Deployment Infectious Disease Threats: IDCRP Initiatives and Vision Forward

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ABSTRACT Background: Infectious diseases pose a significant threat to health and readiness of military personnel deployed globally during wartime and peacekeeping activities. Surveillance and improvement in mitigation through research of infectious disease threats remain an integral part of Force Health Protection. Herein, we review research efforts of the Infectious Disease Clinical Research Program related to deployment and travel-related infections. Methods: The objectives of the Deployment and Travel-Related Infections Research Area are to (1) provide epidemiologic and clinical data, including pathogen-specific estimates of disease incidence among deployed troops, (2) execute clinical trials and effectiveness studies to improve recommendations regarding prevention and treatment of infections during deployment, and (3) evaluate the knowledge and practice patterns of health care providers engaged in deployment/travel medicine and the impact on outcomes. The centerpiece protocol of the research area is the Deployment and Travel-Related Infectious Disease Risk Assessment, Outcomes, and Prevention Strategies cohort study (TravMil), which was initiated in 2010 and collects data on a broad range of deployment-related infections. Results: To date, 4,154 deployed military personnel and traveling Department of Defense (DoD) beneficiaries have been enrolled in TravMil. Surveillance data collected through the TravMil study provide assessment of deployment and travel-related infectious disease threats, and the effectiveness of mitigation strategies. The incidence of travelers’ diarrhea, influenza-like illness, and undifferentiated febrile illness is 20.48%, 9.34%, and 6.16%, respectively. The cohort study also provides necessary infrastructure to execute clinical trials. The TrEAT TD clinical trial evaluated the effectiveness of single-dose antibiotic therapy for travelers’ diarrhea in the deployed setting. When compared to levofloxacin, azithromycin was not inferior; however, inferiority was not demonstrated with use of single dose of rifaximin. The trial findings supported the development of a deployment-related health guideline for the management of acute diarrheal disease. A clinical trial evaluating the effectiveness of rifaximin for prevention for travelers’ diarrhea was underway. Conclusions: The research area has proven its ability to conduct impactful research, including the development of field-expedient diagnostics, the largest DoD multi-site travelers’ diarrhea randomized control trial in peacetime and combat settings, and informed Force Health Protection guidance. The research area continues to provide surveillance data to military commands via an established collaborative network of military treatment facilities, DoD laboratories (both within and outside the continental United States), foreign militaries, and academia. The conduct of clinical and translational research in a deployment setting presents significant challenges, most notably in recruitment/enrollment and compliance with study-related procedures during deployment.

BACKGROUND

United States (U.S.) military combat, humanitarian assistance, and other activities in developing countries expose forward deployed troops to infectious risks that significantly

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The views expressed are those of the authors and do not reflect the official views of the Uniformed Services University of the Health Sciences, and negatively impact operations. The changing nature of regional risk based on climate, emergent/re-emergent pathogens, and shifting of military areas of operation over time highlights the need for ongoing surveillance efforts to

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determine the risk for infectious diseases at discrete locations, impact on mission readiness, and the effectiveness of mitigation strategies to reduce lost duty days. Recent epidemics in the Geographic Combatant Commands (e.g., Ebola outbreak in West Africa in 2014 and ensuing Operation United Assistance,1 and the Zika and Chikungunya epidemics in U.S. Southern Command [SOUTHCOM], U.S. Africa Command [AFRICOM], and U.S. Indo-Pacific Command [INDOPACOM]) highlight the military and public health relevance of long-term surveillance efforts. Although outbreaks of vector-borne diseases among deployed forces (e.g., cutaneous leishmaniasis in Operations Enduring Freedom [Afghanistan] and Iraqi Freedom [Iraq] and malaria during Operations Restore Hope [Somalia] and Enduring Freedom) are infrequent, the occurrence of one significantly impacts military operations.2-4 In contrast to outbreaks, common, self-limited, high-prevalence infections, such as travelers’ diarrhea (TD) also have a considerable impact on operational readiness. In a recent systematic review, the incidence of deployment-related TD in U.S. forces was 30.3 cases per 100 person-months, resulting in substantial short-term morbidity. The median duration of symptoms prior to treatment was two days, with only 30% of deployed personnel seeking treatment and 23% being incapacitated or placed sick-in-quarters.5 It is estimated that one complete duty day is lost per TD episode,6 creating transient critical shortages that impact operational readiness, while increasing health care utilization and adding to deployment-related costs.

