and commitment, these heroes applied their talents to the benefit of all.

Through the stories selected for this anthology, HJF aims to spread the news of the positive impacts military medicine and partnering agencies made through their response to the pandemic, both with programs HJF supports and with others. Our goal through highlighting these stories from military medicine is to help readers learn about this important work and the military's commitment to protecting and serving the Nation and the world, now and in the future.

Foreword

The Department of Defense has consistently prioritized protecting a worldwide deployed military force and providing world-class health care to their families. The military medical research system has successfully delivered a wide variety of solutions for both battlefield medicine and general health. Additionally, in times of crisis, Our Nation has called upon military medical research and innovation to augment responses to public health emergencies. And military medical research has always answered the call and done what our Nation has needed.

The COVID-19 pandemic is perhaps the best large-scale example of military medical research providing critical contributions. This anthology tells the story of military medical technology and processes that were leveraged for the COVID-19 response. Most importantly, it highlights individuals and teams, featuring the selfless servants of military medicine and how these people, with years of training and mentorship, delivered for both service members and the general public.

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“It Can Be Done!”

General Colin Powell’s Leadership Philosophy #4

*Colonel (RET) Richard H. Breen, Jr., United States Army and
Colonel (RET) Marcus Gmehlin, United States Air Force*

Thinking outside the box can be an overused cliché. It just can. But when the COVID-19 pandemic hit the United States in early 2020 and the President of the United States declared COVID-19 a national emergency on March 23, thinking outside of the box is just what was needed. Planning that originated in January 2020 with the Military Health System and the Defense Health Agency turned to action as the enterprise executed their crisis medical planning for the entire department. Now, it was the MHS and the DHA that became the center of gravity in responding to this attack to provide the best health care services and information to their beneficiaries throughout this crisis.



When a medical crisis hits in the Department of Defense, the Military Health System is called upon to lead the attack and defeat this invisible enemy. There were numerous initiatives developed over the course of the COVID-19 pandemic including expanded capabilities in telehealth and telemedicine, the establishment of a COVID-19 Registry, the consolidation of all Military Medical Treatment Facility websites into a standardized product for consistent messaging, the establishment of the DHA Appointing Tool which allowed beneficiaries to self-book their

COVID-19 vaccine appointments, and the establishment and execution of the DHA’s first Operational Planning Team designed to manage, distribute and track the distribution of the COVID-19 vaccine. These are just a sample of the initiatives developed over the course of the pandemic.

The area of Pharmaceutical Operations was no different. On March 31, 2020, all medical and dental facilities across the MHS enterprise postponed their medical and dental elective procedures for an extended period of time for all their beneficiaries. This policy was designed to meet three main objectives during the COVID-19 pandemic: first, to enhance the safety of military medical staff; second, to prolong supplies of personal protective equipment and ensure its availability for emergency use; and finally, to ensure the military medical staff is available to provide care related to the pandemic.

“One of the things that the DHA is really trying to do outside of standardization is to implement leading practices in medicine,” stated Colonel (RET) Marcus Gmehlin, former DHA Chief of Pharmacy who was instrumental in pharmaceutical innovations in the first two years of the COVID-19 pandemic.

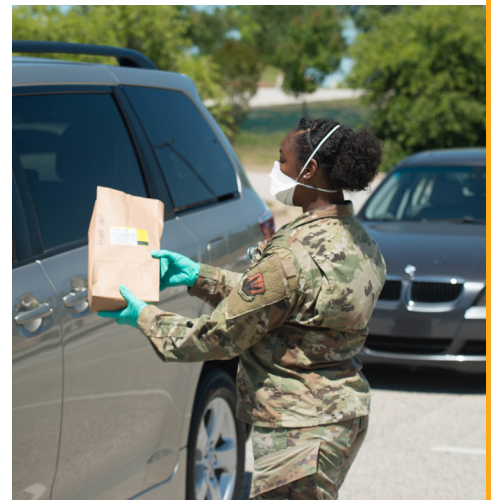
It was at that moment when the DHA Pharmaceutical team began their own innovations for the MHS. The pharmacy division maintains a \$9.7 billion dollar program with 56,000 retail pharmacies in the network, a global multi-billion-dollar mail order contract and 770 brick and mortar dispensing locations within the military treatment facility system. To execute this mission, there must be maximum access to the patients. “Once the pandemic hit, our biggest challenge was ensuring access for beneficiaries to get the pharmaceuticals they needed,” said Gmehlin.

With the dental clinics closed, an idea surfaced to use the dental clinicians to assist with newly established “drive-thru” pharmacy clinics. While not a new practice in the commercial world, this was a new concept for the MTF’s and became a huge success story enabling the beneficiaries to access needed pharmaceutical products and services.

While the drive-thru pharmacy system was a success story, in reality it was not resource sustainable once full medical and dental operations opened back up in the MTF’s. Thus became the birth of the remote pharmacy check-in system. “Instead of physically going to the pharmacy, pulling the ticket, and waiting to be called, now you can enter your DoD ID number and receive a text when your prescription is ready,” said Gmehlin. “This saves the patient time and proves to be efficient and effective. Our goal is to standardize this across the entire DHA worldwide.”

