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The Armed Forces Health Surveillance Center: enhancing the Military Health System's public health capabilities

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Abstract

Since its establishment in February 2008, the Armed Forces Health Surveillance Center (AFHSC) has embarked on a number of initiatives and projects in collaboration with a variety of agencies in the Department of Defense (DoD), other organizations within the federal government, and non-governmental partners. In 2009, the outbreak of pandemic H1N1 influenza attracted the major focus of the center, although notable advances were accomplished in other areas of interest, such as deployment health, mental health and traumatic brain injury surveillance.

Introduction

The center was established by the Deputy Secretary of Defense in February 2008 [1]. The center's mission is to promote, maintain and enhance the health of United States (U.S.) military and military-associated populations by providing relevant, timely, actionable and comprehensive health surveillance information. The center is intended to become the central epidemiological resource for DoD. To achieve that aim, AFHSC combined the resources of the Army Medical Surveillance Activity (AMSA), the DoD Global Emerging Infectious Disease Surveillance and Response System (DoD-GEIS), and the Global Health Surveillance Activity supporting the Force Health Protection Directorate in the Office of the Assistant Secretary of Defense for Health Affairs.

This paper outlines the diverse and unique capabilities of the center. As AFHSC matures, evolves and grows, the capabilities and support provided by its legacy agencies are expanding to meet DoD's needs. The center plays a key role in the collective understanding of infectious disease threats throughout the world, and the impact of these threats on U.S. uniformed and military-associated populations. Today, more than ever, DoD has a more complete picture of the health of American men and women in uniform.

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Background

The center traces its founding to two major policy developments in the 1990s. In the wake of the Persian Gulf War in 1990-91, DoD lacked the ability to address health-related issues in any comprehensive or cohesive manner. Among other initiatives, DoD designated AMSA at the U.S. Army Center for Health Promotion and Preventive Medicine as the department's Center for Deployment Health Surveillance [2]. AMSA operated and maintained a longitudinal relational database that tracked soldiers' health-related events throughout their military careers. The effort later evolved into the Defense Medical Surveillance System (DMSS) [3] as an Army Medical Department DoD Executive Agency.

The Defense Department established requirements for documentation of the health status of servicemembers immediately before and following deployment on major operations [4-10]. DMSS was designated as the repository for this information. The Defense Medical Epidemiological Database, a subset of DMSS, is intended for remote user analysis. The database allows authorized users to access de-identified aggregate data on ambulatory visits, hospitalizations and reportable events of active-duty military personnel spanning the previous 10 years. Meanwhile, the DoD Serum Repository contains more than 56 million serum specimens drawn from individuals serving on active duty since the late 1980s [3]. The specimens, maintained at -25 degrees Celsius, are linked with individual DMSS data, as well as augmented by epidemiological studies of military and

operational relevance. The information is especially useful for developing precise estimates of prevalence and incidence of infectious diseases in the armed forces.

Another major theme in the years preceding establishment of AFHSC was the recognition of the global health threat posed by emerging and re-emerging infectious diseases [11] and the important role DoD, through its network of clinical, reference and research laboratories in the U.S. and elsewhere, should play in the national effort [12]. To address these needs, DoD-GEIS was established in 1996, with a central hub at the Walter Reed Army Institute of Research. As in the case of AMSA, DoD-GEIS operated as an Army Medical Department DoD Executive Agency.

In 2009, AFHSC and its partner organizations were presented many opportunities to build on this proud legacy and make important health surveillance contributions, many of which are described below in relation to the singular public health event of the year, the influenza H1N1 pandemic.

Response coordination

Upon recognition of the novel influenza virus H1N1 in April 2009, AFHSC mobilized the military public health community by convening a series of teleconferences linking community of interest, surveillance and public health professionals at armed forces public health centers, Centers for Disease Control, Combatant Commands and staffs of the Service Surgeons General to share information and resources and to standardize the collective approach to surveillance, case reporting and disease control. The center provided a consolidated DoD pandemic H1N1 report on a weekly basis for the remainder of 2009, as the epidemic spread through military population worldwide. Additionally, AFHSC staff augmented those of the Naval Environmental and Preventive Medicine Unit 5 in evaluating an outbreak of pandemic H1N1 aboard the USS Boxer in July 2009.

Reporting of public health emergencies of international concern

As the Defense Department's lead public health agency, AFHSC is positioned to play a key role in coordinating the reporting of DoD public health emergencies of international concern (PHEIC), in accordance with International Health Regulations as updated in 2005. In general, DoD is responsible for identifying PHEICs in its population, including events occurring in military communities abroad, and reporting these through appropriate U.S. government channels to the World Health Organization (WHO).

The onset of the influenza pandemic forced the early exercise of this role, and facilitated its clarification as the year continued. DoD Instruction 6200.03 (Subject: "Public Health Emergency Management within the Department of Defense," March 5, 2010), formalizing this role, had not yet been completed, and the experience of the center through the initial months of the pandemic helped define and resolve some policy issues regarding roles, responsibilities and communication links.

Development and promulgation of military public health surveillance standards

Public health information becomes more meaningful when data can be compared across multiple agencies over time. Counts, rates and conclusions drawn from the information are rendered more valuable when agencies share common definitions for key terms and adopt standard procedures for calculating important indicators using these definitions.

The center has been charged with leading the U.S. military public health community in the adoption and promulgation of numerous important health surveillance standards. For several years, military medical departments have used a common set of definitions for reportable medical events requiring individual case reports to service public health centers and AFHSC. As a result, this list includes approximately 70 conditions of military public health interest, including infectious diseases, such as malaria and leishmaniasis, as well as noninfectious conditions, such as heat and cold injury and lead exposure. The center coordinated the most recent update of this list, adopted in June 2009 [13], culminating the efforts of a multiservice work group during the previous year. In a similar manner, AFHSC worked in close coordination with staff of the DoD Centers of Excellence for Psychological Health and Traumatic Brain Injury (especially the Defense and Veterans Brain Injury Center), to develop surveillance case definitions for traumatic brain injury.

As the influenza pandemic of 2009 progressed, the surveillance requirements appropriately changed from an initial approach that emphasized individual case finding, laboratory confirmation and documentation of spread to previously unaffected areas, to one that focused on vulnerable populations and clinical severity measures. The center, working with partners in the Services and elsewhere, coordinated DoD's effort to ensure that the pandemic was tracked in a standard, appropriate and timely manner, while yielding vital statistics required by senior leaders.

Seminars, exercises and symposia

Epidemiology is AFHSC's core competency, since another of its mission areas is training and continuing education in epidemiology and public health. The center was especially active during 2009 with symposia on

sexually transmitted diseases, H1N1 lessons learned, civil-military cooperation in public health and pandemic influenza tabletop exercises [14]. The tabletop exercises, held in conjunction with the annual Force Health Protection Conference, were targeted to train public health emergency officers and afforded the military medical community with an opportunity to receive continuing medical education credits.

Throughout 2009, AFHSC sponsored rotations for residents in preventive medicine graduate medical education programs at the Walter Reed Army Institute of Research and the General Preventive Medicine residency program at the Uniformed Services University of the Health Sciences. Approximately half of the resident projects resulted in a report published either in the Medical Surveillance Monthly Report or refereed medical literature.

Epidemiological analysis and reporting

The center provides timely information to a wide spectrum of stakeholders. Its epidemiologists use data in the DMSS—augmented by the Theater Medical Data Store (health outcomes among personnel deployed in southwest Asia), and other datasets as needed—to produce numerous routine and ad-hoc analyses and reports. Routine periodic reports include the DoD Installation Injury Report, featuring specific rates of injuries among the assigned military population on installations (military bases). and DoD Lost Duty Time Application, which similarly includes counts and rates of health events and the resulting cost of these events in terms of lost workdays. Both reports are maintained on the center's website at http://www.afhsc.mil.

Targeted reports provide statistical support for DoD health quality, deployment health and other important Military Health System metrics. The center also provides analysis products upon request to meet a variety of operational and technical requirements. Finally, AFHSC supports limited research efforts, mission permitting.

A number of reports were developed to support the influenza pandemic, including periodic and ongoing surveillance for adverse events potentially associated with immunization against seasonal or pandemic strains. The Medical Surveillance Monthly Report (MSMR) (http://www.afhsc.mil/msmr), published by AMSA from April 1995 to March 2007, is the center's most widely read and well-known publication. Its original purpose, as described by AMSA in 1995, is the dissemination of medical surveillance information of broad interest. As stated at the inception of the MSMR, "The ultimate goal ... is to provide readily available information necessary to inform, motivate, and empower commanders, their surgeons, and medical staffs to design, implement, and resource programs that enhance health, fitness, and readiness." [15] That purpose remains relevant today.

Fifteen years and more than 100 issues later, the monthly publication, now published by AFHSC, has emerged as DoD's public health periodical of record, providing current information and analysis on a wide variety of operational health topics, including trends of communicable and vector-borne diseases, traumatic brain injury, mental and behavioral health issues, and chronic diseases that affect the active-duty military population.

The future

The center provides DoD with a unique centralized epidemiologic capability to assemble and analyze disease patterns among U.S. military personnel and beneficiaries worldwide. Integral to AFHSC's role is the ongoing monitoring of the prevalence, incidence and trends of infectious diseases in time, person and place. As a result of these efforts, estimates of operational impact and disease burden can be determined and recommendations can be provided to key decision makers within DoD for implementation of control measures in support of force health protection.

The release of the President's Policy Directive addressing the Strategy for Countering Biological Threats [16] in November 2009 marked the recognition that strong capabilities in emerging infectious disease surveillance and response provide substantial security value to the nation and the world. With key contacts throughout the world, AFHSC is well positioned to significantly contribute to this greater U.S. government initiative. To further support this initiative, AFHSC will pursue new partnerships to ensure that DoD continues to possess the capability to anticipate, detect and respond to a broad array of threats that could threaten the health of the military and military-associated populations, as well as civilian populations around the world.

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Competing interests

The author declares that he has no competing interests.

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The Global Emerging Infection Surveillance and Response System (GEIS), a U.S. government tool for improved global biosurveillance: a review of 2009

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Abstract

The Armed Forces Health Surveillance Center, Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) has the mission of performing surveillance for emerging infectious diseases that could affect the United States (U.S.) military. This mission is accomplished by orchestrating a global portfolio of surveillance projects, capacity-building efforts, outbreak investigations and training exercises. In 2009, this portfolio involved 39 funded partners, impacting 92 countries. This article discusses the current biosurveillance landscape, programmatic details of organization and implementation, and key contributions to force health protection and global public health in 2009.

Introduction and background

Despite optimism in the 1960s that mankind had conquered infectious diseases, the world has repeatedly confronted the reality of its continued vulnerability. Two landmark Institute of Medicine (IOM) reports outlined these vulnerabilities [1,2]. Recent events emphasize the wisdom of these documents, and the fact that the global community must unite to address emerging infectious diseases.

The first of two IOM reports, released in 1992, highlighted the potential role of Department of Defense (DoD) overseas laboratories in addressing the vulnerabilities of emerging infections. DoD has a long history of medical research and development, much of which has been performed through a network of overseas laboratories. Although their geographic locations have changed through time, five laboratories were in operation in 2009: Cairo, Egypt; Nairobi, Kenya; Bangkok, Thailand; Lima, Peru; and Jakarta, Indonesia in 2009 (Figure 1) [3]. Historically, the role of these laboratories was limited almost exclusively to the research and development of products, such as vaccines, antimicrobials or diagnostics, that would benefit the health of DoD forces throughout the world. Surveillance for infectious diseases, however, was minimal. Between 1992 and 1996, numerous documents and communications within DoD recognized the need for global emerging infection surveillance initiatives leveraging these overseas laboratories, and emphasized the commitment of DoD to these endeavors.

In 1996, the Executive Office of the President of the United States issued a Presidential Decision Directive (NSTC-7) stating that current capabilities were inadequate to protect the U.S. or global public health communities from emerging infectious disease (EID) threats [4]. DoD was again specifically noted among various federal agencies as having global presence and expertise that could be leveraged to help improve worldwide EID surveillance and preparedness. With these events, the DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS) was established, thereby expanding the mission of DoD to address threats posed to the U.S. and other nations by newly emerging and re-emerging infectious diseases. This was a timely development: The next decade brought SARS, West Nile virus and avian influenza, to name a few, and more recently, the H1N1 influenza virus emerged in 2009 as a pandemic threat.

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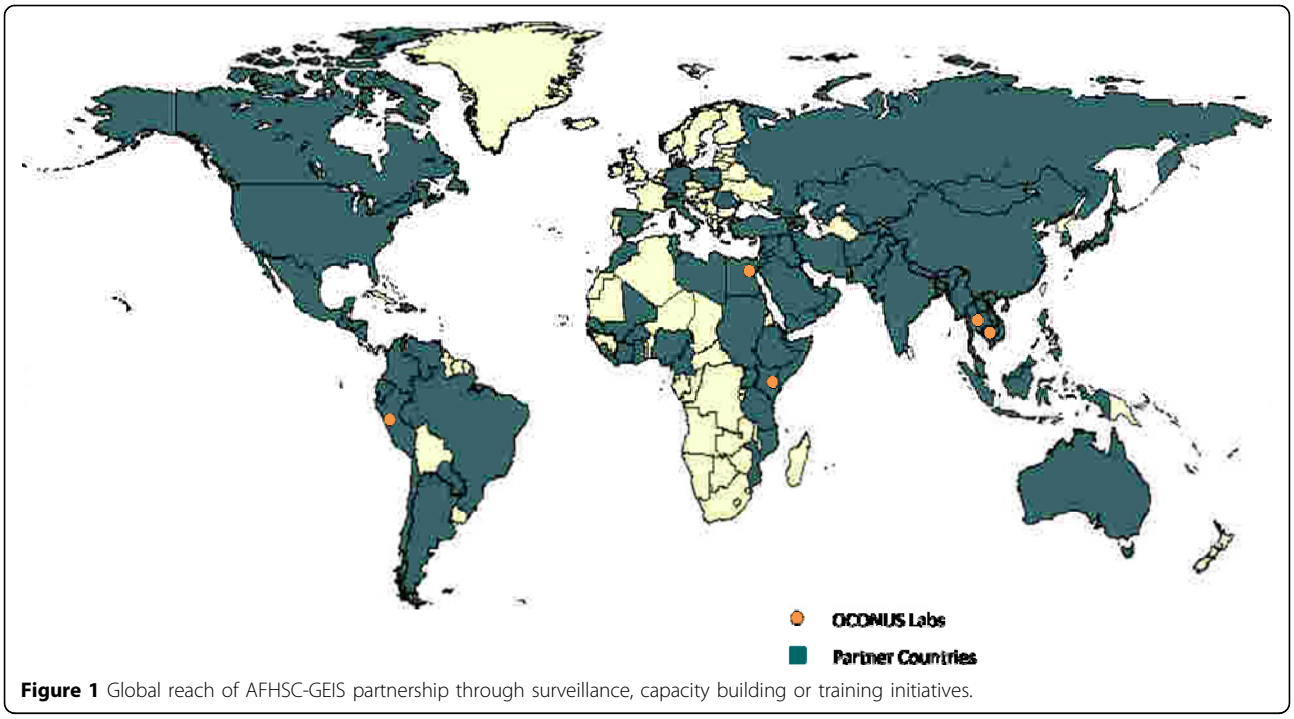

Figure 1 Global reach of AFHSC-GEIS partnership through surveillance, capacity building or training initiatives.

In 2008, DoD-GEIS became a Division of the Armed Forces Health Surveillance Center (AFHSC) by direction of the deputy secretary of defense [5]. This move centralized DoD-wide healthcare surveillance initiatives with domestic and overseas laboratory surveillance efforts. In 2009, AFHSC-GEIS provided direction, funding and oversight to a network of 39 partners (Table 1) at approximately 500 sites. Ninety-two countries were impacted with either active surveillance, capacity-building initiatives or participation in training exercises (Figure 1). This paper will summarize implementation of this global DoD laboratory surveillance network and its contributions in 2009, and discuss potential for the future as the U.S. government becomes increasingly proactive in global biosurveillance.

The current global biosurveillance landscape

In addition to AFHSC-GEIS, many other DoD, U.S. government and U.S. nongovernmental organizations engage in surveillance or capacity-building activities throughout the world [6,7]. In 2009, the U.S. Agency for International Development (USAID) spent more than $1.7 billion on health and over $1.4 billion on humanitarian assistance [8]. Fiscal year 2009 appropriations by the U.S. Congress totaled $33.7 million for the Centers for Disease Control and Prevention's (CDC) Global Disease Detection Program, the principal and most visible CDC program for developing and strengthening global public health capacity to rapidly identify and contain disease threats from around the world. The total budget for CDC's global health programs in fiscal year 2009—including the Global AIDS Program, Global Immunization Program, Global Malaria Program and others—was $308.8 million [9]. The U.S. Department of State's Biological Engagement Program (BEP) received congressional appropriations of $27 million in fiscal year 2009 to engage scientists internationally on issues related to disease surveillance and detection, biosafety and biosecurity. The U.S. Department of Agriculture (USDA) addresses animal health surveillance in the U.S., but is also engaged internationally in capacity building, research and biological control, and outbreak response, with a focus on identifying and evaluating biological agents that could impact global commerce of agricultural products [10]. USDA is also the official U.S. representative to the World Organisation for Animal Health (OIE).

Through Defense Health Program funding, the assistant secretary of defense for health affairs provides $52 million annually to AFHSC-GEIS. The assistant to the secretary of defense for nuclear and chemical and biological defense programs recently embraced emerging infections as a threat to national security, placing global surveillance also within the scope of that organization [11]. Implemented largely through the Defense Threat Reduction Agency, historically that organization's focus has been *threat-agent* reduction and containment in the former Soviet Union. Authorization to extend globally and beyond threat agents is in process and will be conducted in part through the agency's Cooperative Biological Engagement Program. This is likely to result in an additional infusion of

Table 1 Global partners 2009 and region of engagement

	FY09 Funded Partners	Primary Countries Engaged
1	**65th Medical Brigade – Korea**	Republic of South Korea
2	**Armed Forces Institute of Pathology – Washington, DC**	Global U.S. DoD visibility
3	**Armed Forces Research Institute of Medical Sciences – Bangkok, Thailand**	Thailand, Cambodia, Lao PDR, Philippines, Nepal & Bhutan and US Embassies and Consulate offices throughout Southeast Asia
4	**Australian Army Malaria Institute – Enoggera, Australia**	Australia, Vanuatu & Solomon Islands
5	**Center for Disaster and Humanitarian Assistance Medicine – Bethesda, MD**	Numerous with global distribution
6	**DoD Veterinary Food Analysis & Diagnostic Laboratory – Fort Sam Houston, TX**	Overseas food & water production facilities with DoD procurement contracts and US military installations supporting Military Working Dogs and food facilities
7	**University of Iowa – Iowa City, IA**	Thailand, Cambodia, Mongolia, Nigeria & Romania
8	**Johns Hopkins University Applied Physics Laboratory – Laurel, MD**	US military installations; Philippines, Peru & Cambodia
9	**Landstuhl Regional Medical Center – Germany**	US military treatment facilities in Southwest Asia, Germany, Italy, Belgium, Spain, United Kingdom, Turkey, Poland & Ukraine
10	**National Aeronautics and Space Administration – Greenbelt, MD**	Numerous with distribution primarily in Africa, Southeastern Europe and Central Asia
11	**Naval Health Research Center – San Diego, CA**	US military training facilities; 2nd, 3rd and 7th US Naval Fleets and deployed US Naval & Marine Corps personnel in Western Pacific region; US/Mexico border clinics with US CDC
12	**Navy and Marine Corps Public Health Center – Portsmouth, VA**	US military treatment facilities within the military health system (MHS)
13	**Navy Environmental Preventive Medicine Unit – 2 – Norfolk, VA**	US military treatment facilities in Djibouti, Kuwait, Qatar, Bahrain, Iraq & Afghanistan; deployed US Naval & Marine Corps personnel in Southwest Asia & shipboard activities in the Atlantic
14	**Navy Medical Research Center – Silver Spring, MD**	Numerous with global distribution
15	**Navy Medical Research Center Detachment – Lima, Peru**	Eleven countries in Central & South America
16	**Navy Medical Research Unit – 3 – Cairo, Egypt**	Thirty-four countries in West/North Africa, the Middle East & Central Asia and deployed US Forces throughout Southwest Asia and Eastern Europe
17	**Navy Medical Research Unit-2 – Jakarta, Indonesia**	Cambodia, Lao PDR, Indonesia & Singapore
18	**Pacific Air Force – Hickman AFB, HI**	Lao PDR & Vietnam
19	**Public Health Command Region - Europe (formerly CHPPM-Eur) – Landstuhl, Germany**	US military treatment facilities in Southwest Asia, Germany, Italy, Belgium, Spain, United Kingdom, Turkey, Poland & Ukraine
20	**Public Health Command Region - Pacific (formerly CHPPM-Pac) – Camp Zama, Japan**	US military treatment facilities & deployed US Forces in Japan & South Korea
21	**Public Health Command Region - South (formerly CHPPM-South) – Fort Sam Houston, TX**	US military treatment facilities; civilian MoH laboratory centers in Guatemala, El Salvador, Honduras, Nicaragua & Panama
22	**San Antonio Military Medical Center (formerly BAMC) – San Antonio, TX**	US military treatment facilities in Southwestern US
23	**U.S. Army Medical Research Institute of Infectious Disease – Fort Detrick, MD**	US military treatment facilities & overseas VHF laboratory in Sierra Leone
24	**U.S. Army Medical Research Unit – Kenya – Nairobi, Kenya**	Kenya, Tanzania, Uganda, Cameroon & Nigeria
25	**U.S. Northern Command – Colorado Springs, CO**	US military installations & coordination with Mexico and Canadian counterparts
26	**U.S. Southern Command – Miami, FL**	Deployed US Forces throughout Latin America
27	**UCLA/Global Viral Forecasting Initiative – San Francisco, CA**	Cameroon
28	**Uniformed Services University of the Health Sciences – Bethesda, MD**	US military treatment facilities & overseas military research laboratories in Peru, Egypt, Kenya, Thailand, Indonesia & Korea
29	**United States Africa Command – Stuttgart, Germany**	Deployed US Forces throughout Africa
30	**United States Air Force School of Aerospace Medicine – Wright Patterson AFB, Ohio**	US Military MTF sentinel sites around the world
31	**United States Central Command – MacDill AFB, FL**	Deployed US Forces throughout Southwest and Central Asia
32	**United States European Command –Stuttgart, Germany**	Deployed US Forces throughout Europe & Central Asia
33	**United States Pacific Command – Camp H.M. Smith, HI**	Deployed US Forces throughout Far East, Southeast Asia & the Pacific

Table 1 Global partners 2009 and region of engagement *(Continued)*

34	**Walter Reed Army Institute of Research, Division of Bacterial Diseases – Silver Spring, MD**	US military treatment facilities & overseas military research laboratories in Peru, Egypt, Kenya, Thailand & Indonesia
35	**Walter Reed Army Institute of Research, Division of Clinical Trials – Silver Spring, MD**	Support to global system
36	**Walter Reed Army Institute of Research, Division of Entomology – Silver Spring, MD**	Numerous with global distribution
37	**Walter Reed Army Institute of Research, Division of Experimental Therapeutics – Silver Spring, MD**	Support to global system
38	**Walter Reed Army Institute of Research, Division of Virus Diseases – Silver Spring, MD**	Over 35 US embassies & deployed military personnel worldwide; overseas military research laboratories in Peru & Thailand
39	**Walter Reed Army Medical Center - Washington, DC**	Support to military personnel deployed to Iraq & Afghanistan

resources into DoD's global surveillance efforts. Although not directly involved in surveillance efforts, the Military Infectious Disease Research Program (MIDRP) has a mission of protecting the U.S. military against infectious diseases through research and development projects designed to develop products for mitigation, such as vaccines, medications or vector-control systems. Excluding pediatric vaccines, DoD had a major role in developing and licensing 40 percent of currently available vaccines for adults in the U.S. [12]. Most drugs licensed for the treatment of malaria were also products of DoD research and development [13,14]. AFHSC-GEIS surveillance provides baseline infectious disease risk data that directly influences priorities and viable geographic locations for the conduct of various projects within the MIDRP.

Much of the justification for engagement by the U.S. government in this work falls under the category of "health diplomacy." The meaning of "global health diplomacy" can be controversial, but a commonly accepted definition by the University of California at San Francisco is "political change activity that meets the dual goals of improving global health and maintaining and improving international relations abroad, particularly in conflict areas and resource-poor environments."

The involvement of DoD partners throughout the world in implementing this program can clearly be seen as serving a global health diplomacy role. By conducting surveillance and capacity building and assisting with training and outbreak investigations, all integrated into the functions and capabilities of host-country agencies, relationships are forged and trust is developed. International relations abroad are improved. Other DoD organizations work in this broad field of health diplomacy, but less directly in active biosurveillance.

Funding avenues and oversight for these different U.S. government health and surveillance initiatives are independent of each other, and coordination is complex. In a recent publication, the Center for Strategic and International Studies commented that with expanding efforts, agencies should leverage the existing successful programs, and seek a "unity of effort." [15]. The release in November 2009 of the National Strategy for Countering Biological Threats (Presidential Policy Directive-2) also emphasizes the need for coordination: "No single stakeholder can fully address the challenge of biological threats on its own" [16]. This document uses similar terminology as many of the mid-1990s documents that resulted in the development of DoD-GEIS.

Why the Department of Defense?

The global laboratory assets of DoD have long been recognized as valuable platforms from which to conduct biosurveillance. Each laboratory is "sponsored" in-country by either the Ministry of Defense or Ministry of Health. In addition, close working relationships exist with other components of the host and neighboring countries' governments and academic institutions. Leveraging and empowering these relationships is a formula for success with expanded activities. Maintaining personnel at these military laboratories has also proven sustainable over time, when other U.S. government programs found this to be difficult. DoD's unique ability to provide valuable logistical support is a factor, as is its global integrated health care system meeting the health needs of uniformed families throughout the world that can help determine exposures and risk. The synergy between this system and the DoD laboratory system is becoming clear now that both organizations exist at AFHSC.

Another reason for DoD engagement in these endeavors lies in DoD's mission to "deter war and protect the security of our country" [17]. Combat aggressors are but one threat to our security. In the words of James Baldwin, novelist and civil rights activist, "The most dangerous creation of any society is the man who has nothing to lose." Endemic diseases in many resource-poor settings are a cause of instability. Each year, more than 1.6 million people die from diarrheal disease, 800,000 from malaria and 20,000 from dengue fever [18-20]. This burden of known endemic diseases imposes an economic toll and resulting instability. In contrast, emerging infections, whether naturally occurring or the result of human introductions, can result in social unrest and instability on a

scale quite out of proportion to the level of risk they introduce [21]. Though new agents have the potential for high morbidity and mortality, fear can have an even greater impact.

One example is the severe acute respiratory syndrome (SARS) that rapidly spread around the world in 2003. By midyear, 8,098 individuals were known to have been infected with SARS, resulting in 774 deaths. In the scope of international infectious diseases, this toll on human life was minor. However, the economic impact is estimated at between $40 billion and $52 billion [22]. Likewise, 17 infections and five deaths were attributed to the intentional anthrax attacks in 2001. These small numbers do not adequately speak to the crippling disruption of services or huge economic losses incurred. According to a recent IOM report, "Global health and national security are inexorably intertwined" [23].

Considering these facts, the enormous importance of early identification and mitigation of infectious disease threats is a critical component of a national defense strategy to "deter war and protect the security of our country."

Implementation of the AFHSC/GEIS program: methods

The GEIS system functions on a model of "priority pillars" and "strategic steps" (Figure 2). The priority infectious disease pillars include respiratory, gastrointestinal, febrile and vector-borne, antimicrobial-resistant, and sexually transmitted infections. The strategic steps include surveillance and response; training and capacity building; research, innovation and capacity building; and communication of value added. Through integrated implementation of the strategic steps, a comprehensive yet flexible program is created which recognizes the needs of host and partner countries.

Funding for global surveillance initiatives in 2009 was approximately $52 million; $40 million of this was for pandemic/avian influenza initiatives (respiratory pillar), with the remainder available for surveillance in the other EID pillars. In preparation for distribution of these funds, a request for proposals was circulated among partner laboratories in the third quarter of fiscal 2008. A total of 198 proposals were received and evaluated by an internal review board of AFHSC staff. Each proposal was evaluated based on a) potential to fill a critical gap in public health programs, b) likelihood of tri-service or DoD-wide benefits, c) facilitation of timely public health actions, d) responsiveness to critical operational theater or regional needs, e) quality of epidemiology and science, f) leveraging of existing strengths, and g) accessibility of nonfiscal resources needed for execution. In addition, prior performance of the requesting organization and principal investigator was taken into consideration. Proposals were

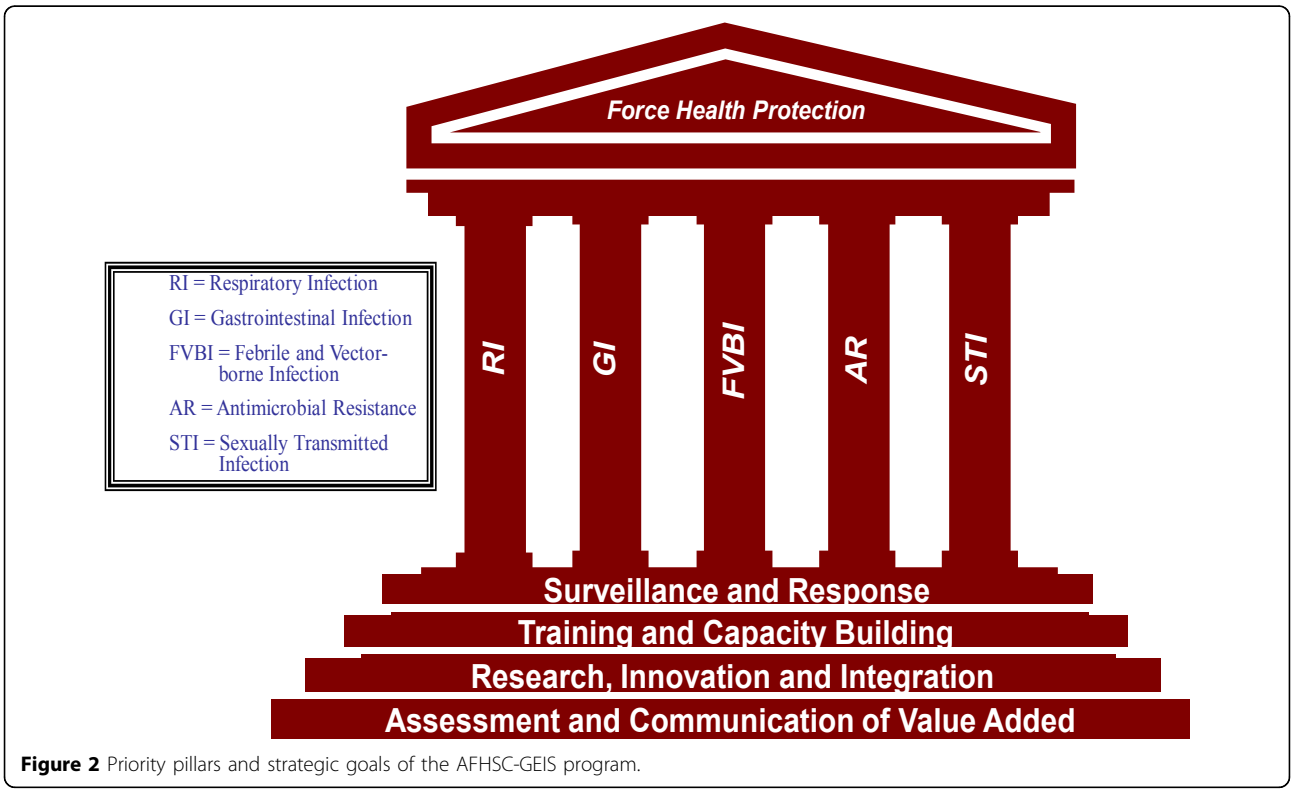

Figure 2 Priority pillars and strategic goals of the AFHSC-GEIS program.

ranked based on scores received, and a cutoff level for funding was assigned based on score and available funding. An external review board, not associated with AFHSC-GEIS and representing all three major uniformed services, reviewed overall funding decisions and provided recommendations. Finally, GEIS and AFHSC directors were briefed and given the opportunity for input. Of the 198 proposals received, full or partial funding was available for the top-ranked 66 percent (130 of 198 proposals), and 56 percent of requested funding was allocated.

Communication of value added

Communication within and outside the network was conducted in a variety of ways: required quarterly reports, monthly conference calls with awarded partners, consolidated DoD influenza reports (with variable frequency from daily to weekly during the emerging 2009 H1N1 pandemic), site visits with program reviews, peer-reviewed publications, and presentations at multiple DoD and civilian international conferences. Results were reported only with local-host or partner-country notification and concurrence. In general, the information requested and shared by the GEIS network was aggregate in nature. GEIS does not archive extensive data sets from partners or host countries. Analysis and interpretation is largely done by the partner conducting the work, in collaboration with the host country, and with ultimate consideration of national sovereignty and transparency in the process.

The central coordination of this global DoD surveillance system afforded multiple opportunities for enhanced utilization of partner capabilities, as well as concise information sharing with other DoD organizations and external agencies (Table 2). The many examples share a central theme of leveraging global visibility and connecting needs with capabilities.

Communication with the World Health Organization (WHO) and CDC is a priority, with a DoD liaison positioned in both organizations to facilitate bilateral information exchange. The value added to these two organizations by the GEIS network is clear in the examples of the WHO reference laboratory status of Naval Medical Research Unit Number 3 (NAMRU-3) in Cairo, Egypt, and U.S. Army Medical Research Unit-Kenya (USAMRU-K). Both laboratories were highly leveraged in training and laboratory capacity building during the 2009 H1N1 pandemic [24]. Numerous influenza contributions to the WHO's Global Influenza Surveillance Network through CDC is another example. These contributions have resulted in numerous examples of viruses isolated by DoD's surveillance network being used as reference strains and the virus seed strain for seasonally available influenza vaccines [25,26].

Table 2 Specific examples of central coordination, fiscal year 2009

1. Funding NMRC for development, production and sharing within partner network of rickettsial diagnostic tests
2. Funding USAMRIID for development, production and sharing within partner network of lassa fever and other select agent diagnostic tests
3. Funding BAMC for development, production and sharing within partner network of leptospiral diagnostic tests
4. Facilitation of sample sharing for advanced characterizations
a. Partner H1N1 samples to WRAIR for full-genome sequencing
b. Shipboard outbreak respiratory and serum samples to NHRC for determination of etiology and immune status
5. Facilitation of ongoing discussions and updates on outbreaks among host-country populations and U.S. military beneficiaries in all regions under surveillance
6. Facilitation of brief summaries and updates of activity related to the 2009 pandemic of A/H1N1
a. Provided a forum for case reporting and regional surveillance findings among network labs and near partners within the countries (InstitutPasteur, PAHO, academic partners)

NMRC: Naval Medical Research Center; USAMRIID: U.S. Army Medical Research Institute of Infectious Diseases; BAMC: Brooke Army Medical Center; WRAIR: Walter Reed Army Institute of Research; PAHO: Pan American Health Organization.

This global DoD surveillance network should not and does not operate in a vacuum. A review of the DoD-GEIS influenza programs by IOM in 2007, conducted after the first year that the network received avian influenza/pandemic influenza (AI/PI) supplemental funds, commented: "DoD-GEIS should further strengthen its coordination and collaboration on pandemic influenza ... with all U.S. partners ... These partners include HHS [U.S. Department of Health and Human Services], CDC,..." [27]. The rapid communication to CDC of the novel H1N1 strains identified by two GEIS partner laboratories before any other public health laboratory (see Table 3) is evidence of the implementation of this recommendation. Though funded partners clearly understand the need for timely processing of samples and expeditious communication, it must be continually reinforced throughout the global surveillance network. Personnel turnover is high, and communication of these ongoing needs is a priority.

Accomplishments: fiscal year 2009

In its entirety, this special supplement of BioMed Central outlines many of the extensive accomplishments of the global GEIS partner network in 2009. Tables 3 and 4 outline the "Top 10 accomplishments of the global network," and the "Top 10 specific localized accomplishments."

Publications and presentations

Another metric for success is the number of publications in peer-reviewed journals and presentations given by network partners. An accurate count is difficult

because the independent network partners leverage funding from various sources for their initiatives. Nevertheless, 112 manuscripts associated with projects partly or wholly supported by AFHSC-GEIS were published in 2009; the number of poster sessions and presentations at various public and private conferences was far higher.

Broadly speaking, 33 peer-reviewed publications encompassed febrile and vector-borne infections and other infectious diseases; 25 were in the realm of respiratory infections, including influenza; 19 described emerging infections; 18 were associated with malaria; nine were about gastrointestinal infection; seven described antimicrobial-resistant organisms; and one was related to sexually transmitted infections. Though populations under surveillance were often a mixture of military and civilian, 28 of these publications were directly related to U.S. or foreign military populations.

These numbers attest to the scientific rigor with which partners conduct their work, their ability to leverage funding to create a relatively balanced portfolio covering all five pillars of infectious disease threats of military importance, and their emphasis on military populations.

The way forward: tools for success

International Health Regulations (2005)

The WHO International Health Regulations, established in 1969, were originally intended to identify several specific diseases of concern (plague, yellow fever, cholera and smallpox) among travelers entering a given country. The events of the past few decades have made it clear that a new paradigm was needed to minimize the global impact of an emerging pandemic and its toll on human life. To this end, the International Health Regulations (2005), or IHR (2005), were formally adopted by the WHO 58th World Health Assembly on May 23, 2005, and took effect on June 15, 2007 [28]. The focus of these new guidelines changed from specific diseases of concern to any event that could be considered a "public health emergency of international concern." Assessments of current capabilities in countries throughout the world were completed in 2009, and compliance with minimum standards of detection and reporting is required by 2012. Building local capability and infrastructure for compliance is the clear goal in IHR (2005), and the regulations acknowledge and encourage countries and organizations that are able to assist resource-poor countries in their compliance process.

Considerable coordination and communication with in-country ministries, academic institutions and other in-country government assets is done by AFSHC-GEIS global partners. However, collaboration and capacity building conducted by DoD partners is being re-examined to comply with a broader U.S. government response, the National Strategy for Countering Biological Threats, and the IHR (2005) framework. The White House National Security staff is playing an active role in this U.S. government coordination. By conducting our program in coordination with this whole of US Government, then our capacity building, outbreak assistance and facilitating in-country diagnostic capabilities with host countries will meet the objectives of all by a) reinforcing amiable relationships between host-country

Table 3 Top 10 accomplishments of the global network, 2009

1. Conducted active infectious disease surveillance, capacity building, training or outbreak investigations in approximately 92 countries and 500 locations through a global network of partners.
2. Served as the primary source for global avian influenza detection. Of globally reported H5N1 infections, 71 percent (37 of 52) were identified or confirmed at DoD partner laboratories funded by AFHSC-GEIS, with the vast majority being performed at the NAMRU-3 laboratory in Cairo, Egypt.
3. Detected the first four cases of novel A/H1N1 through two partner laboratories, the Naval Health Research Center and the U.S. Air Force School of Aerospace Medicine. Communicated results to the CDC.
4. Supported the diagnostic confirmation of the first novel A/H1N1 cases in 14 countries (Bhutan, Cambodia, Colombia, Djibouti, Ecuador, Egypt, Kenya, Kuwait, Lao People's Democratic Republic, Lebanon, Nepal, Peru, Republic of the Seychelles).
5. Centrally consolidated over eight laboratory- and region-specific partner reports into an extremely well-received and informative one-page dynamic document of the "Department of Defense Global Surveillance Summary."
6. Improved infrastructure at 52 laboratories in 46 countries, including eight military and 44 civilian laboratories, with emphasis on influenza, and leveraged capability for other emerging infectious disease initiatives.
7. Sponsored and/or conducted 123 training exercises with more than 3,130 representatives from 40 countries.
8. Responded to more than 76 outbreaks in 53 countries; 24 outbreaks were at U.S. domestic and foreign installations, 36 were in partnership with foreign civilian entities and 15 with foreign militaries.
9. More than 15 reports of first laboratory confirmation of etiologic disease causes in regions where the disease had not been previously reported, including leptospirosis, yellow fever, Q fever, brucellosis, St. Louis encephalitis, Venezuelan equine encephalitis, various rickettioses and other pathogens.
10. Supported partners tested more than 72,000 respiratory samples, of which more than 17,000 (24 percent) were influenza-positive and more than 10,000 (15 percent) were novel A(H1N1).

