



Current AFHSC-GEIS enteric surveillance efforts

AFHSC-GEIS currently supports enteric surveillance activities at the five overseas DoD research laboratories and at the Naval Environmental and Preventive Medicine Unit Two (NEPMU-2) in Norfolk, Va. The reach of these laboratories extends beyond their respective host countries, as each institution has its own network of regional activities, working with neighboring countries as well as their primary host. Table 1 lists some of the accomplishments of the laboratories participating in the AFHSC-GEIS network, including training host nation personnel, providing reference laboratory capabilities and investigating outbreaks. The following vignettes describe representative efforts within this surveillance network, selected based on their diversity and impact.

Pediatric case-control study—Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand

AFRIMS was established over 40 years ago as a tropical disease research and development institution within

DoD. The Department of Enteric Diseases at AFRIMS has a sustained history of conducting collaborative research, epidemiology, and preclinical and clinical trials on enteric diseases. In addition to supporting enteric

Establishment of a reference laboratory for a regional cholera Network—Naval Medical Research Unit no. three (NAMRU-3), Cairo, Egypt

Over the past decade, NAMRU-3 has served as a core laboratory for enteric disease research and epidemiology in pediatric populations through a series of birth cohorts [10-13] and other surveillance studies and clinical trials conducted among U.S. military populations deployed to Egypt and the surrounding region [6-8,14-24]. This track record in enteric disease surveillance and research, modern laboratory and experienced staff has positioned NAMRU-3 as a hub for enteric surveillance activities in the region. In the past year, AFHSC-GEIS has supported pediatric hospital studies at Cairo University, where 140 participants with severe diarrhea have been enrolled in the last year. NAMRU-3 and AFHSC-GEIS, in collaboration with two Egyptian university medical centers, have also initiated a case-control study looking at modifiable risk factors where a total of 164 cases and controls have been enrolled to date. These projects will provide important data about pathogen distribution, and the epidemiological, clinical, economic and molecular characteristics of diarrhea in Egypt. They will also provide the opportunity to explore novel pathogen discovery.

NAMRU-3 has established a *Vibrio cholerae* microbiology and molecular biology reference center for Africa and the Middle East and serves as a reference laboratory for rotavirus characterization in partnership with the World Health Organization (WHO) in an effort to understand and identify the emergence of novel viral strains under vaccine pressure in the region. Both projects have established links with researchers and governmental organizations in countries affected by cholera and rotavirus, and worked to characterize the isolates while providing training opportunities for the host country's public health community. To date, this initiative has established 16 active sites, trained over 53 people, and collected and tested 1,257 specimens. The establishment of this reference center activity is an example of how regional laboratories can serve an important global health surveillance function and build capacity and capability in developing countries.

Enteric disease surveillance among Peruvian Military Recruits—Naval Medical Research Center Detachment (NMRCDD), Lima, Peru

NMRCDD was established in 1983 as a joint enterprise of the U.S. Navy and the Peruvian Navy with a mission to conduct research on infectious diseases of military and public health importance in Peru and Latin America. AFHSC/GEIS supports enteric disease research at NMRCDD through funding of prospective military cohorts, antimicrobial resistance surveillance in enteric

pathogens and a passive surveillance network for febrile diseases including diarrhea.

In collaboration with the Peruvian Army, NMRCDD has conducted a prospective cohort of diarrheal disease incidence and prevalence among Peruvian soldiers in the Peruvian Amazon. To date, over 1,000 soldiers have been enrolled in the study.

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Related enteric projects include the genetic characterization of antimicrobial resistance mechanisms in enteric pathogens from Peruvian children with diarrhea, in collaboration with colleagues at the Universidad Peruana Cayetano Heredia and the Instituto de Investigación Nutricional (both in Lima). Specific activities include the detection of efflux pumps and other fluoroquinolone resistance mechanisms in DEC, and the identification of extended-spectrum beta-lactamases in DEC.

Advanced characterization of enteric pathogens in Indonesian children—Naval Medical Research Unit no. two (NAMRU-2), Jakarta, Indonesia

NAMRU-2 conducts disease surveillance, research, outbreak response, capacity building and training throughout Southeast Asia, including in Cambodia, Indonesia and the Lao People's Democratic Republic. NAMRU-2 contributed to the identification of the first case of rotavirus strain G12 in Indonesia, an important finding for emerging pathogen surveillance [26]. The combination of the P [6] genotype in this rotavirus strain leads to the potential of zoonotic transmission and is important for vaccine development and identification of novel and emerging rotavirus strains. In addition, capitalizing on over 12,000 specimens collected from an Indonesian pediatric diarrhea surveillance effort, NAMRU-2 investigators evaluated the molecular epidemiology and antimicrobial resistance patterns of a number of important bacterial pathogens in this region, better informing empiric treatment strategies for travelers to these regions. One of the most common bacterial genera, *Campylobacter*, was identified in over 300 cases of children presenting with diarrhea. Antimicrobial susceptibility testing to *C. jejuni* identified increasing levels of resistance to ciprofloxacin between 2005 and 2008

