A Shot to Change the World: An Analysis of Process and Partnership in U.S. Military Vaccine Research

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Acronyms & Definitions

AFRIMS: Armed Forces Research Institute of Infectious Diseases
ARDS: Acute respiratory distress syndrome
BIKEN: The Research Foundation for Microbial Diseases of Osaka University
CDC: Centers for Disease Control
CRADA: Cooperative Research and Development Agreement
DOD: Department of Defense
Daly: Disability Adjusted Life Year
FDA: Food and Drug Administration
FSV-1: Malaria vaccine candidate tested prior to RTS,S
GAVI: Non-profit committed to vaccine access
GPO: Government Pharmaceutical Organization
GPO-MBP: Government Pharmaceutical Organization-Merieux Biological Products Co., Ltd.
GSK: GlaxoSmithKline
HAV: Hepatitis A virus
IND: Investigational New Drug
JE: Japanese Encephalitis
KPP: Kampaeng Phet Province Hospital
MAJ: Major
MG: Major General
MIDRP: Military Infectious Diseases Research Program
MSF: Médecins Sans Frontières
MVI: Malaria Vaccine Initiative
NAMRU: Naval Medical Research Unit
NIAID: National Institute of Allergy and Infectious Diseases
NMRC: Naval Medical Research Center
NMRI: Naval Medical Research Institute
NIH: National Institutes of Health
PATH: Global health non-profit organization
RTS,S: Current malaria vaccine candidate under development by WRAIR, GSK and MVI
USPSh: United States Public Health Service
QALY: Quality Adjusted Life Year
USAID: United States Agency for International Development
USAMRIID: US Army Medical Research Institute of Infectious Disease
WARUN: Walter Reed / AFRIMS Research Unit Nepal
WHO: World Health Organization
WRAIR: Walter Reed Army Institute of Research
Abstract
Throughout history, wherever militaries have moved, camped and fought, in peacetime as well as war, disease has followed. Over the past several centuries, as expeditionary movements have become more widespread, the threat infectious disease has posed to military strength has become correspondingly broader. For this reason, the U.S military has long implemented measures to protect the health of its troops; over the past century or so, this has meant research programs intended to develop and test prophylaxis and therapies for the many infectious threats faced by troops. Despite relatively limited resources and funding, the military has achieved ample success, particularly in the realm of vaccine development, which is for obvious reasons the ideal approach to handling disease risk in a large, vulnerable population.

Because of the expeditionary history of the U.S. military, the diseases of interest to military doctors and researchers are often those of interest in the developing world; to this day, diseases prevalent in these areas remain either poorly understood, significantly under-funded, or lacking in effective treatments—often all three. Borne by mosquitoes and other vectors, non-potable water, and overcrowding, many of them are neglected by pharmaceutical companies—which lack a profit motive in poor countries—and by researchers in the areas most affected by them—who often lack the resources to investigate them. Since the 1940s, military researchers have worked closely with allied governments in a number of settings where these diseases are prevalent, from Egypt to Peru to Thailand and beyond. From collaborating on basic science research to conducting major clinical trials in local populations, these multi-national partnerships have been incredibly fruitful for U.S. military research; however, host nations have not always obtained the same benefit from collaborative research as the U.S. military. The mission of these combined research institutes and endeavors, which is unequivocally focused on research achievements for military ends, is one explanation for the disparity in outcomes; the U.S military process for technology production, which is in many ways fragmented and decentralized, is another. Distribution of vaccines within the free market has historically been an afterthought for military researchers, and sometimes barely a thought at all, much to the detriment of the military’s research partners and sometimes to the military itself.

This paper will investigate the history of U.S. military vaccine development, and the current
process and projects. It will explore several case studies that provide a glimpse of those very processes and projects as they unfolded, focusing specifically on the outcome for our military and research partners. And it will present the basics of how the world of public health looks at vaccine accessibility in the developing world. Using this background, I will look to assess the U.S. military process of vaccine development and provide recommendations about how it might be improved to be more equitable to partners, changes that may even be strategically advantageous.
Introduction

Yellow Jack – Disease and Death in the US Military

In the spring of 1862, one year into the Civil War, Union Major General Benjamin Butler arrived in the city of New Orleans with 5,000 troops. The citizens of New Orleans were far from enthusiastic about the unopposed capture of their city and the installation of a Union occupying force in their streets, but these unwelcoming locals were just one of MG Butler’s concerns. The threat posed by yellow fever, which was the source of “the city’s reputation as one of the unhealthiest places to live in the United States” was likely more in the forefront of his mind. Less than a decade earlier, an epidemic had sickened 29,000 and killed nearly 8,000 people—an estimated 10% of the city’s population. (1-3)

Aggressive sanitation efforts were MG Butler’s first priority to prevent the disease in his troops, few of whom had any immunity from past infections. Bitter New Orleans residents recognized this, and many hoped that the scourge of yellow fever would fell a decisive blow on the occupying Northerners and swing the war in favor of the South. Fortunately for Butler, his public health measures were effective in New Orleans that year and subsequent ones. Although the disease raged along the Gulf Coast, affecting Union forces from the Florida Keys to Galveston that year, New Orleans remained relatively unscathed. (4) Indeed, from 1862-1865, yellow fever deaths in the city remained far lower than they had been before and would be after—a total of just 11 deaths over the four years, compared to nearly 5000 in 1858 and over 3000 in 1867. (1)

Despite the relatively mild impact on troops in New Orleans, the significant effect of yellow fever on military operations was well recognized; unfortunately, prevention was hindered in many cases by an incomplete understanding of the disease, its etiology and its treatment. In 1867, Brevet Lieut Col. J.J. Woodward drew the following conclusion in a “Report on Epidemic Cholera and Yellow Fever,” which he produced for the Surgeon General of the War Department highlighting the effect of disease throughout the region:

It is to be regretted that the experience of the army throws no more satisfactory light on the treatment of the disease, but it must be admitted that it is most
instructive with regard to measures of prevention. Besides those general hygienic precautions which are so important in the prevention or mitigation of all epidemic disease, two simple effective measures would appear to be specially indicated by the experience of the army during war and subsequently. The first is quarantine, as a means of preventing the introduction of the disease; the second is the prompt movement of the command to some rural site on the appearance of the fever among the citizens of the town at which it is stationed, or even after the disease has appeared among the men of the command itself. (5)

The report effectively describes not only the epidemiology but also the geography and timeline of disease spread among the military in the late 1860s—199 cases and 79 deaths in Galveston, peaking in September; 823 cases in New Orleans with 219 deaths, peaking just a few weeks later. Ten Army medical officers died. (5) What it does less effectively is identify appropriate strategies to reduce disease transmission—Woodward’s conclusions suggest that he believed yellow fever to be transmissible between individuals, and perhaps related to some environmental or hygiene factors. It would be 33 years before another Army medical officer, MAJ Walter Reed, would provide proof of the etiology of yellow fever—the theory of mosquitoes as a vector had been proposed but had not gained mainstream acceptance years earlier—and modify the conclusions of 1867:

Yellow fever is transmitted to the non-immune individual by means of the bite of the mosquito that has previously fed on the blood of those sick with this disease…yellow fever is not conveyed by fomites, and hence disinfection of clothing, bedding, or merchandise, supposedly contaminated by contact with those sick with this disease, is unnecessary

Reed wrote these words in his 1901 article in the Journal of the American Medical Association. (6) Personal hygiene, then, played little role in disease transmission, although sanitation policies might be useful in destroying mosquito breeding ground; likewise, movement to a rural site might theoretically prevent cases, but not for the reasons Woodward had likely believed. With Walter Reed’s work, a major step-forward in infectious disease medicine in general and military
medicine specifically had been made; generations later, Walter Reed would remain a famous name in medical history, and to this day the most well known military hospital is named for him. His discovery spurred interest in yellow fever, leading quickly thereafter to implementation of vector control measures that would save lives throughout the Americas and later to the development of a vaccine against yellow fever.

The story of yellow fever is just one of many that could be used as a paradigmatic example of the significance of infectious diseases in American military history. Like military researchers who would follow him, Walter Reed had been motivated by the scale of an infectious disease problem he encountered; he used the knowledge of local experts and his ability to work “on the ground” in Cuba to his advantage; he made a significant step forward in understanding and management of the disease; and ultimately, his findings were gained based on models that provided asymmetric benefit. Its overwhelming influence on campaigns shaped the behavior of commanders and limited their tactical and even strategic capabilities. It demanded the attention of military physicians, and each advancement in understanding of the disease had ripple effects across the United States and the world. And ultimately, while intermediate methods of managing the disease had an important impact, development of a vaccine was always the goal, and clearly the most effective approach to turning the disease from a menace to a memory.

**Moving Forward**

With this brief introduction to military research and the role that infectious disease has played in the history of the American military, we will move on to a deeper investigation of the history behind military vaccine research; this will be supplemented with background on the current state of military research. All of this will ultimately allow me to delve a bit deeper into a few case studies that will help us not only to draw conclusions about the process of collaboration with outside organizations, particularly industry, but also to evaluate outcomes of these partnerships. It is no surprise that the military has taken an active role in the development of vaccines and treatments for the infectious disease threats to military operations. As in the past, today's military research efforts focus on the potential infectious threats that the military faces and as in the past, these diseases are significant to public health, particularly in the developing world.
To better elucidate the military’s pathways to research and their relationships with foreign partners, industry, and nonprofits, we will examine research through a series of vaccine case studies. Through these case studies, I will attempt to support the argument that the military has an incredible ability to foster the development of important medical technologies, but that it often fails in its duties to its partners and allies, and should consider how it should support them better not just because it is ethically appropriate, but because it would be mutually advantageous.

The first case, the development of the hepatitis A vaccine, might be ruled a partial success for the military, as a safe, effective, and highly available vaccine has been approved by the FDA and produced by GlaxoSmithKline (GSK) since the early 1990s; however, that availability does not extend to most low and middle income countries, including the one, Thailand, in which it was primarily tested with our research partner organizations. The second story would easily be called a failure, with an effective vaccine being tainted by ethical concerns surrounding its testing in Nepal, and completion of research and testing halted after phase II trials due to a perceived lack of profit potential on the part of industry partner GSK. The third, inspired by both the Thai desire to reduce cases of Japanese Encephalitis and a high profile American death from the disease, might be ruled a success, as both populations involved in its development gained access to the vaccine. The fourth is the ongoing story of malaria vaccination, and it provides an example of how modern vaccine development for a major global disease is fostering the development of new, innovative partnerships among diverse partners. We will follow this section with a discussion of the current policy and ethical milieu surrounding vaccine access and an assessment of the lessons learned from the military experience. Finally, we will close with a discussion of the current state of other, ongoing research projects.
Background

Military Contributions to Infectious Disease Research: A Brief History

The American military, and particularly the Army, has a long and well-documented history of medical innovation, particularly in the realm of infectious disease. As the example of yellow fever shows, the nature of historical and modern conflict has been the driving force pushing the military into this work—not only does combat demand creative solutions to complex injuries sustained on the battlefield, it requires that military physicians face the threat posed by a more insidious and historically deadly foe—disease. (7) In fact, the connection between the American military and medical innovation developed in our nation's earliest days. In 1777, after facing several devastating blows to his combat strength from smallpox—including defeat at the Battle of Quebec after his task force commander and over 50% of his troops became smallpox casualties—General George Washington undertook a campaign to inoculate all new and susceptible troops against the infection. His effort, dubbed by many as the first major military inoculation program in history, ensured the stability of the Continental Army through the end of the Revolutionary War—the British had previously used smallpox in a biodefense capacity, and most been infected as children or inoculated in England. (8, 9) The Civil War saw commanders like MG Butler and his peers struggle not just with yellow fever, but with malaria, smallpox, measles, typhoid, diarrheal disease, pneumonia and numerous others; two-thirds of the deaths in that war resulted from disease rather than combat, and disease may have lengthened the course of the war on the order of several years. (10) The Spanish-American War prompted increased military interest in both typhoid and yellow fevers. In 1900, a military commission established by President McKinley and directed by MAJ Walter Reed made its landmark discovery about the transmission of yellow fever, work that led to improved vector control in Cuba and Central America and had an almost immediate impact during the building of the Panama Canal. Before the late-1904 implementation of massive efforts to rid the isthmus of Panama of mosquitoes, some 85% of canal workers had been hospitalized with infection. Two years later, in late-1906, the disease was essentially under control, with no further deaths after that year. (11) Such major successes in yellow fever prevention—Havana, for example, saw annual deaths from yellow fever drop from 1300 to just 20 over a brief five year span—attracted substantial philanthropic interest in the military's public health efforts. (12) This interest resulted in a yellow fever vaccine
developed by the Rockefeller Institute, and this vaccine was used extensively by the military in World War II (although ironically, it resulted in the large-scale transmission of hepatitis B among vaccinated troops). (13, 14) Typhoid, which killed 1,620 American soldiers and infected ten-times that many during the Spanish-American War, resulted in a vaccine much more quickly, with MAJ Frederick Russell developing one in 1909 that quickly found utility in World War I. In this much larger conflict, infections and casualties from typhoid were ten-fold lower than during the Spanish-American war—227 deaths and just 2000 infections—due to a massive vaccination effort within the military. (8)

World War I represented the last American conflict in which disease would cause more casualties than combat—57,460 deaths from infection compared to 50,280 from combat action.1 Some two decades later, the picture in World War II was starkly different, with disease as a cause of death falling to 1 in 1000 casualties; by this time, the introduction of penicillin supplemented vaccines in controlling infection. (15-17) However, both conflicts inspired continued disease research and vaccine production as infectious disease, even when non-fatal, still had major implications for combat strength and campaign planning. American intervention in World War I coincided with and may have contributed to the influenza pandemic of 1918-1919, and the dramatic impact of the disease on the military—1.5% of the entire military fighting force died from influenza and 20-40% were infected during the height of the pandemic—prompted military research efforts to produce an influenza vaccine. (18, 19) By World War II, vaccination of troops against influenza A (beginning in 1943) and both influenza A and B (by 1945) was underway using vaccines developed from virus isolated by Dr. Thomas Francis, Jr., then director of the Board for Investigation and Control of Influenza and Other Epidemic Disease in the Army (later known as the Armed Forces Epidemiological Board). (18) Similarly, military experience with meningococcal meningitis in World War I prompted the establishment of a research commission at the outset of World War II, although it wasn't until the Vietnam War era

1 While World War I may have been the end of infections killing more troops than combat, the question of non-combat versus combat mortality in war remains significant even today. In the war in Iraq, overall non-combat mortality never surpassed deaths due to hostile action (although there were month to month fluctuations). In Afghanistan, non-combat mortality marginally exceeded combat in the early years of the war, but this pattern reversed in 2005 and never reverted. Although it is difficult to attribute directly to combat, total veteran suicide over the years of these wars would, however, easily exceed combat deaths, and active duty deaths by suicide surpassed combat deaths starting in 2012.
that researchers at the Walter Reed Army Institute of Research were able to isolate and purify the meningococcal polysaccharides that are still used in meningitis vaccines today. (18, 20)

Outbreaks of respiratory disease during World War II prompted studies of acute respiratory distress syndrome (ARDS) in military settings. Identification of adenoviruses—a major cause of ARDS found to infect up to 80% of new military recruits—followed, and by 1958 a vaccine was developed. When problems with the initial vaccine were identified, a new and impressively effective orally administered vaccine was developed by the military (although supply chain problems ultimately led to a long period when the vaccine was unavailable). (18, 20) Military experiences with hepatitis A and B during both World Wars led to passive immunization efforts during the Korean War that conferred temporary immunity to deployed troops; cooperation between the military, NIH, and private industry led to the development of a hepatitis A vaccine in the late-1980s. In addition, military research on Vietnam War veterans established epidemiological proof of widespread Hepatitis B infection in this population, and these data were significant in prompting the development of a vaccine for that disease as well. (18)