The DHA Pharmacy Division was responsible for other initiatives developed during COVID-19. The establishment of dedicated Script Centers, an Amazon-style locker installed at MTF’s, enables a patient to choose a specific pick-up point for their prescriptions. Plans are in development to have these script centers installed at post and base exchanges in the future. This initiative is beneficiary focused to meet their demanding schedules and avoid waiting in line at a pharmacy.

These examples are just the tip of the iceberg of the numerous innovations and creative programs initiated by the DHA during the pandemic. “As we strive for standardization across all our medical services and programs, we must consistently innovate to ensure we provide the best possible services to our beneficiaries,” said Gmehlin. “They expect it, and quite frankly, that is our charge...to be the best in the business.”



60 Days to Stop a Pandemic

Amy Jenkins, Ph.D., DARPA Program Manager, Biological Technologies Office and Shannon Greene, Ph.D., ManTech

Prompted by the launch of Sputnik in 1957 by the Soviet Union, the U.S. Department of Defense (DoD) a year later established DARPA—the Defense Advanced Research Projects Agency—to support a robust and agile technology program dedicated to U.S. national security. In the coming decades, DARPA would contribute to developing GPS, the internet, and other critical technological advancements, including most recently a vaccine for COVID-19.

As a growing number of infectious diseases—Ebola, Zika, and others—increasingly highlighted both the global threat as well as the lack of a public health response, DARPA launched the Pandemic Prevention Platform (P3) program in 2017. As part of DARPA's mission to support U.S. military readiness, the P3 program sought to protect DoD personnel deployed around the world and at risk for highly contagious infectious diseases.

With the objective of containing an outbreak and halting the spread of an infectious disease before it becomes a pandemic, the P3 program focused on ways to dramatically accelerate the development of preventive medical countermeasures, specifically monoclonal antibodies (mAbs). Their goal was to develop a scalable, adaptable, and rapid response platform capable of producing the necessary doses against any known or unknown infectious threat within 60 days. Compared with the four to 10 years typically required to develop antibody therapeutics, this time frame was viewed as highly ambitious, even audacious.

As part of the P3 program, research teams at AbCellera Biologics, AstraZeneca, Duke University, and Vanderbilt University began studying how to most rapidly identify antibodies that would be effective against an infectious virus, as well as ways to deliver the genetic code for producing these protective antibodies so that host human cells could follow the “instructions” and produce the antibodies themselves. This gene-encoded antibody approach had the advantages of being easily manufactured at scale using largely synthetic processes, transported and stored without many of the cold-chain logistics required by traditional medical countermeasures, delivered with near-immediate efficacy, and safely expressed in the body for only a limited duration, causing no permanent alteration to an individual genome.

P3 research initially targeted a wide range of infectious diseases; however, the teams quickly shifted their focus to developing antibody therapeutics and prophylactics for the novel coronavirus when it was first reported in China in 2019. AbCellera Biologics, a Vancouver-based technology company, obtained a sample of blood from a recovering U.S. patient at the end of February 2020 and studied potential antibody candidates after testing them to see how well the mAbs bound to and neutralized the virus.

Among thousands of anti-SARS-CoV-2 antibodies identified by AbCellera Biologics, bamlanivimab (LY-CoV555) was identified as the lead candidate and selected to enter human clinical trials in North America. In May, AbCellera Biologics started working with Eli Lilly on the large-scale manufacturing of this mAb therapy to target the SARS-CoV-2 virus. In November 2020, the U.S. Food and Drug Administration granted emergency-use authorization.

Bamlanivimab (administered on its own as well as in combination with other antibodies) has treated at least 700,000 patients and prevented COVID-19-related hospitalizations and deaths. In addition, bamlanivimab reduced by up to 80 percent the risk of contracting symptomatic COVID-19 among residents and staff of long-term care facilities.

Bamlanivimab was just the first of several success stories for the research teams funded by the P3 program. Another antibody product—a cocktail of two antibodies discovered by Vanderbilt University—was licensed to fellow P3 team AstraZeneca and received Emergency Use Authorization in December 2021 for pre-exposure prophylaxis among individuals at high risk of contracting severe COVID-19 disease. A team at Duke University also discovered several highly potent SARS-CoV-2 antibodies and is planning a clinical study of an RNA-encoded version of their leading candidate. In addition, AbCellera Biologics and partner Eli Lilly developed a second antibody, bebtelovimab, against the most common and fastest-spreading Omicron variants; bebtelovimab received Emergency Use Authorization in February 2022 for use in high-risk individuals.



The development of multiple COVID-19 medical countermeasures by the P3 program shares similarities with other past ground-breaking achievements of DARPA. By taking a transformative—not incremental—approach, the P3 program succeeded in developing a breakthrough technology with impressive speed. Its bold vision also reflected a far-sightedness that saved countless lives. By investing early on in the P3 program, DARPA once again fulfilled its mission of protecting U.S. national security.