The Deployment and Travel-Related Infectious Diseases Research Area of the Infectious Disease Clinical Research Program (IDCRP) focuses on clinical and translational research related to pre-deployment care, exposures and illnesses encountered during travel, and the effectiveness of mitigation strategies. The research area demonstrates several unique features compared with other travel medicine consortia and surveillance efforts at Department of Defense (DoD) overseas research laboratories, which are essential for addressing militarily-relevant infectious disease threats and conducting research in a deployment setting. For example, surveillance networks, such as GeoSentinel and EuroTravNet, rely on provider-based monitoring and are geared towards identifying and responding to sentinel health events.7-8 However, such networks underestimate the incidence of self-limited diseases (e.g., TD and influenza-like illness) that often do not result in a clinic visit, but are militarily-relevant due to the short-term incapacitation of deployed forces and the impact on mission readiness. Similarly, passive surveillance methods that rely on medical record abstraction for syndromic characterization or serologic testing for disease exposure are less able to assess for risk factors during deployment, timing and location of acquisition, etiologic agent, and the severity of illness. The combination of survey data, medical record abstraction and laboratory data used by protocols in the Deployment and Travel-Related Infectious Diseases Research Area provide a robust model for epidemiologic investigations, risk factor analysis, and evaluation of the effectiveness of mitigation strategies. This is also in line with the mission of DoD surveillance networks, such as the Global Emerging Infections Surveillance (GEIS),9 which provide funding support and collaboratively reports study findings to the Force Health Protection officers and Combatant Commands (COCOMs). In addition, observational studies and clinical trials in the research portfolio focus on determining the effectiveness of existing mitigation strategies and the development of new diagnostic, preventive, and therapeutic strategies. Clinical trials in the portfolio have been supported by the Military Infectious Diseases Research Program, which is tasked with developing medical products (e.g., vaccines, therapeutics, and diagnostics) to mitigate infectious disease threats in U.S. service members. Herein, we report on the current accomplishments of the research area, providing an assessment of how these efforts fit within the landscape of research efforts related to deployment infectious disease threats, and discuss future efforts to improve coordination with DoD partners and academia.

The Travel-Related Infectious Disease Risk Assessment, Outcomes, and Prevention Study (TravMil)

This prospective cohort study began in 2010 to evaluate the infectious disease risks and effectiveness of commonly used strategies to prevent and treat travel-related illness among a cohort of DoD active-duty and beneficiaries. To date, the study has enrolled 4,154 subjects (1,764 active-duty personnel on deployment and 2,390 DoD beneficiaries) from eight military treatment facilities (MTFs) both within and outside the continental United States. Study recruitment, enrollment, and follow-up occur in two settings: (i) Deployment setting: at MTFs or outside MTFs at readiness deployment locations where personnel undergo pre-deployment or post-deployment screening, and (ii) Non-deployment setting: non-active-duty DoD beneficiaries seen for pre-travel care at MTF travel clinics. In addition, the study enrolls deployers or travelers evaluated in clinics or hospitalized for a travel-related illness. Active-duty groups enrolled in TravMil include large joint military training exercises such as Cobra Gold (Thailand) and Balikatan (Philippines) in the INDOPACOM Area of Responsibility, as well as deployments (e.g., Special Purpose Marine Air-Ground Task Force deployment to SOUTHCOM and combat support hospital personnel). The regional destinations and disease incidence for 3,757 evaluable subjects (i.e., subjects who completed travel and complied with study procedures) are summarized in Figure 1.