AFHSC-GEIS: Armed Forces Health Surveillance Center, Global Emerging Infections Surveillance and Response System; DoD: Department of Defense; NAMRU-3: Naval Medical Research Unit Number 3; CDC: Centers for Disease Control and Prevention.

Table 4 Top 10 specific localized accomplishments, 2009

1. Of three influenza reference strains provided to WHO (A/California/7/2009, A/California/4/2009 and A/Texas/5/2009) by NHRC and USAFSAM, the A/California/7/2009 was selected as the seed strain.
2. Two biosafety-level 3 (BSL-3) laboratories were commissioned in 2009 at NHRC in San Diego, Calif., and AFRIMS in Bangkok, Thailand; and two BSL-2 laboratories were commissioned, one at the University of Buea, Cameroon, and one on the campus of the Cameroonian Army installation in Yaoundé, Cameroon, under supervision of the Global Viral Forecasting Initiative.
3. NAMRU-3 partners reported the first definitive evidence of human cutaneous leishmaniasis from *Leishmania major* infections in Ghana.
4. AFRIMS published the first report of clinically significant *Plasmodium falciparum* malaria resistance to the potent artemisinin antimalarial drug class, spurring WHO, Bill & Melinda Gates Foundation and host national malaria control officials to institute aggressive measures to contain and eliminate artemisinin-resistant malaria in Southeast Asia.
5. The first documented cases of Venezuelan equine encephalitis, brucellosis, dengue and Q fever in Ecuador were reported by NMRCD-Lima, and the first laboratory-confirmed cases of leptospirosis in the border areas of Thailand and Myanmar were reported by AFRIMS.
6. AFRIMS provided timely outbreak response services to the Nepali National Public Health laboratory, ultimately characterizing (by pulse-field gel electrophoresis) nearly 6,000 cases of multidrug-resistant typhoid fever originating from a single point source, and uniformly quinolone-resistant.
7. NAMRU-3 worked closely with WHO to conduct novel A/H1N1 laboratory diagnostic training for 73 participants representing 32 different countries in a strategic and timely two-week period in May 2009.
8. NEPMU-2, NAMRU-3, and AFHSC collaboratively supported CENTCOM efforts in establishing in-theatre novel A/H1N1 testing and isolation of servicemembers deployed or deploying to sites around the world.
9. The WRAIR/USAMRU-K Malaria Diagnostics and Control Center of Excellence, established in 2003, having trained more than 600 malaria microscopists, established new malaria diagnostics training capabilities in Nigeria and Tanzania, leading to a visit by the president of Tanzania to WRAIR to establish new collaborations between the U.S. Army and Tanzania.
10. NMRCD, as part of its expansive febrile-disease surveillance network in the Amazon basin, published the first comprehensive study of the etiologies of undifferentiated febrile illness in Ecuador, documenting the first laboratory-confirmed cases of Venezualan equine encephalitis, brucellosis, dengue and Q fever in Ecuador.

WHO: World Health Organization; NHRC: Naval Health Research Center; USAFSAM: U.S. Air Force School of Aerospace Medicine; AFRIMS: Armed Forces Research Institute of Medical Sciences; NAMRU-3: Naval Medical Research Unit Number 3; NMRCD: Naval Medical Research Center Detachment; NEPMU-2: Navy Environmental Preventive Medical Unit Number 2; AFHSC: Armed Forces Health Surveillance Center; CENTCOM: U.S. Central Command; WRAIR: Walter Reed Army Institute of Research; USAMRU-K: U.S. Army Medical Research Unit-Kenya.

government public health assets and DoD partners; b) developing the capability to report "public health emergencies of international concern," whereby the entire global community and DoD learns, and world preparations to minimize impact can proceed in a unified and transparent manner; and c) improving DoD's situational awareness through close, transparent, trusting relationships with host countries, even if an actual public health emergency of international concern does not occur.

Military-to-military cooperation and collaboration

As briefly discussed in the biosurveillance landscape section of this paper, many U.S. government organizations are becoming involved in global biosurveillance. The mission of DoD's overseas laboratories necessitates continued engagement with in-country public health authorities. However, with rapidly increasing involvement of other U.S. government agencies, a unique niche that U. S. uniformed officers throughout the world can and should expand engagement is with their global uniformed counterparts. In many cases, militaries are the major providers of health care in their countries, with abilities that far exceed their civilian programs. Despite political agendas, remarkable progress in facilitating open lines of communication can occur when two researchers or public health professionals, regardless of cultural or economic background, establish mutual rapport for a mutual interest: optimal health of their uniformed service members.

Although many military-to-military lines of communication and collaboration currently exist (Table 5), another mechanism AFHSC used to facilitate increased activities in 2009 began with an expanded relationship with the International Committee of Military Medicine (ICMM). ICMM was established in 1921 by Belgian and U.S. medical officers (Commander Medical Officer Jules Voncken and Captain William Bainbridge) after World War I "revealed the importance of closer cooperation between armed forces medical services worldwide" [29]. With 104 member countries, ICMM is an unbiased, transparent organization with the goals of maintaining and strengthening the bonds between all medical services of member states, promoting medico-military scientific activities, and developing and participating in humanitarian operations.

Because of its unbiased membership policy, ICMM is the only military organization with a formal in-force memorandum of agreement with WHO. Through direct engagements or indirect facilitation and empowerment with ICMM, opportunities are being explored to work with foreign militaries, to further facilitate IHR (2005) compliance, and to facilitate force health protection and global public health in concert with WHO. Joint initiatives include co-sponsoring a forum titled "Emerging

Table 5 Fiscal year 2009 military-to-military partnerships by AFHSC-GEIS (14 countries)

Country	Focus of Collaboration	Nature of Exchange
Cambodia	Influenza surveillance & EID lab training	Standardization of laboratory procedures (QA/QC)
Cameroon	Influenza surveillance & EID lab capability	Influenza & EID reporting capability
Kenya	Influenza surveillance	Influenza reporting capability
Lao People's Democratic Republic	Influenza surveillance & EID lab training	Standardization of laboratory procedures (QA/QC)
Malaysia	Influenza surveillance & EID lab training	Subject-matter expert
Nigeria	Influenza surveillance & EID lab capability	Influenza & EID reporting
Pakistan	Influenza surveillance & EID lab capability	Subject-matter expert
Peru	Electronic disease surveillance	EID and influenza laboratory
	Influenza & EID lab capability	capacity & training; disease reporting capability
Poland	Influenza surveillance & EID lab capability	Influenza & EID reporting capability
Singapore	Influenza surveillance, EID lab capability & disease surveillance	Standardization of laboratory procedures (QA/QC)
Tanzania	Influenza surveillance & EID lab capability	Influenza & EID reporting capability
Thailand	Unit-based electronic surveillance	EID and influenza laboratory
	Influenza & EID lab capability	capacity & training; disease reporting capability
Uganda	Influenza surveillance	Influenza reporting capability
Vietnam	Influenza surveillance & EID lab training	Standardization of laboratory procedures (QA/QC)

EID: emerging infectious diseases; QA/QC: quality assurance & quality control

Infectious Diseases: the Military's Role under International Health Regulations (2005)" in September 2010 in St. Petersburg, Russia, and movement toward development of a military public health network to coordinate and provide access to training, resources, and expertise in public health practice and epidemiologic techniques for member state use.

Conclusions

U.S. DoD has a long and impressive history of infectious disease research and product development. The GEIS program was developed at a time of need by DoD-sponsored U.S. and overseas research laboratories. The wisdom of establishing improved global DoD EID surveillance capabilities is reinforced by numerous contributions to global outbreaks, most recently the 2009 H1N1 pandemic. The greatly increased interest by other DoD organizations and the U.S. government as a whole also reinforces this wisdom.

For optimal preparedness, surveillance is an ongoing process, not one that is implemented only in times of public health emergency. Sustaining these programs also avoids negative perceptions by foreign governments of U.S. involvement only with the "surveillance priority *du jour*." The right mix of empowering surveillance activities with capacity building is important to mitigate perceptions of taking but not giving. With the framework of current U.S. government guidelines, such as the National Strategy for Countering Biological Threats and IHR (2005), the world is closer than ever to truly working together on surveillance and control of infectious diseases without consideration of borders.

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Disclaimer

The opinions stated in this paper are those of the authors and do not represent the official position of the U.S. DoD.

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Competing interests

To the best of their knowledge, the authors report no competing interests.

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REVIEW Open Access

A growing global network's role in outbreak response: AFHSC-GEIS 2008-2009

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Abstract

A cornerstone of effective disease surveillance programs comprises the early identification of infectious threats and the subsequent rapid response to prevent further spread. Effectively identifying, tracking and responding to these threats is often difficult and requires international cooperation due to the rapidity with which diseases cross national borders and spread throughout the global community as a result of travel and migration by humans and animals. From Oct.1, 2008 to Sept. 30, 2009, the United States Department of Defense's (DoD) Armed Forces Health Surveillance Center Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) identified 76 outbreaks in 53 countries. Emerging infectious disease outbreaks were identified by the global network and included a wide spectrum of support activities in collaboration with host country partners, several of which were in direct support of the World Health Organization's (WHO) International Health Regulations (IHR) (2005). The network also supported military forces around the world affected by the novel influenza A/H1N1 pandemic of 2009. With IHR (2005) as the guiding framework for action, the AFHSC-GEIS network of international partners and overseas research laboratories continues to develop into a far-reaching system for identifying, analyzing and responding to emerging disease threats.

Background

A central objective of disease surveillance systems is the early identification of infectious disease outbreaks to facilitate rapid implementation of effective control measures for minimizing disease transmission and morbidity. Although outbreak response has come a long way since John Snow's investigation of cholera and the Broad Street pump in 19th century London [1], effective outbreak response continues to be challenging. Today, a particular challenge is the interconnected nature of our global society. Diseases cross international borders and present themselves in unique ways through a continuously changing landscape, making it difficult to rapidly identify, analyze and respond to disease outbreaks. Appropriate and effective monitoring of newly recognized disease clusters requires an established, standardized and well-maintained global surveillance system with a flexible framework for identifying and responding to such events.

In 1997, the U.S. Department of Defense (DoD) established the Global Emerging Infections Surveillance and Response System (GEIS) in response to the Presidential Decision Directive NSTC-7, which identified the need for more robust global disease surveillance [2]. In 2008, GEIS was integrated into the newly formed Armed Forces Health Surveillance Center [3]. As the name implies, the primary mission of AFHSC-GEIS is global disease surveillance and response. A large portion of this mission is accomplished through DoD overseas research laboratories, which were initially established within partner host countries to conduct research on infectious diseases of bilateral concern [4]. This capacity has subsequently been leveraged by AFHSC-GEIS for the purpose of disease surveillance and response.

Currently, five DoD overseas research laboratories serve in this capacity: the Armed Forces Research

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Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand; the U.S. Army Medical Research Unit-Kenya (USAMRU-K) in Nairobi, Kenya; the U.S. Naval Medical Research Center Detachment (NMRCD) in Lima, Peru; the U.S. Naval Medical Research Unit No. 2 (NAMRU-2) in Jakarta, Indonesia; and the U.S. Naval Medical Research Unit No. 3 (NAMRU-3) in Cairo, Egypt. Additionally, the AFHSC-GEIS network includes substantial contributions from three U.S.-based research laboratories and a major regional medical center in Europe. The Naval Health Research Center (NHRC) in San Diego, California, conducts population-based surveillance among basic military trainees at eight of the 10 major training centers in the United States; disease surveillance among shipboard service members in the 2nd (Atlantic), 3rd (Pacific), and 7th (Far East) U.S. Naval fleets; and infectious disease surveillance in six clinics and two hospitals along the United States-Mexico border [in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) and the County of San Diego Health Department]. The U.S. Air Force School of Aerospace Medicine (USAFSAM) in San Antonio, Texas, which serves as the Air Force's clinical reference laboratory and public health center, is the lead organization for the U.S. military's installation-based, influenza sentinel surveillance program. The Walter Reed Army Institute of Research's Division of Viral Diseases (WRAIR-DVD) in Silver Spring, Md., provides full-length genomic sequencing capability and conducts surveillance among U.S. civilians assigned to Department of State embassies overseas. Additionally, Landstuhl Regional Medical Center (LRMC) and the United States Army Public Command Health Region-Europe (PHCR-Europe) in Landstuhl, Germany, function as a regional military medical center and support surveillance for respiratory pathogens and other emerging infectious diseases (EID) within the U.S. European Command. Additionally, AFHSC-GEIS has been a member institution and contributing partner in the WHO's Global Outbreak Alert and Response Network since 1999.

Rapid identification of outbreaks and support of timely response efforts are key components of complying with the World Health Organization's (WHO) International Health Regulations (IHR) (2005), and are core focus areas and strategic goals of the AFHSC-GEIS network [5]. Support for these efforts, provided in response to host country requests for assistance with new or ongoing outbreaks, consists of a wide range of functions, such as field team support, epidemiology or consultative support, and laboratory diagnostic support. These efforts and collaborative exchanges strengthen relationships, build and maintain trust, and are a critical component of the long-standing relationships between the network partners and their sponsor host countries. Many of the partnerships between the United States and host country militaries (mil-mil) partnerships that have developed over the years have served to empower the host country military's role in supporting outbreak response activities within their own countries [6].

In late 2006, Chretien et al., provided a detailed breakdown of how the broad-ranging DoD's global disease surveillance network could potentially serve as a model for other global public health entities to adequately identify and respond to these complex threats [7]. This paper describes how the AFHSC-GEIS network has significantly contributed toward effective outbreak identification and response and capacity building within partner host countries [8] under the guiding principles of the WHO's IHR (2005) [9]. For clarity and for the purposes of this assessment, we will describe the accomplishments of the AFHSC-GEIS network during fiscal year 2009 (Oct. 1, 2008 through Sept. 30, 2009) through two categories: respiratory disease outbreaks and non-respiratory EID outbreaks.

Accomplishments

General

The AFHSC-GEIS network responded to 76 outbreaks (Table 1, Figure 1) in 53 countries during the 2009 fiscal year (FY09), several in direct support of the IHR (2005). The most common diseases investigated were influenza (47), cholera (four), dengue fever (four) and hepatitis (three). Human disease was present in all but one of these outbreaks, and specific causative agents were identified in 69 (92 percent) of them. The population affected ranged from less than 10 individuals to several thousand, and support efforts were often ongoing engagements beyond the initial investigation. The type of population supported also varied, depending on the relationship and the nature of the mission of the laboratory partner. Thirty-six (48 percent) of the outbreak investigations involved partners supporting civilian entities through formal bilateral requests or as part of their role as a WHO regional reference laboratory (NAMRU-3, AFRIMS and USAMRU-K). In the majority of these instances, testing of samples from civilian populations was performed. Twenty-four (32 percent) of the partner responses involved outbreaks among U.S. troops stationed in the continental United States (CONUS) or at overseas locations, while 15 (20 percent) of the responses involved investigations in collaboration with foreign military partners and multinational forces involved in peacekeeping activities or exercises. One investigation involved influenza testing of U.S. expatriates through the U.S. Embassy clinic in Jakarta, Indonesia.

Response activities included a range of efforts from the provision of simple consultative services to comprehensive outbreak packages that included field

Table 1 Diseases and agents investigated throughout 2009 among AFHSC-GEIS global partner laboratories and institutions

Disease or Agent	Number of Outbreaks
Adenovirus	1
Campylobacter	1
Chikungunya	1
Cholera	4
Cyclospora	1
Dengue fever	4
Hepatitis (viral)	3
Influenza	
Pandemic (2009) H1N1	42
Seasonal Influenza	4
Avian Influenza (H5N1)	2
Malaria	1
Norovirus	1
Rickettsiosis	1
Rift Valley fever	1
Salmonella typhi	1
Group A Streptococcal (GAS) pneumonia	1
Syphilis	1
Unknown etiology	
Conjunctivitis	1
Gastrointestinal syndrome	2
Respiratory syndrome	1
Hemorrhagic syndrome	1
Vampire bat bites	1
Total	76

support, epidemiologic consultation and laboratory diagnostic support. In 27 (36 percent) of the outbreaks, personnel were provided for field support, 44 (59 percent) outbreaks received epidemiologic or clinical consultative support, and laboratory diagnostic and testing support was provided to 68 (91 percent) of the outbreak support requests. Many AFHSC-GEIS partner responses were a combination of the above and 27 (36 percent) of the outbreak investigations provided a fully comprehensive response effort with support from all three categories.

Respiratory disease outbreaks

Beginning in 2006, the DoD's global disease surveillance network has worked to enhance the existing surveillance infrastructure to prepare for a potential influenza pandemic. The goals of these expansion efforts included broadening the network to monitor and detect increasing numbers of avian (H5N1) influenza outbreaks around the world and identify new infectious disease threats [10]. This expansion of capacity and function was both appropriate and fortuitous as AFHSC-GEIS network partners at NHRC and USAFSAM were the first in the world to detect the novel influenza A/H1N1 strain in April 2009 in San Diego, California, and San Antonio, Texas. This rapid detection during the end of the influenza season allowed the appearance of this novel strain to be identified and reported as a Public Health Emergency of International Concern by the CDC, a WHO

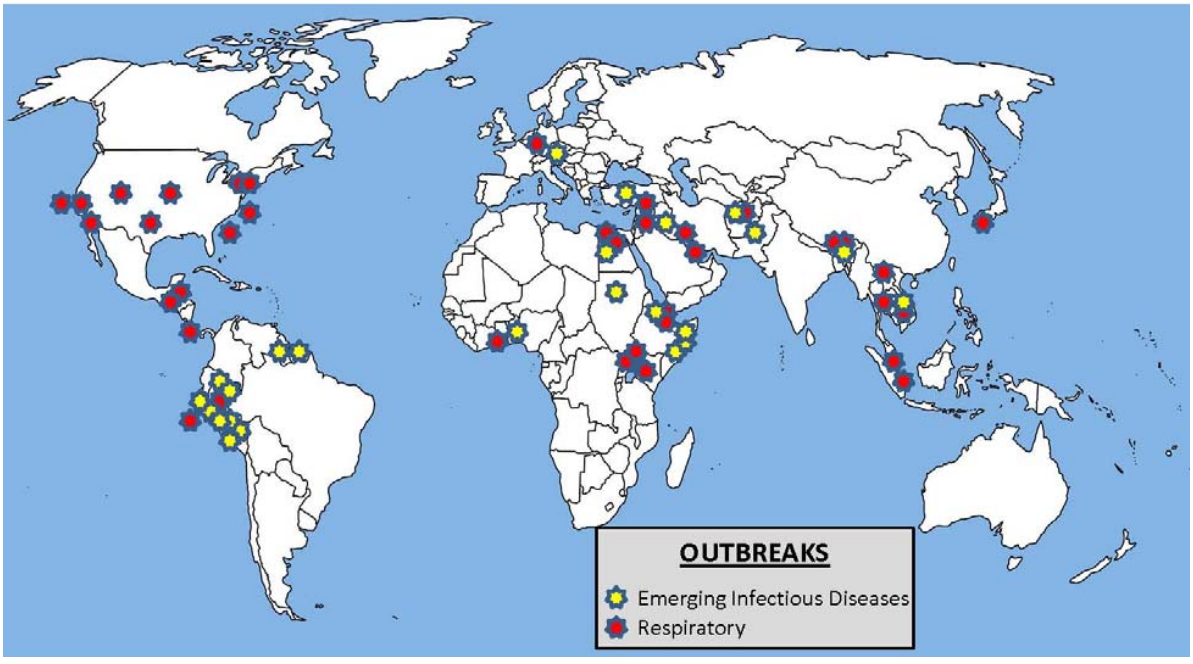

Figure 1 Global Snapshot of Emerging Infectious Diseases and Respiratory Diseases Outbreaks. October 2008 to September 2009.

Collaborating Center, in compliance with IHR (2005). With the onset of this influenza A/H1N1 pandemic in April 2009, substantial efforts were made by AFHSC-GEIS network partners to assist the global health community in responding to this threat. Fifty-one (67 percent) of the 76 outbreaks responses involved respiratory diseases, 41 (80 percent) of which were due to novel influenza A/H1N1.

Beginning in April 2009, with the onset of the influenza pandemic, disease surveillance and investigative support activities were dominated by novel influenza A/H1N1-related responses. As with other investigations, the activities for novel influenza A/H1N1 were wide-ranging and involved different populations and situations. The AFHSC-GEIS network supported the diagnostic confirmation (directly in DoD lab or through support of host-country laboratories) of the first cases in 14 countries (Bhutan, Cambodia, Colombia, Djibouti, Ecuador, Egypt, Kenya, Kuwait, Lao People's Democratic Republic, Lebanon, Nepal, Peru, Republic of the Seychelles and the United States), again demonstrating direct support for increasing compliance with IHR (2005). The non-U.S. activities were a result of the respective AFHSC-GEIS partner laboratory's roles as regional reference testing centers and the bilateral collaborations with host-country Ministries of Health. These bilateral relationships resulted in support of 17 large-scale outbreaks among civilians in 13 countries.

U.S. service members and beneficiaries were affected by the pandemic from the beginning. In the first wave (April through August 2009), AFHSC-GEIS network partners actively investigated 18 different outbreaks on U.S. military installations and among previously defined high-risk groups [11]. These high-risk groups included deployed or deploying personnel, shipboard personnel, new accessions (basic and advanced military trainees and service academy students), health care workers, children and staff in daycare centers, and pregnant women. Stressful military environments, highly mobile missions and complex troop dynamics helped to propagate pandemics in the past and have drawn the attention of the military's operational leadership and leaders of civilian sectors within host countries. These investigations involved from a few dozen cases to more than 1,000 cases tested.

Shipboard investigations involved a number of responding units and included ships at sea in the Atlantic and Pacific Oceans, and the Persian Gulf, as well as vessels in port in major cities around the world. Shipboard investigations have benefitted from the ongoing surveillance of respiratory disease on large U.S. Navy ships [12]. Patients meeting the case definition of febrile respiratory illness (FRI), temperature > 100.4°F and cough or sore throat, undergo throat swabs and the specimens are stored in liquid nitrogen or -80°C freezers. This surveillance, conducted by NHRC, has facilitated timely specimen collection and pathogen identification in a number of shipboard respiratory outbreaks in recent years. The surveillance system detects a wide variety of circulating influenza types as these ships make numerous worldwide port stops over a short time period. In general, the specimens are saved and processed at the end of a ship's deployment, which usually lasts six months. However, in the case of an outbreak, febrile respiratory illness (FRI) specimens from immediately before the outbreak onward can be processed onboard the ship with specific polymerase chain reaction (PCR) testing or shipped overnight to NHRC for 12- to 24-hour turnaround molecular testing and culture.

Shipboard investigations ranged from simple identification of the novel influenza A/H1N1 virus to detailed epidemiologic investigation and testing [13]. NMRCD, in partnership with the Peruvian Navy, investigated a shipboard outbreak in June through July 2009 aboard a 355-crew Peruvian Navy ship at sea in the Pacific Ocean. During the four-week investigation, team members confirmed 78 of 85 (92 percent) febrile acute respiratory illness cases as novel influenza A/H1N1. The attack rate aboard the ship during the time of the outbreak was 22 percent. Early detection, through an active shipboard surveillance system modeled on the NHRC program, played an important role in the rapid detection and subsequent control of the outbreak [14].

The USS Boxer (LHD 4), with a complement of more than 2,200 U.S. Sailors and Marines, was docked at Phuket, Thailand, from June 23 through 29, 2009. On June 30, four of 14 patients with ILI tested positive for influenza A by PCR. By July 9, 102 individuals had provided respiratory specimens (throat swabs in viral transport media) that were sent to NHRC, where 69 were confirmed as novel influenza A/H1N1. Overall, more than 200 cases were identified in a five-week period and 177 personnel were isolated with FRI for an average duration of 3.6 days (Figure 2) [15].

As part of the deployment process, troops usually transition through pre-deployment training at what the U.S. Army refers to as power projection platforms (PPP). These are usually large installations with thousands of individuals transferring to the deployed setting each year [16]. The first wave of novel influenza A/H1N1 included outbreaks among deploying service members from nine of the 15 PPPs and subsequently resulted in two large-scale outbreaks in the operational theatre (Iraq and Kuwait). The most notable PPP outbreaks were at Fort Riley, Kansas (n=33), Fort Hood, Texas (n=44), Fort Lewis, Washington (n=144), and Fort Bliss, Texas (n=188). Response activities at each of the PPPs varied based on the reality on the ground

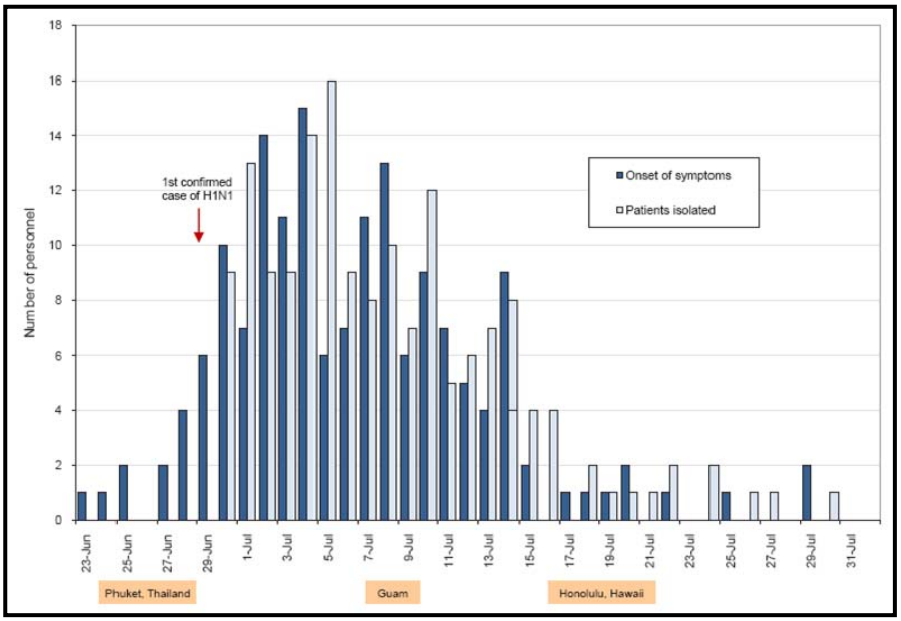

Figure 2 Epi curve of cases, isolated patients during A/H1N1 outbreak aboard the USS Boxer. Summer 2009.

and timing in the pre-deployment process. Sites with large numbers of individuals in the latter stages of pre-deployment were forced to take much more aggressive steps to screen and monitor the symptoms of illness for departing troops.

Military service academies were particularly hard hit by novel A/H1N1 outbreaks during the first wave. Notable outbreaks requiring outside assistance and support took place at the U.S. Air Force Academy (USAFA) [17] (Figure 3), U.S. Coast Guard Academy, U.S. Military Academy and U.S. Naval Academy. Response efforts ranged from diagnostic support for cadets and midshipmen in isolation to comprehensive outbreak support. The response effort for USAFA was unique because it was the first to provide information on the different aspects of the disease in such a high-risk setting. The USAFA investigation team conducted retrospective and prospective surveillance to describe the epidemiology of the outbreak and to define and implement effective control measures. Extensive education and hygiene efforts were implemented and ill cadets were isolated from non-ill cadets to decrease transmission. The team documented confirmed (n=134) and suspected (n=34) novel influenza A/H1N1 cases among basic cadet trainees, with an outbreak period incidence rate of 11 percent. The peak of the outbreak occurred on July 6 and was likely propagated by a Fourth of July social-mixing event (Figure 4). The investigation team obtained serial nasal wash samples from patients and published the first report of virus shedding duration determined by virus culture. Follow-up nasal wash samples taken seven days from illness onset and from asymptomatic patients (≥24 hours) contained cultureable virus in 24 percent and 19 percent of the samples, respectively. The USAFA investigation made a significant and novel contribution to the general public health knowledge on the transmission dynamics of this disease and demonstrated a high proportion of asymptomatic, sub-clinical disease among cadets in this setting.

Remarkably, while notable novel influenza A/H1N1-related outbreaks occurred at all of the basic military training centers, overall, military recruits were only minimally affected during the first wave of the pandemic (Figure 5). Subsequently, the burden of disease shifted almost entirely to recruits at these installations in early fall (August-October) 2009, although the disease burden of novel influenza A/H1N1 among recruits during the entire time was significantly smaller than the ongoing epidemic of adenovirus respiratory diseases among U.S. military recruits [18].

In addition to the novel influenza A/H1N1 outbreaks, four seasonal influenza outbreak investigations were undertaken: one among deployed U.S. troops in Djibouti, one in a refugee camp in Nepal, one onboard a U.S. Navy submarine, and one among newly arrived Japanese military trainees in Camp Pendleton, California. Two H5N1-related investigations occurred, along with an ongoing investigation of human H5N1 cases in Egypt and assistance with human testing during an outbreak of influenza in birds in Nepal in November of 2008. Additionally, two respiratory illness outbreak investigations occurred among basic military trainees, while the U.S. Army Public

Figure 3 U.S. Air Force Academy swearing-in ceremony (Photo Courtesy of Official U.S. Air Force Academy website).

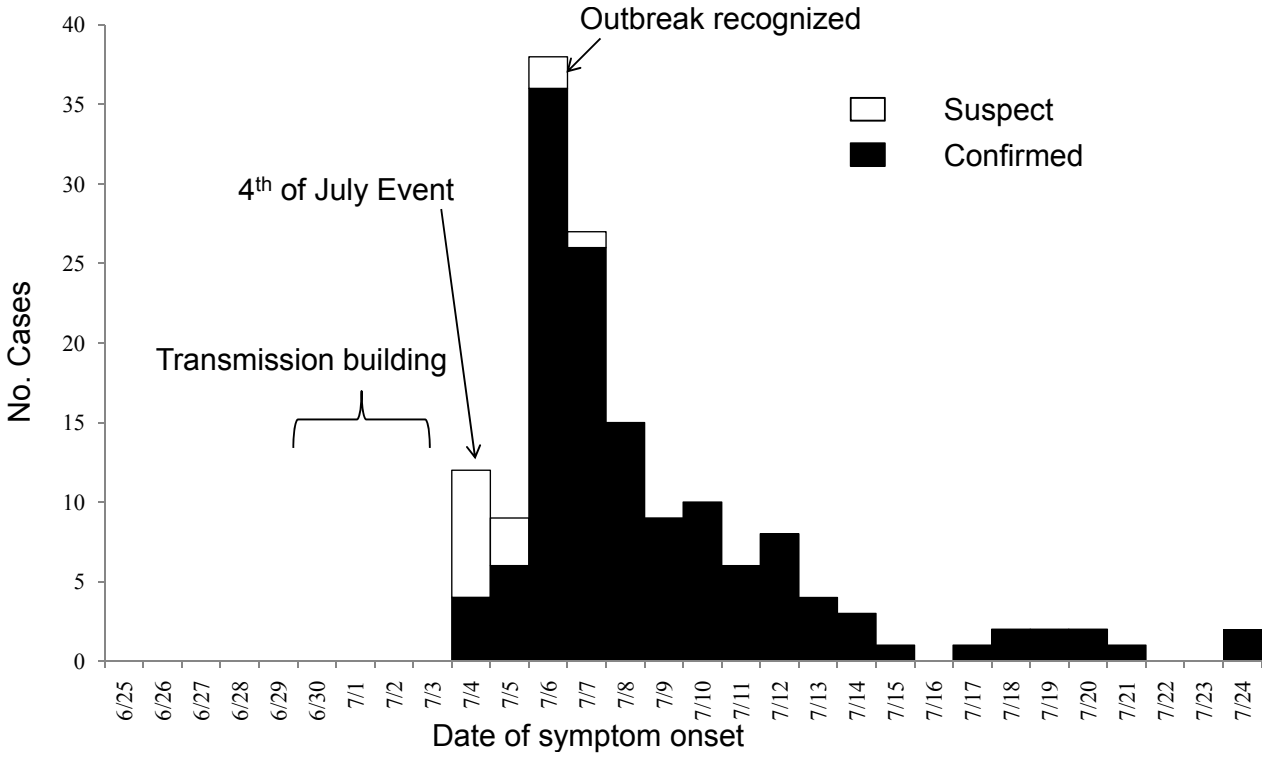

Figure 4 Confirmed, suspect cases of A/H1N1 virus infection at U.S. Air Force Academy, 2009 [17].

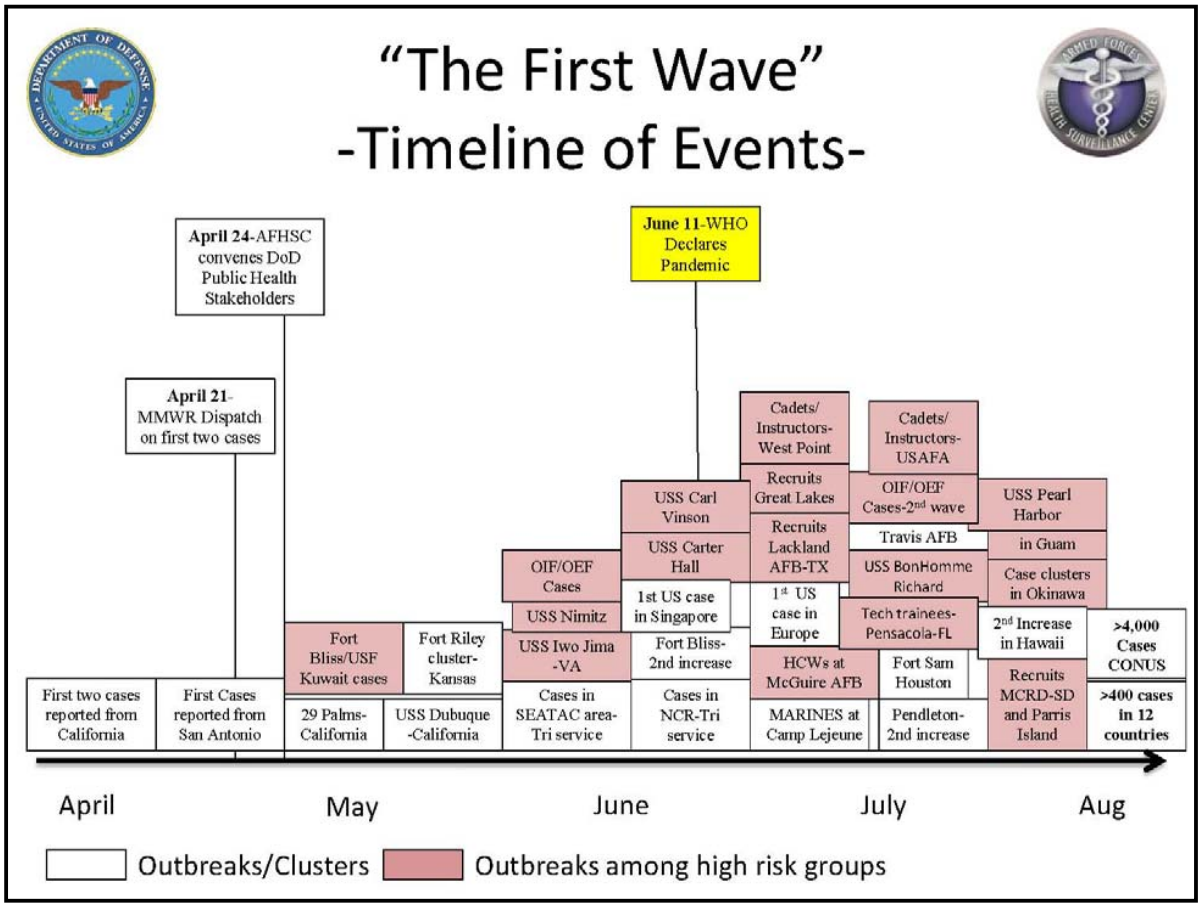

Figure 5 A/H1N1 epi curve, timeline for outbreaks and clusters among U.S. service members and beneficiaries.

Health Command (Provisional) investigated an outbreak of Group A Streptococcus at Fort Leonard Wood, Missouri. An adenovirus type B14 was investigated at the U.S. Coast Guard Training Center in Cape May, N.J. Both outbreaks took place in March 2009 and were supported by the laboratory at NHRC.

Overall, the AFHSC-GEIS global disease surveillance network response remained strong through the end of the first wave and well into the second fall wave of the pandemic. At that point, efforts across the network primarily shifted from outbreak response to systematic surveillance (monitoring and representative sampling) of affected sites, along with more complex characterization of the viruses and close tracking of the global circulation patterns of all influenza viruses.

Non-respiratory, emerging infectious disease outbreaks

The AFHSC-GEIS EID surveillance program includes five program pillars or disease focus areas: respiratory diseases, febrile and vector-borne illnesses, enteric diseases, sexually transmitted infections and antimicrobial resistant organisms. Outbreaks involving all five pathogen/illness categories occurred in the one-year timeframe of this report. Global surveillance network partners responded to 20 outbreaks involving non-respiratory EIDs where the disease agents were identified, including four dengue fever, four cholera, three viral hepatitis, two gastrointestinal syndrome, and one each of *Campylobacter*, chikungunya, *Cyclospora*, malaria, Norovirus, rickettsiosis, Rift Valley fever, *Salmonella typhi* and syphilis. Additionally, partners conducted individual outbreak investigations of conjunctivitis and viral hemorrhagic syndrome, while one response activity examined bites from vampire bats. Overall, these response activities took place in 14 countries.

From May to September 2009, a diarrheal disease outbreak occurred in western Nepal, with reports of nearly 70,000 patients treated and over 350 deaths. The National Public Health Laboratory of the Ministry of Health and Population for Nepal requested assistance from the Walter Reed/AFRIMS Research Unit Nepal (WARUN) in determining the etiology. WARUN received 158 stool samples from eight districts in western Nepal; 45 percent from

children <15 years and 61 percent from female patients. WARUN in Nepal and AFRIMS in Thailand analyzed the samples using real-time PCR and culture. Eighty-two of the outbreak samples were positive for *Vibrio cholerae* (01/0139) by PCR. Many of the PCR positive samples subsequently grew *V. cholerae* serogroup 01 serotype Ogawa in culture. Antibiotic sensitivity analysis of the *V. cholera* isolates showed universal resistance to nalidixic acid, colistin, streptomycin, sulfisoxazole, and trimethoprim/sulfamethoxazole but sensitivity to the commonly recommended antibiotics azithromycin, ciprofloxacin, ampicillin and tetracycline. The National Public Health Laboratory performed the initial culture on these stool samples, and the WARUN and AFRIMS laboratories eventually verified and confirmed the cause of the outbreak. The effort enabled local health authorities to institute appropriate treatment and prevention measures in a timely manner.

Department of Defense resources have also been directed toward the investigation or characterization of other phenomena that may threaten public health other than the disease incidence. For example, AFRIMS and NAMRU-2 investigators were among the first worldwide to recognize that increases in *Plasmodium falciparum* treatment failures to the powerful artemisinin combination therapies signaled the onset of resistance to the last remaining class of malaria treatments in widespread deployment today. As a result of these findings, worldwide efforts are under way to contain spread of drug-resistant forms of the parasite from what is hoped to be a relatively constrained area in Southeast Asia along the Thai-Cambodian border [19].

Although many methods may be used to detect outbreaks, most often an astute clinician or laboratory worker identifies an unusual occurrence or an increased frequency. However, syndromic or electronic surveillance may serve as another method to augment, but not replace, traditional disease surveillance efforts [8]. AFHSC-GEIS partners at NMRCD have implemented a near real-time electronic disease surveillance system based on highly cost-effective and sustainable strategies affordable in resource-constrained, developing countries. This system is called Alerta and was first implemented in the Peruvian Navy population in 2002, the Peruvian Army three years later and more recently the Peruvian Air Force. Currently, Alerta covers 98 percent, 99 percent and 95 percent of the Peruvian Navy, Army and Air Force population, respectively, and receives over 200 notifications per week. The system has been useful in outbreak detection, identifying over 20 outbreaks in the last year, six of which were for influenza. Eighty-six reporting units operate nationwide, including border units, hospitals, infirmaries and ships incorporated in the Peruvian Navy surveillance system. Due to this previous experience, the Peruvian Army's expansion has been faster, currently receiving reports from 120 units throughout the country.