For more information, see:

Nature, Jan. 12, 2021: How COVID Unlocked the Power of RNA Vaccines

The Washington Post, July 30, 2022: How a Secretive Pentagon Agency Seeded the Ground for a Rapid Coronavirus Cure

WRAIR Diagnostics and Countermeasures Branch Contributions to the COVID-19 Pandemic Response

Dr. Sheila Peel and Janice M. Darden

Globally, the diagnosis of SARS-CoV-2 infection has relied extensively on molecular testing to identify cases, guide isolation and contact tracing, and rationalize infection control measures during the COVID-19 pandemic. The WRAIR Diagnostics and Countermeasures Branch (DCB) plays a critical role in developing, evaluating, and deploying diagnostic technologies to detect and monitor SARS-CoV-2 infections in DoD personnel, their dependents, and U.S. populations.

Within the first year of the pandemic, DCB validated and deployed a laboratory developed assay to confirm the presence of actively replicating virus in SARS-CoV-2 infected personnel. This test facilitates medical decision making, specifically return to duty status of military personnel. DCB also validated the performance characteristics of a laboratory-developed test for the quantification of SARS-CoV-2 viral load in infected personnel. Both of these tests were deployed on a commercial high-throughput platform for rapid turn-around of test results.

Results from these tests provide critical data for monitoring SARS-CoV-2 infection, helping to support patient medical management in clinical settings. The use of these laboratory developed tests in U.S. Army clinical diagnostic algorithms decrease Warfighter time away from their units, permitting more rapid re-integration or elimination of COVID-19 isolation and quarantine requirements.

DCB expedited the development and deployment of novel diagnostic assays to quantify SARS-CoV-2 virus in support of vaccine development efforts.

While diagnostic testing is critical for detection of SARS-CoV-2 infection, the emergence of novel SARS-CoV-2 variants of concern underscores the need for next-generation vaccines and therapeutics that confer protection against COVID-19. DCB expedited the development and deployment of novel diagnostic assays to quantify SARS-CoV-2 virus in support of vaccine development efforts. Use of SARS-CoV-2

immunoassays to assess immune responses to vaccine candidates in development is critical for down selection of the most effective candidates.

WRAIR efforts to fight this global public health threat involved the development and evaluation of a SARS-CoV-2 Spike trimer ferritin nanoparticle (SpFN) vaccine adjuvanted with Army Liposomal Formulation QS-21 (ALFQ). DCB collaborated with WRAIR's Emerging Infectious Diseases Branch (EIDB) and a commercial entity, Meso Scale Diagnostics, Inc, to develop a serological approach to evaluate immune responses to COVID vaccine countermeasures against the latest variants of concern in human, nonhuman primate and small animal models.

In addition to supporting WRAIR's vaccine development, this testing capability has also been leveraged to determine the effectiveness of vaccination with other available COVID-19 vaccines in a population of active-duty U.S. Military personnel. Specifically, DCB tests are being used to assess SARS-CoV-2 vaccine protection against both clinical and subclinical SARS-CoV-2 infection; assess the kinetics and durability of the immune response to SARS-CoV-2 vaccines; and to characterize "breakthrough" infections. This data is critical to understanding the social and epidemiologic factors that may be related to new SARS-CoV-2 infections within vaccinated U.S. Military personnel. In addition, these quantitative tests developed, validated, and deployed by DCB to evaluate experimental SARS-CoV-2 vaccines may be rapidly pivoted for other militarily relevant projects.

In collaboration with commercial partners, DCB also developed a systems approach to pooled SARS-CoV-2 testing that entails the combination of independent specimens into a single sample for testing. The DCB-led study specifically established protocols and defined test characteristics for pooled sample testing of SARS-CoV-2 specimens from symptomatic and asymptomatic U.S. Military personnel for surveillance purposes. Results from DCB's efforts, which combined five specimens into one test sample (5:1 pooling), maintained high agreement with individual specimen testing while offering substantial high throughput test benefits. These efforts, which were initiated early in the pandemic, expedited, and expanded COVID-19 surveillance testing for the U.S. Military and conserved critically constrained reagents and consumable supplies.

Diagnostic subject matter experts at WRAIR were detailed to DoD and White House Diagnostic Task Forces to facilitate expansion of diagnostic testing capacity for DoD and U.S. populations. These efforts expanded U.S. diagnostic capacity by three- to four-fold throughout the early stages of the pandemic. DCB advisors also served on Operation Warp Speed and U.S. Government Operation working groups for the development of SARS-CoV-2 vaccine and therapeutic countermeasures which helped develop effective tools for virus prevention and intervention.

For more information, see:

<https://www.wrair.army.mil/biomedical-research/diagnostics-and-countermeasures>

Contributing author: Jamie Livengood



By Closing COVID-19 Knowledge Gaps, IDCRP Paves The Way Toward Better Prevention and Treatment Strategies

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The Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) Research Center based at the Uniformed Services University of the Health Sciences (USU), conducts clinical research focused on military-relevant infectious diseases such as COVID-19. IDCRP was chartered under an interagency agreement between 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 (HJF).