In more recent history, infectious disease research coupled with improvements in field hygiene and medicine have improved the military's ability to overcome infectious diseases. Nonetheless, even in the past decade disease has challenged the successful execution of military operations around the world, and research continues. A series of vaccines have been created for Japanese encephalitis, all based primarily on military research and development and licensed to various private corporations for production. The impetus for American research into Japanese encephalitis dates to the attack at Pearl Harbor in 1941, with the first form of the vaccine developed during World War II. (18, 20, 21) The current form, approved by the FDA in 2009, continues to be administered to soldiers, sailors and marines deploying to Asia. (22) Since the Gulf War and through the wars in Iraq and Afghanistan, cutaneous leishmaniasis—a parasitic disease spread by sand flies—has presented a persistent problem. With no effective prophylaxis and requisite evacuation to Walter Reed Army Medical Center for treatment, the infection is of significant concern, and in the first year of conflict in Iraq, some 600 infections occurred. (23) During the same timeframe, a far smaller deployment of 225 Marines to Liberia to provide embassy support resulted in 80 cases of malaria, 44 of which required evacuation to American military hospitals. Although ineffective employment of prophylaxis was implicated in the
infections, the effect on mission was unchanged, underscoring the importance of preventative methods that are effective, easily employed, and not hampered by side effects. (24) In fact, some speculate that the failure of Marines to use prophylaxis while in Liberia was the result of the unfavorable side effect profile of mefloquine (itself developed by the military in the 1970s), which now carries a black box warning due to the potential for neurological and psychiatric side effects. (25, 26)

Military Research Institutions: Early Development at Home

At the time of Walter Reed, much research happened in the field—his was primarily conducted in Cuba—but a framework had been established for a centralized home for military research in the United States. Founded in 1893, the Walter Reed Army Institute of Research (WRAIR), which today represents the oldest and largest medical research organization in the United States military (the famed Armed Forces Institute of Pathology would be several decades older had it not closed in 2011), recently celebrated its 120th anniversary. At the time of its founding by then surgeon general BG George M. Sternberg, WRAIR was known as the Army Medical School, in recognition of the vision that it should be a center of professional education, and its first dean was the illustrious Walter Reed. Although it focused heavily on its education mission in early years, the Army Medical School also served as a hub for various research commissions and panels, including the 1898 Typhoid Board (leading to the development of the first typhoid vaccine), the 1899 Philippine Tropical Disease Boards, and the 1900 Yellow Fever Commission.

Originally housed on the National Mall, in 1910 the Army Medical School began the first of three moves, the last of which found it housed at Walter Reed General Hospital, located in Washington, DC. It was during the period between the World Wars that the research mission of the school (by that time, known as the Army Medical Department Professional Service School) truly began to evolve from its roots as an educational institution. More research goals were identified and as doctors in training increasingly spent their time in the hospital, the school became less and less a hub of graduate medical education. During the Korean War, the Institute recognized the importance of research on global infectious diseases, since war could result in American troops being deployed to any part of the world; it also expanded its mission to include a new Department of Neuropsychiatry. In 1958, the WRAIR Pilot Bioproduction Facility was
established, with the express goal of developing and producing experimental vaccines; it continues to provide production capabilities for phase I clinical trials. (27) By this time, the institute had a truly research-focused mission, and was beginning to expand its efforts to establish research sites and partnerships abroad. In 2001, WRAIR moved to its current home in Silver Spring, MD, and is now located alongside the Naval Medical Research Center, which was founded in 1942 in Bethesda, MD and has been located in Silver Spring since 1999.

The Army also maintains the 750-employee US Army Medical Research Institute of Infectious Disease (USAMRIID) in Fort Detrick, MD, where it has operated since its founding in 1956. Initially known as the U.S. Army Medical Unit, it first functioned as a center for all forms of biodefense research, including work on offensive biological warfare. In 1969, the U.S. mission to conduct offensive research was completely discontinued and all biological weapons at the site were destroyed. Simultaneously, the center took on its new name, and USAMRIID has been the center of military biological defense research since that time, working on pathogens such as Anthrax, Botulism, Plague, Ebola, Marburg, Hantavirus, Lassa Fever, Tularemia, Ricin and Staph toxins. Work at USAMRIID has resulted in vaccines for Tularemia, Venezuelan, Eastern and Western Equine Encephalitides, Botulinum Toxoid, and Smallpox; work continues on additional vaccines, including those for Plague, Hantavirus, Ricin, Burkholderia, Ebola, Marburg, Staph Enterotoxin B, and a new Anthrax vaccine. (28, 29)

The Navy maintains its own research efforts through the Naval Medical Research Center (NMRC), currently collocated with WRAIR in Silver Spring. Originally housed on the campus of the National Naval Medical Center in Bethesda, MD, the Center was founded in 1942 and was originally known as the Naval Medical Research Institute (NMRI). Early research focuses included not just Navy-specific subjects, such as dive medicine, but infectious diseases as well—in 1943, the center was already focusing on preventing typhus and malaria, including the effectiveness of improved insect repellents. (30, 31) From its founding, the NMRI took part in infectious disease research projects alongside the Army, and the military services are united in their infectious disease research efforts by the Military Infectious Diseases Research Program (MIDRP), an umbrella organization with some 300 doctoral level scientists employed at one of the many military research sites in the United States and abroad. (32) In an expansive report on
military research, the Institute of Medicine has proposed that the NMRC and WRAIR programs should be integrated, but that has yet to occur. (33)

**International Partnerships: U.S. Military Research Overseas**

Although informal military research had been conducted abroad since before the founding of formal institutes, beginning during the World War II era the military began to sponsor research laboratories in foreign countries, since overseas locations often provided the best opportunities for the study of infectious diseases of interest. These foreign labs now represent "the most broadly based international facilities of their kind supported by the United States." (34) The first foreign laboratory, started in 1942 as the Navy Medical Research Unit 3 (NAMRU-3), has been in continuous operation in Cairo, Egypt since the time of its formal founding in 1946 and remains the largest overseas military research facility.² Originally developed as a partnership with the Abbassia Fever Hospital to conduct research as part of the United States Typhus Commission, today the research unit focuses on a wide range of infectious disease research, including serving as the regional WHO lab for rotavirus and malaria. (35) There is an affiliated detachment in Ghana founded in 1996, which initially began as an affiliation with the Navrongo Health Research Center in Northern Ghana, and now works with medical centers throughout West Africa on investigation of leishmaniasis, influenza, malaria, STDs, and Lassa fever, among other diseases. (36, 37)

The Navy also has several smaller foreign labs. NAMRU-6, founded in 1983 and located in Peru, is headquartered in Lima and Iquitos and has an additional laboratory facility in Puerto Maldonado. The unit works in affiliation with the Peruvian Navy and routinely partners with a number of government organizations and universities within the country on dengue research and surveillance, malaria, yellow fever, leishmaniasis, Chagas, and enteric diseases. (38) The Navy also sponsors two research efforts in Asia. NAMRU-2, first located in Guam during World War II, then in Taiwan starting in 1955, has since moved between Manilla (1979), Jakarta (1991), Pearl Harbor (2010), and Phnom Penn (2013). Activities in the region focus on drug-resistant

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² NAMRU-1, now defunct, was founded in 1934 and operated in Northern California until its closing in the 1970s. NAMRU-2, discussed later, was also founded during World War II but has moved several times since its founding and did not include a formal laboratory at its opening.
malaria and infectious disease surveillance throughout Southeast Asia. (39) The U.S. Naval Medical Research Center - Asia (NMRC-A) was established as the center of Asian research in 2013, with headquarters moving to Singapore from Pearl Harbor. (40)

The Army, through WRAIR, also maintains a number of overseas laboratories. In 1958, the U.S. military founded the Army’s first, the Thai Cholera Research Laboratory, renamed the South East Asia Treaty Organization Medical Research Laboratory (SMRL) a year later, and the Armed Forces Research Institute of Medical Sciences (AFRIMS) in 1977. The research institute, which is a joint effort between the U.S. and Thai militaries, is run by a Thai military commander and an American Army officer under the command of WRAIR and the U.S. Army Medical Research and Materiel Command; there are over 300 staff of both nationalities currently working at the institute. (41, 42) Although the headquarters of AFRIMS is located in Bangkok, research activities are conducted throughout the country and region. A major field station, founded in 1980, is located Kamphaeng Phet Province (the Kamphaeng-Phet-AFRIMS Virology Research Unit, KAVRU). Surveillance for influenza and emerging infectious disease is conducted in eight border provinces (surveillance is also a major mission at other Army research labs throughout the world) and several other provinces host research projects and clinical trials, including for dengue, HIV, scrub typhus, and diarrheal diseases. Outside of Thailand, AFRIMS has additional field sites in Bangladesh (studying malaria drug resistance and shigella), Bhutan (studying malaria drug resistance), Cambodia (studying diarrheal diseases and malaria), Laos, Maldives (studying diarrhea), and Vietnam (studying HIV, plague, and enteric disease). They also have more major research facilities in Nepal (Walter Reed/AFRIMS Research Unit Nepal, WARUN), founded in 1995, and the Philippines (Philippines-AFRIMS Virology Research Unit, PAVRU), established in 2006. (42)

Outside of Asia, WRAIR affiliated labs in Africa conduct substantial research on HIV and malaria. The U.S. Army Medical Research Unit Kenya (USAMRU-K), located in Nairobi and affiliated with the Kenya Medical Research Institute (KEMRI), was founded in 1969, and is affiliated with two field stations in Kericho and Kisumu, Kenya. The Institute employs 12 U.S. Army members and over 600 Kenyan researchers and support staff. Through 2011, the Institute has published over 300 articles. (43) In Uganda, Walter Reed has also maintained a partnership
with Makerere University in Kampala to conduct HIV research since 1998. WRAIR also has a European research unit, founded in 1977, dedicated to psychiatric and behavioral health research, and in the past it had additional units—in Saigon, Vietnam from 1965 to 1970, in Brasilia, Brazil from 1973 to 1999 and in Korea from 1988 to 1993.3

**Funding for Military Research**

Funding for military research comes from a number of sources. Most directly, the U.S. Army Medical Research and Materiel Command funds the efforts of the MIDRP (the collaborative body that unites research efforts among the services), and total funds have declined over recent decades, from roughly $73 million in 1998 through 2002 (with approximately $40 million for vaccines) to $48 million in 2005 and $41 million in 2010 (adjusted for inflation). Of note, HIV has its own independent source of funding through the United States Military HIV Research Program, which was established in 1986 by Congress (44-46) The MIDRP also receives funds through several other government sources, including the Small Business Innovation Research Program, Congressional Special Interest funding (which will “sponsor scientifically meritorious biomedical research as requested by Congress;” in 2014, it had $500 million appropriated to specific research areas, none of which were clearly related to infectious disease research), Interagency Agreement funding (such as from the NIH) and funding from industry through cooperative agreements related to specific projects (described below). (47) Biological defense research, primarily conducted at USAMRIID, had a separate budget of approximately $70 million in 2010. (48) It should be noted that the military’s funding for research is minute compared to other government organizations. As a point of comparison, the National Institute of Allergy and Infectious Disease, a frequent collaborator with military researchers that also has a biodefense mission, had a budget of $4.6 billion in 2014—including over $1.3 billion for biodefense specifically, or almost twenty times the budget of USAMRIID, the Army’s designated

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3 The degree to which overseas military labs are made available to researchers from other government agencies is difficult to quantify, although the military’s extensive overseas network of partners and facilities could certainly be useful to these organizations. There are some indications that the largest scale programs for malaria and HIV have more inter-agency coordination than for smaller projects, but there still appears to be a significant amount of siloing.
biodefense research laboratory. (49)

Public and Private Collaboration: Background on the Development and Licensing Process

The military's ability to identify a problem and then narrowly focus research efforts along each step of the path to a solution has undoubtedly played a part in its research success, even in the face of its relatively small personnel and budget allotments. Still, although the military has an impressive record of research achievements, including development of numerous vaccines, none of its work has been accomplished in a vacuum. Frequently, the complexity of translating basic science research into medical technology, as well as the cost and difficulty of clinical trials and vaccine manufacturing, has led military researchers to collaborate with other organizations—some within government, some in the private sector, and some representing non-governmental organizations and philanthropic interests. (50) Indeed, the MIDRP not only cites private collaborators as an important source of funding, but also recognizes that:

One of MIDRP’s major strengths is the recognition by industry collaborators of its neutrality (lack of profit motive) as it pursues its service mission. The trust that this engenders facilitates collaborations that could not otherwise be contemplated, allowing the sharing of trade secrets and the testing of many promising new technologies. (51)

Long before outside collaborations can be formed, though, the military has to prioritize its projects and set its research agenda. In the Army, the process of funding a research project begins with annual evaluations of research objectives submitted by Army research organizations and laboratories. The Assistant Secretary of the Army for Acquisition, Logistics and Technology selects specific projects for identification as Army Science and Technology Objectives (STO), and these projects receive priority and funding, sometimes allotted for multiple years. It is pertinent to note again that, because of its nature as a Congressionally-directed program, HIV research is funded differently than other military research. Approximately 30 of 200 STO projects in any given year are medically focused; in addition, some projects with less well-

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4 Admittedly, NIH biodefense research does include an even wider range of pathogens and pursuits than the military, including emerging infections such as MERS and influenza and drug-resistant strains of infectious diseases (such as TB and S. aureus), as well as programs focused on immunology.
defined goals are funded under the Science and Technology Evaluation Program (STEM), and may eventually qualify for STO classification. As vaccine research progresses, additional analysis is performed to define a project's military necessity. If approved, this analysis, defined within an Operational Requirements Document, qualifies a research project for advanced development—for vaccines, this generally coincides with Phase I/II clinical trials. (44)

At any point in this process, collaboration with an external organization may be established. Often, these relationships are created to gain additional resources or funding from an outside source when federal funding is limited; when they are made with a private corporation, they may also be the first step in a future agreement to license a developed vaccine for production. Based on the Federal Technology Transfer Act of 1986, directors of military research institutes are authorized to establish their own relationships with civilian corporations when these relationships may be beneficial in furthering research goals. These agreements, known as Cooperative Research and Development Agreements (CRADA), define the extent of research to be conducted between the two organizations and the goals of the collaboration. They also outline the patents that each party provides upon entering the agreement, as well as providing a framework for how future intellectual property development will be treated, although any discoveries or innovations that are made within the CRADA agreement will undergo an individual negotiation process to determine how intellectual property rights are defined. Currently, the MIDRP has over 100 active CRADAs with outside organizations. (51, 52)

When manufacturing of a vaccine technology becomes the next logical consideration, a specific licensing partnership is entered, in which a corporation is given rights to “make, use, develop and vend the invention throughout the U.S. and in exchange for royalties”. (53) Known as a patent license agreement, such contracts are advantageous to the military because they facilitate production of a desirable technology on a scale that will meet the military's needs, since the military does not currently maintain large-scale manufacturing capability of its own. In the case of vaccines, a corporation typically takes responsibility for gaining FDA licensing approval, which also removes a costly burden from the military. However, technology licensing also represents a profit opportunity for a partner corporation, which stands to make money from military or jointly developed technology—often, simply by selling this technology back to the
military or the U.S. government in its final, manufactured form.