Within the one-year period of review, the 76 outbreaks identified by the AFHSC-GEIS network spanned the clinical disease spectrum and involved efforts of international significance. The U.S. DoD has established a robust and flexible global response framework through open collaborations with long-standing host country partners, other global health institutions and agencies such as the WHO, the CDC and Institute Pasteur. In doing so, AFHSC-GEIS, through its global network of partners, is addressing the specific milestones for building sustained capacity for early detection and rapid response as prescribed by the IHR (2005).

Conclusions

The Armed Forces Health Surveillance Center's Division of Global Emerging Infections Surveillance and Response System continues to expand internationally to effectively identify and respond to threats from a wide range of disease agents and geography. The growth and enhancement of this surveillance system in anticipation of pandemic/avian influenza allowed the DoD to identify the current influenza pandemic [20,21] and a number of other infectious disease outbreaks in communities throughout the globe. A multipurpose system with defined goals and pillars of focus, the AFHSC-GEIS network has evolved to become a true model for emerging infectious surveillance platforms at the local, regional and international level. By utilizing this established global system, the DoD is able to provide a common and systematic approach to disease surveillance and a framework for effective response. As emerging and re-emerging threats develop in areas where partners work collaboratively with host countries and global health institutions, the AFHSC-GEIS network stands ready to respond.

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Disclaimer

The opinions stated in this paper are those of the authors and do not represent the official position of the U.S. Department of Defense, local country Ministries of Health or Defense, or other contributing network partners.

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Competing interests
To the best knowledge of the authors, there are no competing interests.

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REVIEW Open Access

Capacity-building efforts by the AFHSC-GEIS program

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Abstract

Capacity-building initiatives related to public health are defined as developing laboratory infrastructure, strengthening host-country disease surveillance initiatives, transferring technical expertise and training personnel. These initiatives represented a major piece of the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) contributions to worldwide emerging infectious disease (EID) surveillance and response. Capacity-building initiatives were undertaken with over 80 local and regional Ministries of Health, Agriculture and Defense, as well as other government entities and institutions worldwide. The efforts supported at least 52 national influenza centers and other country-specific influenza, regional and U.S.-based EID reference laboratories (44 civilian, eight military) in 46 countries worldwide. Equally important, reference testing, laboratory infrastructure and equipment support was provided to over 500 field sites in 74 countries worldwide from October 2008 to September 2009. These activities allowed countries to better meet the milestones of implementation of the 2005 International Health Regulations and complemented many initiatives undertaken by other U.S. government agencies, such as the U.S. Department of Health and Human Services, the U.S. Agency for International Development and the U.S. Department of State.

Background

Capacity building, as it applies to health in this context, can be accomplished through strengthening health systems for delivery of medical care, pursuing medical research initiatives to answer important local or regional health questions, or supporting public health disease surveillance to prioritize which diseases are affecting relevant populations. Within this context, global public health capacity building can be defined as developing laboratory infrastructure, strengthening host-country disease surveillance initiatives, transferring technical expertise and training personnel. Disease surveillance is often the first step in improving public health because it attempts to quantify needs and allocate scarce assets in resource-limited settings, in addition to detecting potential outbreaks of disease.

Though not a new concept, capacity building has enjoyed renewed prominence as the world endeavors to meet requirements of International Health Regulations 2005 (IHR (2005)) [1]. Article 5 of the regulations requires that all countries be able to detect, assess, notify and report on public health issues of international significance and control any potential public health event of international concern by 2012. Some countries are capable now, but most are not and will not be compliant by the deadline unless a significant improvement in local capacity occurs. In general, for capacity building to be successful in the long term, efforts must not be undertaken quickly and need to be implemented through a concerted unified effort, achieving steady, sustainable and measurable progress over time, with the eventual goal being independence from the provider of the capability.

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In 2007, the Government Accountability Office issued a report describing the global infectious disease capacity-building efforts of U.S. government (USG) entities [2]. At the time, three USG entities were identified as providing capacity building for emerging infectious diseases (EID), including the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development and the Department of Defense's Global Emerging Infections Surveillance and Response System (DoD-GEIS). Their efforts included laboratory-based disease surveillance, development and testing of diagnostics, and training such as Field Epidemiology Training Programs, the international version of the famed Epidemic Intelligence Service [3]. Currently, many other USG agencies are engaged in building disease surveillance capacity, including the U.S. Department of State, the Defense Threat Reduction Agency and the U.S. National Institutes of Health [4]. In addition, numerous state, non-state and non-governmental organizations, such as the Bill and Melinda Gates Foundation, the World Bank and Médecins sans Frontières, contribute substantially to capacity-building efforts around the world [5-7].

With the establishment of the Armed Forces Health Surveillance Center (AFHSC) in late 2008, the DoD-GEIS program was transitioned to a division and renamed "AFHSC-GEIS"; however, its mission of working to promote and facilitate national and international preparedness for EID was maintained. Strengthening of U.S. military and host-country disease surveillance and public health laboratory capacity represents a critical step for contributing to compliance with the IHR (2005) detection, reporting and response requirements. During 2009, capacity-building efforts were undertaken in a variety of formats, including enhancement of diagnostic capabilities, expansion of surveillance for militarily relevant infectious and tropical diseases, and deployment of electronic surveillance platforms. These efforts were coordinated with local host-country health officials and geographic Combatant Commands to ensure they addressed country and regional medical priorities as well as to ensure better surveillance and response to disease outbreaks and EID threats to U.S. forces abroad. These efforts focused on influenza and other respiratory diseases, malaria, dengue and other vector-borne illnesses, acute diarrheal diseases, antimalarial and antimicrobial resistance, sexually transmitted diseases, and bacterial wound infections.

Accomplishments

Laboratory infrastructure development

Capacity-building initiatives continued to represent a major component of AFHSC-GEIS contributions to worldwide EID surveillance and response activities. Inadequate laboratory capacity in developing countries has been termed the "Achilles' heel" of global efforts to combat infectious diseases [8]. Thus, many AFHSC-GEIS sponsored activities in capacity building were directed at improving existing infrastructure by renovating current laboratory facilities, furnishing new scientific equipment, and provisioning new or enhanced diagnostic testing systems at overseas U.S. DoD facilities, as well as U.S.-based, DoD influenza reference laboratories, which serve as regional reference laboratories, and host-country laboratories.

Efforts were coordinated with over 80 local and regional Ministries of Health, Agriculture and Defense, as well as other government officials and institutions worldwide in 74 countries. A total of 52 National Influenza Centers (NICs) and other country-specific influenza and EID reference laboratories (44 civilian, eight military) were supported in 46 countries (Table 1). The efforts included support to laboratories in eight regions of the world. Sub-Saharan (east, central and west) Africa were the regions with the most major laboratory capacity-building efforts (in 14 countries), consistent with the identified needs of this region relative to the world, especially as it relates to influenza [9,10]. Among all infrastructure and capacity-building projects (Table 2), the majority supported primarily human health entities (in 67 countries); however, projects also supported animal health entities for zoonotic diseases in eight countries. Training efforts are mentioned, but are presented in detail elsewhere in this supplement [11].

One of the most notable AFHSC-GEIS accomplishments in fiscal 2009 was the establishment of two new biosafety level-3 (BSL-3) laboratory suites within DoD reference laboratories. The Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, completed the first laboratory, which the United States certified and commissioned on July 8, 2009. The suite was officially inaugurated September 16, 2009 and began immediately supporting work in avian and pandemic influenza monitoring, including culture and molecular sequencing capability (Figure 1). This BSL-3 laboratory constitutes the first DoD-certified laboratory of its kind in the region and provides the World Health Organization (WHO), Thailand and other countries in Southeast Asia with a much-needed high-containment capability to conduct research and assist with outbreaks involving select human and animal bacterial and viral strains.

The Naval Health Research Center (NHRC) opened a second BSL-3 (agriculture-enhanced) laboratory suite in late 2009. The facility allows work with zoonotic influenza strains submitted by AFHSC-GEIS partners around the world, including development of new virus neutralization testing capabilities against H5N1 and other highly pathogenic avian influenza strains. Additionally, two BSL-2 laboratories were also established at the Cameroon

Table 1 2009 Major Laboratory Capacity-Building Initiatives by Geographic Region

Geographic Region	Major Laboratory Capacity Building Initiative	Countries Supported
Southeast Asia	NIC & military influenza lab equipment, reagent & training support; EID laboratory diagnostics & disease surveillance systems	Bhutan, Cambodia, Lao People's Democratic Republic, Nepal, Singapore, Thailand
Far East	NIC & military influenza lab equipment & reagent support; EID lab proficiency & equipment support	Japan, Korea, Philippines
East & Central Africa	NIC & VHF lab equipment, reagent & training support; EID laboratory diagnostics	Cameroon, Kenya, Tanzania, Uganda
West Africa	NIC & MoH influenza lab equipment, reagent & training support; VHF lab diagnostics & military EID lab diagnostic testing capacity	Benin, Burkina Faso, Cote d'Ivoire, Ghana, Liberia, Mali, Niger, Nigeria, Sierra Leone, Togo
North Africa, Middle East & Southwest Asia	NIC lab equipment, reagent & training support	Afghanistan, Egypt, Iraq, Jordan, Kuwait, Oman, Pakistan, Sudan, Syria
Central Asia	EID & influenza lab equipment, reagent & training support	Azerbaijan, Georgia, Mongolia
Europe	Military & academic influenza lab equipment, reagent & training support	Poland, Romania
Central & South America	NIC & MoH influenza lab equipment, reagent & training support; leishmania military reference lab equipment, reagent & training support	Colombia, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru

Acronyms: NIC, national influenza center; EID, emerging infectious diseases; VHF, viral hemorrhagic fever; MoH, Ministry of Health.

Army Military Health Research Center, supported by Global Viral Forecasting Initiative in Yaoundé and at the University of Buea (Figure 2). Both facilities will greatly improve the ability to conduct influenza and EID diagnostic work, as well as potentially advanced pathogen discovery work in hard-to-reach locations in Africa.

Efforts were also undertaken to improve laboratory capability for global influenza surveillance and diagnosis, especially regarding the novel A/H1N1 influenza pandemic. To this end, AFRIMS established viral/bacterial pathogen culture and molecular diagnostic capability in their Nepal detachment to support the National Public

Table 2 2009 Capacity-Building Initiatives by Major Regional AFHSC-GEIS Supported Partners and Type

Partner (see text)	Type of Infrastructure/Capacity Building*	Centers/ Hospitals	Field Sites	Countries*
AFRIMS	Influenza & malaria/MDR labs (KH, PH); enteric & influenza lab upgrade (NP, TH); blood culture (NP); influenza testing (BT); influenza antiviral resistance (TH)	22	51	5
NAMRU-2	Malaria, FVBI, enteric, blood culture & AMR testing (KH); influenza & AFI testing (ID, KH, SG); surveillance data management (LA)	4	73	4
NAMRU-3	Influenza, blood culture & AMR testing (EG, JO); Influenza PCR/culture & antiviral resistance testing (32 countries); Joint Biological Agent Identification & Detection System (5 deployed US military sites-CENTCOM**); zoonotic disease & entomology (EG, DJ); AFI, blood/cerebrospinal spinal fluid culture & serology testing (AZ, GE); Leishmania PCR & culture (EG, LR); rotavirus testing (6 countries); cholera & other ADD testing (7 countries); FVBI testing (EG, DJ, AZ, GE)	37	42	34
NMRCD-Peru	Influenza PCR/culture & antiviral resistance testing support (10 countries); AFI & viral culture & serology testing (PE, BO, EC, PY); Leishmania PCR, MDR, urine/vaginal PCR-STIs, Rickettsial PCR & culture (PE); enteric culture, PCR & AMR testing (PE, EC, PY); Alerta electronic disease surveillance system (PE, PA, EC)	23	102	11
USAMRU-Kenya	Malaria/MDR, microscopy & PCR, rotavirus, cholera & other ADD testing, arboviral/VHF PCR & culture, AFIs, blood culture & serology testing, STIs culture (KE); influenza PCR, culture &genotyping (KE, UG, CM); influenza, AFI, FVBI, cholera & other ADDs (KE, TZ, NG)	7	69	5
PHCR-South	Influenza PCR, culture & indirect immunofluorescence assay (US, HN, SV, NI, GT, PA); malaria, Leishmania, & dengue PCR testing (HN)	4	7	6
Univ Iowa CEID	Respiratory & other zoonotic respiratory EID testing & epidemiology (US, TH, KH, NG, RO, MN)	6	~30	6
JHU/APL	Influenza military treatment facilities (PIPM) modeling (US); SMS text & ESSENCE Desktop edition system (PH); Open source Interactive Voice Recognition software surveillance (PE); OpenESSENCE website software surveillance (US, PE); SMS text (PH)	1	~125	3

Acronyms: MDR, multidrug resistance; FVBI, febrile & vector-borne illnesses; AMR, antimicrobial resistance; AFI, acute febrile illnesses (such as dengue, leptospirosis and zoonotic infections); PCR, polymerase chain reaction; ADD, acute diarrheal diseases (such as traveler's diarrhea, campylobacter, shigellosis, salmonellosis); STIs, sexually transmitted infections, including *Neisseria gonorrhea*; EID, emerging infectious diseases; PIPM, Pandemic Influenza Prevention Modeling; SMS, Short Message Service; ESSENCE, Electronic Syndromic Surveillance for Early Notification of Community-based Epidemics.

*Country names are displayed in parenthesis using the International Organization for Standardization (ISO 3166) two-character code (URL: http://www.commondatahub.com/live/geography/country/iso_3166_country_codes?gclid=CPSnst2e5KQCFQqP5god3xzd8A); Countries column represents the number where activities have been implemented; U.S. military deployment sites (such as Iraq, Afghanistan) or U.S. Department of State embassies do not contribute to separate country counts, since they represent overseas locations where U.S. forces and/or civilians are deployed or stationed.

**CENTCOM, U.S. Central Command (forward U.S. troop deployment sites).

Figure 1 AFRIMS BSL-3 Laboratory Commissioning. On September 16, 2009 (from left to right), Major General Krisada Duangurai, director general of AFRIMS; U.S. Ambassador Eric John, together with Colonel James Boles, commander of AFRIMS, officiated the ribbon-cutting ceremony for the AFRIMS BSL-3 laboratory. This facility significantly contributes to the country's capacity to conduct research and investigate outbreaks caused by agents, such as avian influenza, chikungunya virus and other endemic diseases throughout Southeast Asia.

Figure 2 Influenza Surveillance Capacity-Building Initiative with Global Viral Forecasting Initiative and University of Buea, Cameroon. Two biosafety level-2 laboratories were renovated at the Cameroon Army Military Health Research Center in Yaoundé and at the University of Buea, in cooperation with the Cameroon government and military. These laboratories have the capacity to isolate and characterize human and animal influenza viruses, as well as other EID pathogens of unknown origin.

Health Laboratory and also established real-time reverse transcriptase polymerase chain reaction (rRT-PCR) diagnostic capacity for influenza at a main tertiary-care hospital of the Department of Health within the Visayas region of the Philippines.

Developing influenza diagnostic capabilities at other NICs was also supported by the U.S. Naval Medical Research Unit No. 3 (NAMRU-3) in Afghanistan, Iraq and Jordan; by the U.S. Naval Medical Research Center Detachment in Peru (NMRCD-Peru) in the countries of Colombia, Ecuador, Paraguay and Venezuela; and in Kenya, by the U.S. Army Medical Research Unit-Kenya. Finally, in conjunction with the CDC's Central America and Panama center, the U.S. Army Public Health Command Region-South (PHCR-South) provided laboratory technical assistance, reagents and supplies to the Ministries of Health (MoHs) in El Salvador, Guatemala, Honduras, Nicaragua and Panama, resulting in the certification of the Guatemalan NIC and the testing of over 5,000 specimens for novel A/H1N1.

In collaboration with the Peruvian Navy, NMRCD-Peru has built a robust shipboard disease surveillance infrastructure with detection capability modeled very closely on the NHRC shipboard surveillance system. The early detection aspect of this system involves equipping participating ships with real-time PCR diagnostic capability for emerging infectious diseases, such as influenza or adenovirus. Short-term storage of samples allows for more in-depth, follow-up testing at the laboratory in Lima or at other collaborating regional laboratories. Since 2007, this system has successfully identified and responded to numerous outbreaks of respiratory, gastrointestinal and sexually transmitted infections among active-duty Peruvian personnel aboard ships [12]. More recently, this capability was instrumental in identifying and responding to a large outbreak of novel A/H1N1 on board a large deck ship in the Pacific [13].

This investment in laboratory infrastructure development has directly impacted the number of outbreak investigations that the AFHSC-GEIS network has been able to support. The capacity-building efforts contributed to outbreak responses in 76 instances in 53 countries, representing every major populated region of the world, including support for the confirmation of the first cases of novel A/H1N1 in 14 countries (United States, Bhutan, Cambodia, Colombia, Djibouti, Ecuador, Egypt, Kenya, Kuwait, Lao People's Democratic Republic (PDR), Lebanon, Nepal, Peru and the Republic of the Seychelles) [12]. The laboratory infrastructure allows for acute response capability and the ability to monitor ongoing epidemics or shifting EID patterns, such as the identification and continued monitoring of artemisinin-resistant malaria in Southeast Asia by partners from AFRIMS [14] and at the U.S. Naval Medical Research Unit No. 2 (NAMRU-2) or the search for genetic mutations within influenza viruses that may indicate resistance to antiviral medications.

Training

It is important to recognize that capacity building not only involves renovating laboratories and providing diagnostic equipment and supplies, but most important, building human capacity. Through training public health and laboratory personnel, the physical infrastructure could be properly leveraged for optimal support of IHR (2005) compliance. During 2009, AFHSC-GEIS supported 18 partner organizations that conducted 123 training initiatives in 40 countries involving at least 3,130 people, including many host-country personnel, in direct support of assisting with compliance with IHR (2005). Significant expansion of training activities was attained in the areas of pandemic preparedness, outbreak investigation and response, EID surveillance, and pathogen diagnostic techniques.

By engaging local health and other government officials and civilian institutions in training endeavors, the U.S. military's role as a key stakeholder in global public health has improved; and many opportunities for EID-related surveillance, research and capacity-building initiatives have been leveraged to provide a platform for public health training, described elsewhere in this supplement [11].

Electronic surveillance initiatives

Electronic disease surveillance, another important component of a comprehensive global public health disease prevention and control strategy, contributes significantly to capacity building and support for IHR (2005) compliance in partner countries. Using electronic methods for data collection and analysis has the potential to improve the accuracy and timeliness of outbreak detection, as well as to provide situational awareness during, or in the aftermath of, an outbreak or pandemic. The AFHSC-GEIS network has supported numerous initiatives in electronic disease surveillance during the past several years, in partnership with several DoD overseas laboratories, host-country Ministries of Health and Defense and our technical partner, the Johns Hopkins University Applied Physics Laboratory (JHU/APL).

AFHSC-GEIS has relied on the extensive experience that JHU/APL acquired in the design and implementation of the Electronic Syndromic Surveillance for Early Notification of Community-based Epidemics (ESSENCE) system [15]. This electronic disease surveillance system, used worldwide at all DoD military treatment facilities (MTFs), the U.S. Veterans Health Administration system and at least 12 states in the United States, served as a

model for a toolkit approach to deploying electronic surveillance within the AFHSC-GEIS network. Tools have been created to enable data collection from the most sophisticated data sources to remote settings where data have traditionally been difficult, if not impossible, to collect. These tools have far-reaching applicability in any resource-limited setting, whether overseas or after a disaster in the United States. The following describes some of the efforts that have focused on adapting electronic or syndromic surveillance techniques to resource-limited settings.

Two electronic surveillance efforts were developed at AFRIMS in Southeast Asia and optimized in 2009, including a project with the Royal Thai Army (RTA) in remote border areas, as well as a pilot short message service (SMS)-based project in the Philippines, part of a joint effort with JHU/APL and the Cebu City Health Office (CHO). The Thai Unit-Based Surveillance (UBS) project commenced in 2001 and originally covered areas along the Thai-Cambodia border where the Thai MoH did not have disease surveillance capabilities. The project, developed by the RTA with support from AFRIMS and AFHSC-GEIS, reports diseases in both military and local civilian populations by faxing reports or by voice via military radio. In 2009, the Thai-Myanmar border area was added and an additional 497 personnel were trained. Version 2.0 of the UBS simplified data collection from 216 symptoms and categorization into 12 syndromes that are consistent with the Thai MoH's reporting requirements. This updated system added questions about poultry exposure, leptospirosis, novel A/H1N1 infection and chickungunya virus infection. Although no major outbreaks of disease were detected by this system in 2009, it continued to provide situational awareness for the RTA and Thai MoH.

Dengue fever poses a significant health threat in the Philippines. Current hospital-based surveillance is highly valid, but poorly suited for rapid identification of dengue "hot spots" because of delays associated with laboratory confirmation. To capture this important data for the purposes of surveillance, a more rapid, but less specific surveillance method was implemented and compared to the standard sentinel surveillance system. This pilot study implements and evaluates a simple dengue surveillance protocol using SMS text messages to send daily, person-based dengue surveillance data from local Barangay Health Centers (BHCs) to the city health office (CHO) in Cebu City. The pilot activity was originally established in five clinics as of March 2009, but was soon instituted in all BHCs in the city. Beginning July 1, 2009, all BHCs have been identifying all patients reporting to clinic with fever. Each day, BHC personnel send this information to the CHO, creating a text message for each patient with fever. The SMS message contains the date and clinic name, as well as the patient's name, age, gender and symptoms. The message is transferred into a Microsoft Access© database, cleaned, and starting July 2010, reviewed in the ESSENCE Desktop Edition application to identify statistically significant increases in reported fever cases.

Meanwhile, NAMRU-2 continued to support the optimization of the Early Warning Outbreak Recognition System (EWORS) at 11 reference and provincial hospitals in the Lao PDR allowing local MoH officials to monitor the impact and burden of tropical and infectious diseases in the country in real time. The CDC currently funds most of the operating budget for EWORS in Lao PDR. The system, jointly developed by the Indonesian MoH and NAMRU-2 with AFHSC-GEIS funding, is also being used in Indonesia as the national reporting system. EWORS has additionally been used in Cambodia, Peru and Vietnam, although it is no longer in use in these countries because local health authorities favored other surveillance systems.

In South America, NMRCD-Peru supported major efforts in electronic disease surveillance, including continuation and optimization of Alerta, a public-private initiative that has revolutionized surveillance for the Peruvian military during the past seven years. The Alerta system has seen recent expansion to all branches of the Peruvian military, as well as adoption by the MoH of one other country in the region—Panama. This system identified 17 outbreaks during 2009, including influenza, dengue, mumps, malaria, hepatitis A and respiratory disease.

Finally, in collaboration with the JHU/APL group, NMRCD-Peru worked to develop an electronic syndromic surveillance system based on open-source software for use in resource-limited environments. As a result, the system can be sustained without continued major investments or software licensing fees. This effort involved the development of interactive voice response reporting, as well as building a web-based infrastructure and database on an open-source version of the ESSENCE system (OpenESSENCE) in use in the United States. Additionally, NMRCD-Peru supported the systematic evaluation of these electronic surveillance systems and research on ways to improve reporting via electronic systems [16].

These electronic surveillance initiatives constitute a vibrant portfolio that capitalizes on the expertise of the JHU/APL group and numerous AFHSC-GEIS partners at overseas laboratories and within host-country Ministries of Health and Defense. Many of the lessons learned, challenges, successes and failures have been shared within this network of collaborators, and a harmonized strategy is emerging to develop and deploy an electronic disease surveillance system that is modular and responsive to various needs found in developing settings. This approach should assist many countries in complying with IHR (2005) by the 2012 deadline.

Provision of technical expertise/reference laboratory support

In addition to supporting laboratory infrastructure development and new surveillance initiatives, AFHSC-GEIS provided technical expertise in support of capacity-building efforts. In 2009, one of the largest such efforts was the network's global response to the novel A/H1N1 influenza pandemic. For example, NAMRU-3 provided training on laboratory techniques for 73 scientists and technical personnel from 32 countries in western and northern Africa, the Middle East, and central Asia, as well as equipment and reagent support to established NICs in Egypt, Kuwait, Oman, Pakistan, Sudan and Syria. Support for further viral characterization by genetic sequencing and antiviral resistance testing was also performed at NAMRU-3, with reference testing support by the CDC in Atlanta. This virology diagnostic-testing capacity building of national reference laboratories constituted an essential step in establishing the capability for H5N1 and novel A/H1N1 detection and rapid response, and resulted in a better understanding of the epidemiologic patterns of respiratory viruses circulating in the region. It also represented the first step toward NIC accreditation and collaboration with the WHO Global Influenza Surveillance Network in support of influenza vaccine development. By linking countries in regional and sub-regional networks and by fostering participation in WHO missions to assess laboratory testing capacity needs, NAMRU-3 played a direct role in promoting IHR (2005) compliance.

Working closely with U.S. Central Command and U.S. Africa Command, NAMRU-3 and the U.S. Navy Environmental and Preventive Medicine Unit No. 2 (NEPMU-2) provided focused laboratory assessment, training, emergency supplies and quality assurance support to five military, far-forward deployed, influenza testing laboratories in Southwest Asia and assisted with the deployment of the Joint Biological Agent Identification and Detection System (JBAIDS) platform for confirmation of novel A/H1N1 cases in-theater. This capability subsequently proved critical when Expeditionary Medical Forces in Kuwait and Djibouti were able to identify and respond to novel A/H1N1 and seasonal influenza outbreaks, respectively.

Network expertise and competence were important in supporting global influenza testing efforts. For instance, the AFRIMS-supported laboratory in the Philippines was designated by the Philippine NIC as the only other facility authorized to conduct novel A/H1N1 testing, in support of central and southern regions of the country (specifically, Mindanao and Visayas).

Military-to-military (mil-mil) partnerships

Growing collaborative military-military partnerships and surveillance exchanges among global network partners and foreign military counterparts continued to be an area of high interest and priority for AFHSC-GEIS. The network currently supports active military partnerships in 14 countries. These partnerships resulted in a number of collaborative response activities that supported foreign military partners, multinational peacekeepers and observers in joint exercises and missions.

The late spring and summer outbreaks of novel A/H1N1 in military treatment facilities throughout Europe resulted in collaboration between Landstuhl Regional Medical Center and PHCR-Europe and the German Military Reference Laboratory. The long-standing relationship between the U.S. European Command and the German Army's Public Health Service helped assist in disseminating confirmed results through weekly surveillance reports sent to military clinicians, hospital commanders, and other public health officials within the U.S. military and the local German public health infrastructure. This arrangement greatly aided the U.S. European Command's ability to conduct surveillance for novel A/H1N1 within the European military community and assisted German government officials in monitoring the level of disease within their country.

Efforts have been established to collaborate on more expansive and cross-cutting surveillance systems with military partners in Poland and Singapore. These efforts include a wide spectrum of surveillance from electronic early detection systems and routine laboratory-based sentinel surveillance to robust pathogen discovery initiatives and focused public health research endeavors. Collaboratively, these efforts have developed significantly during the past year and have helped serve as a model for other AFHSC-GEIS partners to engage their regional foreign military counterparts. These mil-mil partnerships with allied countries allow for open collaboration, capacity building and transparent dialogue between partner countries, and thus have the potential to develop a meaningful framework to better understand disease dynamics among military populations in different parts of the world. To further foster opportunities for these mil-mil partnerships, AFHSC-GEIS is working with the International Congress on Military Medicine and the WHO by facilitating educational opportunities with regard to IHR (2005) and creation of a portfolio of robust epidemiological tools and training that member countries can access as needed [17].

Future directions and challenges

Significant progress was attained in expansion of worldwide EID surveillance and response initiatives in fiscal 2009 through the capacity-building efforts of the AFHSC-GEIS network described above. At this juncture, however, it is necessary to achieve realistic goals in terms of maturation, standardization and unification of the division's global surveillance efforts. This can best be

accomplished by pursuing the following strategic goals: 1) adopting objective metrics of evaluation, such as timeliness of disease detection and reporting to higher levels, proportion of sites submitting timely weekly or monthly reports, proportion of investigated outbreaks with confirmed laboratory results, and proportion of confirmed outbreaks with nationally recommended public health response [18]; 2) ensuring future standardization of genetic and molecular-based testing platforms (e.g., PCR-based assays) across the network of partners; 3) establishing electronic sequence data repositories for more effective information sharing with the CDC, WHO and local regional health authorities (especially for influenza and other respiratory pathogens); 4) continuing emphasis on collaborative work with host-country partners to empower them to reach IHR (2005) capacity-building milestones by 2012; and, 5) achieving standardized reporting schemes for all AFHSC-GEIS partners in the areas of influenza, enteric diseases, febrile and vector-borne illnesses, sexually transmitted infections, and antimicrobial resistance monitoring. In this manner, the AFHSC-GEIS network will continue to contribute to the global efforts in disease control and prevention through the DoD's laboratory-based surveillance and by enhancing harmonization of efforts with other key USG stakeholders, such as the U.S. Department of Health and Human Services, the U.S. Agency for International Development and the U.S. Department of State.

Many challenges exist to building capacity for public health in resource-limited settings, including achieving sustainability of efforts after support is withdrawn, containing the departure of highly-trained, capable scientists after training, and minimizing the duplication of efforts among multiple sponsor agencies within the USG and with other organizations. Data sovereignty and data sharing are also key issues that require transparency on the part of both the sponsor and recipient in order to optimally conduct disease surveillance that satisfies the spirit of IHR (2005). Solutions to many of these challenges are sometimes difficult and frequently require continuous re-evaluation of best of practice solutions for individual settings.

Through the development of active, mutually supportive relationships with local health officials and the establishment of important protocol-driven clinical and laboratory surveillance projects, AFHSC-GEIS supported scientists have become relevant stakeholders within host-country public health communities and are able to continue to work in the critical development of surveillance, laboratory and communications infrastructure within partner countries. In addition to the IHR (2005), the AFHSC-GEIS global network recognizes the recently released National Strategy for Countering Biological Threats (PPD-2) as another guiding framework for alignment of our program with the larger USG initiatives [19], keeping the maintenance of the U.S. military's health (known as "Force Health Protection") as our unique niche in the setting of improving global public health. Meaningful public health initiatives taking place in any one of the partner countries within the AFHSC-GEIS global network must aim for incremental, albeit sustainable, development of capacity on behalf of their partner host countries and do so in line with the specific PPD-2 objectives and IHR (2005) competencies. In this manner, small improvements in capacity, improved testing abilities, and ultimately, compliance with reporting will lead to benefits for the health of U.S. servicemembers and for the health of the world.

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Competing interests

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Training initiatives within the AFHSC-Global Emerging Infections Surveillance and Response System: support for IHR (2005)

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Abstract

Training is a key component of building capacity for public health surveillance and response, but has often been difficult to quantify. During fiscal 2009, the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) supported 18 partner organizations in conducting 123 training initiatives in 40 countries for 3,130 U.S. military, civilian and host-country personnel. The training assisted with supporting compliance with International Health Regulations, IHR (2005). Training activities in pandemic preparedness, outbreak investigation and response, emerging infectious disease (EID) surveillance and pathogen diagnostic techniques were expanded significantly. By engaging local health and other government officials and civilian institutions, the U.S. military's role as a key stakeholder in global public health has been strengthened and has contributed to EID-related surveillance, research and capacity-building initiatives specified elsewhere in this issue. Public health and emerging infections surveillance training accomplished by AFHSC-GEIS and its Department of Defense (DoD) partners during fiscal 2009 will be tabulated and described.

Background

In order to achieve optimal and coordinated implementation of IHR (2005), each member state must be capable of detecting, confirming, reporting and containing an emerging threat to public health [1] by 2012. To reach these 2012 milestones, member states will need to significantly enhance their laboratory infrastructure, and more importantly, appropriately train personnel who can perform the core-capacity functions defined in Article 5 of IHR (2005). These core capacities include leading outbreaks investigations, correctly identifying a pathogen in the laboratory, rapidly communicating findings to stakeholders at all levels, and most importantly, controlling the outbreak through tested and exercised mitigation efforts.

Front-line public health professionals require the latest knowledge and skills to address the evolving nature of potential global threats to public health. The recent pandemic of novel influenza A/H1N1 clearly illustrates the unpredictable nature of pathogens that require dynamic and evolving public health strategies for surveillance, disease management and mitigation.

Training public health professionals, both host-country and U.S. DoD personnel, to understand, monitor, respond to, control and prevent emerging infections is a foundational goal of AFHSC-GEIS. The center has the mission of conducting surveillance for emerging infectious diseases that could affect the U.S. military [2]. AFHSC-GEIS promotes national and international preparedness for emerging infections through orchestrating a global array of surveillance projects, capacity-building efforts, outbreak investigations and training exercises [2].

Since its inception, AFHSC-GEIS partners and collaborators have made available their overseas laboratory and field study facilities to serve as regional focal points for the training of staff, technicians and epidemiologists within partner host countries [3-5] through a growing collaborative network of U.S. government agency

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partners. A wide range of training has been coordinated at these sites, including programs such as the Centers for Disease Control and Prevention's (CDC's) Field Epidemiology Training and Laboratory Training Programs [6] and the U.S. Agency for International Development efforts through Africa and the Pacific [7,8]. These training opportunities serve as a forum for support, coordination and collaboration with host-country partners as prescribed in Article 44 of the IHR (2005). These efforts are conducted in close collaboration with host-country counterparts utilizing standardized teaching tools and guidelines developed by WHO [9] and other international global health entities to enhance core public health capacities within each partner host country.

In addition, through the Uniformed Services University of the Health Sciences (USUHS) Center for Disaster and Humanitarian Assistance Medicine (CDHAM), educational efforts in support of five combatant commands have been bolstered with AFHSC-GEIS funding. Such training provides much-needed professional expertise and the latest technical information to U.S. military and civilian health care providers, as well as to host-country Ministries of Health, Agriculture and Defense, and other civilian agency collaborators. These initiatives result in significantly improving the professional engagement of host-country officials, as well as further enhancing the U. S. government's role as a key stakeholder in the global health community. Training initiatives encompass such topics as planning and preparedness, outbreak investigation, surveillance and response for a wide spectrum of disease- or syndrome-causing agents. This report summarizes training initiatives and highlights select training projects conducted by AFHSC-GEIS-funded partners from September 2008 to October 2009.

Methods

Authors of this report reviewed all fiscal year 2009 (September 2008 to October 2009) individual project reports, as well as program reports from AFHSC-GEIS coordinators submitted to AHFSC-GEIS, and identified specific training programs conducted by partners. In this review, the authors included training activities such as workshops, academic courses, conferences, tabletop exercises and distance learning. Stand-alone lectures, descriptive program presentations and poster presentations are not included, although these remain an integral part of disseminating program findings and information.

Results

During fiscal 2009, 18 partner organizations conducted 123 training initiatives in 40 countries, reaching approximately 3,130 U.S. military and civilian personnel, as well as host-nation personnel (Additional file 1 and Table 1). These educational efforts covered a wide range of topics. The most common categories were EID laboratory techniques (41 percent), pandemic influenza (24 percent) and disease surveillance techniques (19 percent). Training modalities included workshops (defined here as hands-on, interactive training), academic courses, conferences, tabletop exercises, and on-line and telephonic distance learning. Duration of training ranged from 0.5 hours to six months, with the majority of education efforts lasting two to five days.

Table 1 AFSHC-GEIS-Funded Training Initiatives by Combatant Command Location of Training, October 2008-September 2009

Combatant Command	No. total training initiatives	No. countries	No. trainees*
U.S. Africa Command	15	10	294
U.S. Central Command	17	6	454
U.S. European Command	19	8	1057
U.S. Northern Command	28	1	595
U.S. Pacific Command	35	10	623
U.S. Southern Command	9	5	107
TOTAL	123	40	3130

*Where exact figures are not known, an estimate of the number of trainees is provided.

In terms of AFHSC-GEIS pillars, respiratory infections (namely influenza) represented the majority of training initiatives (68 percent), followed by febrile and vector-borne infections (11 percent), gastrointestinal infections (5 percent), and antimicrobial resistance (2 percent). The remaining 14 percent included various topics (geographic information systems, EpiInfo, field epidemiology, principles and practice of clinical research, outbreak investigation, emerging infectious diseases, lab safety precautions, ecological niche modeling and tropical medicine student rotations) (Figure 1). Training initiatives conducted in fiscal 2009 did not focus on sexually transmitted infections. Training occurred in each of the six Combatant Commands (COCOM). The most occurred in the U.S. Pacific Command (USPACOM) and the least in U.S. Southern Command (USSOUTHCOM) (Table 1). Figure 2 shows the geographic distribution of these initiatives across the globe.

The following sections describe selected examples of training initiatives that highlight the breadth of AFHSC-GEIS efforts in this arena.

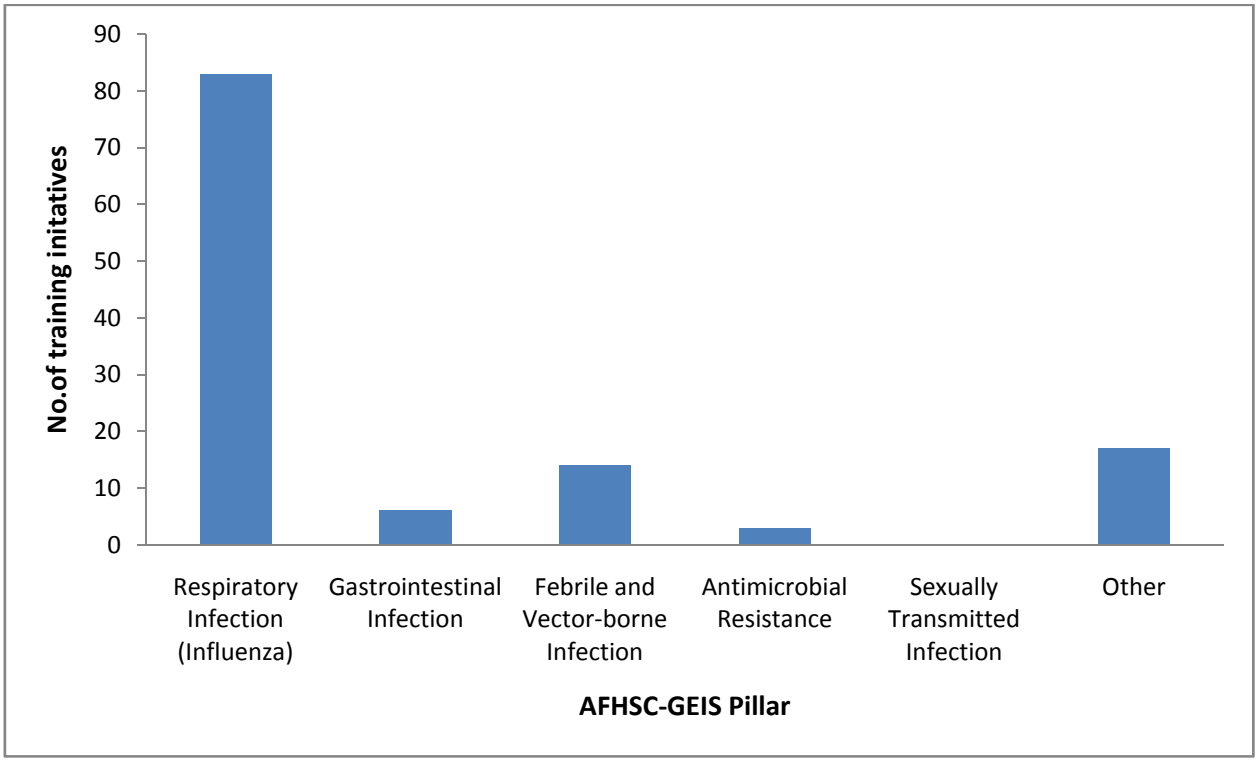

Figure 1 AFHSC-GEIS-Funded Training Initiatives by AFHSC-GEIS Priority Pillar, October 2008-September 2009.

CDHAM combatant command training

All U.S. military initiatives are coordinated by six COCOMs specific to geographic regions of the world: USPACOM, U.S. European Command (USEUCOM), U.S. Northern Command (USNORTHCOM), U.S. Central Command (USCENTCOM), U.S. Southern Command (USSOUTHCOM) and U.S. Africa Command (USAFRICOM). These geographic COCOMs provide U.S. military representation to international and U.S. national agencies within their area of responsibility (AOR).