About EPICC

Following the 2014 Ebola outbreak and the 2015 Zika outbreak, researchers from IDCRP developed an adaptive protocol to study new emerging infectious diseases. This new protocol, known as EPICC (Epidemiology, Immunology and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential), was designed such that researchers could rapidly pivot to study quickly emerging infectious disease outbreaks that could impact the DoD population.

In early February 2020, IDCRP noted that the SARS-CoV-2 outbreak could give rise to a global pandemic. IDCRP quickly revised the EPICC protocol's existing framework to support a study of the SARS-CoV-2 pathogen, as well as COVID-19, the disease associated with SARS CoV-2. EPICC opened for enrollment on March 20, 2020, just weeks after the first cases were detected in the United States.

IDCRP's EPICC study is a longitudinal cohort study (a study that observes a large group of people over an extended period of time) of COVID-19 that enrolls those with COVID-19, COVID-like illness (CLI), asymptomatic individuals with a high risk of SARS-CoV-2 exposure, and COVID-19 vaccine recipients. The study's goals are to characterize the epidemiology, immunology, and clinical characteristics of COVID-19; and examine outcomes of SARS-CoV-2 infections in Military Health System (MHS) beneficiaries. The study eventually expanded to ten enrolling military treatment facilities (MTFs), as well as virtual (online) enrollment across the MHS. Over 2,500 individuals have participated in EPICC across the ten enrolling MTFs, with an additional 5,000-plus online participants MHS-wide.

Over a one year follow-up study period, study participants complete a series of questionnaires to help researchers collect data on COVID-19 risk factors for COVID-19, previous testing, participants' health conditions and medication use, and symptoms or treatments for participants diagnosed with COVID-19. MTF-enrolled participants provide serially collected blood specimens and swabs. Online participants may provide self-collected blood samples. These specimens have been analyzed by a network of immunology and virology EPICC laboratory partners to help EPICC researchers understand the host immune response to infection and vaccination and how this immune response might impact the potential risk of severe disease. Statisticians in the EPICC team are increasingly using artificial intelligence ('machine learning') methods to analyze complex data, and identify patterns and predictors of COVID-19 clinical outcomes.

EPICC has demonstrated major insights into COVID-19 in the MHS to date, including the role of obesity in severe COVID-19, the clinical and virological characteristics of COVID-19 in the vaccinated, the predictors of vaccine-induced immunity, and estimates of the durability of immunity from prior SARS-CoV-2 infections. Over the course of the pandemic, the EPICC study has adapted to new questions—for example, providing rapid information on immunity to new emerging variants such as the Omicron and related strains (e.g. BA.5); EPICC investigators are also examining how the risk of “Long COVID” may change as the SARS-CoV-2 virus evolves and how vaccination mitigates the risk of Long COVID. Recently, EPICC's contributions to Long COVID research was highlighted in the Department of Health and Human Services National Research Plan on Long COVID.

The findings from EPICC have culminated in at least 12 journal publications, over 20 conference abstracts, and briefings to Department of Defense leadership, Military



Treatment Facility stakeholders, the National Institutes for Health, and the U.S. Food and Drug Administration. EPICC is closing COVID-19 knowledge gaps by providing better insight into the progression of SARS-CoV-2 infection, including clinical, virologic, and immunologic determinants of severe disease and long-term post-COVID conditions. Ultimately, the EPICC study aims to improve clinical care for COVID-19 patients, and to advance development of treatment and prevention strategies to benefit both military and civilian populations.

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the Uniformed Services University of the Health Sciences (USUHS) through a cooperative agreement by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been funded in part by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, under an interagency agreement (Y1-AI-5072).

COVID-19 Observational Clinical Studies

Daniel Critchfield, Booz Allen Hamilton and Alex Hillman, JPEO Public Affairs Officer

Since March 2020, the Department of Defense's (DOD) Joint Program Executive Office for Chemical, Biological, Radiological and Nuclear Defense's (JPEO-CBRND) Joint Project Lead for CBRND Enabling Biotechnologies (JPL CBRND EB) and the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF) have collaborated with public and private sector organizations to support several COVID-19 observational clinical studies. The studies, funded through a partnership with the Defense Health Agency (DHA), support the DOD and its partners to understand SARS-CoV-2 and its progression. The studies support the DOD's and its partners' efforts to become better prepared for not only COVID-19, but also future public health emergencies.

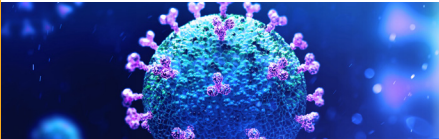
The studies JPL CBRND EB has led for the past two and a half years established a network of clinical sites around the country and the globe. These efforts allow the DOD and its academic and private sector clinical partners (e.g., Duke University, Johns Hopkins University and others) to react quickly to future pandemics by testing, evaluating and understanding the medical countermeasures at the DOD's disposal. Beyond the development and expanded

The studies support the DOD's and its partners' efforts to become better prepared for not only COVID-19, but also future public health emergencies.

use of the mRNA vaccine, there are new technologies that were put to the test through these observational studies, one of the objectives of the observational studies includes enhancing clinical evaluation while mitigating public health risks of disease spread in infected participants. To make this possible, the studies are pushing the decentralization of clinical trials through a device known as Tasso. This device allows for remote blood sample collection, preventing germ spread at testing sites and among infected

patients, a feature that is particularly desirable during the ongoing COVID-19 pandemic or with other highly transmissible viruses. Over 10,000 Tasso devices are deployed at military treatment facilities (MTFs), Veterans Affairs (VA) facilities, and civilian clinical sites with ongoing analyses of the device's effectiveness.