Unfortunately, the military-industry arrangement can represent a potential challenge to the military if a manufacturer perceives a loss in value from product production, or if no manufacturer can be identified at all because of the very limited nature of a given disease. This scenario has played out a number of times and has resulted in gaps in production to support both large-scale vaccine programs (such as hepatitis E and adenovirus) and more targeted vaccine programs (such as Rift Valley fever, along with several others). (44) Multiple sources, including the former director of WRAIR, Phillip Russell, have called this pathway to production into question both for its inefficiency for the military and its failure to appropriately value the fact that the fruits of military infectious disease research have the potential to benefit low-income countries. During a 1984 address to the Annual Meeting of the American Society of Tropical Medicine and Hygiene, Russell discussed the process:

The development of drugs and vaccines and insecticides has been heavily dependent on investment by industry and to a large extent carried out by industrial firms…A notable exception has been the drug and vaccine development done or underwritten by the U.S. Army where government funds covered the early phases of development and subsidized the end-stage industrial development…The heavy reliance on industrial investment for development of the products needed in tropical medicine is, I believe, a thing of the past. I will not go into the reasons for the decline of vaccine production and manufacturing in the United States but it is a well recognized problem, and leaves this country with a serious deficiency in the ability to undertake development of new products such as malaria vaccines, and new viral and bacterial vaccines, especially those needed principally in the developing countries. If we are to exploit the potential of our research, we cannot rely heavily on industry to make the investments. The profit motive is simply not sufficient for many of the potential products needed in the tropical medicine field and disincentives, such as product liability, are great. A greater responsibility for product development must be borne by the public sector through government agencies and foundations. (54)
Nearly 20 years later, the Institute of Medicine performed an extensive analysis of the military vaccine program, and came to a very similar conclusion regarding the current vaccine production paradigm:

DOD’s current approach to vaccines originates with the best intentions, involves skilled individuals, millions (but not sufficient millions) of dollars, and intricate planning. Nevertheless, the committee’s assessment after hearing from many of those involved in the acquisition process, as well as several executives from the companies that manufacture vaccines, is that the current vaccine acquisition process has limitations that make the path from basic research to procurement and use of vaccines both inefficient financially and cumbersome. These limitations result in occasional outright failure (as in the case of the loss of the adenovirus vaccines) and unacceptable delays (in the case of the anthrax vaccine) in vaccine acquisition. The lack of vaccines when and where they are needed risks the success of future military operations and the health of personnel and potentially places national security in jeopardy. (44)\(^5\)

The military’s model of using its limited funding to focus on basic science and translation (and even, frequently, to help with if not fund major clinical trials) has allowed the military to be prolific in its output, but it has not allowed the most widespread and useful application of technology in every case. Unfortunately, although this problem has been recognized for decades, little has changed, perhaps because the task of recreating the system and processes of military research and its cumbersome bureaucracy is not the area of expertise of most people involved in it, all of whom have a huge task simply to solve the scientific questions that some of the world’s most challenging diseases present.

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\(^5\) The “loss” of the adenovirus vaccine refers to the 12 year period between 1996 and 2011 when an adenovirus vaccine, licensed for use in the military and given to all incoming recruits beginning in 1980, lost its manufacturing contract. During the intervening period, no vaccine was produced and by 1999 the vaccine was completely unavailable, resulting in the deaths of several recruits. The military ultimately established a relationship with a new industry partner and paid $100 million for the construction of a new production plant, resulting in the return of the vaccine to the military immunization schedule.
Hepatitis A

I open with the story of the hepatitis A vaccine for several reasons. The military played a significant role in every step of vaccine development, from the basic science of isolating and propagating the virus to creating prototypes vaccines to conducting clinical trials abroad. It also worked in parallel and partnership with two pharmaceutical companies, the Thai government, and the NIH, demonstrating the diverse range of partners needed to bring a vaccine project to completion. The vaccine became a major commercial product in the United States and Europe but was never widely introduced in Thailand, where it was tested, despite the fact that even the military scientists most closely involved in developing the hepatitis A vaccine stated their support for this outcome. This case thus highlights perhaps the clearest example of disparity in the outcomes of military research, while also painting a picture of the industry, government, and international milieu in which military vaccine research is conducted.

The Natural History of Hepatitis A: A Unique Challenge

As a public health problem, hepatitis A presents a unique conundrum that drove the need for a vaccine. Transmitted via the fecal-oral route, it is highly prevalent in areas with poor sanitation and contaminated water supplies—throughout Africa, for example, nearly 100% of the population demonstrates immunity by young adulthood, with over half of children having immunity by the age of 4. In high incidence areas such as Africa, the reported incidence of clinical illness may be as high as 150/100,000 (55, 56) Fortunately, unlike other water-borne infections, hepatitis A presents with no symptoms in some 70% of children and generally only mild symptoms in the remainder. (57) This is not true of adults without prior exposure, however, who are far more likely to become symptomatic on their first exposure to the disease—70% will become jaundiced, for example. Fortunately, long-term sequelae are rare and chronic hepatitis does not seem to result as it does following infection with other forms of hepatitis. (58) Nonetheless, hepatitis A in adults is far from benign, and up to 22% of infected adults require hospitalization for significant symptoms including acute liver failure, with an average length of stay of roughly 7 days. (59)
Because of its close relationship to water and sanitation quality, the epidemiology of hepatitis A changes with improving infrastructure. In the 1970s in the United States, roughly 25% of teenagers and half of young adults had developed antibodies to the disease, but rates of childhood infection and immunity fell quickly thereafter, virtually bottoming out by the time that childhood vaccination was introduced in the 1990s. (55) Through the 1990s, some 270,000 cases per year were estimated in the United States; by 2004, 5 years after the introduction of vaccination, that number had dropped to under 56,000 annually, and to 21,000 by 2009. (60) The military, which implemented hepatitis A vaccination in 1995, also saw a decline in cases, with hospitalizations as high as 4.0/100,000 person years-years in 1991 dropping to below 1.0 in 1997 and below 0.5 in 2001 and beyond. (61)

Prior to the introduction of vaccination, declining pediatric cases of hepatitis A presented a unique challenge for individuals and groups traveling from the United States to higher prevalence areas—travelers and the military in particular—who had no immunity from childhood and were thus at risk of contracting a more significant adult infection. Although the disease rarely results in significant mortality or long-term sequelae, the average adult patient misses thirty days of work in addition to the risk of hospitalization previously noted. In 1997, 63,500 cases of hepatitis A in the United States were estimated to cost $500 million in lost work time and medical care; internationally, with 1.4 million cases estimated annually, that cost is estimated to be as high as $3 billion. (62) The interest in preventing this sort of debility on a vacation, business trip, or military mission was understandable, and drove research into a vaccine. In addition, although mortality has been historically noted to be low, in patients over 50, the mortality rate in the United States is estimated at 27/1000. (63) Worldwide, 102,000 deaths were attributable to acute hepatitis A in 2010—approximately 1/3 of total hepatitis deaths. (64)

As was observed in the United States, as economic conditions improve in hepatitis A endemic areas, the prevalence of disease drops, leaving a susceptible adult population. Thailand, a long-time medical partner of the U.S. military and the location of the hepatitis A vaccine trial that will be described later, is a key example of this transition; it was also the location of the clinical trial that proved the efficacy of the military-developed hepatitis A vaccine. A middle-income country, the epidemiology of hepatitis A in Thailand has changed significantly over the past 30-40
decades. In the 1970s, exposure to the disease reflected the current experience of African nations—over half of children had been exposed and developed antibodies by age 10, and by age 30, nearly 100% of the population was immune. This rate of infection was consistent through the 1980s, before beginning to slow in the 1990s, with only a third of 20-somethings showing immunity by that decade. By the 2000s, fewer than 5% of Thai children and 25% of Thai young adults had been exposed to the disease, with rural numbers somewhat higher. (55) A 2007 study of Thai medical and nursing students showed a 15.3% exposure rate; a similar 2009 study of Thai Army nursing students returned even lower numbers, showing that of 381 students averaging 20 years of age, only 8.9% had anti-HAV antibodies, indicating past exposure. (65, 66) The changing epidemiology of the disease has recently opened the Thai population up to the experience of increasing adult infection, with its higher rates of clinically significant disease, and has increased the number of notable outbreaks occurring throughout the country.

**Hepatitis A in Military History**

Jaundice, understood as a disease synonymous with undifferentiated viral hepatitis and not just as the clinic sign it now refers to, has long-posed an infectious threat to campaigning militaries. In the United States, an outbreak of jaundice was first recorded in conjunction with military history, as a player in the War of 1812. (67) The Civil War resulted in an estimated 20,000-70,000 cases of jaundice due to hepatitis. (68) American forces were relatively unscathed in World War I, but this apparent blessing was ultimately blamed for the failure of the military to prepare appropriately for the threat of jaundice during World War II, during which 200,000 cases were recorded among American forces—numbers “so large as to influence the strategy of the war.” (69) The Mediterranean theater was perhaps most significantly affected, with a peak incidence in U.S. forces of over 18,000 in 1943; during the period of 1943-1945, viral hepatitis was the most disabling infectious disease in the Mediterranean and North African theaters. German forces suffered much more significantly, with millions of cases reported in soldiers over the course of the conflict. (68)

Until the 1940s, the jaundice that affected military units was known only as “epidemic jaundice,” in contrast to serum jaundice (now known as hepatitis B), which was recognized to be an independent disease process. In 1942, Dr. F. O. McCallum coined the term “viral hepatitis, type
A,,” and this subsequently became the preferred term. It was during this time, too, that interest began to mount for identifying the causative agent of jaundice, although efforts to do so were not particularly fruitful in the early period. By the mid-1950s, attempts to propagate the vaccine in a wide array of animals and cell cultures had been tried and had failed, and research efforts through the subsequent decades were no luckier. (70)

Even as basic science research into hepatitis A floundered, the practicalities of protecting troops from it were being addressed independently. The lessons of World War II were not forgotten in subsequent conflicts, but in the absence of a vaccine, protection for deploying troops had to be established through other methods. Beginning in 1964 and continuing through the Vietnam War and subsequently during the Gulf War, passive immunity was established in deploying troops through the use of immune globulin. A working group at the University of Pennsylvania established under the Army Epidemiological Board during the Second World War first demonstrated the protective effects of this method; trials of Ig had also been conducted in the field during military campaigning in Italy, 1944-1945. (71) When applied on a large scale in future conflicts, however, the approach was not without its challenges. In Vietnam, Ig proved less than fully efficacious, with some research questioning whether it affected disease occurrence whatsoever. Due to limited supplies, various stipulations had to be established for which forces would receive it. And it was logistically challenging to administer, as it required periodic re-dosing in order to maintain protection. Despite its use in Vietnam, over 12,000 cases of hepatitis A occurred during the war, resulting in nearly 1000 years worth of work-days lost—roughly one month of convalescent time per sick soldier. (72) During the Gulf War, the large force and rapid deployment again demonstrated the significant logistical challenge of obtaining sufficient Ig for hundreds of thousands of deploying troops. (21) Indeed, the entire U.S. supply was depleted by the need to treat half a million troops with Ig, further reinforcing the military’s need for a safe and effective vaccine—which, incidentally, had been developed and was undergoing testing at that time.

The military medical community was under no illusion that IgG was a long-term solution to the problem of hepatitis A, but into the 1970s, there was no hope that any other solution was imminent either. In a 1975 presentation to the Annual Meeting of the Society of Medical
Consultants to the Armed Forces, Saul Krugman lamented the lack of progress in the area. Dr. Krugman, who remains well known for his research on the hepatitides and was awarded the Lasker Prizer for his work on hepatitis B, received extensive military funding for his work on hepatitis. Of note, he has also been subjected to criticism for the ethics of his research methods, including experimentation on disabled children. (73, 74) It was not until a few years after his speech, in 1979, that scientists at Merck successfully propagated the virus in cell culture; a few years later, WRAIR researchers propagated the virus in primate cells, which became the stepping-stone for their development of the first hepatitis A vaccine. (75)

Towards an Effective Vaccine
Military researchers were not the only ones who recognized the utility of developing an effective vaccine—numerous other research groups were working toward a hepatitis vaccine in parallel with WRAIR, as evidenced by Merck’s success in propagating the virus. In 1979, at roughly the same time as WRAIR’s success in propagating the hepatitis A virus, Merck proved the efficacy of a hepatitis vaccine in marmoset cell cultures from which they had previously propagated the virus. (76) Indicative of the pervasive influence of the military in developing vaccine researchers was the fact that the group was led by Dr. Maurice Hilleman, a pioneer in the field of vaccine development who spent a decade working at WRAIR in the 1940-1950s before being recruited to Merck; this pattern of working for the military before transitioning to industry was not uncommon and would be repeated by numerous researchers over following years. In 1986, WRAIR validated their own vaccine in monkeys, using a cell line that had good evidence for use in producing human vaccines, and a CRADA with SmithKline Beecham came the following year. (75) This primate vaccine used the HM175 hepatitis A strain cultured in MRC5 human diploid cells. Based on its efficacy in monkeys and guinea pigs, researchers gained investigational new drug (IND) approval and the vaccine was tested in 1986 in a group of eight human volunteers at WRAIR, the first such trial in humans. Despite low amounts of antigen in the vaccine, all volunteers developed neutralizing antibodies after four doses and these remained detectable for years. The vaccine subsequently underwent stage I clinical trials in 1988 on an Army base in Fort Lewis, Washington with good results. (21, 77) Researchers at the National Institute of Allergy and Infectious Disease were simultaneously working on vaccine
development, and developed their own CRADAs with Smithkline for a hepatitis A vaccine, vaccine process, and several other developments, including isolation of the HM-175 cell line.

At the time, SmithKline was also working to develop its own vaccine from a Swiss hepatitis strain; ultimately, though, they found that the HM175 strain propagated and used for vaccine development at WRAIR and the NIH was more effective, and they dropped their own research efforts. (78, 79) Ultimately, WRAIR’s early vaccine would serve as a prototype for Smithkline’s Havrix vaccine against hepatitis A; Smithkline developed a final version with more antigen and an adjuvant to increase the vaccine’s effectiveness. (80-82) WRAIR continued to participate in clinical testing of the vaccine, and entered a second CRADA with Smithkline Beecham in 1991. Merck was working simultaneously to test its own hepatitis vaccine and was slightly further along in the process; in 1991 it completed a trial in an endemic population of just over 1000 children in New York, demonstrating that nearly 100% developed antibodies to hepatitis A within a few weeks of vaccine administration. (83) Despite Merck’s head start through the development and testing process, the SmithKline vaccine would still be the first to gain FDA approval.