In fiscal 2009, AFHSC-GEIS funded training programs for COCOMs through CDHAM. Affiliated with USU, CDHAM assisted COCOMs in developing, planning and executing education and training programs for pandemic and avian influenza surveillance and response. As depicted in Additional file 1, in fiscal 2009, CDHAM conducted a total of 12 conferences and tabletop exercises, training 673 individuals in support of four COCOMs: USPACOM, USEUCOM, USCENTCOM and USNORTHCOM. CDHAM conducted two training initiatives in the USPACOM's area of responsibility: a workshop on public health management of pandemic influenza (PHMPI) in Malaysia and the USPACOM Medical Surge Conference, held in Indonesia, which drew 64 participants from India and Indonesia. In EUCOM, CDHAM supported four separate PHMPI workshops in Armenia, Poland, Romania and the United Kingdom involving approximately 190 participants, as well as a European pandemic influenza (PI) Synchronization Conference in Switzerland for 55 participants.

In support of USCENTCOM, CDHAM planned and executed two PHMPI workshops in Kyrgyzstan, which involved 60 participants from Tajikistan, Turkmenistan, the United States and Uzbekistan; and one in Pakistan for 40 participants. These workshops offered a venue for each of the country's Ministries of Defense to present their respective PI plan, focusing on strategies of containment, identifying available resources and existing gaps, and identifying and addressing these gaps with the assistance of the U.S. DoD. The program for this conference comprised three days of lectures, country briefs and breakout sessions.

University of Iowa certificate in emerging infectious disease epidemiology

Developing countries have a strong desire to acquire advanced training in public health from recognized universities in the U.S. and Europe. Many AFHSC-GEIS partners are asked to support this type of training. The University of Iowa developed a certificate program to provide training at an internationally known U.S.

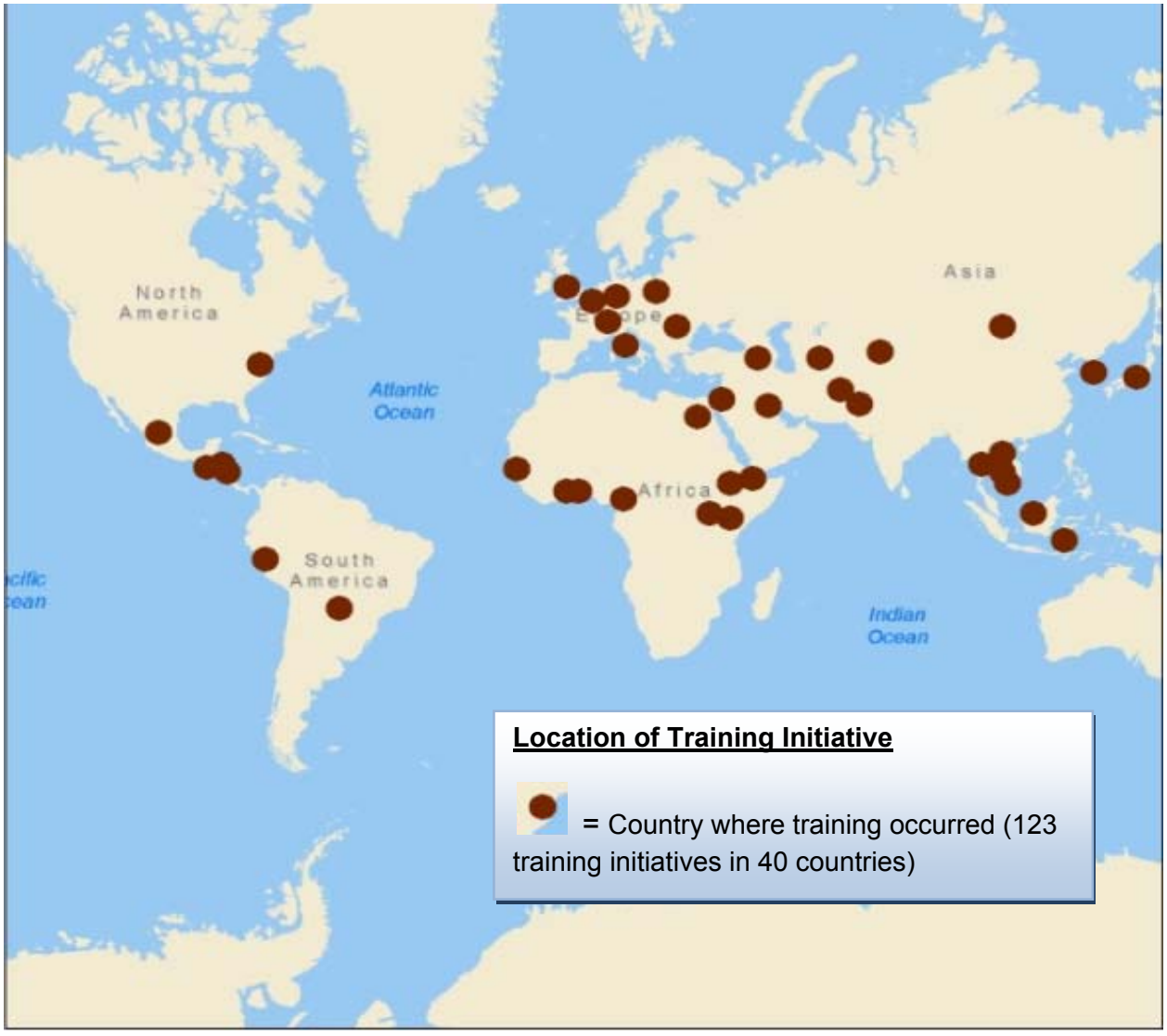

Figure 2 Geographic Distribution of AFHSC-GEIS-Funded Training Initiatives, October 2008-September 2009.

university, through graduate level coursework that trainees could use as an entry to additional graduate studies and potentially the completion of a master of public health (M.P.H.) degree. The certificate program aims to build sustainable epidemiology research capacity in infectious disease by promoting collaborations between international U.S. laboratories and other nations. The program also trained promising young public health officials who will hopefully support public health capacity in their home countries and contribute to the control of local epidemics that may have a global effect.

With AFHSC-GEIS funding, the University of Iowa's College of Public Health created a 12-semester-hour Certificate in Emerging Infectious Disease Epidemiology, nine hours of which may be applied toward an M.P.H. degree. For the summer 2009 class, 33 foreign nationals (from Bangladesh, Egypt, Indonesia, Kenya, Mongolia, Nepal, Nigeria, Pakistan, Panama, Peru, the Philippines, Poland, Rwanda and Thailand) were nominated and enrolled in the certificate program by the DoD overseas research laboratory commanders, AFHSC-GEIS staff, CDC, and U.S. Department of State. Intensive training was conducted in Iowa City for two weeks (six semester hours) that included lectures, tutorials, field experiences, lab exercises, public health demonstrations and written examinations. The remaining credits were earned via web-based curricula [10].

U.S. Army Medical Research Unit-Kenya (USAMRU-K) Malaria Diagnostics Center of Excellence

The continued operation of the Malaria Diagnostics Center of Excellence (MDCoE) in Kisumu, Kenya, provided important contributions in professional malaria diagnostic training. The MDCoE was established in 2004 with AFHSC-GEIS funding. Objectives of the center include training microscopists working in the clinical setting in developing countries and transferring technology to host countries [11].

In fiscal 2009, the MDCoE conducted seven basic malaria microscopy courses, four of which were AFHSC-GEIS-funded, which reached 55 laboratory technicians from Kenya, Nigeria, Republic of South Africa, Tanzania, Uganda and the United States. Each course consisted of 10 days of laboratory practical sessions, lectures, group discussions, demonstrations, take home assignments and pre- and post-course examinations.

By training microscopists who support malaria clinical trials and disease surveillance projects, the MDCoE helped to improve the quality of data generated by these projects. In addition, training of Kenyan clinical microscopists, as well as microscopists from other African countries, will hopefully improve the quality of health care delivery and potentially contribute to a reduction in the malaria disease burden in the local population.

The MDCoE also conducted a mosquito taxonomy and control course, which was taught to 15 Kenyans from the Division of Vector-Borne Diseases in February 2009. This course focused on insect vector taxonomy, identification and control. By teaching this course, USAMRU-K was better able to understand Kenyan vector-control efforts and learn of locations with high risks for vector-borne diseases. They were also able to better identify potential sites for future surveillance activities. The addition of this course expanded outreach potential and should lead to improvement of the quality of their vector surveillance and control programs in Africa.

USUHS–geographic information systems

In the fields of public health and epidemiology, geographic information systems (GIS) have become increasingly popular and beneficial as a tool for tracking epidemics and showing geographic trends of various diseases. In fiscal 2009, USUHS offered important training in the use of GIS for military and civilian students, as well as overseas laboratory personnel.

The University developed and conducted five basic GIS training initiatives, two of which were training courses at the Armed Forces Research Institute of the Medical Sciences (AFRIMS) in Thailand. The first included a two-hour mini-course, presented to 24 project managers, on the use of GIS and remote sensing, or the acquisition of information using either recording or real-time sensing devices, in vector-borne disease studies. USUHS conducted a second one-day course on using global positioning systems in the field and in GIS to 21 technicians.

In addition, USUHS continues to offer an introduction to GIS course as part of its master's degree program in public health. In fiscal 2009, four students enrolled in this course. The University has also provided basic GIS training on an individual basis. University instructors provided basic GIS training to a visiting Thai student, whose dissertation involved examining the distribution of mosquito larvae in Southeast Asia, as well as an analyst in Korea.

Finally, USUHS administered a more advanced two-day course on ecological niche modeling to 17 GIS analysts at AFRIMS. This course focused on creating predictive maps of disease and vector distribution. The use of GIS in public health and epidemiology is an important tool, and the GIS training initiatives of USUHS provide public health students and lab personnel with important skills directly applicable to their field.

U.S. Naval Medical Research Center Detachment (NMRCD)

Like the other overseas laboratories, NMRCD has a long and successful history of conducting innovative training in laboratory methods, epidemiology and research ethics. Each scientific department conducts laboratory training in their respective fields, but the Public Health Training Program within the Emerging Infections Department undertakes the majority of NMRCD training. This group has successfully leveraged U.S. Agency for International Development, CDC and the U.S. National Institutes of Health (NIH)/Fogarty International Center grants, in addition to AFHSC-GEIS funding, to further their training mission in the epidemiology of emerging infectious diseases.

The detachment has used multiple formats to accomplish its training mission. Target audiences included personnel from local Ministries of Health, Agriculture and Defense, academic staff and scientists from Peru and other countries in the Americas, as well as U.S. military and civilian scientists. The countries reached by NMRCD training included Chile, Paraguay, Peru and the United States.

The general approach to training at NMRCD promoted the integrated use of epidemiological, public health and clinical skills, coupled with innovative methods adapted specifically for the region of the Americas. Specifically, this included the continuation of a well-regarded outbreak investigation course in Peru and Paraguay, the introduction of a new course on field epidemiology methods in Peru, and the continued support for the fifth iteration of the NIH's Clinical Research videoconference over three months.

Challenges encountered by partners in conducting training initiatives

Although the majority of AFHSC-GEIS partners did not report challenges in conducting training initiatives, some did encounter difficulties. The most frequent problems noted by overseas partners related to host-nation issues, including political instability and insufficient infrastructure. For example, after the disputed Kenyan presidential elections in December 2007, the ensuing political instability and breakdown of law and order resulted in a burglary at USAMRU-K, where many AFHSC-GEIS program computers were stolen or vandalized. Likewise, political instability in Honduras impeded Public Health Command Region-South personnel from working effectively in the country for several months.

Insufficient host-nation infrastructure reported by AFHSC-GEIS overseas partners included unreliable communications networks and frequent power outages. Other reported challenges of undertaking AFHSC-GEIS projects outside the United States involved acquiring supplies, materials and equipment; finding and training competent personnel; establishing and maintaining collaborative agreements with host countries; and overcoming language barriers. Inadequate English proficiency was the most significant barrier to student performance in the University of Iowa's certificate program in emerging infectious disease epidemiology. Funding delays, as well as the challenge of maintaining continuity of projects with uncertain funding, were also noted by several AFHSC-GEIS partners.

Discussion

Experts note a growing realization that to improve global public health substantially, a training agenda must be developed that will sustainably educate the public health work force. Numerous training efforts now exist, but more comprehensive and coordinated approaches are needed. Some of these current efforts are extremely robust, such as the Field Epidemiology and Laboratory Training Program (FELTP), long considered the gold standard in public health training. However, this program reaches limited numbers of public health officials due to its comprehensive nature [12]. To fill this gap, shorter-term field, laboratory and academic training options are needed [13,14]. These directed training opportunities allow for the rapid acquisition of specialized skills, especially in laboratory techniques, outbreak investigation, and response and control of emerging infectious disease. Importantly, they serve a key role in supporting the implementation of the IHR (2005) and in meeting the local and regional public health needs of developing countries.

Epidemiologic and laboratory training are key components of public health capacity building, and thus, represent an important strategic goal of the AFHSC-GEIS network. From September 2008 through October 2009, the AFHSC-GEIS network, through 18 partner organizations, conducted 123 training initiatives in 40 countries that reached 3,130 U.S. and host-country personnel. Expanded training activities in the areas of pandemic preparedness, outbreak investigation and response, EID surveillance, and pathogen diagnostic techniques have contributed to building robust capabilities at the local level, in direct support of the implementation of IHR (2005).

In addition to documenting the educational initiatives of AFHSC-GEIS partners, this review provides recommendations for improving training activities that merit attention. The first and second recommendations are "global" in nature, requiring action by entities outside AFHSC-GEIS. The third and fourth recommendations are internal to AFHSC-GEIS, relating to quality improvement. Finally, the fifth recommendation requires the action of other entities, as well as AFHSC-GEIS itself.

First, coordinate training initiatives among partners to avoid unnecessary duplication and maximize resources to address gaps. This should be done with other state and non-state entities (CDC and WHO), as well as nongovernmental organizations, academia and other groups involved in global public health education. Training is an essential but time-consuming activity. Training conducted by AFHSC-GEIS partners in fiscal 2009 appear to be largely project-specific and do not seem to be closely coordinated within regions or between partners. As shown in Figure 1, respiratory infections (namely influenza) represented the majority of training initiatives (68 percent) in fiscal 2009. Although these educational efforts targeting influenza were important, especially in light of the recent pandemic, increased coordination and communication among partners may have brought focus to gaps in training, such as in sexually transmitted infections, one of the AFHSC-GEIS pillars (Figure 1).

Second, plan and develop training initiatives in a strategic, systems manner. A strategic and systematic approach to identifying training needs and developing educational initiatives would enhance coordination of efforts, assist in identifying appropriate subject matter experts and lessen the burden on any single organization. Such an approach could allow for increased efficiency and reduce duplication of efforts. Several efforts are under way to catalog or map education efforts, with the intention of fostering collaboration. The efforts include the AfriHealth project and WHO's Knowledge Management for Public Health [15].

Third, enhance the involvement of central headquarters in coordinating and supporting training initiatives. Increased central coordination and scientific

direction for AFHSC-GEIS projects can make existing training activities more efficient, productive and visible. Individual project progress may also benefit from more frequent scientific guidance. Given its ability to set policy and priorities for the global AFHSC-GEIS network and to interface with other interagency partners, AFHSC-GEIS is in a unique position to provide coordination and support of training initiatives.

Fourth, establish a central repository of training materials used in AFHSC-GEIS-funded training initiatives. A central repository of presentation slides, handouts, exercises and information on laboratory training kits would give partners a starting point from which to plan and coordinate their training activities.

Finally, implement evaluation metrics, including measurements of learning objectives and competencies (i.e., pre- and post-tests, self-assessments and learner satisfaction). Evaluation of the training initiatives is perhaps one of the most important steps. Simple pre- and post-tests could greatly enhance the efficiency and effectiveness of the training initiatives and identify the types of training that are the most successful and meaningful to the host country. Assessing the quality of training through a monitoring and evaluation framework across training programs, as well as assessing whether the level of sophistication is appropriate for the target audience, would be helpful.

The widespread realm of topics and geographic regions covered in the AFHSC-GEIS-funded training initiatives build on the center's objective of worldwide emerging infectious disease surveillance and response. The training initiatives mentioned in this review all fall directly under the focus areas and targeted efforts of the IHR (2005) in developing the core competencies to identify, respond to and control public health threats and potential public health emergencies of international concern around the world. These AFHSC-GEIS-funded training initiatives serve as a conduit for member states and neighboring countries to communicate and collaborate on emerging infectious disease planning and development of their national strategies for addressing complex public health emergencies. Funding of training initiatives that enhance global emerging infectious disease planning and surveillance will greatly benefit the world's population by preparing member states to address emerging infectious disease outbreaks in the future.

Additional file 1: AFHSC-GEIS Funded Training Initiatives, September 2008-October 2009 * Training Modality Legend: W = Workshop, A = Academic Course, C = Conference, T = Tabletop exercise, D = Distance Learning, P = Telephone † Where exact figures are not known, an estimate of the number of trainees is provided.

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Disclaimer

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Competing interests

To the best knowledge of the authors, no competing interests are reported.

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Department of Defense influenza and other respiratory disease surveillance during the 2009 pandemic

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Abstract

The Armed Forces Health Surveillance Center's Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) supports and oversees surveillance for emerging infectious diseases, including respiratory diseases, of importance to the U.S. Department of Defense (DoD). AFHSC-GEIS accomplishes this mission by providing funding and oversight to a global network of partners for respiratory disease surveillance. This report details the system's surveillance activities during 2009, with a focus on efforts in responding to the novel H1N1 Influenza A (A/H1N1) pandemic and contributions to global public health. Active surveillance networks established by AFHSC-GEIS partners resulted in the initial detection of novel A/H1N1 influenza in the U.S. and several other countries, and viruses isolated from these activities were used as seed strains for the 2009 pandemic influenza vaccine. Partners also provided diagnostic laboratory training and capacity building to host nations to assist with the novel A/H1N1 pandemic global response, adapted a Food and Drug Administration-approved assay for use on a ruggedized polymerase chain reaction platform for diagnosing novel A/H1N1 in remote settings, and provided estimates of seasonal vaccine effectiveness against novel A/H1N1 illness. Regular reporting of the system's worldwide surveillance findings to the global public health community enabled leaders to make informed decisions on disease mitigation measures and controls for the 2009 A/H1N1 influenza pandemic. AFHSC-GEIS's support of a global network contributes to DoD's force health protection, while supporting global public health.

Background

In response to the 1996 Presidential Directive (NSTC-7), the U.S. Department of Defense (DoD) established the Global Emerging Infections Surveillance and Response System (DoD-GEIS) in 1997, with the mission to monitor newly emerging and re-emerging infectious diseases (EIDs) among U.S. servicemembers and dependent populations [1]. Comparable to their global burden of disease, respiratory infections are responsible for 25 percent to 30 percent of both outpatient illness and hospitalizations among U.S. military personnel [2,3]. Influenza and adenovirus infections are among the etiologies that greatly contribute to morbidity and mortality in military members [4]. During the 1918 influenza pandemic, the U.S. military experienced attack rates as high as 25 percent and case fatality rates averaging 5 percent (ranging from 1 percent to 8 percent) [5].

DoD-GEIS, a division of the Armed Forces Health Surveillance Center (AFHSC) since early 2008, centralized the coordination of DoD influenza and other respiratory disease surveillance efforts beginning in 1998. The program was expanded with 2006 congressional supplementary

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appropriations [6-8]. Subsequent funding in 2007-2009 has maintained this effort. Today, AFHSC-GEIS provides direction, funding and oversight to a system that consists of a network of global partners, including approximately 500 sites in 70 countries (Figure 1).

During the past four years (2006-2009), the AFHSC-GEIS influenza surveillance system increased support for avian and pandemic influenza preparedness to include activities in surveillance and response to newly identified strains and pandemics, such as H5N1 and the 2009 novel A/H1N1. By supporting global surveillance and directing response efforts, DoD serves as a sentinel for local epidemics and can assist in limiting disease transmission. An immediate focus of DoD is decreasing the impact of the novel A/H1N1 pandemic on the armed forces, including reducing recruit- and other training-associated illnesses and deaths, and controlling secondary viral and bacterial associated morbidity. These efforts are similar in intent to those undertaken at the time of the appearance of the new virus strain during the 1918 H1N1 pandemic when efforts were also made to reduce the impact of the virus on the military during World War I.

The AFHSC-GEIS influenza surveillance system plays a major role in the U.S. government's (USG) contributions to the global surveillance of influenza viruses and contributes to the World Health Organization's (WHO) Global Influenza Surveillance Network [9]. Core components of the AFHSC-GEIS influenza surveillance system are a network of specialized diagnostic and reference laboratories in the continental United States, medical treatment facilities within the Military Health System, and five DoD overseas laboratories, along with their respective detachments. The system, built around networks of hub and satellite laboratories, comprises many joint ventures with host countries.

This article focuses on the 2009 activities and accomplishments of the AFHSC-GEIS laboratory-based network regarding global surveillance for respiratory diseases and responding to the novel A/H1N1 influenza pandemic. These activities are described relative to, and by means of, AFHSC-GEIS strategic goals: surveillance

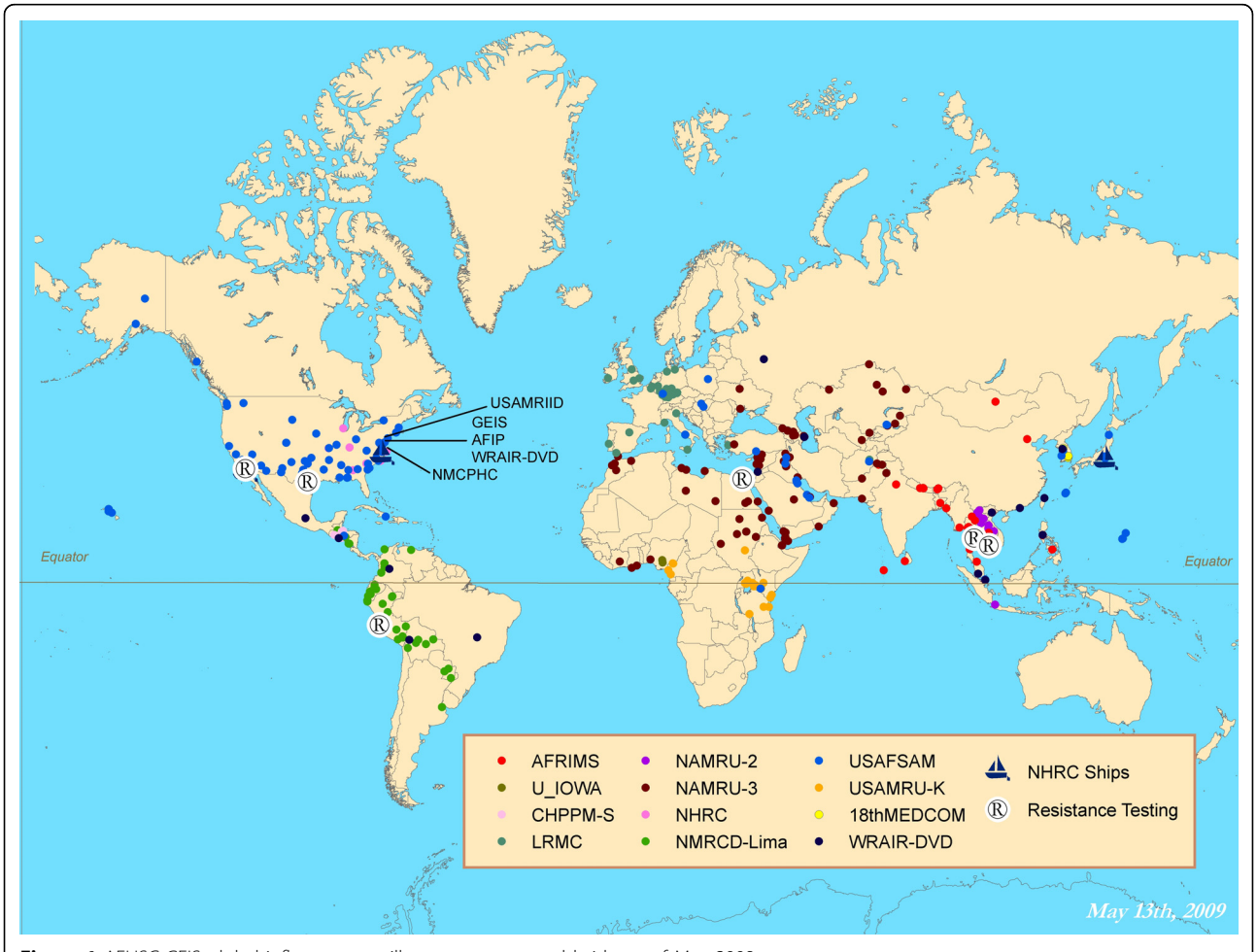

Figure 1 AFHSC-GEIS global influenza surveillance presence worldwide, as of May 2009.

and response; training and capacity building; research, innovation and integration; and assessment and communication of value added.

2009 contributions

Surveillance and response

During April 2009, the first two U.S. cases of novel A/H1N1 were detected in two separate Naval Health Research Center (NHRC) surveillance projects supported by AFHSC-GEIS. In the first instance, NHRC investigators collected a specimen from a 10-year-old DoD dependent who had enrolled in a biomedical trial to test a new influenza diagnostic platform conducted at the Naval Medical Center, San Diego, Calif. Initial results by an external reference laboratory suggested an influenza A/untypable virus [10,11]. At the same time, a 9-year-old female from the U.S./Mexico border was sampled in a collaborative surveillance study with the Centers for Disease Control and Prevention's (CDC) Border Infectious Disease Surveillance Project. NHRC determined infection from an influenza A/untyped virus. Further testing on the IBIS T5000 platform, which infers H and N types from multiple genomic signatures, indicated an influenza A/swine/H1 virus. Samples from both patients were shipped to the CDC for confirmation and characterization.

Shortly thereafter, the U.S. Air Force School of Aerospace Medicine (USAFSAM) detected two near simultaneous cases among military dependents in the San Antonio area. The WHO used three of the strains (A/California/7/2009, A/California/4/2009 and A/Texas/5/2009) as potential strains for the 2009 pandemic influenza vaccine. A/California/7/2009 was eventually selected as the seed strain [9].

In addition to detecting several of the initial cases of novel A/H1N1 within the U.S., AFHSC-GEIS partner laboratories were instrumental in monitoring the global spread of the virus. The Armed Forces Research Institute of the Medical Sciences (AFRIMS) laboratory was the first to detect novel A/H1N1 virus in Nepal and Bhutan, while the Naval Medical Research Unit No. 2 (NAMRU-2) provided support for the initial confirmation on novel A/H1N1 in Cambodia and Lao People's Democratic Republic. The U.S. Army Medical Research Unit-Kenya (USAMRU-K), another AFHSC-GEIS partner, supported initial laboratory confirmation for Kenya and the Republic of Seychelles, and the Naval Medical Research Center Detachment (NMRCD) identified the first cases in Peru and supported initial confirmation in Colombia and Ecuador. Additionally, NHRC diagnosed the first infection in Guam/Micronesia, and the Naval Medical Research Unit No. 3 (NAMRU-3) not only identified the first cases in Kuwait, but also confirmed outbreaks in Afghanistan, Bahrain, Djibouti, Egypt and Lebanon.

Results of AFHSC-GEIS-sponsored influenza surveillance sample testing were reported via host-nation collaborators to their respective ministries to ensure the ministries could make informed and timely decisions about influenza control. The AFHSC-GEIS network surveillance support of the 2009 influenza pandemic was instrumental in the timely tracking and monitoring of the virus. In recognition of AFHSC-GEIS support, the AFRIMS field laboratory in Cebu was made an official Philippine Department of Health testing laboratory, Public Health Command Region-South (PHCR-South) assisted the Guatemalan Ministry of Health Influenza laboratory in becoming a National Influenza Center (NIC), and the Peruvian Instituto Nacional de Salud (National Institute of Health) awarded a commendation medal to NMRCD for its support in the pandemic response.

In addition to the novel A/H1N1 pandemic support provided to foreign host nations, AFHSC-GEIS network partners continued to support influenza and respiratory disease surveillance among military recruits, active-duty servicemembers, and U.S. military beneficiaries. AFHSC-GEIS supported the timely surveillance and rapid diagnosis of circulating influenza and other respiratory viruses within our overseas military populations through its partners in Europe (PHCR-Europe and Landstuhl Regional Medical Center (LRMC)), Japan (PHCR-Pacific and Naval Hospital Yokosuka), and the Republic of Korea (Brian Allgood Army Community Hospital (BAACH)).

Although many network laboratories, such as LRMC and BAACH, could not confirm a novel A/H1N1 infection during the initial months of the pandemic, the facilities provided a strong presumptive diagnosis of novel A/H1N1 based on their findings of untypable influenza A infections. With AFHSC-GEIS support, BAACH became one of the first U.S. overseas laboratories capable of providing on-site diagnosis of novel A/H1N1 for U.S. military personnel and their families. Likewise, the ability of the Navy Environmental Preventive Medicine Unit No. 2, in collaboration with NAMRU-3, to stand up a novel A/H1N1 testing site in Kuwait on short notice also helped provide a timely diagnosis for deployed clinicians. In turn, this effort helped ease tensions between the U.S. military and host countries in Southwest Asia and the Middle East by allowing the rapid identification and subsequent isolation of infected individuals to reduce the likelihood of transmitting influenza virus to local civilians.

A significant challenge for AFHSC-GEIS partners in 2009 was the need to balance their novel A/H1N1 pandemic response with their ability to continue surveillance efforts for other influenza viruses and respiratory diseases (e.g., adenovirus), including potential zoonotic

viruses. Over 50 percent of EIDs are zoonotic, including the H5N1 and 2009 novel A/H1N1 viruses [12]. In 2009, AFRIMS and NAMRU-2 scientists, in collaboration with the University of Iowa's Center for Emerging Infectious Diseases, further strengthened important research of the human-animal interface and epidemiology of influenza viruses by expanding established cohort-based studies and creating new ones in five countries (Cambodia, Mongolia, Nigeria, Romania and Thailand). The endeavor allowed researchers to examine risk factors and transmission patterns of influenza at the human-animal interface.

Likewise, USAMRU-K initiated similar surveillance work in Uganda and continued to conduct migratory bird surveillance to monitor and track the spread of highly pathogenic avian influenza (HPAI). NMRCD conducted similar migratory bird surveillance in Peru. In conjunction with the CDC, NAMRU-3 and NMRCD initiated population-based, influenza-like illness and severe acute respiratory illness surveillance efforts among hospital and community cohorts in Egypt and Peru, respectively (Figure 2).

Finally, AFHSC-GEIS partners provided laboratory diagnosis for 37 of the 52 (71 percent) reported cases of human H5N1 infection worldwide in 2009 [3]. NAMRU-3, serving as the WHO's Eastern Mediterranean Regional Influenza Reference Center (EMRO), provided laboratory diagnosis for 36 of 38 (95 percent) of reported cases of human H5N1 infection in Egypt, and NAMRU-2 identified an additional case in Cambodia [13].

Training and capacity building

Although these initiatives are more fully addressed in other articles within this supplement, the strategic goal of training and capacity building was a significant focus of AFHSC-GEIS influenza funding [14,15]. Nearly all AFHSC-GEIS partners assisted with training and capacity building programs. While the primary objective of these programs is to develop and strengthen global surveillance capacity, the endeavors have the added benefit of improving USG civil-military and military-military relations with host nations. AFHSC-GEIS provided funding to the Center for Disaster and Humanitarian Assistance Medicine at the Uniformed Services University to conduct 14 training sessions for 36 countries. A total of 885 individuals attended the training in support of U.S. Combatant Command partnerships with priority nations.

AFHSC-GEIS funding also supported the Kenyan NIC designation in late 2009 as the WHO East Africa regional influenza laboratory through the assistance of USAMRU-K. Within three months of the novel A/H1N1 virus introduction into the region, the Kenyan NIC received and tested over 1,500 influenza samples from Kenya, Republic of Seychelles and Somalia (Additional File 1). While serving as the WHO's EMRO reference laboratory, NAMRU-3 supported the development of NICs in Afghanistan, Iraq and Jordan, and the sustainment of NICs in Egypt, Kuwait, Oman, Pakistan, Sudan and Syria. In response to the 2009 influenza pandemic, NAMRU-3 also worked closely with the WHO to train over 70 participants from 32 countries in North/West Africa, Central Asia, and the Middle East on real-time reverse transcriptase polymerase chain reaction (rRT-PCR) using the CDC H1N1 assay kits. In the Lao People's Democratic Republic, initial cases of A/H1N1 were tested at the National Center for Laboratory and Epidemiology using equipment and supplies furnished by NAMRU-2 and AFHSC-GEIS funding. All of these efforts helped strengthen the global public health community.

Research, innovation and integration

One of the primary focus areas within the strategic goal of research, innovation and integration is the development of rapidly deployable, field-expedient diagnostic platforms for influenza. Although they generally have a high specificity, point-of-care tests have a poor sensitivity for influenza, especially the 2009 novel A/H1N1 virus [16]. Moreover, while these tests can distinguish between influenza A and B viruses, they are rarely able to subtype specific viruses.

During 2009, AFHSC-GEIS supported the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and the Chemical Biological Medical Systems-Joint Program Management Office transition of the CDC H5N1 and novel H1N1 assays to the Joint Biological Agent Identification and Diagnostic System (JBAIDS). The system had been developed as a ruggedized PCR platform for field identification of priority pathogens of interest. During 2009, USAMRIID successfully optimized and tested the CDC H5N1 assays, and the data will be used in a DoD-sponsored 510K application to the Food and Drug Administration (FDA) for use on the JBAIDS in the future.

In addition, USAMRIID and NHRC successfully optimized the CDC H1N1 assay for use on the JBAIDS platform, and DoD submitted a request to the FDA to extend the current H1N1 Emergency Use Authorization for the JBAIDS H1N1 pandemic influenza assay. The FDA commissioner signed the request on Aug. 24, 2009. As a result, DoD now has the capability to provide a timely clinical diagnosis of novel A/H1N1 in U.S. servicemembers and civilians in deployed and field settings, and is well positioned to extend this capability to include H5N1 influenza diagnosis (Additional File 2).

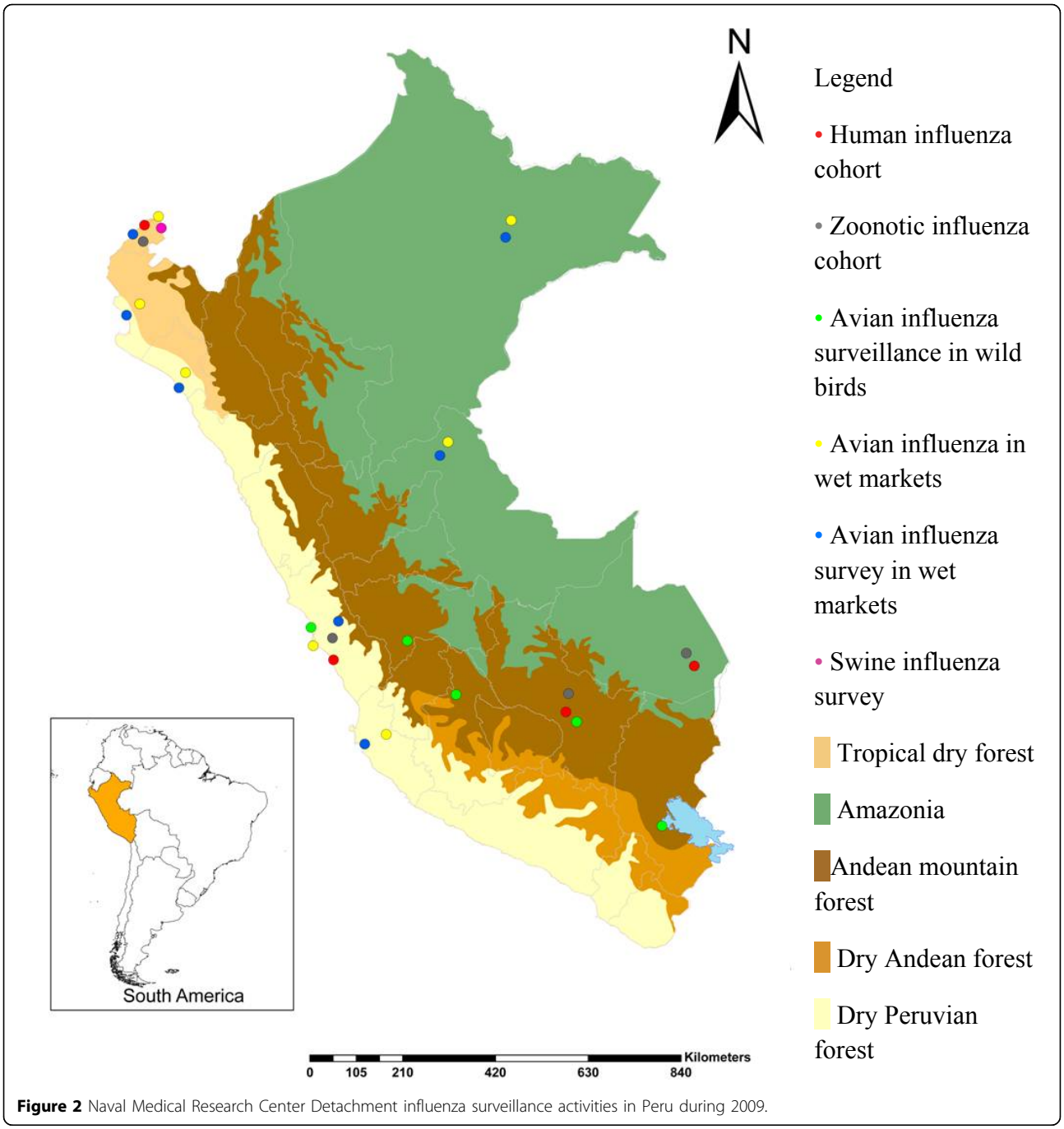

Figure 2 Naval Medical Research Center Detachment influenza surveillance activities in Peru during 2009.

In addition to the CDC H5N1 assays, AFHSC-GEIS also supported FDA approval of a rapid avian H5N1 influenza test (Arbor Vita Corp., AVantage™) using NHRC clinical trial data and validation of the National Veterinary Service Laboratory assay for the AI matrix, H5N1 and H7N3 strains on the JBAIDS by the DoD Veterinary Food Analysis and Diagnostic Laboratory at Fort Sam Houston, Texas. These capabilities will help to further increase DoD's capacity for HPAI surveillance and outbreak response in remote settings.

In 2009, AFHSC-GEIS also sought to integrate influenza full genome sequencing within DoD. To this end, the Walter Reed Army Institute of Research (WRAIR) established full-length and ultra-deep, high-throughput genome sequencing. Twenty-six viruses (two seasonal A/H1N1, two A/H3N2, and 22 novel A/H1N1) from six

countries were fully sequenced and submitted to GenBank. In turn, this sequencing provided valuable information on current viral mutations to DoD and the global public health community.

Assessment and communication of value added

By utilizing data from the Defense Medical Surveillance System, AFHSC conducts assessments on influenza activity, safety of the novel A/H1N1 influenza vaccine and effectiveness of influenza vaccine. Influenza activity among all DoD beneficiaries is monitored weekly and summarized in a weekly report disseminated to service-specific public health centers, preventive medicine physicians and DoD leadership. In addition, AFHSC-GEIS generates a weekly summary of all influenza surveillance reports from DoD laboratories, service-specific public health centers, Combatant Commands and other AFHSC-GEIS partners. The weekly report is posted on the DoD Pandemic Influenza Watchboard (http://fhpr.osd.mil/aiWatchboard/). Both reports are valuable in providing DoD decision makers and global public health leaders with a timely and succinct accounting of influenza activity, severity and geographic distribution.

AFHSC has also partnered with the Military Vaccine Agency, CDC and FDA to provide weekly safety assessments of the novel A/H1N1 influenza vaccine among active component servicemembers. AFHSC provides the only data within DoD for this collaboration. As a result, the center plays a valuable role in the country's assessment of the safety of this vaccine.

Each year, AFHSC-GEIS conducts mid-season assessments of the effectiveness of the seasonal vaccines, and during 2010, will examine the effectiveness of the novel A/H1N1 influenza vaccine. Initial estimates of seasonal vaccine effectiveness against novel A/H1N1-associated illness have been presented at scientific meetings and have been published. [17] Mid-season evaluations generated in January and February 2010 aimed to provide crucial information to the Vaccine and Related Biologic Products Advisory Committee and the public health community at large.