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interest in acute enteric diseases, with several well-organized surveillance activities being established among widespread populations in the developing world (Table 2). These activities include disease-focused networks, such as the WHO-supported regional Rotavirus Surveillance Networks (RSN) [36-38] and the recently established CHOLDInet for cholera and other causes of diarrheal diseases [39]. Under the CDC Global Disease Detection Program, several International Emerging Infections Program (IEIP) sites have been established throughout Africa, Asia and Central America. These programs conduct population-based surveillance to track diseases of global public health importance, including diarrhea.

Two additional research efforts—the Global Enteric Multi-Center Surveillance (GEMS) study and the Network for the Study of Malnutrition and Enteric Diseases (MAL-ED)—are designed to provide data needed to guide the development and implementation of enteric vaccines and other public health interventions to reduce the morbidity and mortality of diarrheal diseases, as well as to study the relationships between malnutrition and enteric infections.

Beyond the focus on specific diseases and pediatric populations of the developing world, other surveillance activities focus on acute enteric infections within the United States. These include the Foodborne Diseases Active Surveillance Network (FoodNet) [40] and the National Antimicrobial Resistance Monitoring System (NARMS). The GeoSentinel Network (GSN), established in 1995 by the International Society of Travel Medicine (ISTM) and the CDC, is a worldwide communication and data collection network for the study of travel-related morbidity conducted through participating travel clinics worldwide [41]. The DoD Military Infectious Diseases Research Program (MIDRP) has a primary mission of developing vaccine countermeasures to prevent the major infections, including bacterial diarrhea, encountered during deployment. Within this sustained research and development program, surveillance and epidemiological research are long-standing components; MIDRP's support to the overseas laboratories helps assess the pathogen-specific burden of disease and the establishment of field sites for interventional studies in military and host-national pediatric populations. A number of these efforts are designed for sustainment of activity (RSN, IEIP, MIDRP, FoodNet, NARMS, GSN) while some have only been recently established (CHOLDInet, MAL-ED), and others are likely time-limited (GEMS, MAL-ED). It is within this context that the AFHSC-GEIS mission to strengthen the surveillance and response capabilities of the United States to infectious diseases that threaten to global public health and military readiness should be considered.

Strengths, weaknesses, opportunities and threats

The strengths of the current AFHSC-GEIS system include its extensive laboratory infrastructure and technically proficient personnel (Figure 1). Furthermore, the current surveillance activities are leveraged not only by other AFHSC-GEIS initiatives but also by other DoD programs (e.g., MIDRP) with related missions such as field epidemiology and diagnostic test evaluation.

Alongside these strengths, there are also important weaknesses. Whereas some laboratories have principal investigators with special expertise in enteric disease epidemiology, this is not universal across the entire AFHSC-GEIS network. An overall lack of strategic guidance within the enteric diseases program was found in a program review nearly a decade ago [42]. The overseas laboratories are quite diverse and have had consi(d)-9(r-b4(e8-12(i)ste

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Although the attributable fraction of IBS caused by domestic foodborne illness is unknown, it is likely large

high-risk areas overseas [9,54,55]. To meet the needs and mission of the DoD and the global public health community, many of the traditional beliefs about the preferred types of surveillance activities may need re-evaluation. For example, the value of year-to-year tracking of antimicrobial drug resistance among enteric pathogens needs to be assessed. While it is true that resistance to enteropathogens may complicate the therapy of diarrhea, most of these infections currently go untreated and generally are self-limited in nature [56]. A surveillance strategy is needed that considers the scope, frequency of assessment, target populations and regions of interest.

While surveillance among U.S. military and adult traveler populations may be considered ideally aligned with the AFHSC-GEIS mission, there are challenges in consistent availability of these populations. Often it is attractive to perform regional surveillance among local populations as a surrogate for understanding disease burden and risks; however, the data collected from these efforts, specifically related to enteric diseases, are not able to be generalized to deployed U.S. military or adult traveler populations in the region. Secondary benefits in conducting studies among local populations include capacity building and improved host nation relations. While children in developing countries may serve as good surrogates in terms of immune naïveté, there may be important differences in pathogen exposure, environment, host-response and risk behavior that may impact the direct generalization of risk to U.S. military populations. For example, among studies conducted by NAMRU-3 in deployed military personnel participating in Operation Bright Star exercises in Egypt, the common

outbreak response throughout the world in both military and non-military populations; and the intangible benefits through medical diplomacy. The challenges in executing networked studies with operational significance in U.S. military populations include initiating multi-center sur-

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