Testing of the Smithkline hepatitis A vaccine began in Thailand that year, during what was incidentally the natural transition period of the illness from highly prevalent among Thai children to increasingly uncommon. Smithkline had initially lobbied for a U.S. trial of the vaccine; however, military researchers proposed a trial in Thailand. The military had a robust, decades-old partnership with Thai medical researchers at Kamphaeng Phet Province Hospital (KPP) via the Armed Forces Research Institute of Medical Sciences located in Bangkok, had recently completed a Japanese Encephalitis vaccine trial with this group, and had also established that Thai children had falling but nonetheless notable rates of hepatitis A—a 1.1% annual infection rate in the region where the trial was conducted—making it an ideal location to test a vaccine. (84)

The 1991 Thai trial was a double-blind, randomized controlled trial involving 40,119 children (aged 1-16 years) in the Kamphaeng Phet province, some 200 miles north of Bangkok. Control participants received a hepatitis B vaccine; all patients received a total of 3 doses of vaccine. 17
months after the start of the trial, a crossover was undertaken, with all participants ultimately receiving both hepatitis A and B vaccines. The results were notable: protective levels of antibodies to hepatitis A were established in 94%, 94%, and 99% of participants at 8, 12, and 17 months after the first vaccine dose. Among all participants, 40 cases of hepatitis A occurred during the trial—38 among controls, and 2 among vaccine recipients (both of which were exceedingly mild compared to control cases when measured by illness duration, clinical presentation, and peak ALT). Adverse effects (compared to the hepatitis B control) included local tenderness/redness/swelling, headache, disturbed sleep and fever; no serious adverse effects were observed. The results of the trial were considered a success, and were published in JAMA in May 1994. (85) This achievement represented the culmination of well over a decade of concerted effort by military, SmithKline and NIH scientists. The military, for its part, had been the first to propagate the virus in primate cell culture; developed the primate vaccine that would serve as a model for the human product developed with SmithKline; conducted the first human hepatitis A vaccine trial; and spearheaded all subsequent clinical trials for the vaccine.

Figure 1: A child being interviewed as part of the Thai hepatitis A vaccine trial. (86)
Approval for Americans

The GSK Havrix vaccine, as it came to be known commercially, was approved by the FDA in 1995 for adults and children two and older; approval for a Merck developed hepatitis A vaccine, Vaqta, followed the next year. In the first few years following approval, the CDC and American College of Physicians recommended vaccination for travelers, high risk patients (homosexual men, IV drug users, patients with liver disease, and those at occupational risk), and children living in areas of the U.S. with high rates of infection—at the time, significant regional differences existed in infection rates, with Native American and hispanic populations significantly more at risk of infection, and incidence rates ranging from 0-4/100,000 along the East Coast to >20/100,000 along the Pacific Coast and in the Southwest.

Over time, the definition of regions at high risk broadened—an initial recommendation for vaccination of children in areas with incidence of 700-1000/100,000 changed to a recommendation for vaccination in areas with more than 20/100,000 cases (encompassing 11 states, including populous California), and a recommendation to consider vaccination in states exceeding the national average of 10/100,000 (an additional 6 states, including Texas). (68) By 2004, a survey of 2-3 year olds demonstrated 54% vaccination in children living in high-incidence states. (87) In 2006, following the approval of Havrix for babies older than 12 months (approval had previously begun at 24 months) the CDC adjusted its recommendation to two doses of the hepatitis A vaccine for all children in the country—the first given at 12-23 months of age, the second 6-18 months later. (87, 88)

In Thailand, the story was different. Almost a decade after the completion of the Thai trial that led to Havrix approval in America, the first major cost-effectiveness analysis of vaccination in Thailand was published; prior to this, there appears to be no documentation of a formal consideration of including hepatitis A on the Thai vaccine schedule. This 2002 analysis conducted by researchers at Chulalongkorn University in Bangkok found that hepatitis A vaccination would not be a cost effective public health intervention in Thailand. Basing their analysis on a cost of 1840 baht for the two dose series (approximately $56.00 in 2014, essentially identical to the cost of the vaccination in the U.S.A.), they found that the vaccine series would have to cost less than 586 baht ($18) for it to be cost effective to vaccinate all children. (89)
Now, over a decade later, the vaccine is still not part of the Thai pediatric vaccination schedule, although it is recommended on the expanded schedule, meaning that those with private insurance may receive it. (90) Interestingly in 2004, around the same time as the first cost-effectiveness analysis was conducted, hepatitis B vaccination was added to the Thai National Vaccine schedule. At the time, TWINRIX, a combined vaccine for hepatitis A and B made by GSK, had been FDA approved for several years, but this was apparently not considered an option for Thailand, almost certainly because of price. In addition, Thailand, in conjunction with Sanofi-Pasteur, was producing a hepatitis B vaccine under the name of Euvax for several years by the time it was added to the national schedule; Sanofi did not have any product equivalent to TWINRIX. (91, 92) Had GSK been Thailand’s production partner, it is possible that more comprehensive cost-effectiveness analysis would have been conducted and a case built for using the combined vaccine in the Thai market.

**Disease Disparities**

The Thai decision regarding hepatitis A vaccination is in keeping with the WHO policy, which provides strong support for vaccination in countries where its use is cost-effective. In its position paper on the hepatitis A vaccination, the World Health Organization articulates the key fact of hepatitis A infection, which are directly applicable to the Thai experience:

> In most middle-income regions there is a mix of intermediate and low prevalence and here, a substantial proportion of adolescents and adults are susceptible. HAV infection in these age groups is associated with a higher rate of severe clinical manifestations and hence, transition from high to intermediate endemicity may result in increased incidence of clinically significant disease and mortality from hepatitis A. (93)

Their position on vaccination is strongly supportive of the use of vaccination, and they state that, if indicated on the basis of cost-effectiveness, it should be incorporated into national vaccine schedules. They additionally include the vaccination on their list of essential medications. (94) Interestingly, in 1991, the lead author of the 1994 Thai hepatitis A clinical trial—Dr. Bruce
Innis, an AFRIMS researcher who now works for GSK—published another paper, making a similar statement on behalf of the Thai people:

Thailand is undergoing a profound economic transition. With increasing prosperity, it is experiencing lower rates of hepatitis A in its largest urban areas, the focus of much of its phenomenal growth. There also seems to be a decrease in hepatitis A transmutation within many rural communities…what is worrisome about this trend is that a falling rate of childhood hepatitis A infection places the population at a greater risk of more severe infection later in life, when the economic consequences of illness are more profound…uniform economic development is a long-term solution to this problem. However, hepatitis A immunization may have an important role as well. Progress in vaccine development has been steady. Both live attenuated and inactivated hepatitis vaccines are awaiting or are under evaluation in volunteers….Development of a safe, effective, inexpensive vaccine for hepatitis A prevention should prompt a reevaluation of immunization priorities for schoolchildren, adolescents, and young adults for both types of hepatitis. (84)

A 1998 review of declining hepatitis A prevalence in southeast Asia drew a similar conclusion, saying “Vaccination could prove to be a public health measure of considerable benefit for SE Asian countries experiencing improved age-related HAV seroprevalence patterns in parallel with socioeconomic development.” (95)

As the WHO makes clear, cost-effectiveness is essential to establishing the utility of vaccination in any population; however, it is clear that not all cost-effectiveness analyses are created equal. As policy recommendations for vaccination in the United States have changed, multiple studies have evaluated the cost-effectiveness of vaccinating the American population—first high risk group (1995), than regional risk areas (1999), then all babies (2005). Analysis completed in 2006, following the expansion of U.S. vaccination to include all children, determined that routine vaccination of all American children at age 1 would cost $28,000 per quality-adjusted life year—deemed by the authors to be an appropriate amount consistent with other common public health
interventions, such as HIV screening in the general population ($42,000 per QALY), and below the threshold of $50,000 per QALY commonly used in the United States. (96, 97)

Even beyond the fact that the U.S. and Thailand have different QALY thresholds based on their differing GDPs, the differences between the Thai and American analyses are significant, and raise questions about disparities in even the most basic preventative health measures. The Thai analysis assumed incidence of disease far above what had been previously deemed inappropriate in the U.S. under the regional vaccination policy—from 45/100,000 for adults to 76/100,000 for adolescents—as well as a fulminant hepatitis rate of 0.1% in adults. In the United States, regional vaccination had been implanted initially in areas with over 20/100,000 cases per year, and later in areas over 10/100,000 cases. The Thai analysis also accounted for work-day/productivity loss—one of the largest costs in the U.S. cost-effectiveness trial—in a much narrower sense than U.S. cost effectiveness analysis, including only days spent in the hospital and one day for vaccination in the calculations. For comparison purposes, the U.S. analysis estimated extensive productivity losses amounting to $37,000,000—almost identical to the total cost of medical care for hepatitis A patients. For a disease that often requires several weeks to a month of convalescence, productivity cost is certainly not an inconsequential cost to consider. (89) In addition, the American analysis included the cost of 20 liver transplants resulting from fulminant hepatic failure, at an average cost of $575,000 each. (98) Although liver transplantation is performed in Thailand, its cost was not included in the cost-effectiveness analysis. Finally, the Thai study did not assess QALYs, but instead did a pure cost-effectiveness analysis—whether universal or targeted vaccination would be cheaper than the costs of disease. One study that analyzed the cost of hepatitis A outbreaks in developed countries found that the economic impact of such outbreaks can be significant, are often due to indirect costs, and that “for vaccination strategies against infections that occur predominantly in outbreak situations, incorrect estimation of these costs could lead to misleading cost effectiveness.” (99)

An Ethical Dilemma

Beyond an assessment of whether cost-effectiveness was appropriately assessed in the Thai setting, there remain significant ethical questions related to the lack of Thai access to a technology they helped to develop. The ethics of clinical trials, including those of this trial...
specifically, have been explored before. Two principles—“reasonable availability” and “fair benefits”—are particularly cogent in this case as they define how populations that participate in trials should be treated. In a 2004 report by the Hastings Center, the Havrix trial is described as an example of a “paradigmatic case” of an exploitative trial on the ground that it was conducted “without assurance from research sponsors or others that the intervention being evaluated will be made ‘reasonably available’ to the population of the host country after the trial.” They do counter with the idea that substantial benefits were received (the ‘fair benefits’ framework) from the conduct of the trial itself, including well over 40,000 participants and researchers receiving the hepatitis A and hepatitis B vaccines, as well as receipt of other durable equipment and training. Nonetheless, there were many within Thailand (and beyond) who opposed the trial and did not see the benefits as appropriate (although unlike the example of hepatitis E will show, this opposition did not seem to relate directly to the involvement of the U.S. military). (100)

The ethical debate may also extend to the fact that the Thai trial was conducted under the auspices of an enduring partnership between U.S. and Thai researchers at KPP and AFRIMS. The mission of AFRIMS is “medical research, disease surveillance and development and evaluation of medical products for militarily important infectious and tropical infectious diseases.” While the Thai military undoubtedly views the partnership as a beneficial one, the obligation of the more powerful party to respect the best interests of the host nation should not be overlooked. In 1959, when the partnership was first proposed, then Thai King Bhumibol was savvy to this issue. Responding to Dr. Joseph Smadel, the chief of the American team visiting Thailand to negotiate the start of the collaboration, the King asked “Yes, Dr. Smadel, but how will the research help my people?” (101)

Even from a pragmatic standpoint, creating a precedent of medical testing on the Thai people without a strong track record of the fruits of that research reaching the larger population is probably unwise. As the case of hepatitis E will demonstrate, host populations are far from naïve about the priorities of foreign researchers. In the case of a long-term partnership (and one where the same region is called upon to repeatedly participate in clinical trials, as Kampaeng Phet has been), it seems both ethically appropriate and in the self-interest of the U.S. military to build good will with their host—in the case of hepatitis A, this might include supporting appropriate
cost-effectiveness analysis or making a strong case for their commercial partner to provide the vaccine at a reduced cost.

**Populations and Profits**

A final consideration in the ethical analysis of Thai access to the hepatitis vaccine is the issue of pharmaceutical profits resultant from the trial. This would be an issue in any scenario, but is made more pertinent by the fact that the technology was largely developed and testing facilitated by the U.S. government, ultimately at the taxpayer’s expense. It is true that vaccines have not historically been the biggest profit-producers for the pharmaceutical industry; they are also perceived as risky, and are increasingly the target of naysayers who blame them for autism and other ills (despite a clear lack of evidence). Indeed, regarding the hepatitis A vaccine, “doubts over the size of the market seemed to plague their [Merck and SmithKline hepatitis A vaccine] development program” up to the time that phase 3 clinical trials were about to commence. (81) Certainly, compared to “blockbuster” drugs such as Lipitor, revenue for which topped $12 billion in 2005, the WHO’s estimate of $1 billion in annual sales for GSK’s hepatitis vaccines (A and B) is relatively paltry. (102)

Vaccines are nonetheless not inconsequential earners, particularly if they become part of standard vaccine schedules. Some, including the Economist, have gone so far as to suggest that “a renaissance” is underway in terms of vaccine profitability and attention from pharmaceutical companies. (103) The United States hepatitis A vaccination program provides an example of likely sales for that vaccine. In 2013, 3,957,577 babies were born in the U.S.A.; if all received vaccination with the hepatitis A vaccine at the price of $29.74 per dose, as recommended, the profit would amount to over $227,000,000 for that annual cohort of babies. (104) However, we must assume lower profits based on some children not receiving the vaccine, and many others receiving it at the discounted CDC price. On the other hand, some babies undoubtedly receive the Twinrix vaccine, which combines inoculation for hepatitis A and B at a price higher than receiving the vaccines individually—$121.59 for five shots (two hepatitis A, three hepatitis B) versus $277.50 for three shots (the combined Twinrix vaccine). Plus, children internationally also receive GSK’s hepatitis A vaccine, which has been approved in Europe since 1993. And adults—for whom the vaccine costs more than double the pediatric price—continue to receive
the vaccine, primarily for travel. Based on this, the WHO’s assessment of $1 billion sales annually for GSK’s hepatitis vaccines seems not far off the mark. This figure represents a small but not inconsequential fraction of GSK’s 2013 sales—$26.51 billion. (105)

The research-stunting effect of placing restrictions on industry is often cited as an argument for allowing large corporate profits, and it probably also accounts in part for why the military has historically not acted to protect the interests of partner governments; conflicts of interest between the military, government and industry are perhaps also a significant player, although measuring them is understandably difficult. Indeed, the military may be hesitant to place stipulations on agreements with private industry for fear of driving them away from a potential agreement—the government is well aware of the importance of market forces and profit potential in attracting corporate partnerships. Nonetheless, in an extensive report on vaccine acquisition by the U.S. military, the Institute of Medicine acknowledged the significance of military research in global health:

Of note are instances in which a vaccine developed by the Army might have international use that is greater than its direct use to the DOD (e.g., Rift Valley fever).…Many of the vaccines developed to protect deployed U.S. forces may also be of benefit to the world’s poorest populations, perhaps compelling DOD interest in a wider range of vaccine development efforts than might be dictated by market forces alone. The committee observes that, overall, the availability of a vaccine for military use is subject to many complex and changeable interests within—and external to—DOD. (44)

**Conclusion**

Currently, the hepatitis A vaccine is approved and available in Thailand, although its use is limited primarily to controlling outbreaks and to those with private health coverage, and even in these instances its use is far from pervasive. Since the approval of the hepatitis A vaccine in the U.S.A. in 1995, numerous outbreaks caused by contaminated food or water have been noted in Thailand, many of them among adults. One paper analyzing the molecular characteristics of hepatitis A in Thailand identified 11 outbreaks between 2001 and 2005. (106) A large outbreak
occurred in Northern Thailand in the summer of 2012, along the border with Laos, resulting in 1600 hospital visits and some 500 hospitalizations. The authors of a paper analyzing the outbreak noted that, “Hepatitis A virus vaccine was not routinely given to the community during the outbreak owing to limited budget but offered as one of the choices for preventive measures.” They went on to point out the proven utility of universal vaccination in other middle-income countries, and to argue for its utility in both pre- and post- exposure prophylaxis, ultimately concluding that “A routine hepatitis A vaccination program should be adopted and incorporated into the national program to prevent large-scale outbreaks.” (107)

The story of hepatitis A shows the military’s vaccine development mechanisms in a mixed light. It is clearly a resounding and impressive success in some ways, particularly as a clinical testing achievement—the military conducted the first human vaccine trial and, independently and in collaboration with the Thai government, the subsequent trials for the SmithKline vaccine. On the other hand, the fact that the vaccine remains largely unused by the country in which it was tested and that this injustice is recognized by those most familiar with the disease and yet no improvement in Thai access has been made over 20 years is disheartening and reflects an example of the lack of a thoughtful process for supported our research partners and military allies. (108)
Hepatitis E

Although it shares a name with hepatitis A, hepatitis E is like a younger sibling—recognized as a distinct clinical entity later, given less attention and research support. The military’s involvement was more focused, with some contributions in the early, basic science stages, but the most substantial support coming from the military’s conduct of clinical trials—the area in which it had been arguably the most successful in developing hepatitis A. In the case of hepatitis E, trials were undertaken in Nepal, but were marred by local conflict and ethical debate, and this foreshadowed later ethical concerns about access to the vaccine. Unfortunately hepatitis E represents perhaps the largest failure along diseases of military focus—despite time and money invested that resulted in an effective vaccine, it never completed development or reached a single customer. The world has only recently gained access to a hepatitis E vaccine, thanks to independent Chinese research efforts, which resulted in an approved vaccine in 2010. It remains to be seen how widely this vaccine will be made available in low-income countries, like Nepal, where it is most needed.