JPL CBRND EB uses other devices that are also advantageous for warfighters in austere environments. The studies test biomarker devices to help medical personnel make informed decisions. New technologies are able to monitor patient vitals, which helps medical professionals make informed decisions and determine appropriate treatment courses, including if a current countermeasure treatment is working, or if patients need additional intervention in a hospital or other setting. Although these devices are being tested for warfighters, they have a lot of potential to be used for civilians too.

COVID-19 testing is a significant component of the observational clinical studies. For example, the longitudinal study of COVID-19 Vaccine Effectiveness and Immunogenicity in Active-Duty Military Population (VIRAMP) evaluates post-vaccination protection against symptomatic, asymptomatic and breakthrough COVID-19 cases. VIRAMP uses twice-weekly home saliva testing to determine immunity to different COVID-19 strands. With nearly 1,000 participants enrolled in the study, the evaluation period is following participants for up to two years to determine vaccination effectiveness and the impact of the emerging variants on the vaccines.

These COVID-19 observational studies are still ongoing. Aside from having a better understanding of the protection that the various vaccines provide against COVID-19, the studies also aim to build clinical networks worldwide to respond quickly to the next pandemic or future biothreat. The studies aim to test medical countermeasures more rapidly than in the past and in various types of environments. Therefore, no matter the setting, medical professionals will be prepared to treat patients at home and in areas lacking resources needed during a pandemic.

The COVID-19 observational clinical studies support the DOD's and its partners' efforts to become better prepared for not only COVID-19, but also future public health emergencies.

The response effort to COVID-19 and any future pandemics do not stop with these observational studies. In April 2022, JPEO-CBRND collaborated with JUST EvoTech Biologics (JUST) to provide the United States government priority access to the JUST facility for the next seven years. This effort aims to strengthen the DOD and thus the Nation's rapid response capabilities. Rapid response capabilities were established and used during the COVID-19 response to manufacture monoclonal antibodies for use in clinical trials. The innovative continuous manufacturing processes implemented at JUST, in collaboration with DOD, enabled an over sevenfold increase in the number of doses produced compared in the same period using standard manufacturing processes. In a rapid response context, this means fielding sevenfold or more doses out of the first production lot—a highly significant achievement and capability. This increase in productivity will also result in reduced cost per dose for routinely produced antibody medical countermeasures.

JPEO-CBRND's Generative Unconstrained Intelligent Drug Engineering (GUIDE), an artificial intelligence machine-learning program, initiated a retargeting campaign in December of 2021, and began establishment of a revolutionary integrated computational drug development toolset. Even with early versions of molecular design tools, GUIDE was able to modify a clinical stage antibody that had lost effectiveness to the Omicron variant, and accomplished the redesign in under three weeks. The tools enable not only a retargeting to the new variant, but also maintained critical product quality attributes to improve safety and manufacturability. One of the retargeted antibody candidates, Omicron-199, has proven effective against all COVID-19 variants that have emerged to-date. In mid-July 2022, the GUIDE team transferred the Omicron-199 material to AstraZeneca for additional testing and potential product development work. The antibody could be one of the first computationally retargeted antibodies to be further developed. This is promising and may lead to regulatory engagements with the U.S. Food and Drug Administration, and if approved, it could lead to future clinical trials. In short, the JPEO-CBRND's JPL CBRND EB team may have helped uncover a potential antibody that could be effective against all SARS-CoV-2 variants thus far, which could also be an essential countermeasure for the continuing global COVID-19 response.



Acknowledgements: Nicky Dorsey, Bruce Goodwin, Col Jessica Cowden, Col Jameson Voss, Rich Totten, Danielle Clark, Carlyle Gollogly, LightDeck Diagnostics and Tasso, Inc.

Clinical Device Images:



Figure 1. LightDeck Diagnostics



Figure 2. Tasso Sample Collection

Novel Technologies to Quickly Act on Outbreak Data

Dr. Danielle Clark

The COVID-19 pandemic exposed critical weaknesses in our ability to rapidly develop, deploy and evaluate medical countermeasures, as well as novel technologies in an outbreak setting. Prepositioned teams and pre-approved, flexible protocols are needed, as well as an improved, integrated suite of technologies to enable more efficient clinical trials and inform response efforts.

Through the HJF Outbreak Clinical Trials program, we are evaluating novel technologies to detect clinical disease, predict disease severity and risk of long-term sequelae, and provide early indication of infection to guide clinical decision-making and inform more efficient clinical trials for medical countermeasure

development. We have deployed a suite of technologies including: (a) Tasso microneedle self-blood collection devices; (b) Point-of-care biomarker assay platforms (LightDeck); (c) Wearable biosensors; and (d) Portable Ultrasound.