Additionally, network partners at NHRC and USAFSAM also evaluate vaccine effectiveness among important subpopulations throughout DoD. NHRC has established a framework for evaluating influenza vaccine effectiveness among basic military trainees that has served as a valuable tool in the larger effort to monitor this important indicator. USAFSAM works diligently each season to identify and molecularly analyze viruses from cases considered potential vaccine breakthroughs (e.g., cases occurring ≥14 days after vaccination) as determined by the surveillance questionnaire data collected as part of routine sentinel surveillance. The Defense Department is well positioned to determine the overall effectiveness of both seasonal and pandemic vaccines in military populations. However, results of these evaluations may not be generalizable to the population at large, given the young, healthy and highly vaccinated nature of military populations. This function is viewed favorably and of great value to the vaccine and public health communities.

Discussion

Although many goals were accomplished during this past year, the novel A/H1N1 influenza virus pandemic of 2009 presented unique management challenges for AFHSC-GEIS and its network of partners. The first significant problem centered on "sensitivity" in terms of reporting cases to host-country health authorities, while simultaneously providing U.S. military and civilian health agencies with the reports. Although the identification of cases was important, many host-country officials perceived that reporting of cases could be detrimental to their economy or community. In tandem with the high visibility of reports, laboratory testing associated with the large increase in processing specimens presented a challenge in terms of local and regional expectation of timely results that each partner needed to address. The consolidation of testing results was found to be challenging, thus, the authors see a pressing need for standardization of reporting in the future. Other challenges occurred in terms of achieving effective ongoing strain-sequencing analysis and reporting to CDC and WHO officials. Lastly, given the high volume of testing required during a pandemic, the program must take a closer look at changing the paradigm of testing whereby only a representative portion (i.e., 10 percent to 20 percent), instead of every sample, is given priority. For example, researchers could test severe cases (e.g., SARI, hospitalized, pneumonia) to more effectively provide reliable estimates of the virus' impact.

A primary focus of the AFHSC-GEIS influenza surveillance system in 2010 is the continued monitoring and tracking of novel A/H1N1 virus for changes in severity, antiviral resistance or transmissibility, particularly in our special populations (e.g., recruits, deployed and shipboard personnel) within the military. Sentinel-based surveillance by our partners (e.g., USAFSAM, LRMC, BAACH) will continue to remain a key component of the surveillance program, as will the population-based surveillance at eight of 10 military recruit-training centers and the Pacific Rim Surveillance at Naval Hospital Yokosuka by NHRC.

To expand DoD's surveillance efforts within the Military Health System, AFHSC-GEIS is partnering with the Infectious Disease Clinical Research Program to establish an acute respiratory infection consortium at several large DoD medical treatment facilities. This group will

examine the pandemic's impact on the U.S. military health care population and evaluate the effectiveness of potential intervention measures, including vaccine-specific effectiveness and non-vaccine interventions, such as hand washing, febrile screening, cohorting and recruit space allocation.

Besides continued surveillance within DoD, AFHSC-GEIS partners are fostering and developing new relationships for surveillance within other military populations to expand the center's global surveillance program and enhance its contribution to global public health. Examples of potential future collaborations include NMRCD partnerships with Bolivia and Ecuador; AFRIMS surveillance in Vietnam; NAMRU-3 development of a veterinary and human influenza surveillance network in western Africa with Burkina Faso, Cote d'Ivoire and Ghana armed forces; establishment of a central African military alliance by the Global Viral Forecasting Initiative in Cameroon; and expansion of DoD and foreign military influenza and EID surveillance efforts in East Africa (Kenya, Tanzania and Uganda) and Central America (El Salvador, Guatemala and Honduras). Further expansion of AFHSC-GEIS-sponsored partnerships with Ministries of Health will also be explored (e.g., by PHCR-South in Central America) to provide improved surveillance in regions of the world where surveillance is lacking or inadequate.

Surveillance of zoonotic influenza will become more focused in 2010. While waterfowl, especially ducks and geese, can be infected and shed many subtypes of influenza A viruses, viral presence in these species does not necessarily imply a risk to humans due to the potential for species-specific strains and especially a lack of human exposure to the waterfowl necessary for transmission [18]. As a result, instead of focusing on migratory birds, AFHSC-GEIS will concentrate on those areas, such as live-bird markets, abattoirs and large breeding farms, and occupations, such as backyard agricultural workers, where individuals are more likely to be exposed to animals, thus selecting a subset that is at much higher risk of infection with, and transmission of, zoonotic influenza strains.

Finally, AFHSC-GEIS will seek to expand DoD's capability to analyze and characterize viruses in-house. In 2009, AFHSC-GEIS funding was used to equip several laboratories with antiviral resistance testing capacity (genotypically by pyrosequencing and phenotypically by inhibition in culture). The capability will be further developed in the future. Likewise, WRAIR's genomic sequencing capacity and throughput will also increase. Additionally, funding will be provided to expand the JBAIDS influenza capability from novel A/H1N1 and H5N1 to include pan-influenza A, pan-influenza B, H1 seasonal and H3 seasonal viruses.

Conclusions

The 1996 Presidential Directive charged the U.S. DoD with monitoring EIDs in the military population. The directive led to creation of the AFHSC-GEIS influenza surveillance system, which strives to be a valuable asset to DoD and the global public health community. Its specimen catchment area includes regions noted for their regular contribution to global strain circulation, such as Southeast Asia, as well as South America, Africa and the Middle East, where strain circulation information is limited.

During 2009, the AFHSC-GEIS influenza and respiratory disease surveillance network not only detected the first cases of novel A/H1N1 among U.S. military beneficiaries, but also detected the first laboratory-confirmed cases within the United States and many countries throughout the world [19]. In addition to its EID surveillance, the network also assisted with providing a rapid global response to the 2009 influenza pandemic through training and capacity-building efforts with partner nations, developing new surveillance and diagnostic platforms, and timely reporting of surveillance results and disease trends to public health authorities such as the CDC and WHO.

This extensive network is positioned to detect the emergence of new respiratory pathogens or significant mutations in the novel A/H1N1 2009 influenza virus as they transpire. The projects and initiatives in 2010 and beyond will help to further strengthen and maintain this network, and ultimately contribute to the sustainment of force health protection and global public health.

Additional File 1: AFHSC-GEIS supports pandemic H1N1 influenza outbreak response in Kenya and East Africa. Figure - Laboratory-confirmed cases of novel A/H1N1 influenza in Kenya, as of Oct. 8, 2009.

Additional File 2: Deployment of the JBAIDS for diagnosis of novel A/H1N1 influenza in the deployed operations. Figure - Use of the JBAIDS for diagnosis of the novel A/H1N1 influenza virus in a deployed setting.

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Disclaimer
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RLB was responsible for oversight and management of the AFHSC-GEIS Avian and Pandemic Influenza Department and drafted the manuscript. KGV, MCJ and JLS were responsible for regional oversight and management within the AFHSC-GEIS Avian and Pandemic Influenza Department. AAE was responsible for analysis of influenza trends within the U.S. DoD. JAP and RGP provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at AFRIMS. JLM was responsible for program management of the CDHAM pandemic influenza training support to U.S. Combatant Commands. MQ provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at PHCR-South. TP and MJC provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at LRMC and PHCR-Europe. JG provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at PHCR-Pacific. DS and JW provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at USAMRU-K. AW and CCD were responsible for optimizing the avian H5 panel for use on the JBAIDS platform. MLB provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at BAACH. ST, MRK and MW provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at NAMRU-2. JAT and BO provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at NAMRU-3. PJB and AH provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at NHRC. JMM, HR and AL provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at NMRCD. RJS and DAN were responsible for optimizing the H5N1 assay for use on the JBAIDS platform. VHM and TG provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at USAFSAM. TS provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at Navy Environmental and Preventive Medicine Unit-2. GCG provided oversight and conducted AFHSC-GEIS respiratory disease surveillance at the University of Iowa. DLB was responsible for oversight and management of AFHSC-GEIS operations and developed the reporting format. KLR was the director of DoD GEIS and provided oversight and direction of its surveillance activities.

Competing interests
The authors declare that they have no competing interests.

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Enteric disease surveillance under the AFHSC-GEIS: Current efforts, landscape analysis and vision forward

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Abstract

The mission of the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) is to support global public health and to counter infectious disease threats to the United States Armed Forces, including newly identified agents or those increasing in incidence. Enteric diseases are a growing threat to U.S. forces, which must be ready to deploy to austere environments where the risk of exposure to enteropathogens may be significant and where routine prevention efforts may be impractical. In this report, the authors review the recent activities of AFHSC-GEIS partner laboratories in regards to enteric disease surveillance, prevention and response. Each partner identified recent accomplishments, including support for regional networks. AFHSC/GEIS partners also completed a Strengths, Weaknesses, Opportunities and Threats (SWOT) survey as part of a landscape analysis of global enteric surveillance efforts. The current strengths of this network include excellent laboratory infrastructure, equipment and personnel that provide the opportunity for high-quality epidemiological studies and test platforms for point-of-care diagnostics. Weaknesses include inconsistent guidance and a splintered reporting system that hampers the comparison of data across regions or longitudinally. The newly chartered Enterics Surveillance Steering Committee (ESSC) is intended to provide clear mission guidance, a structured project review process, and central data management and analysis in support of rationally directed enteric disease surveillance efforts.

Background

Enteric infections pose a significant risk to the 80 to 100 million travelers from industrialized countries visiting developing countries [1] and are leading causes of death among children in these same developing countries, where they claimed between 1.4 and 2.5 million lives in the year 2000 [2]. From the perspective of the United States Department of Defense (DoD), political instabilities in many parts of the world require that U.S. military personnel must be ready to deploy to austere environments where the risk of exposure to infectious diseases may be significant and where routine preventive health efforts are often impractical. Acute diarrheal illness has played a significant role in the outcomes of military campaigns throughout history [3-5]. Advances in environmental health interventions and effective therapies have been insufficient to eliminate the burden of enteric infections in deployed military personnel, which can result in lost work days, increased health care utilization, and compromised operational readiness and effectiveness [5-9].

For these reasons, enteric disease surveillance was established as a pillar within the AFHSC-GEIS system. This system is intended to unite the resources of DoD research facilities and the military health system to facilitate the rapid recognition and understanding of, and response to, infectious disease threats to protect global health and that of the U.S. forces. Herein, the authors report on past and current accomplishments of enteric surveillance efforts within AFHSC-GEIS, provide an assessment of how these efforts fit within a changing landscape of global enteric disease research efforts, and discuss future efforts to improve coordinated efforts within the program.

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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 surveillance among U.S. troops deploying on military training operations such as Cobra Gold 2009 (Thailand) and Balakatan 2009 (Philippines), AFRIMS, through AFHSC-GEIS support, has continued a project of defining the etiologies of pediatric acute gastroenteritis and antimicrobial resistance patterns among host country populations in South Asia (Nepal) and Southeast Asia (Thailand). Under these surveillance projects, over 2,500 cases and controls were enrolled during the past year. This study has continued to demonstrate the importance of particular bacterial and viral pathogens in these regions and the levels of antimicrobial resistance among the most common bacterial etiologies—providing critical information for treatment consideration in individuals deploying to these regions (e.g., use of azithromycin for empiric therapy among travelers/deployments to Southeast Asia).

Table 1 Recent Accomplishments of DoD Laboratory Partners in Enteric Disease Surveillance Under AFHSC-GEIS

Partner	Clinical Surveillance and Capacity Building	Laboratory Results/Accomplishments
AFRIMS	• Pediatric case-control study • Enteric surveillance in troops deploying to Cobra Gold 2009 (Thailand) and Balaktan 2009 (Philippines) • Defining etiology of AGE and antimicrobial resistance among indigenous populations in South Asia and Southeast Asia	• Sites in Nepal and Thailand have enrolled more than 2500 cases and controls during the past year • High rates of fluroquinolone and TMP-SMX resistance among pediatric and travel-associated *Campylobacter* isolates. • Most *Shigella* species are TMP-SMX resistant
NAMRU-3	• Birth cohort research and epidemiology • Severe diarrhea study at Cairo University • Case-control study of modifiable risk behaviors • Molecular biology and cholera/rotavirus microbiology reference center for the Middle East and Africa • Training workshops and courses for laboratorians from Afghanistan, Djibouti, Ghana, Iraq, Jordan, Libya, Morocco, Sudan • Biennial enteric disease surveillance in Operation Bright Star (Egypt)	• 2223 children enrolled to describe pathogen distribution (2000 to 2005) • 117 cases and 1:1 age-matched controls assessed for risk behaviors including food and water sources • 303 *V. cholerae* isolates archived and characterized—2 serotypes with widespread antimicrobial resistance • 937 stool samples processed from eight countries to date this year in capacity as WHO Rotavirus Reference Laboratory • Norovirus outbreak response support, Incirlik Air Base, Turkey
NMRCD-Peru	• Cohort study among basic combat trainees • Antimicrobial surveillance testing in Lima and five departments of Peru	• Received 2159 specimens for antimicrobial surveillance and confirmed bacterial pathogens in 83 percent of them. • The cohort study enrolled 381 participants with 84 diarrheal cases with bacterial pathogens confirmed in 42 (50 percent).
NAMRU-2	• 12,000 specimens from Indonesian pediatric diarrhea • Surveillance project covered six cities on five islands and identified rotavirus as the leading causative agent	• Advanced characterization of *Campylobacter* spp. and *Shigella* spp.
USAMRU-K	• Movement of Enteric Microbiology Laboratory from Nairobi to Kericho includes all ages case-control protocol at Kericho District Hospital and two additional district hospitals in Kisumu	• Detected and identified bacterial pathogens in 28 percent of diarrheal stool specimens • Renovated infrastructure to enable facility relocation to the new Microbiology Hub in Kericho (MHK) • Five-year surveillance protocol uses case-control approach, broadens testing spectrum, and includes antibiotic susceptibility testing • Clinical and (FDA-approved) molecular epidemiology of diarrheal illnesses
NEPMU-2	• Establishing diagnostic capability for Norovirus VGE collection kits with thermal shipping boxes deployed to 30 ships	• Expected to start processing kits in early 2010

Acronyms: Acute gastroenteritis (AGE), Food and Drug Administration (FDA), trimethoprim-sulfamethoxazole (TMP-SMX), viral gastroenteritis (VGE), World Health Organization (WHO).

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 (NMRCD), Lima, Peru

NMRCD 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 NMRCD 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, NMRCD has conducted a prospective cohort of diarrheal disease incidence and prevalence among Peruvian soldiers in the Peruvian Amazon. To date, over 2,900 participants have enrolled in the cohort alone. Baseline stool and serum specimens are obtained from participants, and active surveillance is conducted to detect and evaluate cases of acute diarrhea. Fecal specimens are tested by means of conventional culture, by PCR-based methods for the detection of diarrheagenic *Escherichia coli* (DEC), and by microscopy and ELISA for parasitic pathogens.

Ongoing results at Vargas Guerra show an annual incidence of diarrhea from 0.31-0.70 episodes of diarrhea per person-year since the project began in 2003. Prior to the establishment of active surveillance at the study site in 2004, 40 percent of diarrhea cases presenting for medical care were confirmed as *Shigella* (primarily *S. flexneri* 2a and 3a) by culture [25]. With active case finding, an increased number of less-severe cases were identified, with the proportion of shigellosis as a cause of diarrhea decreasing to a lower but still significant 24 percent of cases. *S. flexneri* is a pathogen of major military and public health importance and is the target of vaccine development by the Walter Reed Army Institute of Research (WRAIR) and the Military Infectious Diseases Research Program (MIDRP). NMRCD also conducts antimicrobial drug resistance surveillance for enteric pathogens in Peru with support from AFHSC-GEIS. Last year, NMRCD obtained 2,159 isolates from collaborating project sites in five departments of Peru with differing climates and population densities. From the isolates, 1,802 bacterial pathogens were confirmed. Of these 1,802 specimens, 47.8 percent were confirmed as *Shigella* spp., 5.4 percent as *Salmonella* spp., 35.7 percent as *Campylobacter* spp., and 6.7 percent as diarrheagenic *E. coli* (DEC). Among organisms evaluated, *Campylobacter* spp. showed high rates of resistance to fluoroquinolones (91.6 percent), although local rates of fluoroquinolone resistance were much lower in the Amazon basin (28 percent). Overall rates of macrolide resistance were low for *Campylobacter* spp. (azithromycin 1.9 percent, erythromycin 3.0 percent). *Shigella* strains were broadly resistant to trimethoprim-sulfamethoxazole (88.3 percent), with lower but noteworthy resistance rates to that agent noted in salmonellae (19.4 percent). *Salmonella* spp. was generally resistant to erythromycin (90.8 percent) but susceptible to fluoroquinolones (1.0 percent resistant to ciprofloxacin) and azithromycin (7.1 percent resistant). DEC had broadly preserved quinolone susceptibility, with only one EPEC isolate out of 120 DEC noted to be resistant to ciprofloxacin.

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 (21 percent to 65 percent) as well as a moderate level of macrolide resistance among *S. flexneri* and *S. sonnei* isolates (M. Kasper, personal communication). The molecular mechanism of ciprofloxacin resistance in *Campylobacter* spp. was studied using a real-time PCR assay to discriminate between wild-type and mutant alleles that can confer resistance to fluoroquinolones.

Establishment of an enterics microbiology laboratory—U.S. Army Medical Research Unit, Kenya (USAMRU-K), Kericho, Kenya

A consortium of several regional laboratories conducting infectious disease surveillance and research, USAMRU-K recently moved its principal Enteric Microbiology Laboratory from the Nairobi campus to Kericho, designated the Microbiology Hub in Kericho (or "MHK"). This laboratory includes automated bacterial identification and susceptibility testing, rotavirus enzyme immunoassay (EIA), and limited parasite EIA testing. The MHK has 9,200 square feet of laboratory space with the capacity to process over 100 stool specimens per week and an enhanced molecular epidemiology focus on enteric microorganisms. Ongoing expansion at MHK will provide the capacity to perform important regional epidemiology and clinical trials related to enteric and other bacterial diseases. In addition to supporting clinical microbiology services at Kericho District Hospital, a new protocol was implemented in September 2009 to conduct a case-control study among local residents presenting to Kericho and Kisumu District Hospitals with diarrhea. This project will be expanded with funding from military research programs to support the development of potential field sites for enteric vaccine studies and to conduct observational and clinical trials in military and similar traveler populations throughout the region.

Establishment of a norovirus reference laboratory to support shipboard and recruit population surveillance—Naval Environmental and Preventive Medicine Unit no. 2 (NEPMU-2), Norfolk, VA

Outbreaks of acute viral gastroenteritis, particularly norovirus, among U.S. military deployed forces, as well as recruit and training populations, are a potential threat to mission capacity and operational readiness, though complete epidemiologic information on the frequency and magnitude of these outbreaks is lacking [5,27-34]. A study by Baily *et al.* reported that outbreaks of acute gastroenteritis were frequent among U.S. and British forces deployed to Iraq and Afghanistan from 2002 to 2007, and of 11 identified outbreaks, 10 had a proven viral cause [35]. Of 84 viral pathogens identified in this series, nearly three-quarters were norovirus. Despite the accumulation of disease threat data, DoD lacks diagnostic capacity under current shore-based and fleet platforms. To remedy this fact, NEPMU-2 is establishing a diagnostic capability for norovirus by developing its laboratory and establishing prospective detection and response activities with recruit training centers, deployed forces and Navy vessels. Collaborative partnerships with the NEPMUs in San Diego and Hawaii have also been developed to enable future surveillance worldwide. Further, the first viral gastroenteritis collection kits containing outbreak guidance, basic epidemiologic collection materials, viral transport media (VTM) supplies, and a thermal shipping box have been deployed for an initial distribution to 30 ships. Data collection for outbreaks during 2010 is anticipated.

Landscape analysis

AFHSC-GEIS in the context of global enteric disease surveillance efforts

A growing number of scientific and non-governmental organizations outside the military are showing a growing

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 considerable latitude for the past decade in study design and the target surveillance populations. This has resulted in varied and successful studies but also in a system with a limited ability to compare data across regions.

This diverse network could be strengthened with an alternative system that uses standardized case definitions, eligibility criteria, basic demographic and clinical data, and advanced pathogen characterization including antimicrobial resistance testing. Such an approach could continue to meet individual laboratory missions while increasing the quality of study design, with the goal of being able to generalize findings across populations and over time. Eventually, the AFHSC-GEIS network could develop into an integrated platform for multi-center studies, with emphases to include novel diagnostic testing and new pathogen discovery.

Other major areas of future interest for AFHSC-GEIS include the link between acute enteric infections and chronic sequelae. More than 50 years ago, the initial descriptions of post-infectious functional bowel disorders were reported [43,44], and two recent systematic reviews have reported that roughly one out of 10 people who develop travelers' diarrhea will go on to acquire post-infectious irritable bowel syndrome (PI-IBS), despite normal preexisting bowel habits [45,46]. Though PI-IBS may not be as debilitating as some other, less common sequelae of infectious diarrhea such as reactive arthritis [47], the Guillain-Barre syndrome [48] or inflammatory bowel disease [49], the attributable burden of PI-IBS in terms of impact on individual servicemember health, as well as medical readiness, needs consideration similar to other important long-term impacts of combat such as traumatic brain injury and posttraumatic stress disorder. PI-IBS has been described to persist in 57 percent of patients after six years in one study and in 76 percent after five years in another [50,51]. These illnesses decrease the quality of life of those afflicted, and the economic impact is considerable [52].

Table 2 Landscape of Current Enteric Disease-Focused Surveillance and Epidemiological Activities

Surveillance System	Lead Institution (s)	Description	Target Populations	Year Established
Rotavirus Surveillance Networks (RSN)	CDC, WHO	Epidemiological support for accelerated rotavirus vaccine introduction. Five networks have been established aligning with WHO regional organizations.	Pediatric populations, global	2000
Cholera and other diarrheal infection network (CHOLDInet)	WHO	Strengthen laboratory capacity for monitoring and rapid detection of cholera and other causes of diarrheal diseases to advance the application of control measures.	Pediatric populations, developing world	2009
International Emerging Infections Program (IEIP)	CDC	Six sites established in Asia (Bangladesh, China, Thailand), Africa (Egypt, Kenya), Central America (Guatemala) with various activities related to enteric surveillance including demographic health surveillance systems and acute diarrhea surveillance.	Adult and pediatric populations, developing world	2001
Global Enteric Multi-Center Surveillance Study (GEMS)	UM-CVD, BMGF	Five-year, multi-center study in Asia (Bangladesh, India, Pakistan), Africa (Gambia, Kenya, Mali, Mozambique) funded by the Bill & Melinda Gates Foundation to quantify the burden and identify the microbiologic etiology of severe diarrheal disease among children 0-59 months of age living in developing nations, for the purpose of addressing limitations of current epidemiology.	Pediatric populations, developing world	2006
Network for the Study of Malnutrition and Enteric Diseases (MAL-ED)	Foundation for NIH, Fogarty International Center, BMGF	Five-year ($30 million), multi-site (eight) project in Africa (South Africa, Tanzania), Asia (Bangladesh, India, Nepal, Pakistan), and South America (Brazil, Peru) with aims to incorporate epidemiology and pathophysiology in a longitudinal study of children from birth to 24 months, to better understand pathogen-related undernutrition and impairment of gut and immune function.	Pediatric populations, developing world	2009
Foodborne Disease Active Surveillance Network (FoodNet)	CDC, USDA, FDA	Multicenter network (10 U.S. sites) with active surveillance for foodborne diseases and related epidemiologic studies designed to help public health officials better understand the epidemiology and burden of foodborne diseases in the United States and disseminate information that can lead to improvements in public health practice.	All ages, U.S.	1995
National Antimicrobial Resistance Monitoring System (NARMS)	FDA, CDC, USDA	Prospective monitoring of the occurrence of antimicrobial resistance of zoonotic pathogens from human diagnostic specimens, retail meats and food animals, many of which are the leading pathogens causing acute enteric illness in the United States.	All ages, U.S.	1996
GeoSentinal Network (GSN)	ISTM, CDC	A multi-site network of 48 globally dispersed medicine clinics on all continents (17 in the United States and 31 in other countries) with aims of worldwide communication and data collection network for the surveillance of travel-related morbidity. The GSN is based on the concept that these clinics are ideally situated to effectively detect geographic and temporal trends in morbidity among travelers, immigrants and refugees.	Adult travelers, global	1995
Military Infectious Diseases Research Program (MIDRP)	DoD	This is a DoD-mandated research program with the purpose of developing effective vaccines and other countermeasures against leading causes of infectious diarrhea in deployed Army, Navy/Marine Corps, and Air Force personnel. This research program includes basic science/discovery efforts, pre-clinical and clinical development, as well as supporting epidemiological studies and clinical trials at the DoD overseas laboratories.	U.S. military and other traveler populations	1970s
Infectious Diseases Clinical Research Program (IDCRP)	DoD	With a mission of conducting research in clinically important infectious disease threats to the warfighter and military community, the IDCRP has established a multi-site travel medicine prospective study that includes an epidemiological study of travelers' diarrhea and its post-infectious sequelae. The study creates a platform to conduct interventional and diagnostic studies.	U.S. military and beneficiary traveler populations	2006

	Helpful to achieving the mission	Harmful to achieving the mission
Internal attributes of the DoD-GEIS system	**Strengths** • State of the art laboratories and information infrastructure • Technically proficient and trained personnel • Representative geographic locations of operations • Other DoD programs with similar mission (e.g., MIDRP)	**Weaknesses** • Lack of adequate staff possessing specific enteric disease expertise • Lack of guidance, standardization and coordination of efforts • Cultural & political need for maintenance of independence in research activity • Incomplete analysis of data
External attributes of the DoD-GEIS system	**Opportunities** • Growing interest in enteric surveillance efforts due to global vaccine initiatives and industry interest • Increased interest on military-to-military collaborations • Establishment of an Enteric Surveillance Steering Committee to focus and support efforts	**Threats** • Relatively low emphasis (funding) compared to other major surveillance foci • Development of other surveillance activities with duplicative goals • High turnover of investigators

Figure 1 Strength, Weakness, Opportunities and Threats Analysis Matrix for a AFHSC-GEIS Enteric Surveillance Network.

Although the attributable fraction of IBS caused by domestic foodborne illness is unknown, it is likely large given the frequency of these illnesses [53]. The impact of these infections on deployed servicemembers and on the residents of developing countries, particularly children, remain unclear, and their study may provide AFHSC-GEIS with an important potential avenue of investigation.

While the strengths and weaknesses of the AFHSC-GEIS system will factor in the future direction of enteric surveillance, there are a number of external factors that may also influence the ultimate surveillance strategy. Interest in the area of enteric diseases is growing, with new private industry and philanthropic interest in developing vaccines for military and civilian populations (including diarrhea vaccines). The DoD has placed a higher-level emphasis on conducting more military-to-military engagements. If appropriately aligned, these trends could represent new opportunities and garner additional external support.

Currently, the DoD funding allocated to enteric disease surveillance activities is relatively lower than that allocated to other AFHSC-GEIS disease pillars. Given the real and ever-present impact of diarrheal diseases experienced by deployed military troops, and the appearance of additional burden associated with chronic disease sequelae of these acute infections, an effort to re-emphasize the critical importance of understanding and preventing these infections is needed. In recent years, the enteric disease research and epidemiological landscape has changed significantly with the establishment of GEMS, MAL-ED, and CDC IEIP sites as previously mentioned. These multinational well-funded initiatives may be seen as overlapping with many AFHSC-GEIS activities. A strategic assessment is needed to determine the future goals of AFHSC-GEIS, given limited resources and a potentially constrained fiscal environment.

Future vision

The knowledge gained through studies of deployed military populations has directly contributed to our understanding of acute enteric infections and their burden among military personnel and families stationed in

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 enterotoxigenic *E. coli* toxin phenotypes were heat-labile toxin (LT) 17 percent, heat-stable toxin (ST) 56 percent, and LTST 26 percent; and predominant colonization factor prevalences were CS6 (32 percent), CS3 (8 percent), and CFA/1 (5 percent) [16-18,22,57]. This is in contrast to studies among Egyptian pediatric populations less than five years of age in Egypt, where the toxin prevalence (LT 36 percent; ST 51 percent; LTST 12 percent) and colonization factor profiles (CS6 9 percent; CS3 0.6 percent; CFA/1 8 percent) were quite different [10,58-61]. The implications of the varied prevalence of ETEC strain phenotypes in two different populations with disease from the same region is critically important, not only in design considerations of current ETEC vaccines under development by the DoD, but also in the selection of appropriate surveillance populations. Furthermore, while host nation military personnel may seem to be a surrogate target population, the acceptability of surveillance in these populations is complicated by their higher probability of acquired immunity to many pathogens, an often-high prevalence of chronic parasite carriage, and potential sensitivities in collaborating with an institution that may not have a broadly favorable reputation within the country. Nonetheless, given limited DoD funding and resources, the value of which target populations are best matched for which objective under an AFHSC-GEIS mission needs further consideration.

The leadership at AFHSC-GEIS has recognized the importance of this assessment and the need for refinement of this program and has established the charter of an Enteric Surveillance Steering Committee (ESSC) to guide the current laboratory network into the future. The development of a true network—implying coordination and standardization in a broader context—would add significantly to the value and achievement of the AFHSC-GEIS mission. However, a cautious approach is needed because each laboratory has variable expertise, available populations and interests. Strategies to achieve a coordinated network could range from providing guidance on laboratory methodology to a common core data element which could be collected on all case patients enrolled in the various studies (e.g., similar to what is done with FoodNet reporting sites) to run global and longitudinal analyses. While comprehensive standardized protocols (e.g., similar to RSN) might be difficult to implement in today's landscape, certain aspects including microbiological methods, antimicrobial resistance testing and clinical data capture could be harmonized across surveillance protocols at each of the sites. The relatively low funding for enteric disease surveillance compared to other disease pillars needs to be addressed. Given the real and ever-present impact of diarrheal diseases experienced by local populations and deployed military troops, the critical importance of enteric infections needs to be re-emphasized. This importance, as well as identified gaps that can be filled, should be met with dedicated programmatic funding allocated to enteric research.

Conclusion

A review of AFHSC-GEIS global enteric surveillance efforts for the most recent fiscal year (2009) shows a diverse network needing refinements in vision and standardization, and a strategically directed surveillance effort. Recent changes in the global enteric disease surveillance and research landscape provide the necessary impetus. The strengths of the DoD laboratory network and individual investigators have generated a number of positive contributions including: longitudinal data on emerging antimicrobial resistance; expansive surveillance activities in multiple countries in practically all regions of the globe; the important threat information been obtained from direct study of deployed populations in Iraq and Afghanistan; the capability of supporting

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 surveillance protocols in new host countries with varying regulatory requirements, and the shifting allocation of resources and emphasis away from enteric diseases to other concurrent public health treats (such as with avian influenza/pandemic influenza). However, these challenges are countered by the benefit of achieving a true global network of laboratories aligned in mission and outcome in mitigating the enteric disease threat.

Future efforts in enteric disease surveillance by AFHSC-GEIS will be shaped by its newly established ESSC. As recommended in a prior AFHSC-GEIS program review [42] and explored in this landscape analysis, areas for direction include: (1) provision of specific guidance to laboratories regarding the goals of AFHSC-GEIS and the qualities that AFHSC-GEIS projects are expected to possess, in addition to active assistance of laboratories in developing project plans and periodic scientific guidance for projects under way; (2) a mechanism for structured project review that permits adequate time for project conduct between reviews, results in timely feedback to investigators and is carried out by a diverse panel of experts; (3) consistent interaction with staff directing AFHSC-GEIS projects to monitor project progress, potential for collaboration and needs for assistance; and (4) an improved means of collecting and distributing surveillance data and other information in a timely manner.

These recommendations will guide the focus of the newly chartered ESSC as its members identify strategic issues, develop new goals, create implementation plans and evaluate future progress. The task that lies ahead for the ESSC is to answer the questions of "What do we do?", "For whom do we do it?", and "How can we do it well?" The enhanced coordination and improved scientific review possibilities of the ESSC will help AFHSC-GEIS build upon its past successes in enteric disease surveillance, continuing to take advantage of the DoD laboratories' history, experience and global reach to answer these questions and achieve the AFHSC-GEIS mission.

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Competing interests

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Antimicrobial resistance surveillance in the AFHSC-GEIS network

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Abstract

International infectious disease surveillance has been conducted by the United States (U.S.) Department of Defense (DoD) for many years and has been consolidated within the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) since 1998. This includes activities that monitor the presence of antimicrobial resistance among pathogens. AFHSC-GEIS partners work within DoD military treatment facilities and collaborate with host-nation civilian and military clinics, hospitals and university systems. The goals of these activities are to foster military force health protection and medical diplomacy. Surveillance activities include both community-acquired and health care-associated infections and have promoted the development of surveillance networks, centers of excellence and referral laboratories. Information technology applications have been utilized increasingly to aid in DoD-wide global surveillance for diseases significant to force health protection and global public health. This section documents the accomplishments and activities of the network through AFHSC-GEIS partners in 2009.

Introduction and background

Antimicrobial resistance is a growing threat to the control of infectious disease globally and within the United States. Lethal organisms once thought to be on the decline are re-emerging with resistance to commonly used antimicrobials. Resistant organisms once acquired exclusively in hospital settings are now widely circulating in communities. Infections with resistant organisms not only result in greater severity and higher rates of morbidity and mortality, but also increase health care treatment costs and long-range expenses related to research and development of new drugs.

Since its inception, AFHSC-GEIS has a legacy of antimicrobial resistance surveillance. This activity continues as one of the five key focus areas for AFHSC-GEIS. Although few of the annual AFHSC-GEIS-funded proposals are singularly devoted to antimicrobial resistance, over several years the organization's partners have developed diverse surveillance programs that often involve studies of microbial sensitivities to antibiotics. Many of these projects include outcomes that not only direct appropriate use of antimicrobials for individual patients and regional health planners, but are also aligned with DoD efforts of medical diplomacy with capacity building and investments in outbreak detection and response. These activities often involve collaborations with the host-nation civilian and military clinics and hospitals, as well as university systems. Other antimicrobial resistance-related programs represent collaborations within DoD for identification and tracking of infections at military medical facilities. Taken together, these activities are beneficial to both force health protection and the host nation in many interconnected levels. The following is a synopsis of selected partner activities from 2009.

2009 contributions

Pathogens in Southeast Asia

Over the last several years, a dramatic rise in antibiotic resistance of enteric pathogens, including enterotoxigenic

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Escherichia coli (ETEC), *Shigella*, *Salmonella* and *Campylobacter* has been documented in Southeast and South Asia [1]. Many hospitals and laboratories in this region lacked the essential infrastructure and capability to isolate and identify enteric pathogens and to reliably test antimicrobial resistance. Several U.S. Naval Medical Research Unit Number 2 (NAMRU-2) projects involved laboratory-based microbiologic surveillance of patients presenting for the care of febrile illnesses in host-nation civilian and military clinics and hospitals scattered around the regions. These efforts not only help determine the etiology of febrile illnesses and antimicrobial sensitivity patterns in these areas but also provide essential host-nation laboratory capacity building and training.

In an effort to determine the epidemiology and etiologies of acute febrile illness of unknown origin among persons seeking medical care in Cambodia, NAMRU-2 established a five-year hospital-based surveillance study commencing in December 2006. Depending on the patients' presenting complaints, nasal/throat swabs, serum samples, blood cultures, malaria smears and stool samples were obtained from 4,751 patients with fever at as many as nine different health care centers over the years. Although the most prevalent pathogens isolated among Cambodian patients were influenza, dengue and malaria, the studies also identified diseases such as leptospirosis, hantavirus and hepatitis A, B and E, as well as diseases caused by rickettsial infections. Bacterial organisms collected from these studies were analyzed for antimicrobial resistance. The surveillance also identified the first cases of multidrug-resistant *Salmonella typhi* with reduced susceptibility to fluoroquinolones in Cambodia [2].

Another NAMRU-2 effort, the Indonesian Pediatric Diarrhea Surveillance program, links six distinct geographic sites on five islands of the Indonesian archipelago. The ongoing multi-year collaborative effort has collected more than 12,000 specimens from patients with acute diarrhea symptoms. Bacterial pathogens were identified in 1,142 cases (11 percent), with *Campylobacter* and *Shigella* species being the most prevalent etiologies isolated. *Vibrio cholerae* was the most common *Vibrio* species identified. Shigellosis was identified as the cause of diarrhea in 300 (2 percent) of the cases. Antimicrobial susceptibility testing of *Shigella* samples demonstrated very high levels of resistance to trimethoprim-sulfamethoxazole, often used as the first-line antibiotic to treat children with diarrhea in Indonesia [3].

Campylobacter species were identified in 314 cases of children presenting with diarrhea to participating hospitals and health clinics in Jakarta, Makassar and Mataram. Antimicrobial susceptibility testing to *C. jejuni* identified rates of ciprofloxacin resistance as high as 65 percent with several cases exhibiting macrolide resistance. Similar patterns were observed for isolates of *C. coli*. An increase in minimum inhibitory concentrations (MIC) for several antibiotics, including ciprofloxacin, was found when analyzing results over the time span of specimen collections. NAMRU-2 implemented a real-time polymerase chain reaction (PCR) assay to discriminate between *Campylobacter* isolate wild-type and mutant alleles that can confer resistance to fluoroquinolones. The study found the majority of resistant isolates possessed this mutation. Several strains that were negative by PCR but resistant by MIC testing are being further characterized by sequence analysis of the quinolone resistance-determining region in an attempt to identify other novel mutations that may confer resistance [3].

Cholera surveillance

Investigators at the U.S. Armed Forces Research Institute of Medical Sciences (AFRIMS) responded to a large outbreak of severe diarrhea that affected over 70,000 people in 2009. They found 52 percent of the 158 samples were positive for *Vibrio cholera* strain O1, 18 percent were heat-labile toxin-expressing ETEC and 13 percent were heat-stable toxin-expressing ETEC. All *V. cholerae* strains isolated from the outbreak were resistant to nalidixic acid and trimethoprim-sulfamethoxazole, but they were sensitive to tetracycline, ciprofloxacin, norfloxacin and ampicillin [4].

The *V. cholerae* and rotavirus reference center for the Middle East and Africa established by the U.S. Naval Medical Research Unit Number 3 (NAMRU-3) performed antibiotic sensitivity testing of 303 archived *V. cholerae* samples. The center's studies demonstrate widespread resistance to streptomycin, trimethoprim-sulfamethoxazole and nalidixic acid. Resistance to ampicillin and chloramphenicol was observed only in isolates from Somalia, and resistance to tetracycline was limited to single isolates from Qatar and Somalia [5].

Health care-associated pathogens

Health care-associated infections and antimicrobial resistance have emerged as important public health problems in both developed and resource-poor countries, as well as among DoD personnel. Increased surveillance in hospitals in developing countries may determine risk factors (e.g., overuse of antibiotics, counterfeit drugs or deficiencies in local patient management guidelines and policies) that are different from those in developed countries. This may also define high-risk medical practices and enable the hospitals to tailor and implement intervention plans to reduce infection rates in resource-limited settings. These surveillance activities may become examples that other developing countries can follow in their attempts to reduce nosocomial infection rates and increase the safety of health care systems in

regions where U.S. personnel and travelers visit frequently. Furthermore, knowledge about the genetic determinants of antimicrobial resistance can be very important for tailoring antibiotic policies and tracing the nosocomial spread of pathogens. Molecular characterization studies are essential tools that may help reduce nosocomial infection mortality rates and the cost of treating antibiotic-resistant infections, and limit inappropriate antibiotic use.

More than 30,000 U.S. military personnel have been wounded in action while serving in Iraq or Afghanistan [6], and many of these patients are at risk for serious complications. Wound infections have been a common complication of these injuries and, as in previous wars, are often caused by gram-negative organisms. Minimal information is available about the mechanism of antimicrobial resistance of bacterial infections in Middle Eastern countries. Working with various regional host-nation partners, the laboratories have been able to document the geographic spread of antimicrobial resistance in common organisms. This vital information is used to effectively advise local and national health care leaders about necessary changes to antimicrobial formularies and provides important information on appropriate antibiotic treatment for troops deployed in the Middle East [7]. Extended spectrum beta-lactamase-producing gram-negative rods and *Acinetobacter baumannii* are major causes of infections in health care settings. Many of these nosocomial infections are difficult to treat with antibiotics, and the antibiotic-resistant organisms that cause them are increasingly being seen in community-acquired infections [8].