A Disease Without a Name: Identifying Hepatitis E and its Scope

In 1980, a young physician from India published the results of two years of work in Kashmir, India, suggesting that an epidemic of jaundice in that region over the period may be the result of a novel form of hepatitis. The idea of a non-A, non-B form of hepatitis had been proposed 5 years earlier, based on observations of blood transfusion recipients, hemophiliacs receiving factor VIII and dialysis patients, subsets of whom had developed hepatitis. But Mohammed Khuroo recognized that the epidemic he was investigating was different than the blood-borne disease that would ultimately be called hepatitis C. Clearly waterborne, the illness Khuroo observed affected mostly young, healthy adults, and the Kashmir epidemic resulted in 52,000 cases and 1,700 deaths. Epidemic wasn’t a common presentation for hepatitis A or B, nor was Khuroo’s finding when he analyzed serum and stool from cases, all of which lacked the typical serology markings to show they had been infected with either hepatitis A or B. (109, 110)

Nearly simultaneously, an American researcher from the NIH had come to the same conclusion about waterborne epidemics of non-A, non-B hepatitis. His work was based on examination of samples collected from a 1950s outbreak of jaundice in New Delhi in which 35,000 patients had
been sickened. At the time of the epidemic, doctors had assumed this outbreak was caused by hepatitis A—it was clearly a waterborne pathogen, and despite the fact that hepatitis A rarely caused large outbreaks in endemic areas, no better explanation could be found. Some proposed that the hepatitis A immunity victims had acquired from childhood was beginning to fade, opening them to increased infection risk in young adulthood. (111) The hepatitis A story stood for decades, as hepatitis A and B were the only known forms of the disease until the 1980s. But upon examination of samples decades after the outbreak, researchers in India and at the NIH discovered, like Khuroo, that serum samples from affected patients had no evidence of acute hepatitis A or B infection. They also noted different characteristics of this form of hepatitis, including a longer incubation period, increased fatality among pregnant women, and frequent cholestasis. (112)

In 1983, a Soviet researcher by the name of Dr. Mikhail Balayan infected a volunteer (reportedly himself) with virus particles from stool of a group of patients suspected of having non-A, non-B hepatitis. Dr. Balayan had a documented history of hepatitis A infection and antibodies, but
nonetheless became clinically ill 36 days after ingestion of the virus, within the normal 3-8 week incubation period. Through this process, he was able not only to collect large amounts of virus, but also to identify viral particles in his own stool using electron microscopy. (113) In 1987, an outbreak of jaundice in a military college in Sargodha, Pakistan, led to the involvement of researchers from WRAIR, which was able to prove that the new virus, now known as Hepatitis E, was involved in the outbreak. (114, 115) This relationship presumably developed via the Pakistan-U.S. Laboratory for Seroepidemiology, located at the Army Medical College and Hospital in Rawalpindi. At that time (and despite Dr. Balayan’s ambitious work), the pattern of hepatitis E excretion from stool had not been well established, and even when viral particles were obtained, correlating them with a recent infection was challenging. (110, 114) For this reason, WRAIR’s formal connection of hepatitis E with an ongoing outbreak was a significant milestone in research. Indeed, Mohammed Khuroo, the original author describing the new hepatitis, later described the period from 1983 to 1990 as “the most frustrating long 7 year halt in the story of hepatitis E” because of the significant challenges associated with isolating the elusive hepatitis E from stool. In 1987, epidemiological studies showed that non-A, non-B hepatitis was estimated to cause three-quarters of all cases of acute hepatitis in Pakistan.

Simultaneously, Mrigendra Srestha, chief medical officer at the Walter Reed AFRIMS Research Unit (WARUN) located in Kathmandu, Nepal, identified the virus on liver necropsy, and the military’s involvement in hepatitis E research was solidified. (116, 117) The Army formally established a field laboratory in Kathmandu in 1995, in affiliation with AFRIMS.

By the early 1990s, “hepatitis E” was coming of age. Now recognized as a distinct clinical entity, it was being increasingly written about in the medical literature and increasingly appreciated as a cause of epidemic illness in countries without widespread access to clean water. As hepatitis E grew in the literature—from one article calling it by name in 1989 to 20 in 1990 to over 300 in 2014—recognition of its clinical significance also grew. Since its identification, the disease has since been recognized as the far-and-away leading cause of jaundice in South Asia. It is endemic throughout not just Pakistan and Nepal, where early research was conducted, but through much of Asia and Africa as well, and is estimated to sicken 14-20 million people per year worldwide, resulting in anywhere from 56,000-300,000 deaths—many of them pregnant women, in whom the death rate is as high as 25%. (116) It also causes 5200 stillbirths annually. (86) Its prevalence
in developed countries is just beginning to be elucidated, with studies in Germany suggesting that some 16% of the adult population has been exposed; studies in the United States have confirmed similarly high rates of anti-HEV antibodies in the population. (118, 119) Since the vast majority of clinical infections are asymptomatic, it is easy to under-diagnose the disease, particularly in areas where epidemics are uncommon. However, there is increasing evidence that immunocompromised patients who are exposed to the virus are at risk of developing chronic hepatitis as a result—a significantly different outcome than the old conventional wisdom that hepatitis E was generally self-limited. This finding makes hepatitis E a disease of potentially greater import in developed nations than was once believed. (120)

Since hepatitis E wasn’t recognized as a distinct entity until the 1980s, determining its influence in historical conflicts is not entirely straightforward, although some authors have speculated about the role it played in the World Wars. (68, 121) In recent conflicts, the Soviet military experienced high rates of disease during the Afghan War of the 1980s. In fact, this was where research attention was first drawn to the disease, and the researcher who identified the pathogen obtained his sample from infected Soviet troops. (122) This experience was not replicated in American forces during the current conflict in Afghanistan, with one study showing exceptionally low rates of exposure among deployed troops. (123) It is speculated that this is more a reflection of the lack of exposure to local culture experienced by most American troops—food and water for coalition forces is almost universally safe—however, some experts have reiterated the risk of deployments to endemic areas. (124) Indeed, deployments of allied militaries to Africa in recent decades have demonstrated that the risk of hepatitis E outbreaks exists, even when food and water supply chains are tightly regulated. Risk of exposure in deployed troops seems to correlate with timing of outbreaks in the civilian communities nearby, meaning that exposure would not be consistent across deployed groups. (125)

**The Need for A Vaccine**

In the 1990s, AFRIMS began to build a convincing case for the need for a Hepatitis E vaccine and for Nepal as an ideal area to study it, first establishing the risk to travelers in endemic area and then determining the burden on local populations. Researchers initially identified both Hepatitis A and E as endemic to the Kathmandu region of Nepal, then argued that over half of
those sickened with hepatitis in the region (and surrounding countries) suffered from hepatitis E. Those afflicted lost, on average, over three weeks of work time and, for wage-earners, 20% of their annual income due to their illness when lost wages and medical expenses were considered. (126, 127) In a country with a poverty rate of 25% and a gross national income of $730 annually, these losses are far from inconsequential for the average family. (128) In addition, theoretical cost-effectiveness analysis for endemic countries found universal vaccination to be more cost-effective than both screening with vaccination or no vaccination. (129)

By the late 1990s, scientists at the National Institute of Allergy and Infectious Disease, some of whom had also worked on hepatitis A vaccine research, had developed a vaccine for hepatitis E. Quickly thereafter a partnership formed with SmithKline Beecham for clinical trials. (130, 131) The vaccine was created from genetic material isolated during the Sargodha, Pakistan outbreak, which had first spurred forward military research over a decade earlier. (132) WRAIR formed its own agreement with SmithKline to support clinical development of the vaccine. Phase I safety trials were conducted in the United States at WRAIR with 88 U.S. Army volunteers and subsequently an additional trial was conducted among a small group of volunteers in Nepal. (132, 133) For larger trials, it was clear that an endemic location was needed, and Nepal provided an optimal location for a clinical trial of a hepatitis E vaccine. An Army research lab had been established there since 1995, and a portion of the phase I trials had been completed there in 1998. The Nepali army had worked with U.S. military researchers investigating hepatitis E, Japanese encephalitis and other diarrheal diseases, as well as conducting influenza surveillance over a 13-year partnership, and 19 publications had resulted by 2000. (42) In addition, as military researchers had established, the disease was endemic in the population, with past studies showing 30-40% of the young adult population had been infected in the past. (127, 134-136)

The trial was initially approved for conduct in the civilian population, with 3000 participants to be chosen from the city of Lalitpur, south of Kathmandu in central Nepal. Several papers have explored what happened next. The civilian population of the region, wary of the mission of the U.S. military in developing a vaccine—and understandably concerned about the degree to which they would benefit from the outcomes of the research—stood in protest. At the time, as Jason
Andrews clearly points out in his bioethical evaluation of the trial, messages were mixed. Nepali government officials stated that the motivation for vaccine development was not profit but rather saving lives, while military officials openly acknowledged the military mission to protect the lives of American soldiers and the pharmaceutical industry goal of a successful vaccine for travelers. (136, 137) In the period leading up to the proposed start of recruitment, the issue became increasingly contentious, with many Nepalese expressing frustration that the real solution to their hepatitis E problem was clean water, not a vaccine. In fact, WARUN chief Rob Scott admitted that Thailand would have been the go-to location for a hepatitis E vaccine trial, but, “WHO’s international year of potable water in Thailand in the 1980s was a success. ‘Thailand took that very seriously’, Scott told me, ‘and their hepatitis rates plummeted which is why we couldn’t run the trial there’.” (116)

As a result of the controversy and their general lack of confidence that the benefits of research
would be shared with the community, local government officials ultimately blocked conduct of the trial, with the mayor of Lalitpur stating “Nepal should not be made a laboratory for the interests of the American Army.” (116) Instead, the trial was carried out in 2000 Nepali military service members in Kathmandu. Although the military participants were volunteers, the ethics of conducting the clinical trial in a foreign military population—at a time when the Nepali government was receiving military aid from the United States to support an ongoing civil war—has also been a topic of debate among bioethicists. (138, 139) Beginning in 2001, 898 participants received the three-vaccine hepatitis E series. The participants were followed until 2004. The vaccine was found to be 95.5% efficacious and adverse events were equivalent between the two groups. The results were also suggestive but not conclusive that protection may be afforded after two doses of vaccine. Unfortunately, conducting a study in the Nepali military population meant that the study population was almost entirely male—not necessarily representative of the highest risk group, pregnant women. The results of the trial were published in 2007 in the New England Journal. (135)

**Shelving The Vaccine**

What happened next should not have been a surprise to those involved in research and development for the vaccination. The vaccine’s development went no further than the completion of the Nepali trial for financial reasons—GSK had decided that it did not have enough profit potential, even as a traveler’s vaccine, for development, and it and the U.S. military were unable to find anyone else to pay for its production. According to some news reports, GSK knew that the vaccine would not have commercial potential even before it began the Nepali trial, begging the question that several commentaries have brought up—why conduct the trial at all? There may have been, and likely was, hope that funding would come from another source to fill the gap for GSK—perhaps from the U.S. government who was, after all, involved. Other reports suggest, however, that as late as 2008, GSK was still optimistic about the vaccine and hoped to find a partner to subsidize further development. Genelabs, which had isolated the hepatitis E virus in the early 1990s and had also had a relationship with GSK, reported to the SEC at the end of 2007 that “GlaxoSmithKline advised us that they have decided to continue development of the investigational [hepatitis E] vaccine for which they plan to undertake extensive clinical and manufacturing efforts.” (131)
Ethicist Jason Andrews addresses the issue of the shelved vaccine as well, calling the partners into question for waiting so long to present their results publicly, which they did in December 2005—almost two years after the conclusion of data collection, and a year before the results were finally published. He suggests that this delay—the cause of which is unclear—hampered efforts to find a partner to fund production. (140) Andrews and several of his colleagues addressed a thoughtfully worded letter to GSK in 2006, pointing out their ethical concerns and identifying GSK as the party responsible for ensuring distribution of the vaccine. (141) In 2007, in response to this and several other letters questioning the ethics of a trial in the Nepali military population and the access local populations would receive to a vaccine, senior study authors (including Dr. Bruce Innis, the architect of the hepatitis A trial who had since transitioned from working from the military to GSK) responded:

GlaxoSmithKline, along with U.S. government agencies, has supported rHEV vaccine research, because the company recognized the value of developing vaccines and medicines against diseases in the developing world—efforts it has undertaken for more than 20 years. Bhattarai asks about access to the vaccine after the trial. We affirm that GlaxoSmithKline embraces the principle of distributive justice and is committed to continue development of the rHEV vaccine so that it can be available in Nepal. Nevertheless, since control of infectious diseases is a global public good, we call for international financing for the introduction of the rHEV vaccine through partnerships similar to those developed for rotavirus and pneumococcal conjugate vaccines.