Decentralized Trials and Self-blood Collection

The need to reach potential research subjects outside clinical centers grew urgent during the COVID-19 pandemic, as hospitals became overwhelmed with surges in cases and many isolated at home. Our team partnered with the Naval Health Research Center (NHRC) and Tripler Army Medical Center (TAMC) to develop and deploy a decentralized study of ambulatory COVID-19 cases and their close contacts. Research subjects enrolled at NHRC never set foot in a clinic for study visits, nor did they have in-person contact with the study team. Blood collection was enabled using a novel technology, the Tasso micro-needle self-blood collection device.

The Tasso Serum Separator Tube (SST) (Tasso Inc., WA, USA) is a single-use, sterile, disposable, integrated device for self-collection of capillary blood by the user. The device comprises a lancet assembly and a detachable reservoir collection unit, designed to collect up to 300 μ L capillary blood that can be processed to generate serum at a central processing lab for downstream analysis.

Point-of-care biomarker assay platforms

Triage decisions became critical during the pandemic, but clinicians had very little to guide them on which patients to admit to the hospital and which to discharge to isolate at home. We set out to develop a rapid point-of-care test for the risk of hospitalization of recently diagnosed COVID-19 patients. This technology aims to quickly classify those patients recommended for hospitalization versus those who could isolate at home. We partnered with LightDeck, as their technology platform has unique capabilities for point-of-care (POC) host-response biomarker assays. We evaluated potential COVID-19 host-response biomarkers for outcomes using a bank of clinical samples covering both hospitalized and non-hospitalized patients. Out of that evaluation, we demonstrated that two specific markers, C-reactive protein (CRP) and inducible-protein 10 (IP-10 or CXCL-10) are markedly elevated in those patients who are hospitalized. Hospitalization risk prognosis/triage could provide significant benefit during pandemics or biothreat events when resources (e.g., nurses, ICU beds, ventilators, etc.) are limited.

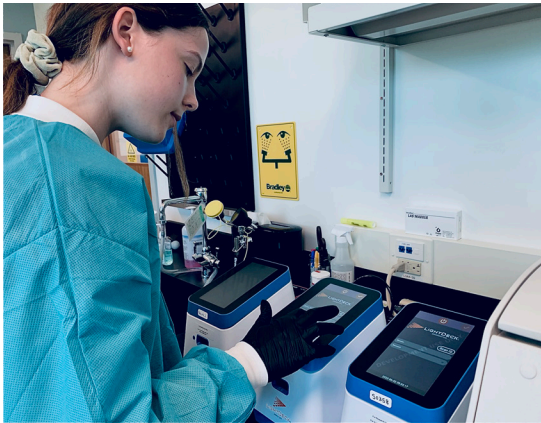
Wearable biosensors

Remote monitoring of vital signs with sophisticated personalized algorithms has the potential to provide a non-invasive means to assess disease progression and provide early indication of infection. We have partnered with PhysIQ, a company that specializes in collecting and analyzing continuous physiological data acquired from wearable biosensors, as well as NHRC, TAMC, Duke University, and Johns Hopkins University to deploy wearable biosensors in subjects with COVID-19 and their close contacts. Among the specific objectives of the study are to use continuous physiological data to characterize immune response to infection, evaluate novel machine-learning-enabled diagnostic and prognostic tools, and evaluate the efficacy of emergency investigational new drug therapies that may be administered to enrolled participants.

POCUS

From austere to tertiary care settings, Point-of-Care Ultrasound (POCUS) is an emerging technology that could guide life-saving treatment for the Warfighter. POCUS could be used to identify both lung pathology and causes of shock in the field. However, algorithms to guide clinicians and medics on the appropriate use of this promising tool are needed.





HJF has developed and modified clinical research protocols for the deployment of POCUS. Deployment included training of study personnel, collection of associated clinical data and imaging, establishment of required agreements, as well as engagement of subject matter experts for training and annotation of images.

Technologies that help health care providers make informed treatment decisions as well as those giving patients ways to provide information to their

caregivers remotely have the capacity to improve outcomes for service members as well as the general public, whether in a pandemic situation or not. ACESO is committed to furthering such studies and creating results that bring these benefits to life.

Founded in 2010, the *Austere environments Consortium for Enhanced Sepsis Outcomes* (ACESO) is a consortium consisting of U.S. Government, non-profit, academic and industry partners. ACESO's mission is to improve survival for patients with sepsis through development of host-based diagnostic and prognostic assays and evidence-based clinical management. ACESO is specifically focused on developing solutions to guide clinical decision-making in settings where a modern intensive care unit (ICU) is not available, including military deployments to areas with long medical evacuation chains, medical centers in low- and middle-income countries, and pandemic or other public health emergency settings.

The HJF/ACESO team leveraged our advances in sepsis at the start of the COVID-19 pandemic to rapidly translate and deploy technologies to better understand COVID-19 and develop solutions.