The inclusion of a “non-deployment” arm comprised of traveling DoD beneficiaries and active-duty personnel traveling for reasons other than deployment (e.g., going on vacation or visiting friends and relatives) is important as these
travelers comprise a significant proportion of beneficiaries seen for pre-travel care within the DoD Travel Medicine clinics, and data from this cohort improves the generalizability of findings to the adult travel population. For example, DoD beneficiaries in TravMil tend to be older (median age of 41 vs. 29 years for deployed personnel) with a higher proportion of females (42% vs. 18% for deployed personnel) and a shorter median duration of travel compared to the deployment population (approximately 2 weeks vs. 1 month). A combination of prospectively collected clinical data, surveys (i.e., pre-travel survey, a travel illness diary, a post-travel survey, and an extended follow-up survey at three and six months for long-term sequela), and a large repository of specimens for laboratory testing (e.g., paired pre- and post-travel sera and self-collected stool smears prior to and during travel) are used to evaluate the epidemiology, prevention, and treatment of high-impact, deployment-related infectious disease. Lastly, collaborations with both DoD laboratories and academic institutions with expertise in state-of-the-art infectious disease diagnostic technologies are used to develop specimen collection and testing methods that are conducive to research in the deployment setting. Data collected from the TravMil study is reported back to the local units to support planning for future deployments. Another unique aspect of TravMil is its ability to provide rationale and study design for clinical trials targeting priority concerns, as well as provide infrastructure needed for study execution in a deployment setting. Estimates of TD incidence, time to first unformed stool, and disease severity are used to inform sample size estimates for clinical trials targeting preventive and treatment strategies.

Among 3,272 TravMil subjects who completed a travel illness diary or post-deployment/travel survey, 20% reported TD (Figure 1). Key findings from TravMil studies are summarized in Table 1. In one analysis of adult and pediatric DoD beneficiaries who traveled outside the continental United States for a duration of ≤6.5 months, 24% of 1,120 participants developed TD for an incidence rate of 5.3 cases/100 person-weeks. The highest rate was among travelers to Africa (8.6 cases/100 person-weeks) followed by South, Central, and West Asia (6.1 cases/100 person-weeks). Female gender and travel to Africa for reasons of vacation, visiting friends/relatives, or business were independently associated with risk of TD, while dietary indiscretion (e.g., eating food from street vendors, use of ice in drinks, and consumption of poorly cooked meat) was not a TD risk factor. Patients with moderate or severe diarrheal illness were more likely to have suboptimal self-treatment. Influenza-like illness was the focus of another TravMil study that assessed 2,932 trips. Approximately 11% of the trips were complicated by an influenza-like illness with risk independently associated with female gender, older age, and duration of travel. Vector-borne illness, including Zika virus (ZIKV), Dengue virus (DENV), and Chikungunya virus (CHIKV), are another focal area of TravMil. In one TravMil analysis, cross-reactive binding antibodies from a DENV-naïve, ZIKV-infected subject was compared to a subject with high levels of neutralizing antibodies against both DENV and ZIKV. Serum from the latter subject was found to enhance DENV-2 infection in K562 cells at a higher dilution compared with the DENV-naïve, ZIKV-infected subject, suggesting that enhancement of DENV-2 infection may be prevented by high levels of cross-neutralizing antibodies. Compliance with mosquito preventive measures and mosquito exposure (64% reporting seeing mosquitoes, 53% reporting ≥1 bite) among travelers to regions with risk of vector-borne diseases have also been assessed in TravMil studies with 53% of travelers being compliant for repellent use on skin (16% compliant for repellent use on clothing).

Clinical Trials to Evaluate the Efficacy of Mitigation Strategies for Travelers’ Diarrhea in the Deployment Setting

Conducting a clinical trial in a deployment or travel setting presents a distinct set of challenges, including maintaining subject accrual despite changes in deployment schedules, variable risk of disease acquisition depending on itinerary and exposures during travel, ensuring compliance with study procedures, and obtaining specimens in a field setting. As noted above, the IDCRP infrastructure includes research personnel at MTFs that work closely with military commands, data collection using electronic and paper-based surveys, application of quality checks, and collaborations with a large network of DoD laboratories and academic partners. All these elements are critical for executing a clinical trial in a field setting. In collaboration with the Naval Medical Research Center, DoD overseas laboratories, and the United Kingdom (U.K.) Ministry of Defence, IDCRP investigators completed a Phase III randomized trial evaluating the effectiveness of singledose antibiotic therapy (levofloxacin, azithromycin, and rifaximin) for treatment of TD during deployment (Trial Evaluating Ambulatory Therapy for TD [TriEat TD], ClinicalTrials.gov Identifier: NCT01618591). Clinical cure at 24 hours occurred in 81.4%, 78.3%, and 74.8% of the levofloxacin, azithromycin, and rifaximin arms, respectively. Compared with levofloxacin, azithromycin was not inferior ($p = 0.01$); however, non-inferiority was not demonstrated with rifaximin ($p = 0.07$). At 48 and 72 hours, efficacy among the regimens was equivalent. Following conclusion of the trial, an expert panel workshop was held with the objective of developing a DoD Deployment Health Guideline for management of acute TD and the consensus guidelines have since been published in Military Medicine (Figure 2).