We emphasize that GlaxoSmithKline is seeking public-sector partners who also are committed to the long and challenging endeavor to add the rHEV vaccine to immunization programs in high-risk countries. Despite competing public health priorities, we remain optimistic that the 95% protective efficacy of the rHEV vaccine can attract support. Adoption of rHEV vaccination programs in Nepal would be a fitting outcome for our trial’s volunteers and our many colleagues who since 1987 have examined options to identify and control hepatitis E. (142)
As of 2015, GSK has yet to find a partner and the vaccine remains unused in Nepal and elsewhere. Some of this is probably related to the international view of hepatitis E, which often places it as a low-priority public health concern. The WHO established a working group in 2013 and will publish its first position paper on hepatitis E vaccination in 2015, well after GSK’s vaccine success. Lack of WHO attention to hepatitis E undoubtedly reflects its historically low profile compared to other public health threats, and this likely made it harder to identify a partner willing to fund it—indeed, CDC researchers have commented that “hepatitis E is so neglected, it’s left off the lists of neglected tropical diseases”. Nonetheless, the outcry related to a clinically tested and efficacious vaccine being shelved has not been subtle, but thus far it has had little impact. Commentary in the Lancet and other journals (including an article by AFRIMS researchers) in the years following the 2007 Nepal trial questioned what had happened to a vaccine that had come so far and yet done so little for the greater good:

The New England Journal of Medicine (2007): The effectiveness of the rHEV vaccine generates hopes for prevention of disease among high-risk populations. But will the population at risk in Nepal benefit from this vaccine? Experience shows otherwise. International travelers benefit from the parenteral Vi capsular polysaccharide typhoid vaccine, which was tested among natives of Kathmandu. However, Nepalese natives do not benefit from the vaccine, probably owing to the vaccine’s high cost and short-term protective efficacy. Such examples discourage community support for research. The rationale of medical research cannot be justified if the population in which the research was carried out does not benefit from the results of the research. In this regard, the investigators need to clarify the usefulness of the rHEV vaccine in preventing and controlling disease in the native population of Nepal. (143)

Transactions of the Royal Society of Tropical Medicine and Hygiene (2008): Since vaccination appears to be both a highly effective and feasible tool to reduce HEV-associated morbidity and mortality, governmental, philanthropic and international health organisations as well as pharmaceutical industries
should make a concentrated effort to develop strategies to bring an effective vaccine to the people who need it. (144)

The Lancet, 2010: Years have passed since the development of this (hepatitis E) vaccine, with no real gain for the people in the country where it was tested nor across the wider global community…if GSK (and) Walter Reed Armed Forces Institute of Medical Sciences were not going to develop these vaccines or make them available after their successful testing in Nepal…why were they tested? And if these organizations will not develop them further, is there a responsibility to make them available to others who might? (145)

The Lancet, 2010: Because no treatment exists for HEV infection, development of a vaccine is the best way forward in developing and developed countries. However, developing countries are unlikely to have the resources needed to develop and test vaccines. So why have companies invested their resources in creating vaccines such as those for HEV that are safe and seem effective, and then not developed them when they are urgently needed? The answer might be that pharmaceutical companies do not think an HEV vaccine is commercially viable. (146)

Liver International, 2014: the publication of this first successful clinical trial of an efficacious HEV vaccine generated enthusiasm and optimism. However, this vaccine has not reached the market because of concerns regarding its ability to generate sufficient revenue…Too often, the decision to develop a drug, or in this case a vaccine, is profit driven. Such profits are generally generated in the West and not in developing countries. However, our medical ethics should also motivate us to develop therapies for diseases which wreak havoc in developing countries, but not in the West. (129)

The ethics of a military trial and the ultimate shelving of the vaccine combine to raise questions about the U.S. government’s relationships with their Nepalese allies, and what kinds of support are valuable in such a partnership. The United States has a historic relationship of military
support with Nepal through the International Military Education and Training (IMET) program, which provides modest amounts of annual funding to help improve training, build stability and support democracy in partner nations (Thailand is also an IMET partner). In the early 2000s, at the time of the hepatitis E trial, Nepal was also a beneficiary of special Foreign Military Funding, which provided much more substantial amounts of funding—the State Department requested some $27,000,000 from 2002-2004—with the intent that “FMF in Nepal will help its government cope with a brutal communist insurgency, restore enough stability to permit elections, and prevent the countryside from becoming a haven for al-Qaida and other terrorist groups.” (Foreign Military Aid) Most notably, Asia is only becoming a more important strategic focus for the U.S. military. Recent years have seen a concerted shift in military strategy toward Asia; in a 2012 report on strategic priorities for the 21st century, policy makers emphasized:

While the U.S. military will continue to contribute to security globally, **we will of necessity rebalance toward the Asia-Pacific region.** Our relationships with Asian allies and key partners are critical to the future stability and growth of the region. We will emphasize our existing alliances, which provide a vital foundation for Asia-Pacific security. (147)

While direct military aid is one way to support our relationship with Nepal, “softer” support through a humanitarian program such as providing hepatitis E vaccination might be an effective grassroots mechanism to garner good will in the Nepali military. It would also undoubtedly improve military readiness. Outbreaks of hepatitis E are far from uncommon in the military population, a factor that was taken advantage of in the vaccine trial. Given the international engagement of most militaries, there are also ripple effects of allowing troops to go unprotected from diseases such as hepatitis E. Indeed, the Nepali military is among those blamed for introducing hepatitis E to Haiti as part of a UN peacekeeping mission in 1995; before a vaccine was available, but all the more reason that . (134) Interestingly, Nepalese soldiers serving in a peacekeeping capacity were also implicated in the 2010 cholera outbreak in Haiti—cholera represents another disease with a history of military interest and vaccine development. (8, 148)
A Chinese Vaccine

While the GSK owned vaccine remained shelved, it took an entirely separate research and development in another country to finally bring an effective hepatitis E vaccine to the world market. In 2010, Chinese researchers published the results of a Phase III clinical trial of a new vaccine against hepatitis E, the HEV 239 vaccine. Much like development in the United States, the vaccine (commercially known as Hecolin) was an effort in partnership between private industry, academia and the government. Work on the vaccine began at Xiamen University, but was spurred on by investment from the Yangsheng Group. The Group paid $1.8 million in 2000 to develop a joint laboratory, which was ultimately recognized by the Chinese government as the National Institute of Diagnostics and Vaccine Development in Infectious Diseases. Yangsheng also created a subsidiary company, Innovax, to produce the vaccine. (149)

Over 100,000 participants from Jiangsu Province were involved in a randomized controlled trial to test the efficacy of the vaccine. The vaccine was 100% efficacious after 3 doses with no serious adverse effects. (150) In December 2011, the State Food and Drug Administration in China approved Hecolin, paving the way for use throughout China and for its evaluation by the WHO for use by its myriad programs. All told, the vaccine cost $80 million to develop, much of which came from the Chinese government, and it will be sold for approximately $18 per dose, with $10 million in sales anticipated in 2013. (149)

The Chinese hepatitis E model shows that collaborative models will likely be the way of the future in bringing much needed vaccines to market. The challenge will be for countries like Nepal—whose government may not have nearly $80 million to pump into development, and whose average citizens may not be able to pay $18 for each of three doses of vaccine—to find a way forward. Indeed, what if, like hepatitis A in Thailand, cost-effectiveness analysis doesn’t pan out? Previously described cost-effectiveness data was based on a vaccine cost of $9.86, which is substantially lower than the predicted cost for Hecolin. (129) It is unclear whether China or the WHO will support vaccine implementation in countries, like Nepal, where market forces would not otherwise bring the vaccine’s price to a cost-effective level.
Conclusion

Outbreaks of hepatitis E continue to garner headlines—in 2014 alone, outbreaks were reported in Nepal (6000 infected), Uganda, India, and among refugees in Ethiopia and Sudan. (148) One 1998 study identified hepatitis E carrying UN peacekeepers as the introducing source of hepatitis E in Haiti, with serum analysis showing that Pakistaini, Indian, and Nepali soldiers serving in the country carrying the highest rates of infection based on serum analysis—62%, 37% and 37% respectively. (134) The idea that traveling militaries have the potential to spread hepatitis to previously unaffected areas is a disturbing one, but not unlikely given the potential for large groups from various areas to work in close quarters for extended periods of time, and for military members to be drawn from a wider demographic than international travelers in general. Indeed, the same phenomenon has been noted for cholera in Haiti—a major 2010 outbreak in that country was introduced by UN peacekeepers, ironically from Nepal. (148) In addition, the ethical debate surrounding testing of the hepatitis E vaccine in Nepal shows that local populations are not ignorant of what their participation in research means. If the U.S. admits that its strategic goals include building bridges in Asia and limiting the hold of terrorist organizations in counties such as Nepal, presenting the U.S and its military in a positive light—not in an exploitative one—would be wise. In a country such as Nepal, which has both military and medical partnerships with the United States, appropriate reciprocation for participation in a vaccine trial may not simply be ethically appropriate, it may be strategically advantageous—an intervention with the potential to be highly “cost-effective” for the United States government and military.
Japanese Encephalitis

Japanese encephalitis has been on the U.S. military radar as a disease of interest since at least World War II, when military scientists developed the first vaccine against the disease, which became the basis for vaccination of Asian children for decades after the war’s conclusion. The military also initiated, in conjunction with their Thai partners, the clinical trial that led to the vaccine’s approval in both countries (albeit decades after its development), and they also helped to develop a newer vaccine, which is the only other approved in the United States—but it rarely used due to its high cost. The story of JE provides an example of an alternative outcome for our partners—in the case of the JE vaccine, Thailand not only implemented the vaccine in a cost-effective manner, but also has benefited financially from industry partnerships that have allowed them to produce both new and old JE vaccines in-country. Differentiating the nuances of what made Japanese Encephalitis a success story for Thailand, in opposition to the failures of hepatitis A in Thailand and hepatitis E in Nepal, is complex and gets to the heart of the problem of vaccine access.

Japanese Encephalitis Epidemiology

Unlike hepatitis A and E, Japanese Encephalitis is a vector-borne, zoonotic disease, carried by the *Culex tritaeniorhynchus* mosquito (and occasionally other *Culex* species) and perpetuated by amplifying hosts such as swine and birds. (151) As a mosquito-borne illness, management of the vector and water supplies is an important component of public health efforts to manage the disease; unfortunately, this can be exceedingly difficult in rural areas. Rice paddies are a common breeding ground, and complex water management techniques are required to have an impact on mosquito populations. Unfortunately, even with the best management, mosquitoes are quick to re-infest areas they have been cleared from. Likewise, management of the vector with pesticide has not generally proven useful—because of logistic and cost-effectiveness reasons, pesticide is nearly impossible to apply on a large enough basis to adequately control mosquito populations, and thus disease. (152) Efforts to reduce human infections by interfering with swine infection, including using vaccination, have also proven less useful. (153) Difficulties in environmental management have long made human vaccination the ideal public health approach to Japanese Encephalitis, as articulated by PATH:
Interventions other than immunization have not significantly reduced morbidity and mortality from JE disease. Although good quality care improves outcome, there are no antiviral medications available to treat JE. Mosquito and pig-control methods have shown very limited impact, have significant limitations, and are not recommended as a focus for JE control. Immunization is the only reliable and effective method to control disease. (154)

Compared to hepatitis A and E, Japanese Encephalitis is a disease of smaller clinical scale but more significant consequences. Approximately 30-50,000 reported cases occur annually throughout Asia, where it is endemic in 24 countries; one WHO estimate of total clinical cases placed the actual incidence closer to 68,000 per year. (151) The actual infection rate is certainly much higher than this; however, the majority of Japanese encephalitis infections are asymptomatic, such that anywhere from 25-1000 times as many infections occur as become clinically significant. (155) What is notable about the virus, and what makes it such an important public health concern, is its high morbidity and mortality. With a fatality rate of up to 30% among those who are symptomatic and a disability rate of up to 50% among survivors, it causes 10,000 deaths and results in serious disability in 15,000 people per year (151, 154) Throughout Asia, the current burden of disease varies significantly, however, with annual disability adjusted life years ranging from 0 in Japan, where human vaccination programs have been in place for decades, to over 30/100,000 in Laos, Cambodia, and Pakistan, where vaccination is uncommon and the population remains more rural. (156)

Because it is vector-borne and not related to clean water supplies, Japanese Encephalitis affects developed and developing nations much more equally than hepatitis A and E, although vaccine access now serves as a cause of disparity in place of clean water. Indeed, it is likely that the significant potential for disease in wealthy countries accounts for why a vaccine has been in use for decades in Asia. Despite exceptional control for decades and reduction of many of the environmental factors that perpetuate the vector, Japan, Taiwan and South Korea continue to recommend vaccination of all children against the disease. Even in low-income countries,
vaccination has been proven to be very cost effective, with a cost of just $28 per DALY prevented. (154)

**History**

As its name implies, Japanese Encephalitis originated, or at least was first appreciated, in Japan, although it is not unique to that area. Summer epidemics of Japanese encephalitis were recognized in Japan as early as the 1870s, but it and other forms of vector-borne encephalitis were not fully characterized until the 1930s, when the virus was isolated from the brain of a patient. This was too late for its impact on military campaigning to be measured in conflicts prior to World War II. (155) In the lead-up to that war, concern over deployments to Asia and the Pacific led to recognition of the threat posed by Japanese Encephalitis, but relatively little was known about the disease by American scientists, and they weren’t in a position to obtain information from the more knowledgeable Japanese. Nonetheless, a rapid and concerted effort was made to develop a vaccine, and by 1942, one had been developed by passage of the
“Nakayama” strain of virus in infected mouse brains; this now-famous strain had been isolated from a fatal case in 1935. Major Albert Sabin, of polio fame, was the creator, and the vaccine was developed under the auspices of the Commission on Neurotropic Virus Diseases of the Army Epidemiology Board.\(^6\) (158, 159) Unfortunately, it was unclear whether this early vaccine was entirely effective, and as an unpurified vaccine derived from mouse brain cells, the vaccine also caused periodic encephalomyelitis.

At the end of World War II, a cluster of Japanese Encephalitis cases occurred among the U.S. military serving in Okinawa, Japan, in the context of a larger epidemic in the area. The Sabin vaccine was used on close to 70,000 military personnel in the region in an attempt to control the epidemic; however, a controlled trial of its efficacy was unable to be undertaken at the time, and in hindsight, it appeared that vaccination might have started too late to have a major impact on the outbreak anyway. Observations by Sabin on the outbreak and vaccination effort suggested that at the very least, the vaccine did not produce significant side effects—although fears of this were not completely dispelled. (160) Overall, however, rates of infection remained mercifully low through the war, although an additional 250,000 personnel did receive vaccination following the Okinawa outbreak. (161)

In the years following the war’s end and extending through the Korean War there were small numbers of cases among American service members each year, including an outbreak of 300 cases in Korea in 1950. (162) All military personnel serving in the region during this period received vaccination with a modified vaccine, which used both mouse brain and chick-embryo derivatives. (161) Military cases of Japanese Encephalitis also occurred throughout the Vietnam War—24 in 1967, 57 in 1969, and 61 in 1970. (22, 163-166) One such case occurred in 1972, when an American Marine stationed at an airbase in Thailand fell ill and drew the attention of AFRIMS researchers, who had been working on Japanese Encephalitis in Thailand since 1969. During this period, no vaccination was given to deployed Soldiers, although this was not for lack of perceived need—the official military history of the period noted “The continuing yearly epidemics in Vietnam and the still unresolved problem of late sequelae in subclinical infection

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\(^6\) Incidentally, Dr. Sabin also developed a dengue vaccine during his time in the military (1944), and these two efforts are his first vaccine successes, albeit not his most famous.
warrant serious consideration of the development of protective immunization for individuals assigned to endemic areas; this would be a realistic approach to recurring epidemics worldwide.” (164)

Figure 5: An AFRIMS team sets out for the day during the 1970 JE study in Chiang Mai, Thailand. (101)

**Vaccination for the West and the Rest**

The history of Japanese Encephalitis vaccine development and implementation traces a continuous path from its origins during the Second World War. Despite questions about the Sabin vaccine’s efficacy, at the conclusion of the Second World War the vaccine technology was passed to the Japanese government, which continued its use among the nation’s children and also conducted research to improve the vaccine technology. Much of this work was conducted at the Research Foundation of Microbial Disease at Osaka University (“BIKEN”). While the U.S military ceased use of both forms of vaccine after 1951 based on unproven efficacy, in Japan, trials using the mouse-brain/chick-embryo were conducted on children in Okinawa in the second half of the 1940s, with over 50,000 children vaccinated and followed for several years. These trials showed lower rates of infection in vaccinated children, although the results were not uniformly significant. (162)
In 1965, this unpurified vaccine was tested in a massive Taiwanese clinical trial conducted in the northern counties of the country, where disease incidence was highest. Over 250,000 Taiwanese children were randomized to receive the JE vaccine or placebo; a small subset of each group received one dose, while the majority received two. Through the study, the participants were compared to unvaccinated children in the region. Over two decades after the original vaccine had begun to be used in large numbers of Japanese children, the Taiwanese trial finally proved both the safety and relative efficacy of the Japanese Encephalitis vaccine—two doses of vaccine gave 81% efficacy and a statistically significant decrease in morbidity compared to placebo. (167)

Simultaneously, Japanese researchers had developed a purified version of the vaccine that reduced the risk of encephalopathy. Almost immediately and despite no clinical trial evidence of the vaccine's efficacy, this became a routine vaccination for Japanese children between the ages of 3 and 15. Because of this vaccination program and increasingly aggressive vector control
efforts, the disease quickly became uncommon in Japan, falling from a rate of 2.5/100,000 in the 1950s and 1960s to 0.01/100,000 by the 1990s. (154) To put this remarkable decline in other terms, in the 1920s, a single epidemic killed nearly 4000 people; by the early 1970s, fewer than 100 cases occurred annually in Japan, and that has dropped to under 10 per year over the past two decades. (168, 169) The newest studies have confirmed that developed countries like Japan have no more than a handful of clinical cases per year. (165, 170) Interestingly, much like the earliest vaccine, which was used for decades without strong evidence of its efficacy, the vaccine that prompted these steady decreases in disease incidence was also used without a randomized trial. A clinical trial to prove the efficacy of the vaccine was attempted in Korea in 1968, but few cases occurred that year and the trial was inconclusive.