For more information, see:

<https://www.aceso-sepsis.org>

<https://www.hjf.org/news/hjf-filter-covid-19>

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Photo subject: Claire Wilson, Laboratory Technician, ACESO/HJF

Photo credit: Kathryn McKean, Communications Coordinator, ACESO/HJF

Existing Partnerships Accelerate Diagnostic and Treatment Development

Denver Beaulieu-Hains and Scotty Hogan

Before the global pandemic, the term *first responder* only referred to law enforcement and emergency medical personnel. COVID-19 may have changed that.

Working with the leaders at the Joint Services, Defense Health Agency, Office of the U.S. Army Surgeon General, Walter Reed Army Institute of Research, the U.S. Army Medical Materiel Development Activity (USAMMDA), the Department of Defense's product development, systems management and acquisition organization, rapidly equipped units with critical care equipment and solutions to mitigate the loss of life and ensure readiness.

After Congress passed the Coronavirus Aid, Relief and Economic Security (CARES) Act, the funding provided allowed USAMMDA to pursue diagnostic and treatment options in the fight against COVID-19. The development of new diagnostics and treatments for infectious diseases falls under the purview of the Warfighter Protection and Acute Care (WPAC) Project Management Office (PMO), and the office quickly engaged with



its industry partners to begin the development process. In particular, for the military services to continue their mission, there was an immediate need for diagnostics to detect COVID-19 and treatments for the virus and the side effects it caused.

Established partnerships were beneficial. “We worked closely with U.S. Army Medical Research Acquisition Activity (USAMRAA) which allowed us to get new contracts awarded quickly due to the emergency situation and having pre-existing relationships with the companies made getting the contracts finalized a lot easier, said Dr. Kendra Lawrence, project manager for WPAC PMO.”

“As soon as we learned that DHA CARES Act funding was available, we had briefings with the DHA,” said Dr. Lawrence. “We had three programs in our portfolio that we believed we could leverage to support COVID-19 response. We reached out to those

The Warfighter Expeditionary Medicine and Treatment PMO found their niche in ensuring safe and reliable Personal Protective Equipment (PPE)

“There was a need for a lot more swabs than what was commercially available at the time, and there was funding available for manufacturing solutions,” said Christine Parker, project manager at USAMMDA’s Warfighter Expeditionary Medicine and Treatment PMO. “We worked with all the various stakeholders [every single service] to coordinate our response to ensure that the response and procurements were compliant with what was allowed under the EUA through FDA. We wanted to have the capacity organically within the services to produce some of the testing equipment, without having a negative impact on the public-private sector.”

partners and asked, what we could do to get on contract quickly, what we could do to get moving quickly and what we could accomplish with the DHA CARES Act funding?”

One of the first technologies, developed by InBios International, Inc., leveraged its lateral flow technology for the development of a SARS-COV-2 Antigen (Ag) Detect and Serology (Ab) Detect rapid test. InBios received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) for its SARS-COV-2 Ag Detect test within 10 months. By August 2021, a second EUA authorized human serum, plasma, venous whole blood or finger-stick and provided results in about 20 minutes. Later, during November of 2021, the home test was available and expanded access to include individuals 14 years or older.

Another technology solution from a partner under contract with USAMMDA included BioFire Defense’s FilmArray®, a PCR test which evolved through the pandemic, receiving multiple EUAs as its capabilities and sample types were expanded.

WPAC PMO also worked with Ophirex, Inc., on treatment for one of the leading causes of COVID-related deaths, Acute Respiratory Distress Syndrome (ARDS). Ophirex is developing a broad-spectrum snakebite antidote to treat snakebite envenoming, caused by the same molecule thought to trigger ARDS, so the WPAC team and Ophirex decided to repurpose the drug to treat the condition

in COVID-19 patients. A clinical study began on June 30, 2021, to test Varespladib’s viability as a treatment for COVID-19-related ARDS. The study is ongoing and currently in its second phase, with a planned completion date of December 2022.

As an integral part of the U.S. Army Medical Research and Development Command (MRDC) and Army Futures Command, by January 2022, USAMMDA's Force Health Protection Directorate had treated more than 22,000 treatment courses with the investigational COVID-19 treatments Remdesivir, convalescent plasma and monoclonal antibodies, and COVID-19 therapeutics worldwide. Additionally, ongoing efforts to field and replace critical patient care equipment and materiel remain a priority.

“While we worked on efforts to respond to COVID-19, we also had to ensure all of our other Department of Defense and Army priorities were moving forward [despite COVID-19]. We had to find solutions,” said Lawrence. “Everyone pulled together and looked for ways to leverage technologies as potential applications against COVID-19.”