In Egypt and Jordan, NAMRU-3 has been engaged in surveillance of health care-acquired infections and antimicrobial resistance with emphasis on intensive care units [9]. Researchers analyzed 124 highly resistant gram-negative rods that were collected as part of this surveillance network. Isolates were characterized phenotypically by standard bacteriological procedures and antimicrobial susceptibility profiles were obtained using Clinical and Laboratory Standards Institute (CLSI) criteria. Major mechanisms of antimicrobial resistance in isolates confirmed as either extended-spectrum beta-lactamase-producing bacteria or *Acinetobacter baumannii* were further characterized by pulsed-field gel electrophoresis (PFGE), plasmid profiling, PCR amplification and DNA sequencing.

The resulting antimicrobial resistance profile classified 46 (37 percent) of the isolates as multidrug-resistant organisms. Nineteen isolates (15 percent) were resistant to imipenem and 20 (16 percent) were resistant to meropenem. Sixteen isolates (13 percent) were resistant to both carbapenems. All isolates were sensitive to colistin and were also sensitive or intermediately sensitive to minocycline. Antimicrobial resistance testing using the Etest® strip method indicated production of metallo-beta-lactamase in 18 (14 percent) of isolates.

The NAMRU-3 surveillance of health care-acquired infections and antimicrobial resistance demonstrated that gram-negative organisms constituted the majority of isolates in both countries (61 percent in Egypt and 65.2 percent in Jordan) [8]. In Jordan, *Klebsiella* species were the most commonly isolated gram-negative pathogens (17.4 percent of all isolates), whereas in Egypt, *Klebsiella* species and *A. baumannii* were equally prevalent among the gram-negative bacilli with each organism accounting for 15.4 percent of the isolates. Not surprisingly, high rates of antimicrobial resistance were reported in hospitals in both countries. Extended-spectrum beta-lactamase producer rates among *E. coli* isolates were 64.3 and 66.7 percent in Egypt and Jordan, respectively. *Klebsiella* species showed extended-spectrum beta-lactamase producer rates of 57.1 percent in Egypt and 75 percent in Jordan. In Egypt, resistance of *Pseudomonas aeruginosa* to imipenem was 58.8 percent, and almost 88 percent of *Staphylococcus aureus* isolates were resistant to methicillin. The higher rates of antimicrobial resistance in specific intensive-care units (ICUs) encourage the establishment of better-informed antimicrobial use policies and implementation of stricter infection control practices. These mitigations help decrease antimicrobial resistance rates and reduce the risk of spread to the community.

Acinetobacter infections

Antimicrobial-resistant strains of bacteria threaten U.S. military personnel deployed in the Middle East and Afghanistan from combat- and non-combat-related infections caused by these highly resistant pathogens [10]. *Acinetobacter baumannii-calcoaceticus* complex, *P. aeruginosa*, *Klebsiella* and *E. coli* are common pathogens, but, compared to past wars, the acquisition of multidrug-resistant isolates appears to be significantly increased [11]. *A. baumannii* is a common nosocomial challenge in Egypt and has emerged as one of the important opportunistic pathogens in hospitalized patients throughout the world. Additionally, these infections plague DoD and Veterans Affairs medical treatment facilities and contribute to prolonged hospital stays. Outbreaks of *Acinetobacter* infections are becoming increasingly common among patients in ICUs, surgical units and burn units [12].

The severe impact of an *Acinetobacter* outbreak on hospital operations requires a quick assessment of the potential spread of these infections. Comparison of *A. baumannii* PFGE patterns from Egypt with isolates collected at military treatment facilities in the U.S. showed high levels of genetic variability among collections. The majority of the *Acinetobacter* isolates cultured

from hospitalized injured personnel have been multi-drug-resistant, limiting the use of some empiric antibiotics for treatment of wound infections [11].

Continuous surveillance with genetic characterization of *Acinetobacter* is the ideal method to direct infection-control measures or altering of antimicrobial regimens. Molecular genotyping of these isolates enhances infection control of personnel wounded in the Middle East and the possible nosocomial transmission of these organisms within the DoD hospital system. Characterization of the multi-drug resistant organisms via PFGE genotyping will help identify possible sources of infection and lead to strategies for employing appropriate antibiotics and isolation practices.

Landstuhl Regional Medical Center (LRMC) has an active surveillance protocol for *A. baumannii*. All incoming patients from Operation Iraqi Freedom, Operation Enduring Freedom and Africa are screened for colonization of *Acinetobacter*. Between October 2008 and March 2009, more than 500 *A. baumannii* isolates were processed. Three main clusters of 90 percent similarity were identified and account for 66 percent of the strains examined. This comparison of *Acinetobacter* genotypes significantly benefits infection control efforts by helping identify potential sources of spread, particularly those that occur during the evacuation chain from the battlefield to U.S.-based hospitals. This genotyping data has been used for infectious disease surveillance and infection control at LRMC and thereby improved total patient care.

In January 2009, an increase in the number of *A. baumannii* infections with similar antibiograms in the LRMC ICU was observed [13]. The three strains were shown to be genotypically similar. While the actual source was not determined, the infection control team adopted additional measures, and further spread did not occur. The data from the *Acinetobacter* studies, including the PFGE, antibiotic susceptibility and plasmid profiling, will provide valuable information regarding the epidemiology and evolution of *A. baumannii* from the onset of Operation Iraqi Freedom.

Collection of this data allows researchers to identify strains of interest for further detailed molecular work (e.g., genome sequencing). The PFGE data collected at LRMC is shared with other military treatment facilities. The DiversiLab and PFGE data generated at LRMC allow AFHSC-GEIS and DoD to make more informed funding decisions by comparing the two systems in terms of cost, ease of use and quality of data.

A unique three-year collaborative effort championed by Dr. Luther Lindler, the GEIS Acinetobacter Surveillance Initiative, established standard operating procedures for PFGE of *Acinetobacter* species among laboratories at Brooke Army Medical Center (BAMC), Walter Reed Army Institute of Research (WRAIR), Walter Reed Army Medical Center and LRMC. Some of the samples processed were sent to BAMC and WRAIR for comparison with the samples of all participating military treatment facilities. Some samples processed by each of the partner laboratories were sent to BAMC and WRAIR for analysis, generating a systematic collection of PFGE patterns-identified strains infecting DoD personnel. This enhanced the capabilities of DoD to determine the initial geographic location of contamination as well as the spread and prevention of virulent strains of gram-negative organisms originating from wound infections. Specific isolate information coupled with patient outcomes led to the identification of specific virulence factors within particularly virulent strains and guides the use of specific or novel antibiotic treatments [14].

Drug resistance studies at Brook Army Medical Center

The primary objective of the Center of Excellence for Leptospirosis at BAMC is developing reliable molecular diagnostic techniques based on PCR for the disease. The center has also assessed the antimicrobial therapies for leptospirosis using *in vitro* and *in vivo* models. After developing a calorimetric system to test antimicrobial resistance by an *in vitro* model to various leptospiral strains from around the world, the center has continued to collect novel strains from around the world to test while assessing a broad array of serovars against older and newer antimicrobial agents.

Antimicrobial agents that have been tested to date include older agents such as amikacin, cefazolin, ceftazidime, cephalexin, colistin, fosfomycin, gentamicin, metronidazole, minocycline, polymyxin, rifampin, sulfamethoxazole, tobramycin, trimethoprim, imipenem, and vancomycin [15-18]. Newer and novel agents including tigecycline, doripenem, cethromycin, CEM-101 and CEM-102 also have been tested. In addition, the more active *in vitro* antimicrobial agents have been characterized further in a lethal hamster model for *in vivo* activity. This work has enabled the center to respond to specific requests by clinicians in the developing world to determine if older more commonly used antimicrobials not used in the U.S., such as chloramphenicol, have activity.

Additionally, BAMC has maintained a referral laboratory at the San Antonio Military Medical Center (Texas) to support DoD outbreak investigations and other epidemiological investigations and research. This center provides centralized molecular biology support to characterize multidrug-resistant bacteria pathogens and has been involved in multiple studies. BAMC developed a collaborative research relationship with Fort Sill (Oklahoma) to support a methicillin-resistant *Staphylococcus aureus* (MRSA) colonization study supported

through AFHSC-GEIS and an Infectious Disease Clinical Research Program-sponsored project of chlorhexidine-impregnated cloths to prevent skin and soft tissue infections in U.S. Marine officer candidates. Additionally, they performed resistance and virulence factor gene analysis for *Klebsiella pneumonia* and developed and analyzed numerous multidrug-resistant pathogens and possible outbreaks including analysis of MRSA isolates recovered from the U.S. Army Institute of Surgical Research burn unit during the past 25 years [19,20].

Further studies at BAMC evaluated the resistance mechanisms of *Enterobacteriaceae* as well as extended-spectrum beta-lactamase-producing *Klebsiella* isolates and their impact within a burn unit. They also studied the efficacy of topical agents for *Klebsiella*, *Pseudomonas*, MRSA, and *Acinetobacter baumannii-calcoaceticus* complex in the burn unit [21,22]. These projects included the study of multidrug-resistant *Klebsiella*, *Acinetobacter baumannii-calcoaceticus*, and *Pseudomonas* infections over time within a patient and between patients. A major focus of the BAMC group is to further characterize antimicrobial activity against *Acinetobacter baumannii-calcoaceticus* complex [23].

Clinical laboratory testing methods and broth microdilution were used to define the susceptibility phenotypes of 107 single-patient isolates from blood and wound infections to 15 antimicrobial agents. Genetic relationships were determined by PFGE, and isolates were screened for selected resistance determinants. The isolates were resistant to an average of nine agents and four antimicrobial classes, with 92 percent meeting a definition of multidrug-resistance.

The most active agents were colistin (MIC_{90} 0.5 μg/mL, 99 percent susceptible) and minocycline (MIC_{90} 4 μg/mL, 90 percent susceptible). Carbapenems, traditionally reserved for multidrug-resistant infections, were relatively inactive (imipenem MIC_{90} 0.5 μg/mL, 38 percent S). Fifty-two percent of isolates carried the OXA-23 carbapenemase, which substantially degraded the activity of imipenem (78.4 percent S without, versus 1.8 percent S with OXA-23 present). Rifampin has promising *in vitro* activity (MIC_{90} 4 μg/mL); however, no susceptibility breakpoints have been defined. Aminoglycosides also had very limited activity (amikacin $MIC_{90} \geq 256$ μg/mL, 16.8 precent S; gentamicin $MIC_{90} \geq 32$ μg/mL, 4.7 percent S; tobramycin $MIC_{90} \geq 32$ μg/mL, 27.1 percent S). Aminoglycoside-modifying enzymes were heterogeneous in these isolates, and poorly predictive of the aminoglycoside susceptibility phenotype.

Nearly half (49.5 percent) of the isolates carried the class 1 integron, a marker for the acquisition of cassettes containing multiple antimicrobial resistance genes. Of 107 isolates, 106 (99 percent) carried at least one resistance determinant. Significant inaccuracies were found in some clinical testing methods for tetracyclines, aminoglycosides and, to a lesser extent, carbapenems. Identifying the most prevalent resistance mechanisms, optimal susceptibility testing and judicious use of antimicrobial agents may help preserve the last remaining agents with activity against multidrug-resistant bacteria.

Overall these projects have enabled BAMC to leverage its various programs to collaborate with internal and external partners to improve treatment of combat-related injury infections and multi-drug resistant infections by assessing local delivery of antibiotics in animal models and characterizing novel resistant bacteria. It has also enabled better characterization of multi-drug-resistant infection rates throughout the military health care system from point of injury through tertiary care referral hospitals in the U.S.

Antimicrobial resistance in military trainee populations

Another ongoing AFHSC-GEIS-supported activity at Naval Health Research Center (NHRC), San Diego, characterizes the clinical isolates of *Streptococcus pyogenes* from U.S. military basic trainees [24]. Group A *S. pyogenes* (GAS) infections are common in young adults and may present clinically as pharyngitis, scarlet fever or invasive disease. GAS is also associated with post-infectious sequelae, including rheumatic heart disease and glomerulonephritis. Acute GAS infections remain susceptible to penicillin but resistance to macrolide antibiotics has been noted in recent years.

Antibiotics are frequently used for prophylaxis of recruits against infections; therefore characterization of GAS isolates is necessary in these populations. Ongoing surveillance since 1998 has demonstrated continued susceptibility to penicillin and low-level resistance to macrolides and other antibiotics in GAS isolates collected at nine recruit training sites.

Macrolide resistance is of particular concern because this class of antibiotics is often used for prophylaxis and treatment of individuals who are allergic to penicillin. NHRC tested 2,837 GAS isolates from recruits since the study's inception in 1998. Among 240 isolates collected in 2009, in comparison with previous annual studies, lower resistance was seen with erythromycin (6.6 percent), while higher resistance was seen for tetracycline (7.0 percent), clindamycin (4.3 percent), and levofloxacin (6.5 percent). Higher levofloxacin resistance was seen in 2009 at Marine Corps Recruit Depot, Parris Island (South Carolina) and higher clindamycin, erythromycin and tetracycline resistance was seen at Fort Benning (Georgia). Additionally, M protein gene (*emm*) typing of *S. pyogenes* performed by NHRC has demonstrated associations of certain *emm* types to resistance and virulence. Other *emm* types have been shown to be more likely associated with outbreaks among U.S. military trainees.

Monitoring high-risk populations such as recruits for emergence of potentially virulent strains could lead to early interventions that may prevent outbreaks and reduce morbidity. The most common *emm* gene types among trainees were 3, 5, 44, 6 and 75. *Emm* type 75 was associated with increased levels of erythromycin resistance, but without apparent increased virulence. *Emm* type 5 was less common but is one of the potentially more virulent strains and was implicated in several outbreaks in 2006 and 2007. A high degree of correlation exists in the temporal distribution of strain patterns between multiple sites suggesting a concerted strain turnover pattern occurring on a larger scale.

These results demonstrated the sensitivity and specificity of a recently developed, rapid, high-throughput strain identification technology and provided the basis for a method of rapid inferential prediction of clinically relevant characteristics using rapid strain typing methods. This surveillance also provided information on circulating strains for GAS vaccine development initiatives.

Electronic surveillance of antimicrobial resistance

A completely different approach using electronic data sources for antimicrobial resistance surveillance was undertaken by the Navy Marine Corps Public Health Center (NMCPHC). NMCPHC developed algorithms and tools to interpret Health Level 7 (HL7) data derived from the DoD Composite Health Care System for surveillance of diseases significant to public health [25]. Use of this data for the surveillance of antibiotic resistance feeds data into BacLink and WHONET, tools developed by the World Health Organization (WHO). Using its experience with inpatient and outpatient encounter records, laboratory and pharmacy data, and other medical and personnel databases, NMCPHC explored trends in disease burden and antibiotic-resistant microorganisms.

The DoD-wide HL7 electronic microbiology laboratory data were restructured to rapidly identify and monitor emerging antimicrobial resistance in organisms, such as *A.baumannii*, *K. pneumoniae*, *P. aeruginosa* and other pathogens of public health concern. The HL7 data stream provides an opportunity for active surveillance of trends in antibiotic resistance and near-real-time response to significant health threats, especially in high-risk populations.

These capabilities were used to enhance surveillance and understanding of trends in emerging pathogens and antibiotic resistance as well as to answer requests for information about invasive MRSA and *S. pneumoniae* in the Military Health System beneficiary population and describe skin and soft tissue infections among DoD members. More than 175,000 skin and soft tissue cases were identified among DoD active-duty military service member medical encounters between October 2006 and May 2008.

Seventy-four percent of cultured skin and soft tissue infection cases were associated with *S. aureus*, followed by coagulase-negative *Staphylococcus* (6 percent), *E. coli* (2 percent), *P. aeruginosa* (1 percent) and *Proteus mirabilis* (1 percent). More than half of the *S. aureus* isolates tested for oxacillin sensitivity were defined as MRSA. MRSA isolates were not only resistant to oxacillin but also to erythromycin (90 percent). Methicillin-sensitive *S. aureus* (MSSA) isolates were sensitive to other commonly-used antibiotics, including trimethoprim-sulfamethoxazole and vancomycin. HL7 outpatient pharmacy data showed that the antibiotics used to treat both types of infection were very similar; trimethoprim-sulfamethoxazole was prescribed frequently for both MRSA (67 percent) and MSSA (52 percent).

The first iteration of an NMCPHC antimicrobial-resistant organism surveillance website displays antibiograms and high-profile organism counts, as well as similar data broken out by service and region [26]. The project includes the use of WHONET to generate facility-specific, DoD-wide and regional antibiograms for comparison and assessment of trends external to their own patient populations. The methodology used to restructure antimicrobial data was validated by comparing the sensitivity profiles prepared by military treatment facilities to the NMCPHC sensitivity profiles from the restructured data. The validation process is ongoing.

The importance of electronic surveillance is demonstrated further in the NMCPHC analysis of the study, *Acinetobacter* species Infections: Trends in Active-Duty Servicemembers. The investigation identified more than 6,300 *Acinetobacter* isolates found in 2,467 DoD active-duty servicemembers between 2005 and 2008. *Acinetobacter* species isolates from wound specimens made up 34 percent of active-duty servicemember isolates (n=2,138) and showed levels of susceptibility between 45 percent and 80 percent to all of the commonly prescribed antibiotics reviewed throughout the study time period; 95 percent of these isolates were *Acinetobacter baumannii-calcoaceticus* complex [25].

Isolates identified from blood specimens made up 6.5 percent of all active-duty service member isolates (n=409). Overall susceptibility of these isolates to amikacin was 36 percent, imipenem susceptibility was 57 percent and colistin susceptibility was 33 percent. Meropenem results for these isolates were quite limited, with only 15 isolates tested and an overall susceptibility of 7 percent [25].

A similar electronic study of upper respiratory infections and antibiotic resistance among U.S. Navy recruits with upper respiratory infection-associated medical encounters and microbiology records document

isolation of *Streptococcus* in 92 percent and *P. aeruginosa* in 3 percent of 1,022 laboratory specimens [25].

Future direction and initiatives

Since the inception of DoD-GEIS and now AFHSC-GEIS, multiple partners have studied various aspects of antimicrobial resistance with a multitude of methods. This section documents the 2009 partner accomplishments and activities.

The increasing prevalence of emerging antimicrobial-resistant infections remains one of the greatest threats to global health and will continue to be a major concern for AFHSC-GEIS. To successfully counter this threat, the global network will need to be united and coordinated. The three-year GEIS Acinetobacter Surveillance Initiative demonstrated the value of standardized operating procedures and central specimen archives in expanding the knowledge base for these unique, but all too common, infections. AFHSC-GEIS-funded partners will need to develop closer collaborations to best understand the various components involved with global antibiotic-resistant organism surveillance. AFHSC-GEIS has begun initiatives such as subject matter expert steering committees to better direct and coordinate funded proposals as a means of identifying surveillance gaps, avoiding redundancies and assuring state-of-the art technologies.

The creation of an Antimicrobial-Resistant Organism Steering Committee is planned for fiscal year 2011 and will help develop a unified global surveillance plan to combat this common enemy. Increased and sustained surveillance capabilities that can rapidly identify genetic and phenotypic patterns of resistance are essential tools for surveillance in the ever-changing field of microbiology and antimicrobial resistance.

The ability to track antimicrobial resistance in organisms causing disease in DoD beneficiaries is essential for infectious disease and public health leaders to formulate policy and determine appropriate actions for mitigation. AFHSC-GEIS will continue to fund studies that increase its knowledge of the forces and mechanisms that create resistant organisms so that the battle against antimicrobial resistance can be waged more effectively.

Conclusion

Infectious diseases have always been a major threat to U.S. military forces and global public health. Antimicrobial resistance surveillance has been a pillar of military force health protection and global public health for AFHSC-GEIS since its creation in 1998. AFHSC-GEIS funding has enhanced the ability of partner laboratories to maintain robust infectious disease surveillance.

A significant spin-off of these efforts is the acquisition of multiple isolates of microorganisms infecting patients from various regions of the world which can be further analyzed for antimicrobial resistance. The rate and spread of antimicrobial resistance can be tracked and helps to direct patient care, antibiotic prescribing practices and national policy.

To better understand the global picture of infectious disease, it is essential to use standardized nomenclature and laboratory procedures in order to correctly identify the causative microorganisms. Additionally, the various reports must be collated if the data is to be relevant to DoD populations spread around the world. AFHSC-GEIS-funded partners have continued to contribute greatly to essential research and development of techniques that further the investigation of disease causing organisms. Rapidly changing technologies and computer applications speed the process of analysis of the organisms and allow more educated and informed policies and interventions to better treat and prevent infectious disease threats. This report has provided a synopsis of recent antimicrobial resistance surveillance accomplishments achieved by AFHSC-GEIS partners.

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Competing interests

The authors declare that they have no competing interests.

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REVIEW Open Access

Malaria and other vector-borne infection surveillance in the U.S. Department of Defense Armed Forces Health Surveillance Center-Global Emerging Infections Surveillance program: review of 2009 accomplishments

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Abstract

Vector-borne infections (VBI) are defined as infectious diseases transmitted by the bite or mechanical transfer of arthropod vectors. They constitute a significant proportion of the global infectious disease burden. United States (U.S.) Department of Defense (DoD) personnel are especially vulnerable to VBIs due to occupational contact with arthropod vectors, immunological naiveté to previously unencountered pathogens, and limited diagnostic and treatment options available in the austere and unstable environments sometimes associated with military operations. In addition to the risk uniquely encountered by military populations, other factors have driven the worldwide emergence of VBIs. Unprecedented levels of global travel, tourism and trade, and blurred lines of demarcation between zoonotic VBI reservoirs and human populations increase vector exposure. Urban growth in previously undeveloped regions and perturbations in global weather patterns also contribute to the rise of VBIs. The Armed Forces Health Surveillance Center-Global Emerging Infections Surveillance and Response System (AFHSC-GEIS) and its partners at DoD overseas laboratories form a network to better characterize the nature, emergence and growth of VBIs globally. In 2009 the network tested 19,730 specimens from 25 sites for *Plasmodium* species and malaria drug resistance phenotypes and nearly another 10,000 samples to determine the etiologies of non-*Plasmodium* species VBIs from regions spanning from Oceania to Africa, South America, and northeast, south and Southeast Asia. This review describes recent VBI-related epidemiological studies conducted by AFHSC-GEIS partner laboratories within the OCONUS DoD laboratory network emphasizing their impact on human populations.

Introduction

Vector borne infections (VBIs) such as malaria, dengue fever, yellow fever, scrub typhus, and plague comprise a significant proportion of the global infectious disease burden. These diseases account for more than half of the priority diseases in the Special Program for Research and Training in Tropical Diseases, a scientific collaboration of the World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the United Nations Development Program and the World Bank. High priority VBIs include malaria, lymphatic filariasis, leishmaniasis, African trypanosomiasis, onchocerciasis, dengue and Chagas disease, many of which are also considered to be neglected diseases.

Typically defined as infections transmitted from the bite or mechanical transfer of an arthropod vector [1],

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VBIs are of growing importance in an era of global travel. Increasingly blurred lines of demarcation between human and zoonotic disease reservoirs and the unpredictable effect of climate change on the distribution and behavior of arthropod vectors also contribute to the rise of VBIs. Disproportionately high VBI burdens fall in areas with poor health infrastructure, underscoring the need to develop and maintain responsive surveillance systems capable of detecting VBI outbreaks in resource-constrained environments.

The Defense Department has long operated a network of medical research laboratories principally to conduct research and development on diseases of military impact. These laboratories commonly referred to as DoD OCONUS laboratories, have emphasized VBIs in their infectious disease research portfolios. The historical rationale for this emphasis on VBIs is the need to conserve and maintain the health and capacity of troops while operating in a variety of settings with increased exposure to disease-carrying arthropod vectors. The potential impact of vector-borne disease on military populations is illustrated by General Douglas MacArthur, who, referring to the impact of VBI on World War II forces, famously lamented, "This will be a long war, if for every division I have facing the enemy, I must count on a second division in the hospital with malaria, and a third division convalescing from this debilitating disease." [2].

The creation of DoD-GEIS was inspired by the 1992 Institute of Medicine (IOM) report on emerging infections and formally tasked through the June 1996 Presidential Decision Directive (NSTC-7) on emerging infections, which expanded on the original IOM report. The merging of DoD-GEIS with the DoD OCONUS laboratory research mission leveraged the laboratories' strengths—capacity for high-quality hypothesis-driven scientific rigor and established host-nation relationships—and sought to incorporate the additional components of global surveillance, training and response to infectious disease threats. In addition, existing OCONUS laboratory programs oriented toward the development of new vaccines, drugs and diagnostics for diseases in the developing world would benefit from the acquisition of timely surveillance data to help guide their efforts.

The inception and subsequent execution of the program coincides with a period when DoD's public health concerns, expressed by General MacArthur decades ago, increasingly converged with those of the developing world. Since the end of the Cold War, DoD personnel increasingly have been deployed to to render humanitarian assistance in regions of political and economic turmoil and natural disasters. The 2010 Haiti earthquake relief effort, during which several DoD personnel contracted *Plasmodium falciparum* malaria [3], exemplifies this risk.

The AFHSC-GEIS network and its OCONUS laboratory partners conduct VBI surveillance of in arthropod vectors, animals and humans, with emphasis on surveillance of vector-borne diseases in humans, the primary host of interest. The VBI program aims to characterize present occurrences of VBI in humans as well as support the AFHSC-GEIS predictive surveillance program [4] by validating the capability of satellite remote sensing, ecological niche modeling, and arthropod vector and zoonotic reservoir surveillance to predict the risk of VBI transmission to humans. This report reviews the 2009 accomplishments of the AFHSC-GEIS and DoD OCONUS laboratory VBI surveillance network.

Malaria surveillance

One of the world's largest malaria drug resistance surveillance networks is maintained by AFHSC-GEIS, with sites in Africa, South America, the western Pacific islands, and northeast, south and Southeast Asia. The emphasis on malaria drug resistance is well justified. Since World War II, an inexorable pattern of resistance has rendered once-useful malaria treatments, such as chloroquine, sulfadoxine/pyrimethamine and mefloquine, ineffective in large parts of the malaria-endemic world. Despite tremendous progress, there is still no vaccine that prevents infection or disease. This underscores the threat posed by emerging drug resistance and the importance of effective surveillance systems to detect the onset of resistance and assure optimal treatments.

In 2009, the AFHSC-GEIS laboratory network analyzed 19,730 specimens from 25 sites spanning malaria-endemic regions using techniques, such as molecular characterization of resistance genes and *in vitro* drug sensitivity assays to determine inhibitory concentrations against a battery of common malaria drugs. Some sites are also capable of conducting therapeutic efficacy and complex pharmacokinetic *in vivo* studies to better understand drug-parasite interactions.

Today, the most effective anti-malarial drugs are those in the artemisinin class. The artemisinins, derived from *Artemisia annua*, have been used in Chinese medicine for centuries under the name Qinghaosu and eventually incorporated as first-line treatment for *P. falciparum* worldwide. Compared to other malaria drugs such as mefloquine and chloroquine, artemisinin derivatives are vastly superior in terms of safety, tolerability and efficacy, and—until recently—unmarred by resistance. Although the artemisinins have been used on their own as a single-agent therapy, fears over the possible development of resistance have given rise to the concept that malaria treatments should follow the examples adopted for tuberculosis and human immunodeficiency virus (HIV)—that combining drugs with differing mechanisms of action will both optimize patient outcomes and

minimize the risk that resistance will develop. Such artemisinin combination therapies (ACTs) contain a short-acting artemisinin component to quickly reduce parasite burden and clinical symptoms and a longer-acting partner drug to clear remaining parasites. This approach is now recommended by WHO as the first-line treatment for uncomplicated *P. falciparum* malaria in all endemic countries.

The major global investment in ACTs has been threatened recently by increasing ACT treatment failures on the Thailand-Cambodia border, an area historically considered an epicenter of drug-resistant malaria. Between 2002 and 2004, increased parasite clearance times and unusually high failure rates with the ACT regimens artesunate-mefloquine and artemether-lumefantrine were being reported on both sides of the border [5,6] and begged the question of whether resistance to the artemisinin component or its partner drug was the culprit. To further explore this question, the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, conducted a combined *in vivo/in vitro* artemisinin-monotherapy efficacy study to isolate the specific effect that artemisinin resistance may have played in the ACT failures. Although the 28-day cure rate of the artemisinin monotherapy regimen was greater than 90 percent, two subjects failed artemisinin therapy despite the documentation of adequate plasma drug levels, direct observation of medication doses and up to a 4.3-fold higher IC_{50} concentration than the overall mean. This report, the first to document clinical artemisinin resistance, raised serious concerns that resistance to the artemisinin component of ACTs had developed [7].

In 2009, AFRIMS continued to expand its drug-resistance efforts to examine possible countermeasures to combat the potential spread of resistant strains. No previous investigations had been conducted to determine the optimal artemisinin dose regimens that most effectively clear *P. falciparum* parasites. While current dosing regimens in widespread use were effective for relatively sensitive parasites, the specter of artemisinin resistance raised the question of whether higher doses might more effectively clear resistant strains.

AFRIMS conducted a study exploring dose-effect relationships with particular attention to the safety and tolerability limitations imposed at doses higher than previously tested in humans. Subjects with uncomplicated *P. falciparum* malaria were given a total of 14, 28 or 42 mg/kg of oral artesunate divided over a week and followed for clinical and parasitological endpoints. Safety and efficacy findings of the highest dose were particularly critical since demonstration of improved cure rates at higher doses might be critical in designing higher-dose regimens for widespread deployment. Unfortunately, enhanced efficacy was not noted at the high dose arm, either in parasite clearance times or cure rates. Furthermore, transient neutropenia was observed at the 42-mg/kg dose, suggesting toxicity to myeloid progenitor cells. Together, these safety and efficacy findings allowed AFRIMS to characterize an important dose-limiting toxicity of the artemisinins—a valuable data set in light of worldwide deployment of ACTs [8].

To further characterize the artemisinin resistance phenomenon in 2009, Naval Medical Research Unit Number 2 (NAMRU-2) completed a *P. falciparum* therapeutic efficacy study in the Chumkiri District of Kompot Province, approximately 100 km south-southwest of Phnom Penh, Cambodia. In contrast to the areas along the Thai-Cambodian border, where AFRIMS had conducted its drug resistance studies, the Chumkiri site was chosen in part to determine whether ACT resistance had spread to points farther east. The NAMRU-2 study documented an 18.8 percent treatment failure rate employing the national standard regimen of artesunate-mefloquine combination therapy. Treatment failure was associated with increased *pfmdr1* copy number, higher initial parasitemia, higher mefloquine IC_{50} and longer parasite clearance times [9]. This study demonstrated that resistance to the artesunate-mefloquien regimen extended beyond the highly suspected areas of drug resistance along the Thailand-Cambodia border, highlighting the need to expand containment efforts to include Kampot Province.

The increased failure rates of ACTs and the confirmation of resistance to the artemisinin class documented by AFRIMS and NAMRU-2 were regarded as a regional and global emergency. If ACT treatment failures along the Thai-Cambodian border follow the historical precedent of chloroquine (CQ) and sulphadoxine/pyrimethamine (SP) resistance, ACT regimens could be compromised globally within a few years, leading to the frightening possibility of compromising effective treatments for the enormous biomass of *P. falciparum* parasites in sub-Saharan Africa at immense cost to human life. In response, the international malaria community is mounting an aggressive campaign to contain these resistant parasites [10].

This concern is well founded. Specifically, the phenomena of CQ and S/P resistant *P. falciparum* are well described in Africa and been demonstrated to have spread from Southeast Asia to Africa in so-called "selective sweeps" [11,12], suggesting that history may repeat itself with the newly discovered artemisinin resistance phenomenon in Southeast Asia. The Malaria Drug Resistance (MDR) laboratory of the U.S. Army Medical Research Unit – Kenya (USAMRU-K), based in Kisumu, in collaboration with the Kenya Medical Research Institute and Kenya Ministry of Health, has monitored in vitro malaria drug sensitivity and molecular marker profiles across Kenya since 1995. In 2009, *P. falciparum*

drug resistance surveillance efforts focused in western Kenya at three district hospitals in Kisumu, Kericho, and Kisii. A total of 213 *P. falciparum* specimens were collected and frozen for later drug susceptibility profiling against a panel of six to twelve antimalarial drugs. Concurrently, 182 samples were examined for molecular markers associated with *P. falciparum* drug resistance, including Pfmdr1 copy number and select point mutations in Pfmdr1, Pfcrt, and PfATPase6. Data analysis indicates that decreasing but high levels of chloroquine-resistant, low levels of mefloquine-resistant, and no artemisinin-resistant parasite profiles were present among samples assessed. Reassuringly, i*n vitro* drug sensitivity patterns and mutation rates suggest that overall *P. falciparum* drug resistance was stable in Kenya from 2006 through 2009.

Future USAMRU-K drug resistance surveillance efforts will emphasize monitoring artemisinin susceptibility of Kenyan isolates with an integrated approach to correlate *in vitro* drug sensitivity testing with clinical *in vivo* resistance assessments. Artemisinin resistance monitoring is particularly timely in light of the recent adoption of the ACT artemether-lumefantrine as first-line therapy for uncomplicated *P. falciparum* [13]. Timing is optimal to now establish baseline laboratory and clinical resistance data against which future assessments can be compared, both within Kenya and globally.

Malaria surveillance efforts at the Australian Army Malaria Institute (AMI) have focused primarily on the prevalence of malaria infection and incidence of drug resistance within the western Pacific region. Efforts in 2009 concentrated on the Vanuatu and the Solomon Islands. In collaboration with the Pacific Malaria Initiative Support Centre, village-based mass blood surveys were conducted and malaria-positive samples were genotyped to determine the prevalence of chloroquine drug-resistance polymorphism within the Pfcrt gene. Twelve codons of Pfcrt were evaluated and a consensus polymorphic profile was established that allowed for comparison between different countries. The establishment of a consensus "genetic fingerprint" of Pfcrt polymorphisms and its correlation with microsatellite markers, not under immune or drug selection, has provided information on the flow of malaria drug resistance genotypes throughout the region. Current data demonstrate the existence of a common consensus genotype in Papua New Guinea, Vanuatu and the Solomon Islands—distinct from genotypes arising in Indonesia and the Philippines. These findings have implications for the manner in which drug-resistant alleles originating in Southeast Asia may spread throughout the western Pacific.

The AFHSC-GEIS malaria program has also been active in surveillance of *Plasmodium vivax* malaria throughout Asia and South America. As opposed to *P. falciparum*, *P. vivax* treatments are complicated by the need to eradicate dormant hypnozoites. Because of the difficulty in assessing which patients harbor undetectable hypnozoites, it is critical to ensure that radical curative regimens employing chloroquine (CQ) and primaquine (PQ) are optimized. Although highly curative when administered for a two-week course, most malaria control programs acknowledge the real-world effectiveness of PQ for hypnozoite eradication to be inadequate, largely due to insufficient compliance with the protracted regimen. Concerns about G6PD-related hemolysis also limit the incorporation of PQ into national treatment guidelines.

In 2009, malaria scientists at the Naval Medical Research Center Detachment (NMRCD) in Peru reported the results of an efficacy study of abbreviated PQ regimens for the prevention *P.vivax* relapses. Patients were treated under direct supervision in three health centers in Iquitos, the largest city of the Peruvian Amazon Basin, with CQ, 25 mg/kg over three days, plus primaquine, in one of three different randomly-assigned regimens: 0.25 mg/kg daily for 14 days, 0.5 mg/kg daily for seven days or 0.5 mg/kg for five days. The regimens selected represent the WHO-recommended regimen, the Pan American Health Organization (PAHO)-recommended regimen, and a shorter version of the PAHO regimen, respectively. Of the evaluable 491 patients, 48 presented with reappearance of parasitemia due to the same vivax genotype after 35 days of initiating the therapy: 27 (16.0 percent) in the five-day arm, 9 (5.8 percent) in the seven-day arm and 12 (7.4 percent) in the 14-day arm (unpublished data). NMRCD concluded that the seven- and 14-day PQ regimens are similar to each other in efficacy and superior to the shorter five-day regimen in preventing relapse of *P.vivax* malaria [14]. Despite the lower efficacy of the five-day regimen, it likely offers some benefit over regimens without a primaquine component.

Although resistance to malaria chemotherapy has traditionally been more problematic for *P. falciparum*, it is also necessary to remain vigilant for resistant *P.vivax* strains. Chloroquine is nearly universally used as the first-line therapy for *P. vivax* malaria due to its high efficacy and low cost, and PQ remains the only drug capable of eradicating hypnozoites from the relapsing *Plasmodia* species *vivax* and *ovale*. As part of the above-mentioned treatment efficacy study, NMRCD investigators uncovered new evidence of the transmission of CQ-resistant *P.vivax* in the Peruvian Amazon Basin. Of the four patients with reappearance of parasitemia, one was determined to be probably resistant to chloroquine when a whole-blood CQ level at the time of reappearance of parasitemia was measured to be 95 ng/mL and pvmdr1 gene sequencing and neutral microsatellite markers

analysis revealed the same *P. vivax* genotype in the reappearing and original parasites [15].

In the Republic of Korea, similar concerns that CQ-resistant *P.vivax* may have caused an increased caseload from 2005 to 2007 led GEIS partners to conduct a prophylactic efficacy study in 2009. Enrolled into the study were 142 *vivax* malaria patients, most of whom were participants in the Korean Army hydroxychloroquine (HCQ) chemoprophylaxis program. To rule out noncompliance as a cause for prophylaxis failure, plasma HCQ metabolite levels were determined on the day of enrollment. Most soldiers with "breakthrough" *vivax* malaria infections harbored undetectable HCQ levels. Fourteen of 127 (11 percent) of subjects were determined to have HCQ levels >100 ng/mL, meeting established criteria for biological resistance or suspected biological resistance.

The study was the first to describe chloroquine-resistant *P.vivax* prophylaxis failures on the peninsula and raises concerns given the widespread use of HCQ and chloroquine for both treatment and prophylaxis of *vivax* malaria in Korea. Although noncompliance may have contributed to the increased caseload, the widespread use of unmonitored HCQ prophylaxis raised concerns that chloroquine resistance, a phenomenon previously undocumented in Korea, may have contributed [16].

Surveillance of other VBIs in human populations

Although malaria shares common clinical features with other VBIs, the difficulty encountered by clinicians in rendering accurate diagnoses of other VBIs is hampered by the fact that they are not easily diagnosed at the pathogen level. Many studies have corroborated the need for laboratory-based diagnostics in order to distinguish one etiologic cause of undifferentiated fever from another. This is particularly applicable to VBIs, which generally present as undifferentiated fever [17-19].

Throughout the AFHSC-GEIS laboratory network, efforts were made in 2009 to enhance or establish hospital-based febrile illness surveillance platforms in Azerbaijan, Bolivia, Cambodia, Ecuador, Georgia, Kenya, Nepal, Paraguay and Peru in an effort to guide clinical treatments for undifferentiated febrile illness—many of which were caused by VBIs. Working in collaboration with local Ministries of Health and other institutions, such as the U.S. Army Medical Research Institute of Infectious Diseases, Walter Reed Army Institute of Research, and the U.S. Centers for Disease Control and Prevention, specimens collected from patients with acute febrile illness at hospitals and clinics have allowed AFRIMS, NMRCD, NAMRU-2, Naval Medical Research Unit Number 3 (NAMRU-3), and U.S. Army Research Unit-Kenya (USAMRU-K) laboratories to conduct etiological agent identification, monitor the prevalence of VBIs within the AFHSC-GEIS network regions, and better understand VBI epidemiology and geographic distribution.

In 2009, AFHSC-GEIS partner laboratories conducted etiological agent identification of non-malaria VBIs on more than 10,000 specimens from 43 sites in nine countries. The use of techniques such as viral culture, polymerase chain reaction (PCR) assays and enzyme-linked immunosorbent assays (ELISA) led to the discovery of new pathogens and serotypes new to regional areas. For instance, Guaroa virus (GROV) infection, transmitted by *Anopheles neivai*, was documented first in Colombia, and later in Brazil and Panama. Through the febrile illness surveillance study by NMRCD researchers [20], several GROV cases were documented in febrile illness patients from Bolivia and Peru by ELISA detection of IgM-specific antibodies. Prior to this study, GROV infection had not been documented in Bolivia and Peru but should now be considered in the differential diagnosis for febrile illness of unknown etiology in that region.