For decades after World War II the threat of Japanese Encephalitis continued to be recognized by the U.S. military, but little headway was made in vaccination, and the American military was less ambitious than the Japanese government in terms of using untested vaccines. All this changed in the early 1980s, when two Americans—one a university professor, the other a university student—contracted Japanese Encephalitis while in China. Both subsequently died, raising the profile of the disease significantly in the United States; even a few years after the death of 20-year-old student studying abroad in Beijing, the story remained intriguing enough for the New Yorker magazine to write a substantial piece about the death and its repercussions. (153, 171) Indeed, the story was compelling: for the father of John Zeidman, his son’s death became the motivation for a crusade to bring a Japanese Encephalitis vaccine to the United States. By 1982, he had succeeded in having a Japanese-produced vaccine approved as an Investigational New Drug. (172) The vaccine underwent small-scale evaluation by the CDC and was available on an investigational basis from 1983-1987, with some 17,000 doses administered to American travelers through CDC clinics during this period. (165, 166) In June 1987, before it had become approved or generally available, the Japanese manufacturer chose to stop distribution to the United States due concerns over liability, but the tide had nonetheless turned, and American awareness of Japanese Encephalitis was more firmly established. (173)
At roughly the same time, public health authorities in Thailand were debating the use of the Japanese Encephalitis vaccine to reduce cases in their country. The disease had first been reported there in 1961, with annual outbreaks occurring through the 1960s; a particularly heavy rainy season led to the first recorded epidemic in Chiang Mai in 1969. The following year, AFRIMS (then SEATO) researchers collaborated with local medical centers to evaluate the disease in the region. In 1972, their investigation of a case of encephalitis in a U.S. Marine led them to identify a major epidemic and “launch a full-scale epidemiological investigation of what proved to be a major outbreak of this disease.” (101). Their work established the epidemiology of the virus in the area, including the seasonal nature of transmission, the importance of local geography and climatological factors, and the relationship of swine and *Culex* mosquito populations to transmission rates. (175, 176) Through the decades of the 1960s through the 1980s, 1500-2500 cases of encephalitis were reported per year—an incidence of up to 3/100,000 nationally, with most cases concentrated in the Northern provinces during the rainy summer months, where the incidence could rise as high as 20/100,000. (177) The case fatality ratio was consistently 20-30%. (178)
The timeline of Thailand’s Japanese Encephalitis experience is consistent with the rest of the continent. Beginning in the 1970s, the disease began to experience a resurgence in Asia, spreading in range, returning to areas where it had been under control, and increasing in prevalence nearly everywhere. Rapid population growth in Asia, increased land area devoted to rice paddies and growing pork production—in Thailand, area under rice cultivation grew by 14% and pork production increased 80% from 1990-2005—are all theorized to be among the causative human factors. (156) By the 1990s, it had reached never-before affected Pakistan, India, and parts of Indonesia and Australia. (155) Over 44,000,000 people in Thailand now live in endemic areas. Data from one-time serum samples taken in 1989 (when vaccination was available but not widely used in Thailand) showed that among rural children, 7-32/1000 had recently been infected with Japanese Encephalitis. (179)

Beginning in 1973, the Thai government attempted to manage Japanese Encephalitis through vector control and avoidance; but as is well documented throughout Asia, these efforts were “basically ineffective.” (178) Human vaccination was recognized as potentially the only highly effective approach to disease control, but there continued to be concerns about the feasibility of using the vaccine on a nationwide scale, most notably related to cost:

The high cost of JE vaccine ($2.30 per dose in 1988) is a major hindrance to the use of vaccination for JE control in both government and private sectors. The Department of CDC (in Thailand) has been attempting the use of JE vaccine, but the vaccine cost and the characteristic distribution of JEV infection and JE cases have put JE at a lower priority among vaccine preventable diseases whose control costs are to be borne by the Department. (170, 178)

The Thai government ultimately decided to pursue a vaccination strategy to control Japanese encephalitis in their country, but were not prepared to implement vaccination without a trial in their population. AFRIMS, which had researched the disease for over a decade and provided much of the evidence that defined the Thai encephalitis problem, proved the perfect organization to execute a large-scale clinical trial. The timing was also right for American researchers, with demand heightened for an FDA approved vaccine. Beginning in March 1984, children were
recruited to a large clinical trial to study the efficacy of the BIKEN vaccines. Over 65,000 Thai children were ultimately selected to participate, and received two doses of either bivalent (composed of the traditional Nakayama strain plus the Beijing-1 stain, which had shown by various metrics to be more useful in vaccine production), monovalent or placebo vaccine. (81)

Both vaccines had efficacy rates of 91%, with an attack rate for vaccinated children of 5/100,000 compared to 51/100,000 for unvaccinated children. Side-effects were uncommon and mild. In concluding, the authors of the study—which was published in the New England Journal in 1988—acknowledged “immunization of children in Asia against Japanese encephalitis virus remains a difficult problem. Although safe and effective, the vaccine is expensive, and other health problems are pressing in the region.” (177)

**Vaccine Implementation**

The vaccine was licensed for use in the United States in 1992, although it was ultimately removed from the market in the mid-2000s because of supply issues. (180) In 2005, the Japanese
government had discontinued its recommendation for use of the BIKEN vaccine based on largely unsubstantiated safety concerns, and by 2007, production of the long-used vaccine had completely ceased, although newer vaccines have since been developed to replace it in Japan. (181) In 2009, Ixiaro (which was also developed with substantial military contributions) was approved in the United States, and this vaccine continues to be available and recommended for use in American travelers going to endemic areas for one month or longer. (182) The high cost of the vaccine—in the hundreds of dollars and generally not covered by insurance—is a barrier to vaccination, even for travelers from wealthy countries, and also calls into question the cost-effectiveness for travelers. (183, 184)7

Fortunately, unlike hepatitis A and in spite of the high cost of vaccination, the cost-benefit analysis of Japanese encephalitis vaccination in Thailand, and other countries in Asia as well, was favorable. A 1997 analysis of vaccination in Thailand estimated treatment of each acute case of encephalitis would cost $1660, but found that the most substantial savings came from preventing disability, which was associated with profound long-term costs. Each prevented case would represent a savings of $72,922 over the long term. It also compared vaccination of 18-month-olds with that of primary school aged children, and found that infants should be the priority for vaccination. (154, 181, 185) Similar cost-effectiveness evidence has been found in other Asian countries as well, but despite the clear data, vaccination policies throughout Asia vary significantly. Taiwan, Japan and Korea—all wealthy and all with country-wide risk of disease—have the most long-standing and robust programs, with recommendations for childhood vaccination in place since 1968, 1967, and the 1970s respectively. China, with the largest at-risk population in Asia, had an incomplete vaccination program beginning in 1981; it was not until 2008 that it added Japanese Encephalitis to its Expanded Immunization Program for all children in endemic areas. Thailand’s high incidence neighbors, Cambodia, Laos, and Malaysia, have either no or extremely young and limited programs in place. Thailand implemented a vaccination program not long after the conclusion of publication of trial results. (154)

7 The Japanese Encephalitis experience of replacing a long-standing, effective vaccine with a newer, more expensive (but sometimes minimally improved and potentially unavailable) vaccine has been seen in multiple cases—hepatitis B and rabies among them—and begs the question of where precious research resources should be expended.
The Japanese Encephalitis vaccine was included on the Thai National Immunization Program in 1990. Initially, it was recommended for 18-month-old children only in high-risk regions, which was categorized as eight northern provinces. The recommendation gradually progressed to include a larger geographic area. As new provinces were added to the infant immunization schedule through the 1990s, a graduated program of “catch-up” immunization of grade-schoolers was also implemented. In the year 2000, all 76 provinces were incorporated into immunization plan. By 2003, one study documented high rates of compliance with vaccination—among 2-3 year olds, 92% and 87% respectively had received their first and second vaccinations. (186) Incidence of Japanese Encephalitis dropped rapidly after beginning in 1990, from as high as 3/100,000 cases annually to well below 1/100,000. (187) Thailand is one of six countries that is considered to have controlled Japanese encephalitis, with an estimated rate of 0.07/100,000—43 total cases in 2007. (154)

Even before its widespread implementation, Thailand appeared to be strategizing ways to gain access to the Japanese Encephalitis vaccine; they did so through an effective model of partnership with the pharmaceutical industry that significantly enhanced their national vaccine production capacity. BIKEN was the long-time Japanese producer of JE-Vax, the original vaccine and the subject of the 1984 Thai trial. In conjunction with the Japanese government, BIKEN initially supported the vaccine in Thailand through technology transfer and other technical assistance. Beginning in 1985, Thailand started to produce vaccine on a pilot-scale to facilitate trials. Following approval of the vaccine, production was scaled-up and Thailand was eventually able to produce 40% of its national vaccine need at a government owned factory; it imported the remainder from BIKEN in Japan. (188) The factory, the centerpiece of the Thai Government Pharmaceutical Organization (GPO), was founded in the 1930s. Its early mission was to research herbal products, but it soon evolved to produce medications and reduce Thai reliance on importing pharmaceutical products. (189) In 1989, the GPO factory switched from the Nakayama strain vaccine to the recently tested bivalent (Nakayama/Beijing 1) vaccine. (190)

In 1997, French pharmaceutical company Sanofi-Pasteur entered into a joint venture with the Thai government to fund the construction of a vaccine manufacturing plant that was completed in 2002; they subsequently transferred vaccine technology to the Thai Governmental
Pharmaceutical Organization (GPO) through the GPO-Merieux Biological Products Co (GPO-MBP). Ownership of the GPO-MBP is held equally by the Thai government via the GPO and Sanofi Pasteur. The vaccine factory is the only WHO pre-approved facility in Thailand and currently produces vaccines for hepatitis B, rabies, measles, polio, flu and Japanese encephalitis, and has allowed Thailand to meet not only its national needs—in 2006, it produced over 25 million vaccine doses for the country—but to become a vaccine producer for the region and in the case of certain drugs (such as antiretrovirals), for other parts of the world. (191) Sales in 2011 were $349,000,000, and the GPO also succeeded in reducing drug costs within Thailand by 10% that year. (192-194) The GPO continues to conduct research and development on herbal products, medications of local and regional import, and with WHO support recently completed construction of an influenza vaccine plant. (195)

An update to the GPO-Sanofi partnership, with a significant upgrade to the production facility, was announced in 2013 with the goal of producing a tetravalent JE vaccine. In exchange for the upgrade and technology, the Thai Public Health Ministry agreed to purchase six vaccines from GPO-MBP. Thailand will become the regional producer for the Imojev vaccine (also known at Thajev), a live, attenuated, recombinant chimeric Japanese Encephalitis virus vaccine that was approved in Thailand and Australia in 2010. The vaccine, which was originally known as Chimerivax and manufactured by Acambis, is based on the novel method produced by Dr. Tom Monath, a researcher who spent 24 years in the U.S. Public Health Service and U.S. Army, including time as the Chief of Virology at USAMRIID, before moving to the pharmaceutical industry. (181, 196) There are plans for the vaccine to be exported to other Asian countries and Australia. (191, 197-199)

**Other Directions for JE Research**

Even though a clinically tested, effective Japanese Encephalitis vaccine was available in the United States and abroad as of the early 1990s, this did not represent the end of the vaccine story, or of military research. As early as the mid-1980s, while testing of the BIKEN mouse brain derived vaccine was underway in Thailand, WRAIR scientists in the United States were beginning to work on a cell-culture derived vaccine intended to improve on some of the concerns surrounding the mouse brain vaccine—namely, low immunogenicity, difficult production, and
safety concerns. A promising new candidate vaccine emerged in 1986 via a Chinese researcher, Dr. Yu Yong Xin, who had developed a prototype vaccine from a strain called SA 14-14-2 cultured in dog kidney cells, which were used in the measles and rubella vaccines used in the United States. (81) Beginning in the 1990s, this strain of Japanese Encephalitis virus was used in China to vaccinate millions of people, and had been shown in large trials to be efficacious after one dose of immunization. (180) Walter Reed researchers used this concept, but modified the vaccine to culture it in Vero cells. From 2001-2003, WRAIR conducted a phase II trial in 94 participants using a Vero cell derived vaccine produced at their Pilot Bioproduction Facility; they evaluated subjects in four groups, one of which received the older JE-VAX for comparison purposes. The trial showed very high rates of seroconversion with the new vaccine (100% at the highest vaccine doses) with no more significant side effects than the standard JE-VAX. (200)

WRAIR partnered with pharmaceutical company Intercell to develop and produce the vaccine. While early trials and experimental vaccine production were overseen by Walter Reed, phase III trials and commercial scale production were taken over by InterCell after the success of the Phase II trial, with the vaccine technology transferred to Intercell’s factory in Livingston, England. Phase III trials were conducted exclusively by Intercell; unlike other vaccines, where WRAIR’s international partnerships had been useful for completing field trials, JE trials could be undertaken in Europe because “licensure of the JE vaccine did not require field efficacy trials because vaccine-induced neutralizing antibody at a titer of 1:10 or greater is an accepted surrogate of protection from Japanese Encephalitis Virus (JEV)”. (201) Over multiple studies, the vaccine, soon to be known commercially as Ixiaro, performed slightly better than the licensed vaccine, prompting seroconversion in 98% of recipients (compared to 95% of those receiving the older vaccine). (202-204) Ultimately, the vaccine was licensed to several pharmaceutical companies for large-scale distribution: Novartis in the Americas and Europe; Biological E. Ltd. in India and parts of Asia; and Bioterapies in Australia and parts of the Pacific. (181) The vaccine was approved by the FDA 2010 and became one of two licensed Japanese Encephalitis vaccines in the United States, the other being the now defunct BIKEN vaccine.
Conclusion

Japanese encephalitis represents, in many ways, a happy compromise between the interests of the U.S. military, the needs of its foreign research partners, and the best interests of the people of Asia and Thailand in particular. Confronting a significant threat to military readiness and public health, the military developed the technology behind the oldest as well as one of the newest vaccines available, which represent the two licensed in the United States; it contributed to the basic science and epidemiological understanding of the disease, which arguably built the case for childhood vaccination in Thailand; and it facilitated testing that made the vaccine available to the Thai people and to U.S. travelers and service members. The Thai government, for its part, appeared to be the force that drove forward clinical testing, and it not only ensured that its population benefited from the development of a vaccine, but that the national economy benefited from a direct partnership with the pharmaceutical industry. By developing production capacity and enhancing the biotechnology sector in its country, it also paved the way for future growth and greater opportunities in this area. The pharmaceutical industry also benefited, establishing production capacity in a low cost country within the region while building a partnership with an emerging market. And it did all this with a lower prevalence disease.
Malaria

I will focus the last case on an ongoing research project, one which differs in significant ways—including the scale of disease prevalence, funding, and attention—from those discussed already. It is also the most concerted and diverse military partnership of the four examples, involving not just industry (yet again, the military found itself working with GSK) but a new player—a nonprofit—in the team pushing for vaccine development. This model means, uniquely, this vaccine also has a plan for access, even before it is approved clinically. Malaria thus provides what could be a model for other military projects in order to improve access, even for small scale or regionally limited projects.