Another IDCRP clinical trial (Prevent TD; Clinicaltrials.gov Identifier NCT02498301), conducted in collaboration with the U.K. military, evaluates the efficacy of rifaximin for TD prevention during deployment. Rifaximin is a non-absorbable, gut-selective antibiotic, that is currently licensed
for TD treatment in the United States. It also shows great potential for TD prophylaxis due to its good safety/tolerability profile and broad-spectrum activity against enteric pathogens. A recent meta-analysis of five randomized-controlled trials conducted by researchers outside the IDCRP demonstrated efficacy for TD prevention (pooled risk ratio:

### Table I. Summary of Findings from TravMil Studies

| Citation | TravMil Focal Area | Key Finding |
|----------|-------------------|-------------|
| Lalani et al., 2015<sup>10</sup> | Travelers’ diarrhea | Underutilization of self-treatment with antibiotics among travelers with moderate or severe travelers’ diarrhea |
| Lalani et al., 2015<sup>23</sup> | Travelers’ diarrhea – PCR based pathogen detection | Pilot study suggesting Whatman FTA Elute cards may be effective at storing genomic material from many diarrheal pathogens |
| Lalani et al., 2018<sup>19</sup> | Travelers’ diarrhea – PCR based pathogen detection | Using the Taqman Array Card (TAC) results on frozen stool as the reference, the overall sensitivity and specificity of TAC on Whatman FTA Elute cards was 72.9% and 98.0% respectively. TAC on FTA cards demonstrated a decrease in sensitivity with increasing frozen stool quantification cycle |
| Lalani et al., 2016<sup>13</sup> | Vector-borne illness | Poor compliance with mosquito protective measures observed among travelers to regions with risk of malaria, dengue, or chikungunya; compliance with skin repellants associated with female gender, seeing mosquitos during travel, and travel during rainy season |
| Lindholm et al., 2017<sup>14</sup> | Vector-borne illness | Increased mosquito exposure associated with active-duty travelers and travelers visiting friends/relatives; both symptomatic and asymptomatic cases of dengue and chikungunya virus identified |
| Wood et al., 2018<sup>11</sup> | Acute respiratory infections | Female gender, older age, and extended duration of travel associated with an increased risk of developing influenza-like illness |
| Valiant et al., 2018<sup>12</sup> | Vector-borne illness | High levels of dengue cross-neutralizing antibodies may potentially prevent enhancement of dengue infection in Zika virus-convalescent individuals |

**FIGURE 1.** Map of TravMil enrollment sites, number of enrollments to date for each Area of Responsibility and incidence of travel related infections. U.S. Northern Command enrollments comprised of subjects traveling from continental United States to Puerto Rico. Footnotes within the table: (a) Incidence calculated using subjects that completed a travel illness diary or post deployment/travel survey (n = 3,272). (b) Travelers’ diarrhea defined as ≥2 loose stools in a 24-hour period or >1 loose stool with associated symptoms to include nausea, vomiting, abdominal pain, fever or blood in stool. Map modified from image licensed under CC BY-SA 4.0. [https://commons.wikimedia.org/wiki/File:GCCMAP.png](https://commons.wikimedia.org/wiki/File:GCCMAP.png)