Recent reports of vector-borne diseases circulating in Nepal have described the first documented case of dengue virus [21] and the spread of all dengue virus serotypes circulating in 2008 [22]. To further expand on these findings, AFRIMS initiated a hospital-based study to determine etiologies of undifferentiated febrile illnesses at four hospitals in Nepal (two in Kathmandu, one in Pokhara and one in Bharatpur). Through fiscal year 2009, 163 patients had been enrolled.

Although testing is still in progress, laboratory testing has confirmed or suggested a diagnosis in over 75 percent of cases enrolled to date. In addition to non-VBIs detected (*Pseudomonas aeruginosa* (one), *E. coli* (one), *Salmonella typhi* (three), *Salmonella paratyphi* A (four), leptospirosis (37), hepatitis A virus (four), hepatitis C virus (one), brucellosis (16), influenza A H3 (six), influenza A H1Sw (two), influenza B (two) in the initially enrolled patients, 28.2 percent had a VBI: scrub typhus (19), murine typhus (three), Japanese encephalitis (JE) (two), primary dengue infection (12), secondary dengue infection (nine), and malaria (non-*falciparum*) (one). Diagnostic analyses yet to be completed include testing for *Bartonella* infection, which has not previously been determined to be a cause of illness in Nepal, and pathogen discovery for unrecognized viruses. The study continues enrollment through 2010 to determine the seasonal risk for VBI and other infections in Nepal.

Hospital-based surveillance conducted by the AFHSC-GEIS partners provides practitioners with critical information used to treat patients, and for implementing disease prevention and control measures. An example is provided by a 2009 seroprevalence study conducted by NAMRU-3 researchers in Azerbaijan, which surveyed

68 patients for West Nile virus (WNV), *Rickettsia typhi*, hepatitis A, Q fever, leptospirosis and brucellosis serologies. Of 68 patients screened, 8.8 percent were positive for leptospirosis, 7.3 percent were positive for *Rickettsia typhi* IgG, 93 percent contained anti-hepatitis A virus antibodies, 31 percent showed Q-fever IgG antibodies, and 16 percent were reactive in brucellosis screening. The data obtained from the study provided clinicians with a better understanding of the risks and exposures for regionally relevant infections, in turn supporting improved treatments. Ancillary benefits of the study included the training and laboratory infrastructure enhancements that enabled the Azerbaijan Ministry of Health to better meet public health needs.

Human seroprevalence of hantaviruses, arenaviruses, brucellosis, WNV, Crimean Congo hemorrhagic fever (CCHF), leptospirosis, rickettsias, and several other vector-borne and zoonotic diseases have also been conducted throughout the network. For example, in 2005, Nepal experienced an outbreak of JE, and an outbreak response executed by WHO and the Nepal Ministry of Health collected samples from acute encephalitis patients. Serological testing, however, revealed that only 35 percent were positive for the disease. In 2009, using randomized JE-negative samples, AFRIMS researchers tested acute illness serum for the presence of IgM to dengue virus, Chikungunya virus, WNV, *Leptospira* and *Brucella*. Of 286 samples, AFRIMS found 75 patients (26.2 percent) with antibodies against *Leptospira*, 18 (6.3 percent) with *Brucella* antibodies and five (1.7 percent) with Chikungunya antibodies. No samples were positive for exposure to dengue virus or WNV. Although VBIs made up a small percentage of samples not positive for JE, this was the first time Chikungunya infection had been documented in Nepal.

Not only is characterization of pathogens responsible for febrile diseases of considerable assistance to clinicians rendering care to individual patients, but it also allows for temporal and spatial tracking of disease and pathogen strains. In Cambodia, NAMRU-2 investigators have tested specimens collected from 5,362 patients for dengue virus, rickettsial infections, hantavirus infections and other pathogens, and determined dengue-2 and dengue-4 serotypes as the predominant circulating strains by real-time PCR. Determination of circulating dengue virus serotypes is particularly relevant in light of the fact that heterotypic strain infection might increase clinical disease severity through an antibody-dependent enhancement mechanism [23].

Surveillance of VBIs in animals and vectors

While not a major focus of the review, vector and animal surveillance can play a role in mitigating the human impact of emerging infections by triggering measures to limit transmission of vector pathogens from vector and animal reservoirs. In 2009, AFHSC-GEIS continued to conduct arthropod surveillance in Afghanistan, Ethiopia, Kenya, Libya, Peru and Thailand in collaboration with host-nation organizations, including Afghani and Libyan National Malaria and Leishmaniasis Control Programs, Universidad Peruano Cayetano Heredia, Combined Joint Task Force-Horn of Africa, Consortium for National Health Research-Kenya, Cairo University, and several other academic and public health agencies.

Efforts by AFRIMS, NAMRU-3, NMRCD, and USAMRU-K focused on continuing entomology studies for vectors such as mosquitoes, ticks, fleas and mites to test for arboviruses, rickettsiae, and *Leishmania* species. For example, USAMRU-K collected 50,718 ticks and 36,464 mosquitoes to screen for CCHF virus and dengue virus, respectively, in five sites of Kenya: Busia, Kahawa, Kakamega, Kisumu and Isiolo. After initial screening by ELISA for CCHF, three of 16 positive samples were confirmed by PCR and sequenced. Pooled tick samples and mosquito samples were also used for cell culture inoculation for CCHF and dengue virus.

In 2009, AFHSC-GEIS-sponsored animal surveillance activities continued to expand in Kenya, Korea, Peru and Thailand. Tissue and sera from animals, such as rodents and cattle, were collected and screened for the presence of zoonotic pathogens, including arenaviruses, brucellosis, anthrax, leptospirosis and hantaviruses using assays such as Rose Bengal test, Microscopic Agglutination Test, hemaglutinin inhibition assay and ELISA.

A good example of the need for coordinated human-animal surveillance is provided by a seroprevalence study conducted by NMRCD researchers in the Peruvian Amazon region to characterize the epidemiology of spotted fever group (SFGR) and typhus group rickettsial (TGR) infections among humans and domestic pets. From the 1,195 human sera analyzed for SFGR and TGR using anti-SFGR and anti-TGR antibody ELISAs, 521 (43.6 percent) and 123 (10.3 percent) were positive, respectively [9]. Among the 71 canines surveyed for SFGR and TGR, 42 (59.2 percent) were positive for SFGR antibodies and two (2.8 percent) were positive for TGR antibodies. Using a nested PCR, one active SFGR infection was detected among the canines. Among the 17 felines screened, one (7.7 percent) contained SFGR-specific antibodies while none had TGR antibodies. The study demonstrated that prevalence of these rickettsial infections was high within the study population, providing clinicians with a greater awareness of rickettsial infections as a cause of febrile illness in the Iquitos area and that domestic pet owners may be at higher risk [9].

Discussion

The 1996 Presidential Decision Directive NSTC-7 formally codified and expanded the role of DoD—already a well established contributor in tropical infectious disease research—to include the additional components of global surveillance, training and response to infectious disease threats as part of the DoD-GEIS program. Infectious disease surveillance data obtained from the DoD OCONUS laboratory network are shared freely and published in the peer-reviewed literature to inform local, regional and global health program managers irrespective of national or geographical affiliation. This mutual benefit between host-nation public health programs and DoD has arisen in part because of the unique, communicable nature of infectious diseases. As VBIs increase globally, the need to optimally manage surveillance efforts for maximum impact becomes even more critical.

The original DoD-GEIS Emerging Infections Prevention Strategy [24] stipulated the need for "standardized sentinel surveillance" to "strengthen and integrate programs to monitor, control and prevent emerging and zoonotic diseases" among its strategic goals, emphasizing drug-resistant malaria, Rift Valley fever, rickettsial infections and dengue fever. In 1998, following the document's publication, several reviews and panels corroborated the necessity of VBI surveillance [25]. An exhaustive review of global trends in emerging infectious disease attributed 28.8 percent of all emerging infectious disease events to VBIs in the decade following implementation of the original DoD-GEIS Strategy [26]. In 2009, the GEIS VBI surveillance program continued to make significant contributions throughout its global network (Figure 1). However its success, opportunities exist for greater refinement of the program. Enumerated below and in Table 1 are concepts to guide future AFHSC-GEIS VBI surveillance efforts for maximum impact.

Utility of organizing surveillance initiatives: VBIs vs. non-VBIs

As a practical matter, managing AFHSC-GEIS surveillance into a cohesive program under the familiar nomenclature of "vector-borne infections" is desirable since scientists, government public health structures and medical research communities tend to be organized and resourced accordingly. However, the necessity of conducting surveillance of undifferentiated febrile illnesses that do not fall into specific AFHSC-GEIS pillars (i.e., respiratory, enteric, sexually transmitted or antimicrobial-resistant) illustrates the inadequacy of constraining surveillance efforts for "undifferentiated fever"—a clinical description befitting many VBIs, but not necessarily inclusive of all militarily relevant diseases. Hence, strict adherence to the necessity for arthropod vector transmission may not represent the best framework for the comprehensive programmatic surveillance of diseases that threaten DoD personnel and other military populations. For example, omitted from this review is a rather substantial body of work conducted by AFHSC-GEIS partners specializing in leptospirosis, a disease that does not require an arthropod vector component for transmission, but is transmitted through human contact with infected animal urine.

A requirement for vector-borne transmission also excludes another body of work by AFHSC-GEIS partners in Korea who conducted an outbreak response investigation of hemorrhagic fever with renal syndrome [27]. The investigation localized transmission sites to be near the demilitarized zone (where most U.S. and Korean soldiers conducted field training) and led to the characterization of three novel hantaviruses [28-30]. Although not technically VBIs, these leptospirosis and hantavirus surveillance efforts were prospectively supported by AFHSC-GEIS because of their perceived relevance and potential impact on military and developing-world populations. The demonstrated value of these efforts speaks to the need to judiciously support non-VBI surveillance as conditions warrant rather than hewing to a dogmatic requirement for vector transmission as a condition for programmatic management.

Within in the U.S. military framework, prioritizing disease surveillance for VBIs is consistent with the Infectious Diseases Investment Decision Evaluation Algorithm (ID-IDEAL) framework previously proposed by DoD infectious disease officials [31]. The framework was developed as an algorithmic model to prioritize infectious diseases posing the most substantial threats to deployed U.S. military forces and to guide research and development. The model takes into account disease severity and likelihood of infection on a spatial and temporal basis and assigns a Global Severity Risk Index (GSRI) for DoD personnel. Of the top 20 infectious disease threats prioritized by GSRI, half are VBIs (malaria, dengue fever, Rift Valley fever, Chikungunya, CCHF, sandfly fever, O'nyong-nyong, Sindbis virus, scrub typhus and leishmaniasis).

More recently, a panel composed of DoD infectious disease experts and policymakers issued a priority ranking of infectious disease threats to the U.S. military [32], listing many of the same VBIs identified by the ID-IDEAL model. Taken together, the expert panel document and ID-IDEAL's GSRI scores may be considered as doctrinal support for an "infectious disease military impact rank" (Table 2) integrating these two reports to guide future surveillance priorities. Incorporation of this

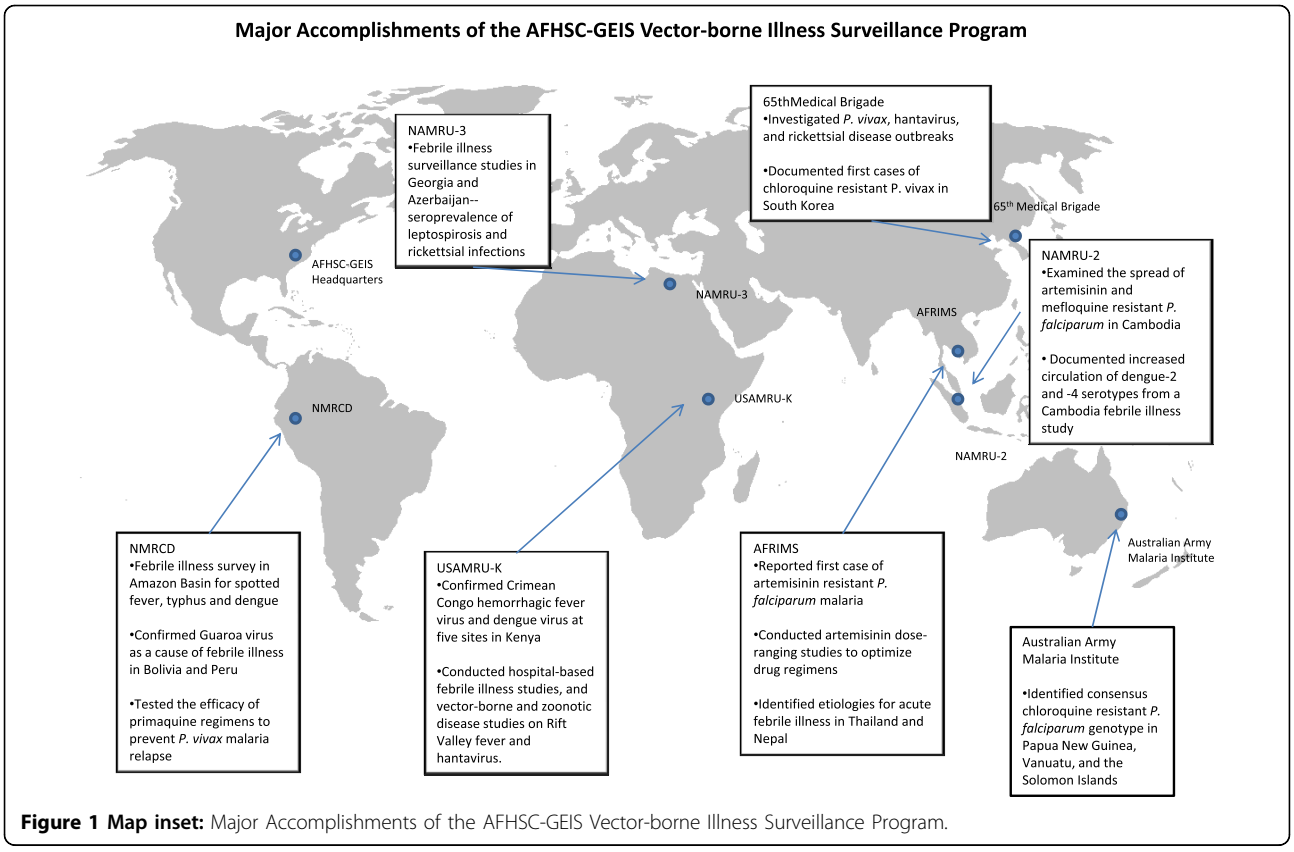

Figure 1 Map inset: Major Accomplishments of the AFHSC-GEIS Vector-borne Illness Surveillance Program.

Table 1 Concepts for the AFHSC-GEIS Vector-Borne Infection (VBI) Surveillance Program

Concept	Rationale
Programmatic organization of surveillance efforts as VBIs is a useful principle to prioritize surveillance efforts	Strict adherence to a VBI-only surveillance program must be balanced with an understanding of prevailing disease threats
VBI surveillance efforts should be closely coordinated with human surveillance	Although disease burden in zoonotic or vector populations is of interest, it is so primarily because of the potential impact on humans
Human VBI case definitions should require laboratory confirmation	Clinical diagnoses of most VBI are of limited sensitivity and specificity; pathogen level identification will guide effective treatment
Case definitions employed should be able to be applied consistently across disparate geographies and longitudinally	If surveillance goal is to map disease in areas of sparse infrastructure, simpler laboratory techniques may be preferable
Advancing technologies should be evaluated continually and incorporated without jeopardizing capability for analysis of longitudinal trend**s**	Balance must be achieved between newer diagnostic technologies and adherence to established laboratory case definitions. Substitution of more sensitive methods may erroneously mimic disease emergence
Standardized laboratory and clinical approaches should be judiciously applied and implemented based on proximal impact on human health	The imperative for a "standardized" surveillance system must be tempered with consideration for the cost-benefit ratio of implementing such standards
To properly power epidemiological studies over a broad geography, laboratory case definitions may diverge from those typically used to guide clinical diagnoses	Example: Studies intended to define the geospatial extent of antimicrobial drug resistance might seek to characterize genotypes from extracted DNA rather than rely on determination of minimum inhibitory concentrations (MICs) from viable organisms, despite the fact that the latter may be more predictive of clinical outcome
Patient samples and associated clinical data must be recorded and maintained in a data and specimen repository in a consistent manner over time	Longitudinal trends can be better assessed if specimens and associated demographic data are catalogued in a manner to allow for retrospective trend analysis
Full use must be made of existing, appropriately collected and catalogued sample sets for retroactive analysis	As technology advances, capability to diagnose previously "undiscovered" pathogens can be applied retroactively to banked specimens to better determine the pace of emergence

Table 2 Military Infectious Disease Impact Rank: Top 20 febrile illnesses ranked by order of military significance

Rank	Disease	Median GRSI Score	Medical Force ICDT Rank	Military Impact Index (GRSI/ICDT Rank)
1	Malaria	4949	1	4949
2	Diarrhea, bacterial	5236	3	1745
3	Dengue	3148	2	1574
4	Norovirus and other viral diarrhea	1964*	7	280
5	Leptospirosis	1745	10	174
6	Chikungunya	2608	16	163
7	Rift Valley Fever	2519	24	104
8	HIV/AIDS	728	14	52
9	Meningococcal meningitis	698	17	41
10	Diarrhea, protozoal	411	11	37
11	Crimean-Congo hemorrhagic fever	430	13	33
12	Leishmaniasis	12	5	24
13	Hepatitis E	402	21	19
14	Hemorrhagic fever with renal syndrome	252	15	16
15	Q fever (*Coxiella burnetti*)	92	6	15
16	Rickettsioses	155	19	8
17	Tick Borne encephalitis	134	23	5
18	Influenza	35	8	4
19	Plague	89	18	4
20	Lassa/other arenaviruses	63	22	2

Index calculated as quotient of Infectious Diseases Investment Decision Evaluation Algorithm (ID-IDEAL) Global Risk Severity Index (GRSI)/Integrated Capabilities Development Team (ICDT) rank for diseases listed in both documents. Adapted from refs 27 and 28.

**Mean of all GSRI scores* for diarrheal diseases.

[+]*Mean of cutaneous, visceral and mucosal leishmaniasis GSRI scores.*

index to guide future AFHSC-GEIS endeavors would emphasize surveillance priorities in terms of health impact rather than by mode of transmission.

Need for "standardization" and requirement for laboratory confirmation

Capitalizing on the expertise resident throughout the OCONUS laboratory network, AFHSC-GEIS's VBI surveillance efforts have traditionally emphasized laboratory characterization to the pathogen level. The non-specific clinical presentation of most vector-borne diseases makes pathogen-level diagnosis difficult even in the hands of highly experienced clinicians. This emphasizes the need for highly trained laboratory scientists and technicians to use established diagnostic methods to enable informed individual and community prevention and treatment strategies.

The use of the adjective "emerging" as a prefix to "infectious diseases" implies the necessity of determining the temporal and geospatial distribution of any given candidate infectious disease, and assumes consistent clinical or laboratory case definitions are applied over time or between surveillance locales for such comparisons to be valid. Development and implementation of such standard methods, particularly in the realm of laboratory-based diagnoses, are almost always easier said than done, given their logistical and financial costs. In addition, once any given standard approach is implemented, the pace of technological development almost assuredly outdates it. Thus, the imperative for a standardized surveillance system must be tempered with consideration of the cost-benefit ratio involved in implementing any given standardization effort.

The single greatest factor contributing to the success of AFHSC-GEIS has been the traditionally collaborative and close relationship between DoD OCONUS laboratory scientists, public health personnel and their host-nation counterparts. Together, DoD personnel and host nations work to identify, conceive and execute emerging infectious disease surveillance activities based on regional DoD and local Ministry of Health priorities. While this approach has its merits, the emphasis on regional flexibility has come at some expense to creating a standardized surveillance system. The desire for standardization to enable the generation of geographically and longitudinally generalizable data must be balanced with the need to remain responsive to host-nation capabilities and priorities.

A more appropriate approach calls for judicious application of proscriptive standards to maximize the applicability of the overarching surveillance product. Additionally, if laboratory samples cannot be transported to centralized reference laboratories (as may be the case due to human

use or regulatory considerations), laboratory approaches that are implementable in both austere and well-developed settings may be more desirable than technologically complex methods if the former approach enables data comparisons between locales. As a corollary, laboratory case definitions for epidemiological studies may diverge from those typically used to guide clinical diagnoses.

Finally, longitudinal comparisons will be optimized if the emphasis on harmonized laboratory approaches is matched with the collation of clinical data and the use of proper information systems to catalog both biological samples and their associated clinical datasets.

Role of vector surveillance

Although this report has focused on surveillance of VBIs in human hosts, entomological vector surveillance also plays a critical role in estimating disease risk and guiding interventions to control transmission. In the absence of a vaccine or prophylactic drug for many VBIs, prevention is reliant on vector control and reduction of infective bites. Optimally, control efforts must be linked with vector and human surveillance data to gauge their effect and estimate disease risk.

A critical distinction between human and vector surveillance is the complexity of vector collection when considering the tremendous diversity of culprit arthropods. In contrast with human surveillance, which generally focuses on disease incidence and/or prevalence in a particular population, unique aspects of vector transmission complicate vector surveillance approaches. For example, for diseases in areas where a specific vector responsible for disease transmission may be unknown or unconfirmed, approaches emphasizing vector identification and transmission competence may need to be prioritized. In other areas where the disease-transmitting potential of arthropod species is well corroborated, targeted characterization of infection rates and vector population densities maximizes the predictive power of field vector surveillance for human VBI cases [33], helping decision makers prioritize vector control efforts and public awareness campaigns [34].

Vector surveillance and control programs face fiscal challenges; they are difficult to sustain because the proportion of infected arthropods may be low and the predictive impact on the acquisition of human disease is difficult to verify. Nonetheless, since surveillance of VBIs in humans is by definition *post factum*, the VBI surveillance approaches must not be neglected since correctly executed vector control measures are uniquely preventive in nature. These factors highlight the need for close coordination between vector and human disease surveillance efforts.

Conclusion

The studies reviewed in this report highlight the prodigious accomplishments of AFHSC-GEIS's VBI surveillance program and the potential impact on vector-borne and other communicable diseases of well conceived, relevant and timely surveillance. This review unequivocally demonstrates the benefit provided to host-nation populations through surveillance activities that transcend traditional nation-state boundaries. The capacity of infectious diseases to affect human beings in unforeseen ways, particularly with the advance of VBIs in an ever-shrinking global community, endangers both military and the developing world.

Future efforts of AFHSC-GEIS's VBI program should center on enhancing the integration of vector, zoonotic and human surveillance activities, continuing to maximize the impact on human diseases of interest to both military and civilian populations, and providing surveillance data that genuinely empowers public health officials. It is essential that the AFHSC-GEIS VBI program remains dedicated to the premise that in the fight against infectious diseases, timely and actionable surveillance data are critical.

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The authors declare that they have no competing interests.

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REVIEW Open Access

The AFHSC-Division of GEIS Operations Predictive Surveillance Program: a multidisciplinary approach for the early detection and response to disease outbreaks

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Abstract

The Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System Operations (AFHSC-GEIS) initiated a coordinated, multidisciplinary program to link data sets and information derived from eco-climatic remote sensing activities, ecologic niche modeling, arthropod vector, animal disease-host/reservoir, and human disease surveillance for febrile illnesses, into a predictive surveillance program that generates advisories and alerts on emerging infectious disease outbreaks. The program's ultimate goal is pro-active public health practice through pre-event preparedness, prevention and control, and response decision-making and prioritization. This multidisciplinary program is rooted in over 10 years experience in predictive surveillance for Rift Valley fever outbreaks in Eastern Africa. The AFHSC-GEIS Rift Valley fever project is based on the identification and use of disease-emergence critical detection points as reliable signals for increased outbreak risk. The AFHSC-GEIS predictive surveillance program has formalized the Rift Valley fever project into a structured template for extending predictive surveillance capability to other Department of Defense (DoD)-priority vector- and water-borne, and zoonotic diseases and geographic areas. These include leishmaniasis, malaria, and Crimea-Congo and other viral hemorrhagic fevers in Central Asia and Africa, dengue fever in Asia and the Americas, Japanese encephalitis (JE) and chikungunya fever in Asia, and rickettsial and other tick-borne infections in the U.S., Africa and Asia.

Background

The morbidity and mortality associated with infectious disease outbreaks, which are directly or indirectly linked to ecologic or climate events and trends, pose a growing problem for global public health [1-3]. Many factors are associated with this growth: disease vector-habitat expansion due to environmental degradation and climate variability; changes in animal and human population dynamics that increase the risk of human exposure to infective pathogens; and the insufficiency of public health infrastructure in resource-limited settings to support and sustain routine infectious disease surveillance, prevention and control activities. The goal of the AFHSC-GEIS predictive surveillance program is to provide DoD decision makers with advanced awareness on emerging infectious disease threats, and thereby promote timely, science-based disease outbreak prevention, preparedness, and control-and-response action. The proof of concept is best exemplified by the recurring outbreaks of Rift Valley fever in Africa. These outbreaks have not posed direct threats to DoD forces, but in Africa and the Middle East they do cause significant agricultural and trade disruptions in addition to human morbidity and mortality. The economic, social and political destabilization associated with Rift Valley fever outbreaks in vulnerable states like Yemen, Somalia and

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Zimbabwe cannot be understated. Geographic stabilization benefits not just those directly affected, but also those, like the US military, who may have to respond to a crisis. In addition, the accidental or intentional importation into the US of Rift Valley fever or other vector-borne human health or agricultural threat would be a disaster to the US economy. DOD involvement in any Federal response to such an outbreak would be costly. Keeping these threats under surveillance and contained outside the US, is in the direct interest of the US [4,5].

The economic and human health devastation of the 1997 Rift Valley fever outbreak in Eastern Africa was not repeated in the 2006-2007 outbreak. This was largely due to the implementation of early, targeted interventions by the affected countries and the international community, prompted by AFHSC-GEIS early alerts. The result was a more contained outbreak and a quicker return to regional economic, social and political stability.

To achieve its predictive surveillance goal, the AFHSC-GEIS has brought together a dynamic team of partners into an integrated, multidisciplinary program with the capability to generate and merge data to produce pre-event advisories and alerts on the emergence of disease outbreaks. Partner activities are organized into three primary predictive components: 1) satellite remote sensing and ecologic niche modeling for ecologic and climatic events, trends and characteristics that otherwise influence the potential for disease outbreaks; 2) arthropod-vector surveillance and geo-spatial mapping for characterizing vector presence, abundance, and disease transmission capability; and 3) animal-host surveillance for detecting vector and pathogen exposure events, and animal-to-animal or animal-to-human pathogen transmission. Another predictive surveillance program component, human-disease surveillance, does not serve a predictive function. Rather it provides evaluation feedback for the overall program's meta-product, predictive information on human disease threats. The predictive surveillance program components are linked to one another by communications and data-processing channels. Program partners use the channels to integrate and analyze surveillance results from the different components for temporal and spatial relevance. This produces progressively targeted information on emerging threats. (Figure 1)

Methods

Program management

The AFHSC-GEIS has oversight and ultimate responsibility for the program's implementation, and therefore, provides its strategic direction based on DoD priorities and Force health needs. The scientific content and scope of program activities are an expression of consensus among subject matter experts working within the predictive surveillance disciplines. In 2009, they were organized into a steering committee that: 1) promotes the generation of quality-controlled, reproducible data from all program participants; 2) cultivates intra- and extra-DoD predictive surveillance-related clinical and laboratory training and operational research; 3) advocates for the use of standardized surveillance and laboratory methodologies, and evaluates new or novel technologies for applicability; and 4) delineates the roles, responsibilities and mutually-supporting relationships among the AFHSC-GEIS predictive surveillance partners.

Program model

The core of the program is a model that groups activities into components that conduct surveillance for critical detection points indicative of eco/climatic anomalies, and weather, disease-pathogen, vector, or animal-host events, which are known to be conducive to, and in aggregate, presage the emergence of disease outbreaks in humans. (Figure 2) Program partners generate and analyze derived data from their component activities, then collaborate and coordinate with each other to aggregate and merge their findings into the context of the entire model. The unifying analysis outcome among and between components is disease transmission potential. The selection criteria for applying the model to an etiologic pathogen and geographic location are that they are of stated DOD priority, and that they have direct or indirect temporal and spatial association with environmental trends and events such as El Niño occurrences. [6] Direct associations occur when the expression of disease is dependent on the environment's direct influence over a pathogen. For example, changes in sea surface temperatures lead to outbreaks of cholera.[7] Indirect associations are most evident for vector-borne diseases, such as Rift Valley fever, where the environment influences the vector's life cycle, and which in turn influences pathogen presence or transmission. To date, this model has successfully predicted outbreaks of Rift Valley fever in Kenya, Tanzania, Somalia, Sudan, Madagascar and South Africa from 2006 through 2008.[8,9] Host-country ministries of health and agriculture, as well as the World Health Organization (WHO) and the Food and Agriculture Organization (FAO), are currently using the program's Rift Valley fever advisories and alerts to prepare for and mitigate the impact of Rift Valley fever outbreaks in Africa.

The AFHSC-GEIS program is expanding the use of its model to other priority vector- and water-borne and/or zoonotic diseases including: leishmaniasis, Japanese encephalitis, malaria, chikungunya fever, and hantavirus infections. The extension also covers different ecosystems such as those in southeastern Europe, central Asia,

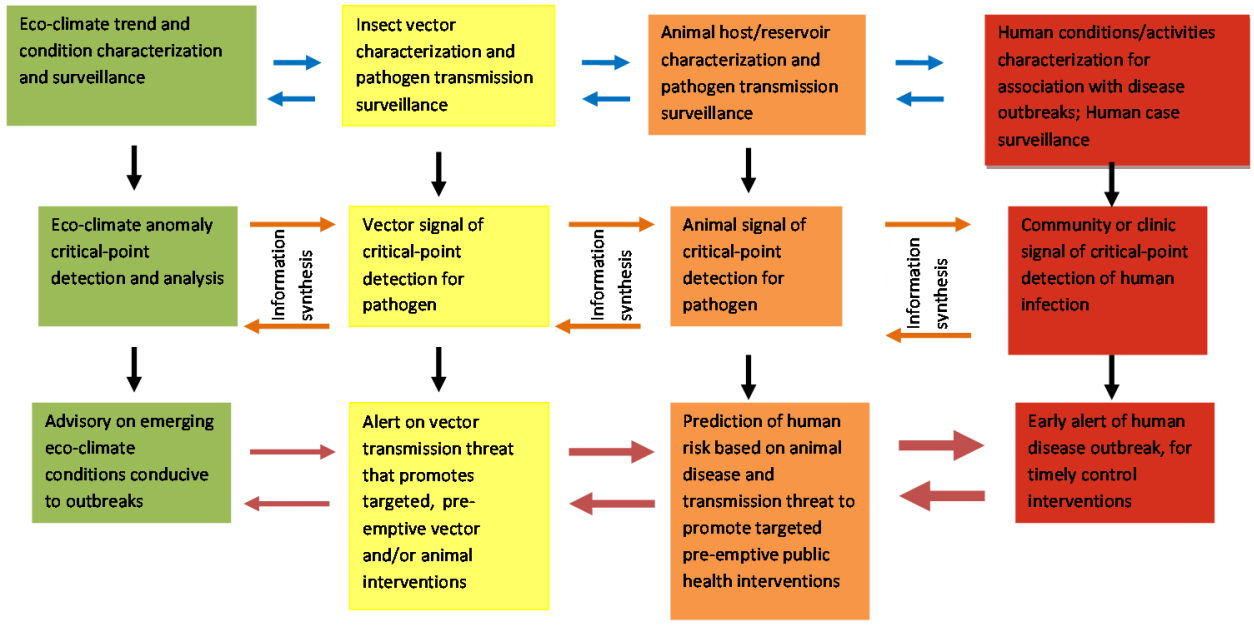


Figure 1 AFHSC-GEIS Predictive Surveillance Program Boxes represent model components: Green – eco-climate, yellow – vector, orange – animal, red – human. Horizontal arrows represent communications and feedback: blue – inter-component communication and coordination, orange – collaboration on generated data and information, red – progression of certainty between reports and feedback for program priorities. Vertical arrows represent component sequence of activities and production of reports.

the Middle East, southeast and northeast Asia, and North America [8]. AHFSC-GEIS is consulting with national and international public health authorities to optimize the delivery of the program's product—comprehensive and reliable information predicting outbreak emergence, through an easily accessible website.

Model components

Eco-climate component

The eco-climatic data used in predictive surveillance are derived from two sources: satellite remote sensing for the macro-level influences of climate and ecology, and ground-based measurements (ground-truths) for the micro-level results of weather and habitat conditions. The latter tend to be more precise, but geographically-localized, quantitative measurements. The former are less precise, more qualitative data that give a broad overview of eco-climate events and trends contributing to disease outbreak potential. Both are used in tandem for meaningful analysis.

Remote sensing

The Global Inventory Modeling and Mapping System (GIMMS) group at the National Aeronautics and Space Administration's (NASA) Goddard Space Flight Center monitors global-scale indicators of inter-annual climate variability, for example the El Niño Southern Oscillation (ENSO). The group performs detailed analyses of satellite-generated datasets on land surface temperature (LST), [10] normalized difference vegetation index (NDVI) [11,12], sea surface temperature (SST), [13] outgoing long-wave radiation (OLR) [14] and rainfall [15]. The group uses time series analyses for assessing macro-level ecologic dynamics that signal the persistence of an eco-climate trend with known association to disease outbreak emergence (Figures 3, 4, 5, 6). GIMMS then produces illustrative maps and graphics that form a risk assessment, the first product of our model's prediction process. For example, in the Rift Valley fever project, GIMMS uses the concurrence of warmer SSTs in the central and eastern Pacific (>1° C), and in the western equatorial Indian Ocean (>5° C), as its analysis' initial critical detection point. Historical observations and expert analyses link these SSTs to excessive rainfall over Eastern Africa. When the resulting greener-than-normal conditions (vegetation growth) continue for longer than a three-month period, an ecology emerges for mosquito-presence and survival [1]. However, because the remote sensing datasets are snapshots of large geographic areas, and therefore are only surrogates for actual weather-related conditions, they must be augmented with quality-controlled direct measurements, i.e., environmental temperature or rainfall volume at representative localities on the ground (Figures 7, 8).

GIMMS' analyses result in advisories based on detections of early shifts in eco-climate trends. As these trends start to produce indicators of rising disease risk

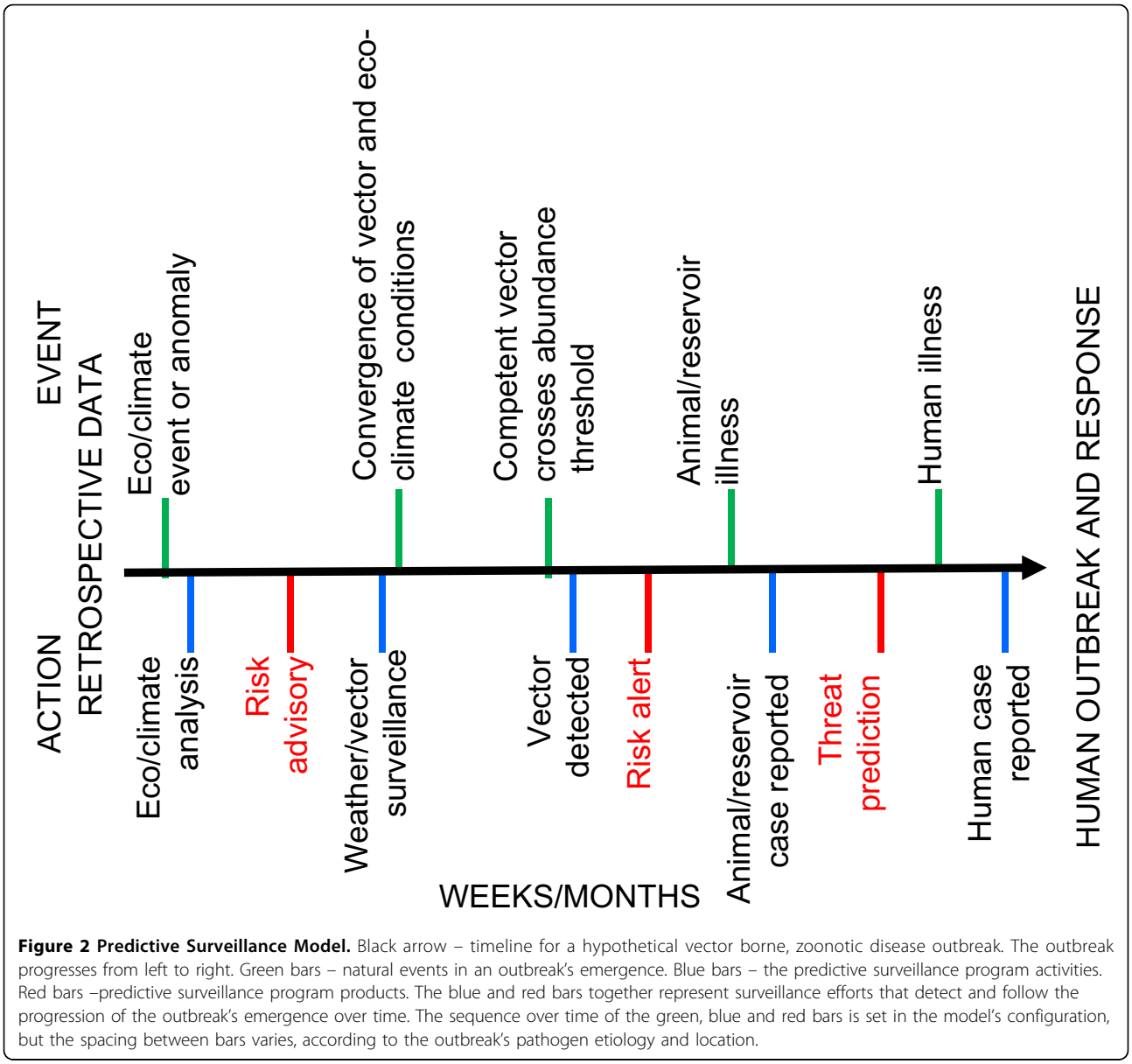


Figure 2 Predictive Surveillance Model. Black arrow – timeline for a hypothetical vector borne, zoonotic disease outbreak. The outbreak progresses from left to right. Green bars – natural events in an outbreak's emergence. Blue bars – the predictive surveillance program activities. Red bars –predictive surveillance program products. The blue and red bars together represent surveillance efforts that detect and follow the progression of the outbreak's emergence over time. The sequence over time of the green, blue and red bars is set in the model's configuration, but the spacing between bars varies, according to the outbreak's pathogen etiology and location.

in specific geographic locations, the advisories transition to more certain alerts of threat emergence. GIMMS disseminates advisories and alerts to Federal collaborating agencies (DoD overseas laboratories and public health and medical research agencies [16], U.S. Agency for International Development, Centers for Disease Control and Prevention, and U.S. Department of Agriculture), and international partners such as WHO and FAO. When used in conjunction with ground-truth information, remote sensing targets subsequent surveillance activities to those locations most at risk. Such targeting permits intensive vector- and animal-host surveillance for pathogen transmission and disease emergence where it is most needed [17]. In August 2009, the GIMMS group issued an early warning advisory on an emerging global disease risk from autumn 2009 through spring 2010 (Figure 9).