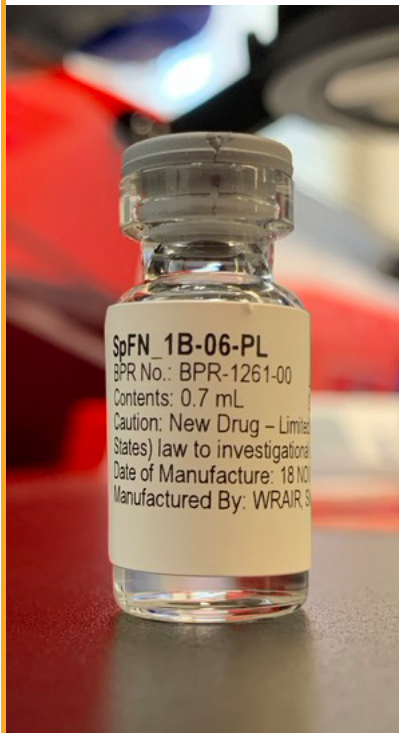
Team USAMMDA might not look like other first responders, but consider this: In addition to services authorized and employed due to the DHA CARES funding, USAMMDA's Warfighter Deployed Medical Systems PMO also supplied Warfighters with portable oxygen generators, T1 Hamilton ventilators, infusion pumps, ultra-sonic cleaners, blood fluid warmers, Next-Generation Diagnostic Systems with COVID-19 test kits, and D-cylinder oxygen tanks. When it comes to COVID-19, USAMMDA developed and delivered!

For more information on USAMMDA and WPAC's impact on pandemic response, go to: https://mrdc.amedd.army.mil/assets/docs/WPAC_Newsletter_Volume_II_20220412.pdf



WRAIR Leveraged to Speed the Development of Safe, Effective Vaccine for COVID-19

The Walter Reed Army Institute of Research (WRAIR) and the U.S. Army Medical Research and Development Command played a key role in U.S. Government's COVID-19 pandemic response. For more than 125 years, WRAIR has been a leader in global efforts to combat the world's most pervasive and high impact infectious diseases, such as malaria, HIV/AIDS, Ebola, and dengue. The Institute played a key role in the development of many vaccines including ones for Adenovirus, influenza, dengue, typhoid, Hepatitis A and B, and Japanese encephalitis.



In the early days of the COVID-19 pandemic, WRAIR infectious disease specialists quickly pivoted to spearhead countermeasure development efforts within the DoD and work in coordination with U.S. Government and private industry collaborators to develop tools to prevent, detect and treat COVID-19.

WRAIR experts partnered with researchers at other U.S. Government agencies and helped provide leadership for the oversight of vaccine development efforts for COVID-19. Subject matter experts at WRAIR joined Federal efforts early in the pandemic, providing critical expertise and guidance to the efforts that then fell under Operation Warp Speed and participated on White House Task Forces and product development teams for candidate COVID-19 vaccines.

WRAIR's unique strengths in clinical research, specifically around community engagement, clinical trial design and immune monitoring laboratory assays, helped guide tremendous efforts to develop and test novel vaccines, diagnostics and therapeutics. As the epidemic evolved, WRAIR also contributed knowledge about the ongoing genetic diversity of the virus and the potential impacts of virus variability on the vaccines in use and in development.

In addition to their contributions to the Federal effort, WRAIR scientists worked closely with industry and U.S. Government partners to develop a "pan-coronavirus" vaccine technology that may potentially offer safe, effective and durable protection against evolving variants of concern and similar coronaviruses that could emerge in the future. This effort to create a broader, forward-thinking strategy was complementary to the landscape of global countermeasures that were developed while fulfilling WRAIR's mission to protect Service members and the global community from the increasing threat posed by emerging infectious diseases. WRAIR scientists took a long-term, strategic

approach by mapping and optimizing the SARS-CoV-2 surface protein structure for presentation on a nanoparticle scaffold, a technology based on approaches developed for an influenza vaccine by the National Institutes of Health.

Different from licensed mRNA and adenovirus vector vaccines currently in use, the WRAIR's SpFN (Spike Ferritin Nanoparticle) candidate vaccine is a recombinant protein subunit nanoparticle vaccine that presents a fragment of the virus to the immune system to elicit a protective response. Ferritin is a naturally occurring iron-carrying protein that self-assembles into spherical cage. Researchers hypothesize that presenting multiple copies of Spike in an ordered array may be a key to inducing a potent and broadly protective immune response. SpFN is different than the recently authorized protein nanoparticle developed by Novavax in that it produces a more highly ordered nanoparticle.

The SpFN vaccine is formulated with ALFQ, one of the Army Liposome Formulation family of adjuvants developed by researchers at WRAIR. An adjuvant is a component of a vaccine that helps activate the immune system and improve immune responses. Preclinical and early clinical studies have demonstrated ALFQ to be safe and strongly potent as a vaccine adjuvant.

Pre-clinical animal studies of SpFN show the candidate vaccine not only elicits a potent immune response but may also provide broad protection against SARS-CoV-2 variants of concern, as well as other human and zoonotic coronaviruses. SpFN entered Phase 1 human trials in April 2021. The findings generated by this trial, expected to be published in late 2022, will provide key insights into SpFN's potency, breadth and durability in humans. The results will also allow the broader community of researchers to compare SpFN's immune profile to that of other COVID-19 vaccines already in use.

For more information, see:

<https://www.wrair.army.mil/biomedical-research/emerging-infectious-diseases>

<https://eidresearch.org/>









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