**TABLE I.** Illness Incidence<sup>a</sup>, Percent Incidence, Incidence Rate (person-months)

| Illness Incidence<sup>a</sup> | Percent Incidence | Incidence Rate (person-months) |
|-----------------------------|-------------------|-------------------------------|
| Travelers’ diarrhea<sup>b</sup> | 20.48% | 0.16 |
| Influenza like illness | 9.34% | 0.07 |
| Undifferentiated febrile illness | 6.16% | 0.05 |
0.478, 95% confidence interval [CI]: 0.375–0.610; p < 0.001). Lower protection rates were observed for travelers visiting Southeast Asia vs. Mexico, likely due to the presence of more invasive pathogens, such as Campylobacter in Southeast Asia. In addition, the daily dose of rifaximin used in the clinical trials ranged between 400–600 mg with differing frequency of administration. The aim of the IDCRP Prevent TD study is to assess the efficacy of 550 mg rifaximin compared with placebo when taken twice daily or once daily to prevent TD in military service members deploying to regions with high risk of TD. The trial focuses on military groups deploying to Southeast Asia, Africa, and Central/South America and evaluates the pathogen-specific epidemiology of TD within each geographic region, including the impact on rifaximin prophylaxis on pathogen distribution. Enrollment (229 U.S. DoD active-duty personnel and 219 British infantry personnel) and follow-up of subjects is complete with planned reporting of results in 2020.

**Development and Validation of Field-Expedient Collection and Testing Platforms for TD Enteropathogen Detection**

The development of field-expedient collection and testing platforms for enteropathogen detection is essential for understanding the regional epidemiology of TD, as well as informing vaccine development and treatment guidelines. The IDCRP, in collaboration with the University of Virginia and DoD partners, developed a customized quantitative polymerase chain reaction (PCR)-based panel (TaqMan Array Card [TAC]) for detection of TD enteropathogens, virulence factors, and antimicrobial resistance genes (Figure 3). The assay
can detect pathogen targets on stool samples or stool smears on Whatman FTA Elute cards (FTA card, GE Healthcare Life Sciences, Marlborough, MA, USA). The specialized filter paper matrix is able to store nucleic acid at room temperature for prolonged periods, thus, facilitating self-collection and transportation in a field setting. The IDCRP Research Laboratory located at Naval Medical Center Portsmouth serves as the principal laboratory for storage and TAC testing of fecal samples and stool smears.

Several IDCRP protocols in the research area have focused on evaluating the performance characteristics of this customized TAC assay on FTA cards. The Stool Card Validation protocol evaluates the performance characteristics of the TAC assay on FTA cards compared to standard microbiologic methods, using 350 diarrheal specimens from the Armed Forces Research Institute of Medical Sciences (Bangkok, Thailand) and Naval Medical Research Unit-6 (Lima, Peru) repositories. The performance characteristics of the TAC assay on smeared FTA cards, using TAC on frozen stool as the reference standard, was also evaluated as part of the TrEAT TD clinical trial. The overall sensitivity and specificity of TAC on FTA cards for enteropathogen detection was 72.9% and 98.0%, respectively, despite storage of FTA cards for a median 2 years at room temperature. Furthermore, TAC on FTA cards demonstrated an increase in sensitivity at higher pathogen loads, measured as the quantification cycle (Cq) value in stool. The results support the use and further development of FTA cards in combination with a quantitative PCR assay for enteropathogen detection in austere environments, where conventional storage and testing of stool samples in not feasible. We are currently testing self-collected stool smears obtained from TD cases vs. asymptomatic controls enrolled in the TravMil study with the TAC assay, to better understand attribution of TD to detected pathogens.

Vector-Borne Febrile Illnesses and Arthropod Exposure

The impact of wartime vector-borne infection epidemics on military operations, along with civilian populations is well recognized. Although advances in vector and disease-control measures (e.g., vaccination, chemoprophylaxis, personal protection, and control measures) have led to a decline in the incidence of infectious diseases during deployment, the emergence or re-emergence of vector-borne diseases such as CHIKV, ZIKV, and the ongoing transmission of DENV demonstrate the need for a comprehensive epidemiological evaluation of arboviral threats, including co-circulation, in the geographic COCOMs. In a TravMil analysis by Lindholm et al., 267 DoD beneficiaries traveling to CHIKV-outbreak regions in the Americas between December 2013 and May 2015 were evaluated for serologic exposure to CHIKV and DENV. Increased mosquito
exposure was associated with active-duty travelers (odds ratio [OR]: 2.6; 95% CI: 1.3–5.4 for seeing mosquitoes) or travelers visiting friends and relatives (OR: 3.5; 95% CI: 1.0–10.0 for high-intensity bite exposure). The composite attack rate for CHIKV and DENV infection was 3.7% of 108 evaluable, immunologically naïve, prospectively assessed travelers. In the absence of effective vaccines and chemoprophylaxis to arboviral infections, ascertaining the proportions of deployers exposed to the infectious bites of specific mosquito vectors in high-risk locations are needed to determine the use and effectiveness of vector control strategies. Given the large repository of paired sera, clinical data, and existing partnerships with DoD research labs, the TravMil study provides an ideal platform for vector surveillance and incidence of arboviral infections using serologic biomarkers.