Ecologic niche modeling

Remote sensing products and climatic averages such as rainfall and ambient temperature are used in ecologic niche modeling (ENM). ENM characterizes those habitat and geographic conditions suitable for maintaining disease vectors and animal hosts, and thus those areas suitable for the transmission of disease pathogens during outbreaks. Estimations of ecologic niches help investigators map precisely where a vector or host may live and

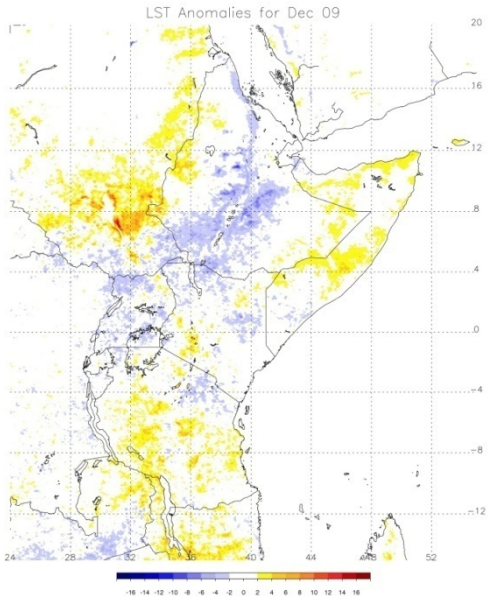


Figure 3 Land Surface Temperature (LST) Anomaly for Eastern Africa, December 2009. Blue – cooler than average land surface temperatures. Yellow/orange/red – warmer than average LST.

thrive, providing vital information for predicting where a vector-borne or zoonotic disease may occur [18-20]. Examples of diseases targeted by the AFHSC-GEIS program's ENM include JE and malaria in the Republic of Korea (ROK) [21-24].

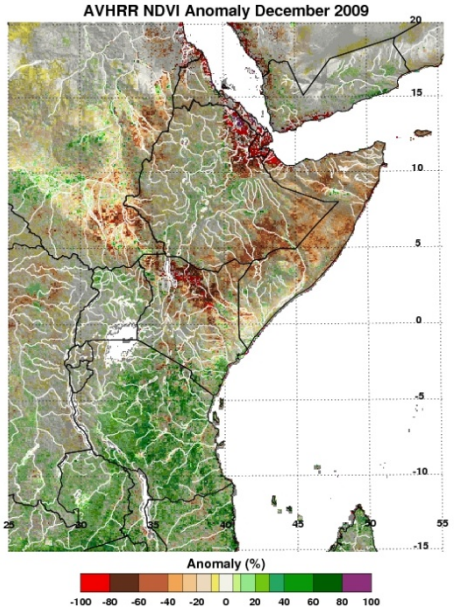


Figure 4 AVHRR-N17 NDVI Anomaly for Eastern Africa, December 2009. Green – greater vegetation growth as a surrogate for sufficient and prolonged rainfall. Brown – less vegetation growth signaling less than normal rainfall.

For JE, the Uniformed Services University of the Health Sciences (USUHS) partners use the maximum-entropy approach, Maxent [25], to model the occurrence of the primary JE vector *Culex tritaeniorhynchus*[19]. This approach uses environmental variables (e.g., average minimum monthly temperature, total monthly precipitation, vegetation indexes, land cover and elevation) and geo-referenced mosquito collections to derive a vector's spatial range. USUHS partners then determine the controlling environmental factors for *Cx. tritaeniorhynchus* abundance, distribution and periodicity. The intended result is the identification of a putative detection point for predicting JE risk to U.S. Forces in the ROK (Figure 10). In the future, USUHS partners will test this ENM application to JE in other countries such as Thailand.

MosquitoMap (http://www.mosquitomap.org) is an AFHSC-GEIS online product that incorporates ENM as a predictive surveillance tool for vector surveillance. At its core is a data-curation process that organizes and standardizes accurate mosquito collection, distribution data, and pathogen-transmission models [26-28]. Using MosquitoMap, its developers at the Walter Reed Biosystematics Unit (WRBU), Walter Reed Army Institute of Research (WRAIR) make accurate, high-resolution distribution maps of where vectors are predicted to exist. MosquitoMap is paired with the Mal-area Calculator (MAC), a raster overlay analytic tool that maps and quantifies the extent of where vectors, disease pathogens, and humans co-occur (Figure 11).

During 2009, WRAIR-WRBU partners focused on validating MosquitoMap's vector distribution models for the ROK [29]. WRAIR-WRBU also began making vector map-layers for Southeast Asia to expand the geographic functionality of MosquitoMap. During 2010, partners will incorporate MosquitoMap into a new application—VectorMap, which will include sand fly and tick data and models (Foley DH, personal communication).

Vector component

The second program component, the vector component, is currently organized to support the niche modeling applications described above, and promote the identification of critical detection points for other vector-borne diseases included in the AFHSC-GEIS predictive surveillance program. While the program's vector surveillance activities historically centered on mosquitoes (focus: Rift Valley fever, JE, malaria), in 2009 they expanded to include sand fly (focus: leishmaniasis) and tick (focus: rickettsioses) surveillance.

Mosquito

To improve Maxent accuracy and broaden its usage, investigators at the Armed Forces Research Institute of Medical Sciences (AFRIMS) adapted an RT-PCR assay

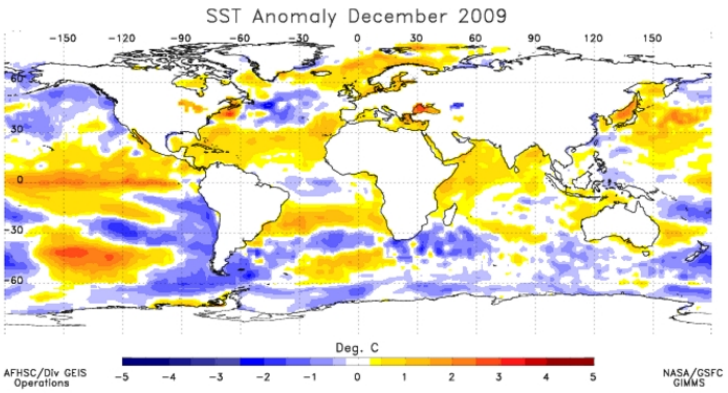


Figure 5 Global Sea Surface Temperature (SST) Anomaly for December 2009. Yellow and orange – warmer than normal SST in the equatorial Pacific and Indian Oceans. This is characteristic of a warm ENSO (El Niño) event.

for detecting JE and other flaviviruses in mosquito specimens. This improved diagnostic capability is used to increase the validity of the vector component's identified critical detection point for JE and other flaviviruses. Also, USUHS investigators are adding a vegetation height evaluation protocol to enhance Maxent's ecologic specificity. Both these efforts are tailored toward using the Maxent application on flavivirus threats in Southeast Asia.

In anticipation, AFRIMS hosted a workshop in 2009 on ENM for 21 scientists from Thailand and the Philippines. The pathogen focus for this workshop was chikungunya virus (CHIKV), the cause of a severe, ongoing outbreak (>48,000 reported cases in 2009) in southern Thailand.[30] (Figure 12) AFRIMS engagement with the Thai Ministry of Public Health (MoPH) in CHIKV field investigations reinforces AFRIMS' reputation as a valued regional partner in mosquito control, risk assessment, and determiner of the driving forces behind this outbreak (e.g., factors in virus transmission, vector competence, and landscape epidemiology). (Figure 13) AFRIMS virologists responded to the outbreak by conducting real-time testing of both human blood and mosquito samples for virus presence and virulence (A226V mutation).[31] Characterization of circulating viruses is possible because AFRIMS has biosafety level (BSL)-3 capability to culture CHIKV. All outbreak information generated by AFRIMS is shared with both the Thai MoPH and Royal Thai Army for their public health decision-making. In total, these efforts not only

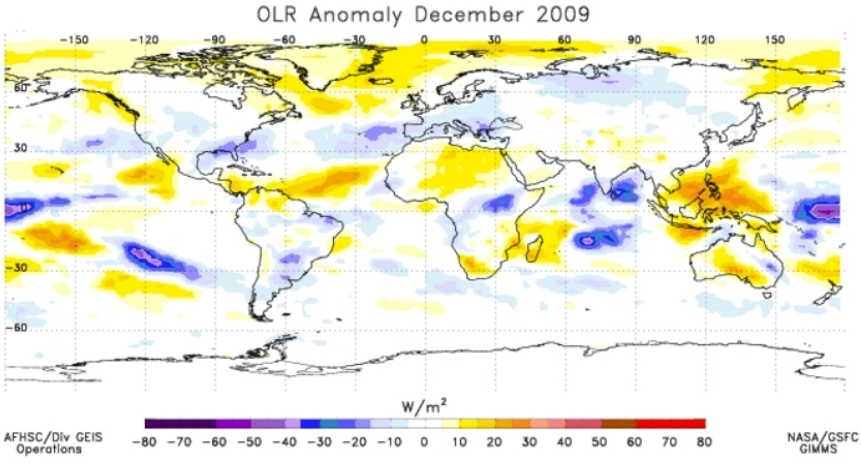


Figure 6 Global Outgoing Longwave Radiation (OLR) Anomaly for December 2009. Blue areas - negative OLR anomalies in the eastern Pacific and Indian oceans and in east central Africa are indicative of higher than normal rainfall in these areas. Yellow to orange – lower than normal rainfall.

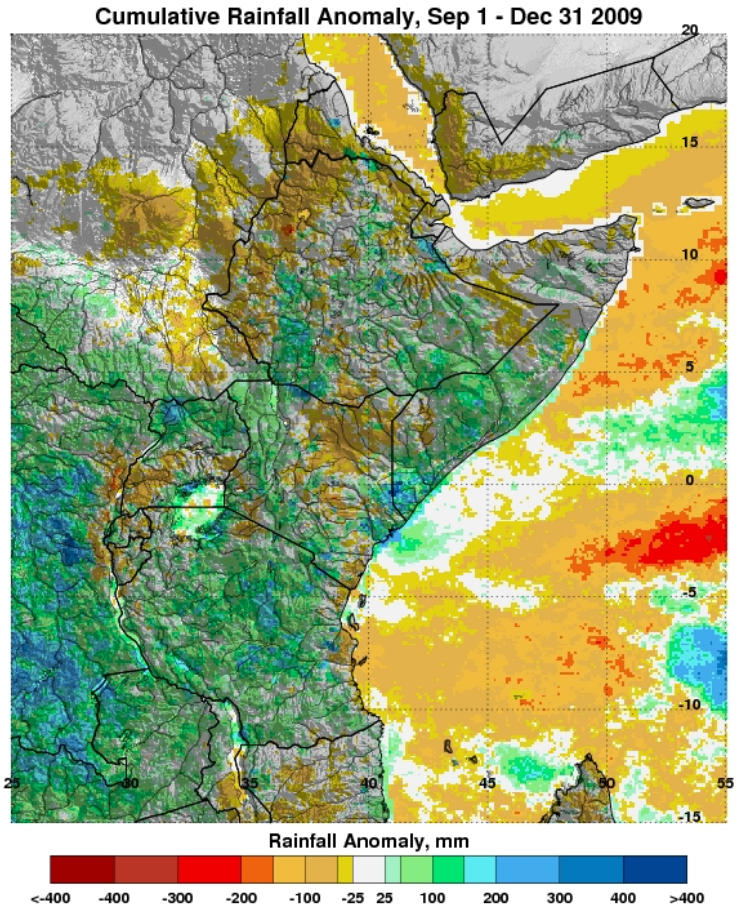


Figure 7 Cumulative Rainfall Anomaly for Eastern Africa, Sept. 1 to Dec. 31, 2009. Blue and green – Rainfall totals of between 100 and 300 mm above normal being detected in nearly all of the region except in north and central Kenya where November rains were light.

contribute to the resolution of this outbreak, they will inform future inclusion of CHIKV in the AFHSC-GEIS predictive surveillance program.

Sand fly

During 2009, USUHS trained a WRAIR entomologist to apply ENM to sand fly surveillance. This represents a first step by the predictive surveillance program to cover non-mosquito vectors of disease. In conjunction with this training, initial investigations were done to test the application of remote sensing to sand fly larval-habitat characterizations, and their use in determining critical detection points for leishmaniasis transmission in the Middle East [32].

At the same time, AFHSC-GEIS partners at the U.S. Army Medical Research Unit-Kenya (USAMRU-K) and the Kenya Medical Research Institute (KEMRI) conducted large-scale surveillance for sand fly presence at over 200 sites in three distinct geographic regions of Kenya. Approximately 3,500 sand flies were identified and tested for *Leishmania* spp. infection using polymerase chain reaction (PCR) techniques. This traditional surveillance work forms the basis for future ENM and predictive surveillance for leishmaniasis in that country and potentially elsewhere in sub-Saharan Africa (Figure 14).

To date, there have been two major findings with epidemiological and predictive surveillance implications in Kenya. First, *Leishmania major*-infected sand flies (species undetermined) were detected in two regions not previously known for leishmaniasis transmission: Isiolo and Lamu (Figure 11). Second, *Phlebotomus orientalis*, a known vector of visceral leishmaniasis (VL) in Sudan, was detected in large numbers in Isiolo and at another site, Garissa (Musila LA, personal communication). Garissa is considered a non-endemic area for cutaneous leishmaniasis (CL) and VL [33-36]. *P. orientalis* is rarely collected in Kenya as a whole [37].

Interestingly, USAMRU-K investigators are receiving reports from the Wajir area in northeast Kenya on possible VL cases among inhabitants and refugees from

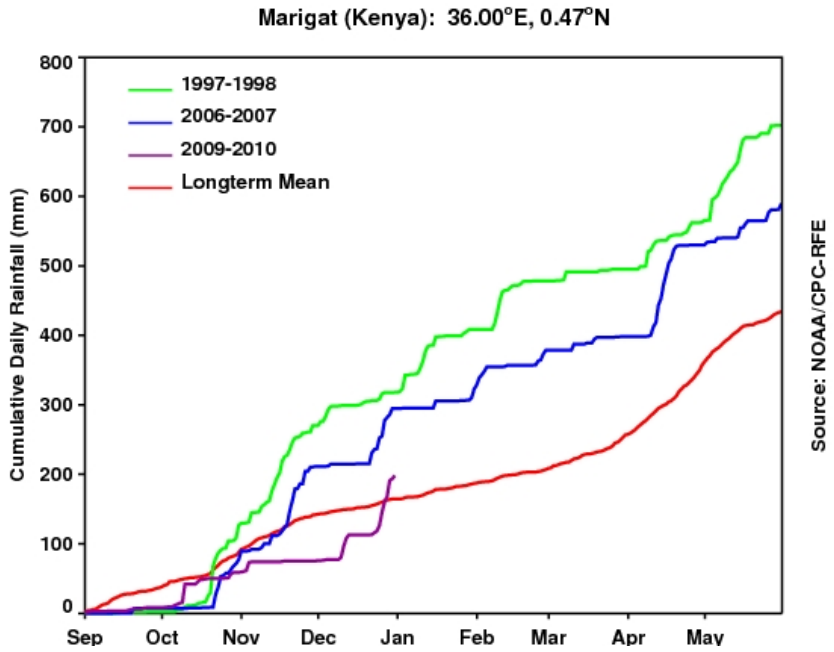
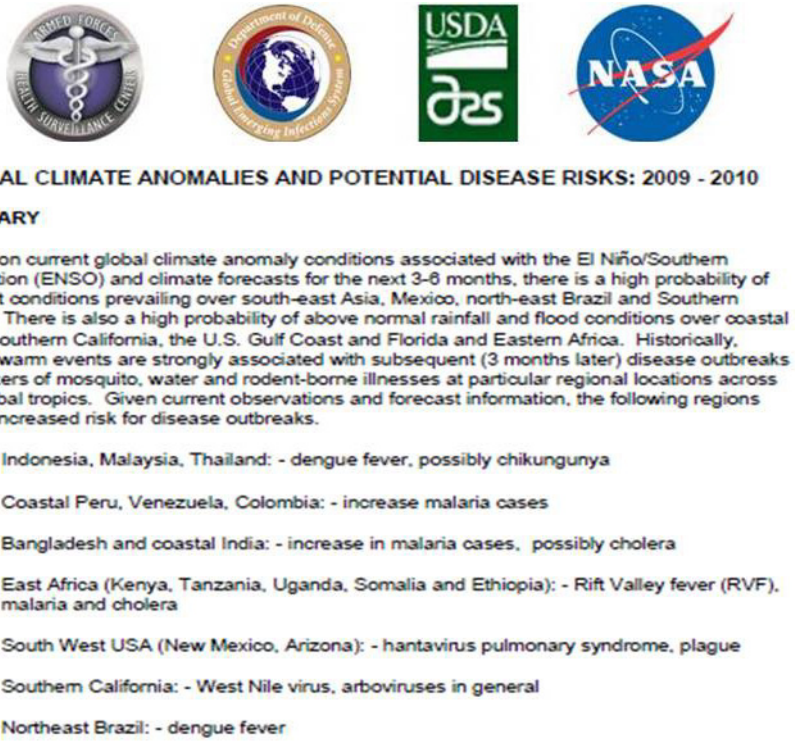


Figure 8 Cumulative Rainfall Totals for Marigat, Kenya. The two most recent El Niño seasons are represented in green – 1997-1998, and blue – 2006-2007. Red – the long-term rainfall mean. Purple – rainfall amount during the 2009-2010 season through Dec. 31, 2009. Not shown – heavy rainfall occurred during the last week of December 2009 at this site and others throughout the central Rift Valley.



GLOBAL CLIMATE ANOMALIES AND POTENTIAL DISEASE RISKS: 2009 - 2010

SUMMARY

Based on current global climate anomaly conditions associated with the El Niño/Southern Oscillation (ENSO) and climate forecasts for the next 3-6 months, there is a high probability of drought conditions prevailing over south-east Asia, Mexico, north-east Brazil and Southern Africa. There is also a high probability of above normal rainfall and flood conditions over coastal Peru, southern California, the U.S. Gulf Coast and Florida and Eastern Africa. Historically, ENSO warm events are strongly associated with subsequent (3 months later) disease outbreaks or clusters of mosquito, water and rodent-borne illnesses at particular regional locations across the global tropics. Given current observations and forecast information, the following regions are at increased risk for disease outbreaks.

- Indonesia, Malaysia, Thailand: - dengue fever, possibly chikungunya
- Coastal Peru, Venezuela, Colombia: - increase malaria cases
- Bangladesh and coastal India: - increase in malaria cases, possibly cholera
- East Africa (Kenya, Tanzania, Uganda, Somalia and Ethiopia): - Rift Valley fever (RVF), malaria and cholera
- South West USA (New Mexico, Arizona): - hantavirus pulmonary syndrome, plague
- Southern California: - West Nile virus, arboviruses in general
- Northeast Brazil: - dengue fever

Figure 9 The AFHSC-GEIS and NASA Predictive Surveillance Advisory, August 2009. Predictive surveillance advisories are sent to AFHSC-GEIS Predictive Surveillance program partners, DoD public health authorities, and other national and international organizations. The advisories also are publicly shared on an open-access website (ftp://rvf:geis@pengimms.gsfc.nasa.gov) when eco-climatic events and trends suggest that disease outbreaks may arise in the coming several months. The August 2009 advisory was not geographically limited because the expected El Niño conditions were expected to have global impact.

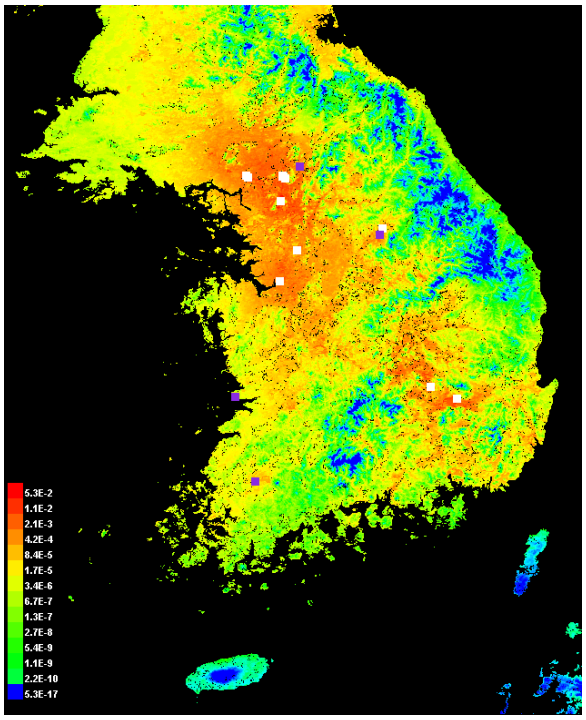


Figure 10 Predicted Distribution of *Cx tritaeniorhychus* in the Republic of Korea. Red and orange – higher probability of *Cx tritaeniorhychus* occurrence. Blue – lower probability of *Cx tritaeniorhychus* occurrence (corresponds to higher elevations). Purple and white dots – mosquito collection sites. White dots were used for model building (training points) while purple dots were withheld from the model and used for testing the accuracy of the model. This work demonstrates that cropland conditions, primarily rice fields and minimum temperature in the summer, are positive factors in predicting this mosquito's distribution; whereas forested hills and mountains >1000 m elevation, are negative factors.

Ethiopia and Somalia. This province is not traditionally considered endemic for leishmaniasis either. However, the area did undergo drought conditions after the 2006-2007 El Niño rains; and similar reports of leishmaniasis were made during the aftermath of the El Niño events of 1997 and 2000-2001 (and possibly historically since the 1930s) [38]. Therefore, USAMRU-K and KEMRI researchers are investigating this apparent environmental association. If a temporal relationship exists between El Niño events, sand fly activity, and leishmaniasis occurrences, it will provide a solid foundation for expanding predictive surveillance capability in Kenya beyond the Rift Valley fever project.

Tick

Tick surveillance is also conducted in the predictive surveillance program's vector component. As an initiation point, the program is using rickettsiae as the pathogen focus. During 2009 at Fort Eustis, Virginia, partners from the Naval Medical Research Center (NMRC) collected three species of ticks known to parasitize humans (*Amblyomma americanum*, *Dermacentor variabilis*, *Amblyomma maculatum*). The ticks were tested for rickettsiae (*Borrelia lonestari* and *Ehrlichia chaffeensis*), using quantitative real-time PCR (qPCR) assays and multilocus sequence typing (MLST).

Researchers tested 108 *A. americanum* ticks pooled in 33 samples, and found that 33 (100 percent) of the pools had positive reactions to *Rickettsia amblyommii* (unknown pathogenicity), two (6.1 percent) for *B. lonestari* (unknown pathogenicity), and one (3 percent) for *E. chaffeensis* (human monocytic ehrlichiosis). All six pools (14 individual ticks) of *D. variabilis* were negative for evidence of rickettsiae. *Rickettsia parkeri*, a newly recognized pathogen, [39] was found in one *A. maculatum* tick. This is significant because until 2002, all confirmed cases of tick-borne spotted fever in North America were attributed to only one pathogen, *Rickettsia rickettsii*, the cause of Rocky Mountain spotted fever. Previously, tick-borne rickettsiae other than *R. rickettsii* were considered non-pathogenic in the United States. Between 2002 and 2006, *R. parkeri* infection was detected in six cases (two DoD beneficiaries) in the southeast United States. This detection and subsequent investigations of *R. parkeri* infection in the U.S. are being used to build future predictive surveillance capability on this and other tick-associated diseases.

Overseas, an astute AFHSC-GEIS partner in the ROK noted that in 2004 two service members presented at the 121st Hospital with eschars typical for spotted fever group (SFG) and scrub typhus group (STG) rickettsial infections. This observation prompted a serology study in 2005 which resulted in the first evidence that SFG rickettsial infections are associated with deployments of U.S. military personnel to Korea, 181 seropositive of 8,918 tested (2 percent).

Animal component

While it is generally accepted that eco-climate trends and events can influence disease transmission from animals to humans [40,41], given the complexity of animal population dynamics, bionomics and behaviors, considerable research is needed to identify the determinants of that association. As a starting point, the AFHSC-GEIS partners working in this component are focusing on rodent-borne hantavirus diseases.

In Kenya, USAMRU-K discovered hantaviruses in live rodents from Marigat and Garissa (Figure 15). These viruses are now being characterized at the U.S. Department of Agriculture, Fort Collins, Colorado, and their presence in Kenya will be analyzed for correlation with the already existing eco-climate data from the Rift Valley fever project. This cross-analysis of datasets will allow investigators to explore how the eco-climate

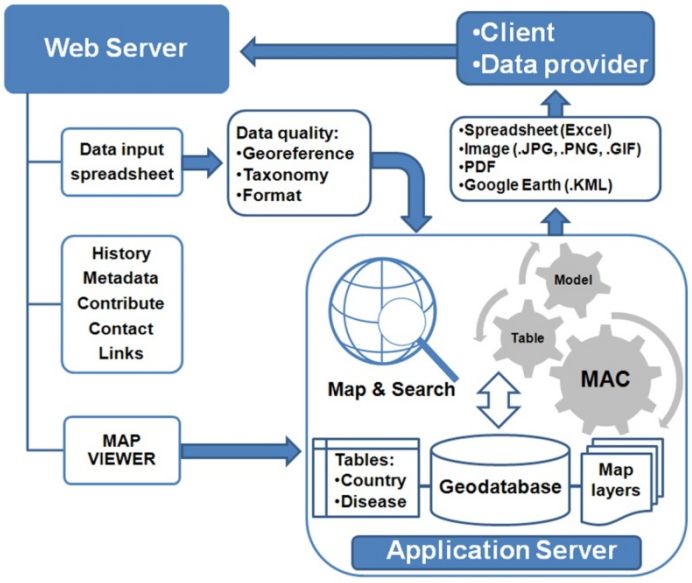


Figure 11 Overview of MosquitoMap. A client or prospective data provider accesses the web server hosting MosquitoMap. A downloadable spreadsheet is available with instructions regarding data requirements. Data can be submitted via email. A link is also available to the map viewer hosted on an application server running ArcGIS Server 9.3. The client can map and search the geodata-base, or use the Mal-area calculator (MAC) to quantify the overlap of models of vector, disease and human distribution. Output is available to the client in various formats. Figure reproduced from Foley et al. (2010).

conditions and trends interface with hantavirus infections in East Africa. It will also facilitate a Naval Medical Research Unit No.3, Cairo, Egypt (NAMRU-3) and NASA analysis of hantavirus outbreaks in the Ukraine. Interestingly, NASA partners observed some geologic similarities between Kenya and the Ukraine. If validated, this observation will be useful in determining the predictive surveillance model's indicators of critical detection points for the emergence of hantavirus outbreaks.

In the ROK, U.S. and Korean partners are conducting small mammal surveillance to elucidate hantavirus exposure-risk at U.S. field training sites. Recently, these investigators discovered three new hantaviruses (Soochong, Muju, and Imjin viruses) [42-44].

To complement the vector component work on rickettsial infections, Naval Medical Research Unit No. 2, Jakarta, Indonesia (NAMRU-2) has found rickettsiae in small peri-domestic mammals on the islands of Java, Kalimantan, Sulawesi and Sumatra in Indonesia. In a total of 491 animals (including shrews, mice and eight species of rats), 26 percent were seropositive for SFG rickettsiae, 14 percent for typhus group, and another 10 percent for STG rickettsiae. Interestingly, *R. felis* and another SFG Rickettsia spp. were found associated with 208 fleas (*Xenopsylla cheopis*) from these rodents. Similar studies were conducted with partners in the ROK [45] and in Peru (37 of 742 {5 percent {ectoparasites from domestic animals were positive for rickettsiae, including *R. parkeri* {Tidewater spotted fever}, *Candidatus, Rickettsia andeanae* {unknown pathogenicity}, and *R. felis* {*flea-borne spotted fever*}).

Human component

As the AFHSC-GEIS predictive surveillance model is framed, the human component comprises two aspects of human-based surveillance and analysis. The first is human disease and case detections from laboratory diagnosis or syndromic surveillance. This human disease surveillance is described elsewhere [46] and will not be discussed here, except to say that it helps the predictive surveillance program focus on its ultimate subject, human disease. It provides the retrospective and prospective epidemiologic information necessary to target, analyze and refine the program's model.

The second aspect, and the one that is integral to the predictive surveillance model itself, is the identification and characterization of those specific human factors that can serve as critical detection points for human-disease outbreak emergence. As an initial pilot study (using a directly-transmitted disease - cholera), the Johns Hopkins University Applied Physics Laboratory (JHU/APL) assessed the demographic, economic, environmental, and climatic variables associated with outbreaks in Africa during 1995-2005. The study's putative contributing factors for outbreaks included qualitative and quantitative sanitation and water source contamination, rainfall, and water

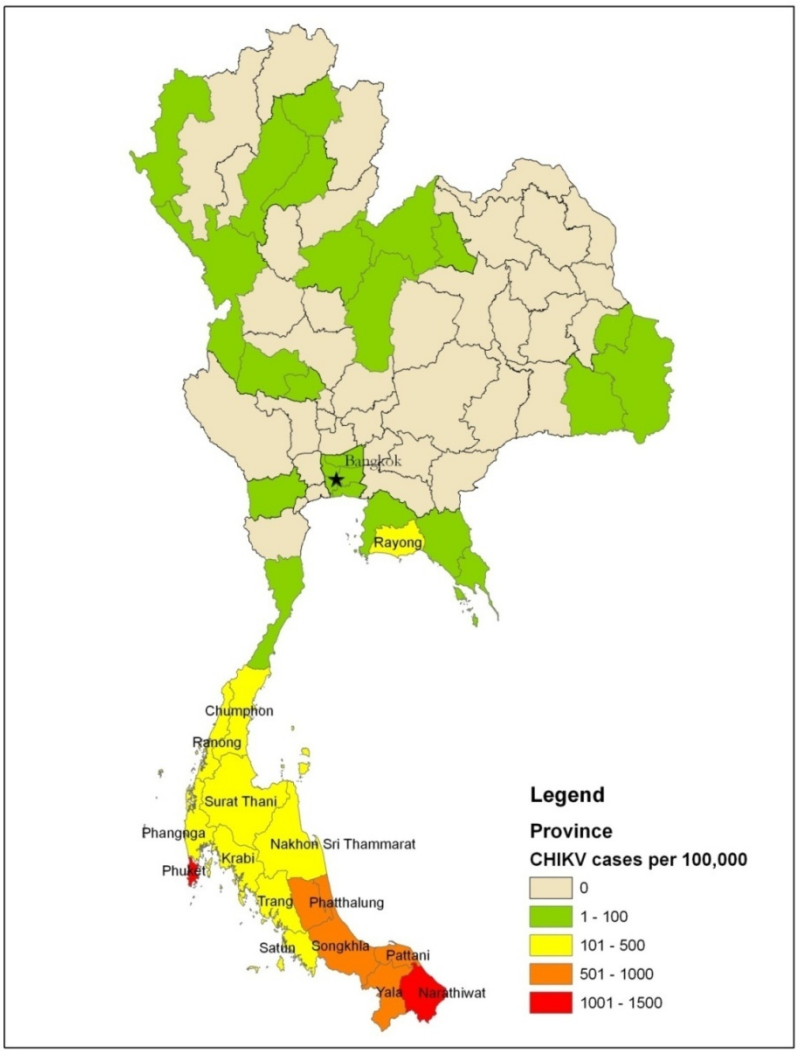


Figure 12 Distribution of 2009 CHIKV Cases Showing a Clear Concentration of Cases in the Southern Peninsula. Data reflects suspected cases (per 100,000 province inhabitants) reported by the Bureau of Epidemiology, Ministry of Public Health, Thailand. Data available at http://203.157.15.4/chikun/chikun/situationy52/chikun_20091231520.pdf (in Thai).

management (i.e., flooding) factors, human housing density and quality (i.e., peri-urban sprawl), and human migration and living-practices associated with displaced persons or refugees. This study showed good correlation between these factors and cholera outbreaks. It also showed that the occurrence of a cholera outbreak in a neighboring province during the previous month could also be a predictive factor [47]. This study sets the stage for the analysis and definition of eco-climate and pathogen transmission factors involved in human disease outbreak emergence.

Cross-component activities

Diagnostic support

As each of the above components strives to identify the critical detection point(s) which signal(s) a potential for pathogen transmission, it is understood that the predictive surveillance model's underpinning is pathogen presence or absence in a geographic area, not the intrinsic behavior of the pathogen itself. This necessitates the inclusion of accurate diagnostic testing capability in the program's activities. During 2009, this aspect of the program was best exemplified by work done by NMRC on rickettsiae detection and characterization.

After developing and producing rickettsiae diagnostic assays, NMRC used them to test arthropod vectors, animal hosts and specimens from human cases for rickettsial infections [48]. NMRC has tested for and confirmed the presence of *Rickettsia felis* (flea-borne spotted fever) in febrile patients from northeastern Kenya. By developing and providing an Enzyme-linked

Figure 13 Inspection of Water Cisterns in Southern Thailand as Part of a Chikungunya Virus Outbreak Investigation. AFRIMS personnel are collecting mosquitoes throughout Thailand as part of a niche modeling effort of CHIKV vector distributions. Vector density and distribution are the likely key drivers of the restricted distribution of CHIKV cases observed in Thailand in 2009.

Figure 14 Sand Fly Surveillance in Kenya. Traps are set on the base of a termite mound in Marigat, Baringo district, Kenya. Termite mounds are one of the natural habitats for *Phlebotomus martini*, a vector of visceral leishmania in East Africa.

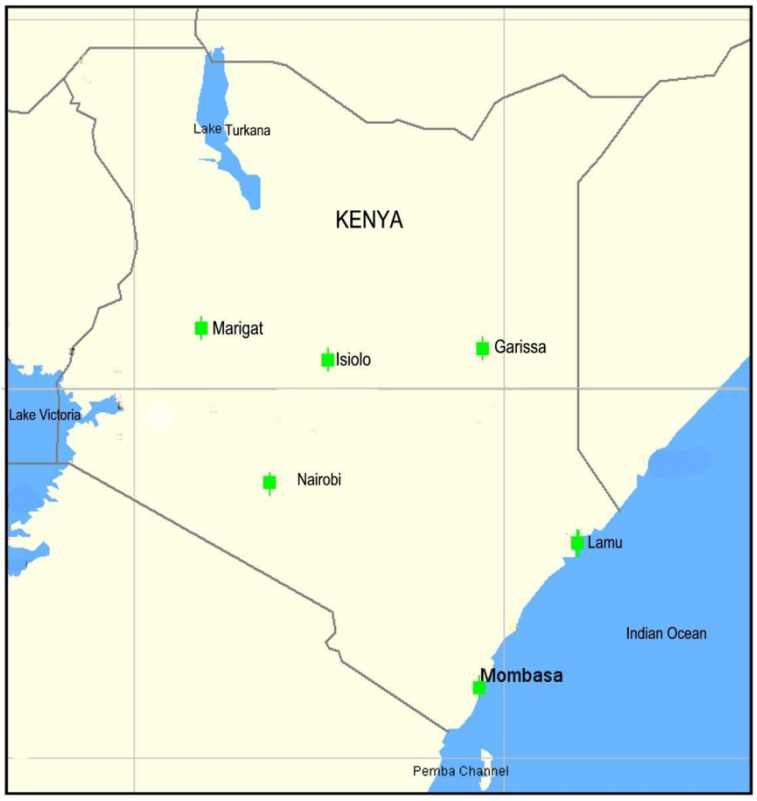


Figure 15 Map of Kenya Showing Surveillance Sites: Arthropod Vectors and Animal Hosts. *Lieshmania major*, a protozoan parasite causing zoonotic cutaneous leishmaniasis, has been detected in Isiolo in the central part of Kenya and Lamu along the northern coast. The visceral leishmaniasis vectors, *Phlebotomus orientalis*, and *P. martini* were detected in Garissa in Kenya's Northeast Province and in the Rift Valley village of Marigat respectively. Hantaviruses have been found in both Marigat and Garissa.

Immunosorbent Assay (ELISA) test specific for SFG rickettsiae antibodies against *Rickettsia conorii*, NAMRU-2 confirmed the presence of SFG rickettsioses among fever patients in Cambodia (Kasper M, personal communication).

NAMRU-2 has also performed SFG rickettsiae-specific ELISA testing on 368 sera collected from residents of Jakarta, Indonesia. In this work, NAMRU-2 found SFG rickettsiae-specific antibodies in 60 serum samples (16.3 percent), and of these, five paired samples showed a four-fold rise in titer indicating acute SFG rickettsiosis. Likewise, NAMRU-2 was able to test pooled ectoparasites from rodents collected in Jakarta, and found 2/40 (5 percent) positive for SFG rickettsial DNA.[49]

Through the predictive surveillance program, NMRC will continue to provide DoD investigators with technical assistance and assays for detecting rickettsial diseases (including Rocky Mountain spotted fever, Tidewater spotted fever, murine typhus, flea-borne spotted fever and other rickettsioses) that present emerging and re-emerging risk to DoD military, civilian, and family members throughout the world.

Dataset standardization

To ensure reliability and validity, the AFHSC-GEIS program is promoting consensus on and the establishment of dataset standards for the program's component activities. Dataset standardization is necessary for conducting meta-analyses on the results of program activities, and merging them into meaningful information for advisories, alerts and predictions. For example, precise taxonomic and geo-referenced collection data are essential for understanding vector and host bio-geography, ecology and distributions, and the impact of environmental changes on them. The data are essential for determining pathogen transmission factors associated with outbreaks. Accurately geo-referenced vector collection data must be matched spatially and temporally with remote sensing data of an appropriate resolution to answer questions about the environmental determinants of vector-borne disease distribution. While the methodology of collecting datasets may vary according to the instruments used, the end results, the language and content of the datasets must be concordant in order to facilitate a seamless progression of surveillance results between

AFHSC-GEIS partners and program components. Partners at WRAIR-WRBU have published recommendations on mosquito collection data standards, and these are being considered as the standard operating procedure (SOP) for mosquito collections sponsored by AFHSC-GEIS [50]. Similar SOPs will be developed for sand fly and tick collections.

Conclusions

Looking to the future, the AFHSC-GEIS predictive surveillance program in its entirety, its management framework of the AFHSC-GEIS Predictive Surveillance Steering Committee, and its scientific model that provides direction to program surveillance and analysis activities, will continue to support the detection and reporting of emerging vector- and water-borne and zoonotic disease outbreaks of importance to DoD.

Under AFHSC-GEIS leadership, the program will refine and expand its model of disease outbreak emergence surveillance. It will build and elaborate upon those component activities that optimize collaborations between partners. It will continue to define those critical detection points that represent the model's signal that an outbreak is emerging. The program will continue to advocate for focused, pre-emptive public health action to prevent or mitigate human morbidity and mortality, as well as the destabilizing effects of infectious disease outbreaks.

In the near term, the predictive surveillance program is expanding upon its initial Rift Valley fever success. It will continue to characterize and validate identified eco-climate anomalies for predictive surveillance application under different ecosystem and habitat conditions. Partners will continue to identify disease-associated vectors and hosts with demonstrated periodic or cyclic disease-transmission pathways that are plausibly associated with eco-climatic events and trends. Partners will investigate vector- and water-borne and zoonotic diseases for which the program's model might be applicable, and most importantly, which present operational risks to DoD force. This expansion is now underway with the program's activities on JE, leishmaniasis, hantavirus and chikungunya fever. The program is initiating pilot activities on Crimea-Congo hemorrhagic fever, Ebola and other viral hemorrhagic fever outbreaks, and malaria.

By continuing efforts in strengthening pathogen detection capabilities, program components are improving the sensitivity and specificity of the model's critical detection points. As the program expands, partners will learn more about the model's capabilities and determine where, for what and under what conditions the model does or does not apply. This will necessitate an incremental growth for the program, subjecting model usage to continuous quality assurance and applicability assessments. As the program matures, AFHSC-GEIS will facilitate the appropriate transfer of the components' operations to those partner organizations best suited to ensure sustainable, quality-assured predictive surveillance.

The success of predictive surveillance will depend on the recognition that it is founded on a meta-system of different surveillance activities, linked by communications, coordination and collaboration between multiple, diverse disciplines, and producing advisories and alerts, which have progressively more certainty over the course of an outbreak's emergence. No single component can provide sufficient information for accurate predictions. Just because we detect an El Niño event, does not mean that a disease outbreak will occur. Similarly, if a vector is present in a locality, it does not mean that the pathogen is present or that disease will be transmitted to humans. Human activities may permit, exacerbate, or prevent human exposure to the risk of disease transmission. It is only when all relevant components of the predictive surveillance model are applied diligently and with scientific rigor to the synthesis of a complete agent-vector-host-environmental scenario, that the program will produce reliable advisories, alerts and predictions.

The role of AFHSC-GEIS in the predictive surveillance program as a whole is to provide an agile, investigative platform for continuously testing different scenarios, combinations of geographic areas, vector- and host-species characteristics, and pathogens to facilitate the development of a stable of predictive surveillance models for an array of different infectious disease outbreak scenarios. In the end, however, even once given, a prediction, advisory, or alert cannot prevent outbreaks. It can only inform the decision-making process for timely, effective public health action.

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