A recent TravMil substudy funded by Armed Forces Health Surveillance Branch (AFHSB)-GEIS evaluated *Aedes aegypti* and anopheline exposure and arboviral infections among 100 active-duty personnel deployed to SOUTHCOM or AFRICOM, using antibody responses to specific salivary proteins: gSGP6-P1, a salivary protein specific to *Aedes aegypti* and anopheline exposure and Nterm-34kDa, a salivary protein specific to *Aedes aegypti* mosquitoes. Higher baseline (pre-deployment) antibody levels were observed among AFRICOM deployers with a history of prior deployments to high-risk areas. Furthermore, higher baseline antibody levels were associated with blunted antibody responses to exposure during deployment. No seroconversions to ZIKV or CHIKV were noted among deployers. Follow-on studies are planned for validation of these novel biomarkers, with the goal of developing a serologic panel to determine both vector exposure and disease incidence in deployed personnel.

**Provider Knowledge Attitudes Practices and Impact on Outcomes**

Although significant variability in the practice of deployment-related preventive measures has been reported, the relative impact of medical provider-level decision making for deployment and travel medicine interventions (e.g., educational, medications, and vaccines) on relevant clinical outcomes is not fully understood. For example, there are differences in malaria chemoprophylaxis prescribing patterns within the Military Health System (MHS) by practice setting (MTF vs. civilian facility), beneficiary status, and provider specialty. Furthermore, temporal trends in prescribing patterns and military Force Health Protection policies suggest that these guidelines may lead to practice changes, impacting all MHS beneficiaries and not just the active-duty forces for whom they are designed. As a result, the Deployment and Travel-Related Infections Research Area initiated the Deployment and Travel Health: Knowledge, Attitudes, Practice, and Outcomes Study (KAPOS), which is a multi-cohort study that utilizes a mixed methods approach to describe the burden of travel/deployment associated diseases, as well as practice patterns related to their prevention and treatment. Using data extracted from the MHS, the initial phase of this effort focuses on describing the epidemiologic, health, economic, and readiness burden of deployment and travel medicine-related conditions and identifying patient and provider cohorts that are more likely to incur deployment/travel-related illnesses. Follow-on analyses will utilize electronic surveys that assess knowledge, attitudes, and reported practices of providers and travelers/deployers to provide more robust context of MHS data. Ultimately these cohorts will be linked to demonstrate relationships and the relative impact of provider and patient knowledge, attitudes, and practice on post-deployment/travel health outcomes.

**Research Area Strengths and Opportunities**

The diagnosis, treatment, and prevention of the major infectious disease threats associated with deployment and international travel is a high priority for the DoD. Several protocols in the research area portfolio directly address these priorities, and their successful execution is largely predicated on partnerships within DoD agencies (e.g., Naval Medical Research Center, Walter Reed Army Institute of Research, Armed Forces Research Institute of Medical Sciences, and the Naval Medical Research Units), the U.K. military, and academia (e.g., University of Kansas and University of Virginia), along with support from unit and command leadership of deployed forces. An important strength of the research area is the availability of site investigators and coordinators with an expertise in travel medicine research that is needed for accurate collection of data and to minimize loss to follow-up in the deployment and travel setting. Furthermore, protocols within the research area are closely linked with standardized questionnaires allowing for specimens and data to be pooled across studies. For example, the incorporation of the epidemiologic objectives in clinical trials, such as stool card collection for PCR testing and serologic testing for arboviral infections allows for pooling of data from the TravMil and other clinical trials.

There are a number of opportunities that will be incorporated in the strategic vision for the research area over the next few years. Increased engagement with the COMC leadership is needed to focus surveillance efforts in deployments or exercises within each of the areas of responsibility. In addition, the research area will focus on engagement with partner nations in U.S. European Command (e.g., UK) and INDOPACOM (e.g., Australia) that deploy forces or participate in joint military exercises in developing countries, to establish a joint disease surveillance program focused on improving military interoperability. Continued collaboration across other IDCRP research areas, such as the Emerging Infectious Diseases and Antimicrobial Resistance, Acute Respiratory Infections, and Sexually Transmitted Infections, are warranted to address related infections in a deployment setting.
Considerable funding and effort have been allocated to the development of field-expedient collection methods and diagnostics for TD, a critical need for surveillance activities and clinical trials in the deployment setting. Interest in enteric diseases is growing, specifically with regards to understanding and manipulating the gut microbiome to prevent TD during deployment and potential long-term sequelae, which could lead to collaborative efforts with both private industry and DoD partners, and help balance portfolio between epidemiologic objectives, clinical trials, and development of field-expedient diagnostics. Additional studies are required to optimize collection and storage methods and refine interpretative criteria for molecular methods. For example, results from the TrEAT TD trial and the Stool Card Validation study suggest that the sensitivity of smeared FTA cards is higher for bacterial pathogens, such as diarrheagenic Escherichia coli compared to norovirus when stored for prolonged duration at room temperature. Approximately 35% of smeared FTA cards were also positive for more than one pathogen, indicating the need for detailed interpretive criteria to discern the relative importance of each pathogen. Thus, future efforts will focus on optimizing field collection and storage protocols for stool smears, as well as defining quantitative cycle cut-offs for pathogen attribution, specifically for pathogens relevant to vaccine development, such as enterotoxigenic E. coli (ETEC), differentiating true pathogen attributable cases, and/or vaccine preventable outcomes.

Enteroaggregative E. coli (EAEC), Campylobacter spp. and Shigella spp. are also common causes of TD worldwide and relevant to DoD enteric vaccine development. Campylobacter is the focus of a new protocol at Tripler Army Medical Center (Honolulu, HI) which aims to describe the etiology and clinical outcomes related to acute infectious diarrhea among active-duty military personnel and DoD beneficiaries, as well as investigate comparative culture independent microbiological platforms, serodiagnostics, immune responses, and short and long-term outcomes. Lastly, follow-on studies from the TrEAT TD clinical trial are characterizing the humoral immune response in patients with Shigella-, ETEC-, enteropathogenic E. coli- and EAEC-associated diarrhea by protein microarray to identify targets that may be relevant for vaccine development. In addition, efforts are underway to understand how TD and antimicrobial therapy may impact the host microbiome.

Apart from efforts related to epidemiology and vaccine development, the research area will continue to focus on alternative mitigation strategies for TD, in the absence of a licensed vaccine. With regards to vector-borne febrile diseases, efforts will be focused on determining vector exposure and the incidence of vector-borne febrile diseases in operational exercises and deployments to regions that are of interest to the military commands. In addition, collaborative projects with the Kansas State University and the Uniformed Services University of the Health Sciences will focus on validating serologic biomarkers to determine Aedes and anopheline vector exposure, with the goal of using the biomarkers to determine the effectiveness of vector control measures during deployment.

As noted earlier, the KAPOS protocol will provide valuable data regarding the burden of travel/deployment associated diseases, as well the relative impact of provider and patient knowledge, attitudes, and practice on post-deployment/travel health outcomes. An emerging area of study referred to as implementation science is viewed as a critical piece of the strategic plan going forward. Defined as the study of methods to promote the adoption and integration of evidence-based practices into routine health care and public health settings, this research is important in identifying barriers to, and enablers of, effective policymaking for the DoD, and leveraging the knowledge to develop evidence-based innovations in effective delivery approaches.

The IDCRP oversees a diverse portfolio of research protocols geared towards the diagnosis, treatment and prevention of major infectious disease threats during military deployment. The success to date is based on prospectively defined strategic goals coupled with strong collaborative ties across the DoD. Several significant contributions to the military and the travel medicine community include field-expedient diagnostics (i.e., filter paper-based collection method and TD TaqMan Array PCR assay), TD management through development of a DoD-specific Deployment Health Guideline, and epidemiologic data regarding deployment-related infections. The challenges of conducting clinical and translational research in a deployment setting includes the need for sustained funding and engagement of military partners and ensuring adequate rates of enrollment and compliance with study related procedures during deployment. Future efforts will focus on refinement and application of surveillance/diagnostic tools, optimizing Force Health Protection infectious disease surveillance, interventional trials to evaluate the efficacy of mitigation strategies, and improving the integration of evidence-based practices into deployment-related health care.

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