Malaria in the Military and the World

Malaria has played a role in American history since the nation’s founding and has likewise been a factor in the Revolution, Civil War, and nearly every military expeditionary action of the last 150 years, resulting in 50 years of military research on the disease—research that has led to a U.S. military influence on half of all malaria vaccine candidates developed worldwide. (45) During the Revolution, both sides were wracked with disease during campaigning in the Southern states, although the British were affected more substantially. Some scholars have gone so far as to credit the heinous effects of malaria with influencing major strategic decisions by the British that affected the outcome of the war. (205) In the 1830s, military campaigns against the Seminole in Florida led to the expansion of the use of large doses of quinine for malaria therapy. During the Civil War, the Union suffered over 1 million cases of malaria and 10,000 deaths; in his memoirs, GEN Ulysses S. Grant mentions the suffering caused by “malaria fevers” during the Vicksburg campaign. MAJ Walter Reed studied malaria outbreaks during the Spanish-American War, and later, while working with COL William Crawford Corgas in Cuba, established the importance of mosquitoes in transmitting infectious diseases. This led to a sharp decline in cases during the construction of the Panama Canal, thanks solely to improved control of mosquitoes. In World War II, there were 600,000 cases of malaria concentrated largely in the Pacific theater, but also in the Mediterranean and the Middle East. GEN Douglas MacArthur apparently stated “this will be a long war if for every division I have facing the enemy I must count on a second division in hospital with malaria and a third division convalescing from this debilitating disease!” (206) In the Korea era, the military set up trials of primaquine, and used it
to treat returning troops. In Vietnam, 100,000 cases were reported, and malaria was “the leading cause of medical disability”. The recognition of chloroquine resistant malaria in Southeast Asia was the instigator of a WRAIR directed malaria program, as “the Army recognized that there was little economic incentive for private pharmaceutical firms to undertake antimalarial drug discovery activities. From a commercial perspective, it makes little sense to produce costly pharmaceuticals for people who cannot afford shoes.” (33, 207)

Figure 10: Army Medical Corps officers investigate standing water for mosquito larvae at Fort Jackson, SC. (208)

Figure 11: A World War II image reminds soldiers about the threat of malaria. (209)
In modern operations, malaria has affected the campaign in Afghanistan, and all forces deployed from March to November are currently mandated to use malaria chemoprophylaxis. (210) Small operations are routinely affected, too—the most memorable in recent memory may be the infection of 80 Marines in Liberia, most of whom were not taking the mefloquine they had been prescribed and half of whom required evacuation back to the United States for treatment. (33) The cost, side effects (including the high profile psychiatric side effects of mefloquine), and difficulties with compliance (in Afghanistan, a 30-56% compliance rate is cited in the literature) associated with malaria chemoprophylaxis have all been cited in the literature and popular media as downsides to this approach to prevention, and are a strong impetus for the ongoing research into an effective malaria vaccine. (211)

The global impact of malaria needs little introduction. The dramatic statistics—which vary according to the source—indicate 200 million cases per year and at least 600,000 deaths, possibly many more. These statistics are perhaps even more notable when compared to those of just a decade ago, when deaths peaked—the WHO estimates over 800,000 deaths in 2004, while an independent group sponsored by the Bill and Melinda Gates Foundation called WHO numbers into question, placing deaths for that year at 1.8 million. (212, 213) In either case, these statistics are astounding, and deaths are far from the only metric by which malaria’s impact should be measured. The societal and economic repercussions of malaria are also notable, with major effects on economic growth—which is significantly lower in countries affected by Plasmodium falciparum—and per capita GDP—which is five-fold lower in malaria-endemic countries. Direct costs from malaria are estimated at $12 billion per year worldwide and the indirect costs and dampening effects on economic growth are significantly higher. (214) Even population growth may be related to malaria—demographers speculate that the high childhood mortality resulting from malaria is also tied to the persistence of high birth rates, which have additional economic effects for a society. (215)

Over recent years, funding for the fight against malaria has been as dramatic as the disease epidemiology. Over the past 7 years, funding for malaria research and development specifically has averaged in the $500-600 million range each year. By 2011, nearly half of that funding came from the public sector, and less than 20%—roughly $105 million per year—from industry. A
more detailed breakdown of average public sector funding over recent years includes major players from the U.S. government—$121,000,000 per year from the NIH, $31,000,000 from the Department of Defense, and $9,000,000 from USAID. NIH funding is topped only by the Gates Foundation, which provides a full quarter of annual research and development funds—$155,000,000. (216) Research funding equates to a mere fraction of the total spending on malaria, which was estimated at $2.55 billion in 2010. (217) U.S. pledges and payments, amounting to over $13,000,000,000 from 2001-2016, account for roughly one third of the funds committed to the Global Fund to Fight AIDS, Tuberculosis and Malaria—which, in turn, provides half of the international funding for malaria funding. (218) The U.S. also contributed an additional $1 billion per year from 2008-2013 as part of individual legislation, and USAID funding reaches into the hundreds of millions each year—$619 million in 2013. (219) Cleary, the price tag of fighting malaria in the present and striving to prevent it in the future is remarkable, and the pressure to develop a vaccine is heavy.

Military malaria vaccine research has received just a tiny fraction of total global funding, garnering between $6-8 million in annual funding through the early 2000s. (220) This amount of funding is on par with the amount USAID spends on malaria vaccine R&D, but a fraction of the $30 million spent by the NIAID. (220) Several independent organizations have called for greater funding for military malaria research, including PATH, which called the DOD “a leader in tropical and infectious disease research” and suggested that “doubling the Army and Navy’s budgets for malaria vaccine development would allow these programs to move candidates already in the vial into clinical testing.” (221) In its comprehensive report on the military malaria program, the IOM concluded, “the DOD should markedly enhance its research and development efforts to produce malaria vaccines suitable for military needs. The large investment (at least $300 million) that is required to give a high likelihood of success in producing a vaccine in the next 10 years needs to be acknowledged and planned for.” (33) Despite the relative budget limitations, the military has been highly productive throughout its 50-year history.

**Developing a Vaccine — A Three-way Partnership**

Before vaccines were considered a possibility, the military turned to prophylactic drugs, using a series of synthetic prophylactic drugs to replace quinine beginning in World War II. First came
atarbine, which was developed in Germany but synthesized independently by American scientists and used extensively during the war. Subsequent military research efforts examined over 15,000 potential compounds for their antimalarial effect, and several successful agents, including primaquine, emerged from these efforts. (206) In 1963, the U.S. Army Research Program on Malaria was established as a subsidiary of WRAIR in response to the need for new drugs to combat chloroquine-resistant malaria. New military research findings and treatments were quick to follow, including mefloquine. The military also funded research at civilian institutions, including landmark work published in the early 1970s demonstrating immunity acquired through the use of irradiated sporozoites. (222) This proof of principle research showed that a vaccine for malaria could be developed, and it occurred just as the American military gained firsthand experience on the effects of malaria in combat—over 100,000 cases occurred among military personnel during the Vietnam War, a rate of just under 1% in 1965, representing a significant impact on combat power. (33)

With evidence of induced malaria immunity, the military devoted itself to finding a vaccine, and by the early 1980s scientists at WRAIR had identified the circumsporozoite protein (CSP), a surface antigen of the malaria sporozoite that could be used as a vaccine target. The gene was cloned and sequenced by scientists at the NIH and WRAIR. With a potential target, WRAIR entered into a CRADA with Glaxo-Smithkline (GSK) in 1984 to produce a malaria vaccine using GSK’s recombinant Escherichia coli expression systems. Together they developed FSV-1, the world’s first malaria vaccine candidate. In 1987, in a small clinical trial, six volunteers were given the vaccine and then exposed to malaria carrying mosquitoes. While FSV-1 was deemed ineffective, one of the volunteers was granted immunity by the vaccine, the first time that a human was made immune to malaria through a simple vaccine. This WRAIR trial was followed by the first malaria clinical trial conducted at an international Walter Reed Project laboratory, this one in Kenya. (223) Over the following few years, GSK and WRAIR both independently conducted additional trials on a number of malaria vaccine candidates, but continued to run up against low immunogenicity.

Through further cooperation, WRAIR and GSK were able to develop the RTS,S malaria vaccine candidate. (224) Unlike previous vaccines, this vaccine utilized a fusion protein from malaria
CSP and hepatitis B surface antigen coupled with a novel adjuvant. (223) Together, WRAIR and GSK conducted monkey trials, following by initial safety trials and subsequently Phase IIa trials at WRAIR. (223) Larger Phase I trials were conducted beginning in 1997 in the Gambia involving 20 male volunteers, and the vaccine was found to be safe and well-tolerated. (225) Additional studies in children were conducted in The Gambia and Mozambique with the same results for safety, and these showed, for the first time, protection against malaria over time—30% efficacy against clinical malaria and 58% protection against severe malaria, maintained over 6-month follow-up. (226) In 2001-2002, with RTS,S in hand and some data on its efficacy, WRAIR and GSK formed a partnership with the Malaria Vaccine Initiative (MVI), a nonprofit organization founded in 1999 as a component of PATH with the support of the Bill and Melinda Gates Foundation. (227) In order to reduce the financial risk it would be taking to develop a malaria vaccine, GSK requested $25 million from the Gates Foundation. The Gates Foundation made a $50 million commitment to the MVI to support development of a malaria vaccine; MVI received another $100 million from the Bill and Melinda Gates Foundation in 2003 and $108 million in 2005. When the vaccine advanced to Phase III trials, MVI committed an additional $107 million to the effort. (223, 228, 229)

Phase III trials were started in March 2009 through collaboration with the governments of seven African countries; the trial was sponsored by GSK and participants included wide ranging interests known as the RTS,S Clinical Trials Partnership, among them KEMRI-Walter Reed scientists. Test sites included Kilifi, Kombew, and Siaya, Kenya (with Kombewa the site of a WRAIR research lab); Nanoro, Burkina Faso; Lambarene, Gabon; Kumasi and Kintampo, Ghana; Manhica, Mozambique; Bagamoyo and Korogwem Tanzania; and Lilongwe, Malawi. (230) The trials focused on testing RTS,S in children, who suffer the majority of malaria deaths, and over 15,000 children in two age groups were enrolled. (231-233) Preliminary results were published in 2011, detailing outcomes in the first 6000 children in older (5-17 months) age group. The trial demonstrated a 55.8% effect against clinical malaria and a 47.3% vaccine efficacy against severe malaria with serious adverse reactions occurring at similar frequencies for the control and vaccinated groups. (231) The following year, results from the younger (6-12 weeks) age group were published, showing lower efficacy for infants—30.1% against clinical malaria and 26.0% against severe malaria. (232) Although the infant results are less impressive
than earlier trials, overall these are nonetheless promising results for a vaccine that could be combined with current malaria fighting techniques to reduce the number of malaria deaths by an estimated 1,000-1,500 lives a day, and the vaccine could also serve as a step forward while a higher efficacy, second generation vaccine is developed. (229)

In late 2013, final results from the RTS,S trial, including nearly 3 years of follow-up, were presented. Results from 18-month follow-up were largely consistent with earlier results, with 46% efficacy against clinical malaria for children vaccinated at an older age and 27% efficacy for infants. (235) Three year follow-up of phase II clinical trial participants showed that efficacy was lost entirely by three years post vaccination. It also found that the vaccine’s efficacy was lower in higher transmission areas. (236) Four-year follow-up showed 29.9% efficacy against a first case of Falciparum malaria and 16.8% efficacy against all malaria exposures over the time period. (237) In July 2014, GSK submitted a regulatory application to the EU for approval of the vaccine; that process is still underway, but GSK suggests that approval and a WHO policy recommendation on use of the vaccine may be completed by late 2015. (238) Based in large part on the substantial funding provided by MVI, Glaxo Smithkline announced in 2010 that it will not seek to make a profit off any sales of the RTS,S malaria vaccine. Instead, it plans to sell the vaccines at a price that will allow it to cover the $350 million that it cites as its costs in
developing the vaccine (it also indicates that it anticipates investing another $260 million in the future), plus 5% overage that it intends to reinvest into additional research projects. (238, 239)

When a vaccine is approved and recommended by the WHO, it seems likely that the vaccine will achieve widespread use in Africa fairly quickly, given the pricing scheme proposed by GSK and the large amount of public and private interest and funding devoted to malaria. GSK’s own promotional materials state “if and when the vaccine is approved, further partnerships and collaborations will be necessary to help facilitate its delivery and implementation across Africa as quickly as possible.” (240) GSK has also provided funding to nonprofit organizations to investigate the cost of implementing malaria vaccination in different African countries. (241) This represents both a philanthropic and a pragmatic choice on the part of the company, as widespread dispersion of the vaccine is in the best interest of GSK, and the high degree of publicity associated with the malaria vaccine means that GSK is certain to be careful about handling media perception of the company and its work. In addition, GSK will certainly seek a more significant profit in the future, from a second-generation, higher-efficacy vaccine.

It should be noted that malaria represents such a significant public health problem, such a profound cause of death and disability the world over that the standard for a successful vaccine is far different than for most other diseases. A vaccine with 50% efficacy wouldn’t be considered a success for many diseases, but for malaria it is exactly what the global health community is seeking at the current time. The Malaria Vaccine Initiative (MVI) “Roadmap,” published in 2006 with their goals for research milestones over the coming years, set the following major milestones: “By 2015, develop and license a first-generation malaria vaccine that has a protective efficacy of more than 50% against severe disease and death and lasts longer than one year...By 2025, develop and license a malaria vaccine that has a protective efficacy of more than 80% against clinical disease and lasts longer than four years.” (242) Even a vaccine with 50% efficacy would be expected to reduce malaria mortality by half, saving hundreds of thousands of lives per year. (243) Cost-effectiveness analyses of the RTS,S vaccine have estimated that it will be cost effective in a variety of settings. An analysis of Malawi found the vaccine more cost-effective than no intervention and than the current standard intervention, insecticide-impregnated bed nets, and it was deemed “very cost effective” by Malawian standards. (244) The fact that a
malaria vaccine has proven technically more challenging than vaccines for some other diseases is another reason that a lower efficacy vaccine is considered acceptable: “malaria vaccine development is hindered by the sheer complexity of the parasite and its life cycle, extensive antigenic variation, and a poor understanding of the interaction between P. falciparum and the human immune system.” (245) Subunit vaccines like RTS,S (which uses the CSP subunit) seem to be an effective approach, but even these have some difficulty stimulating a sufficient immune response to kill the malaria parasite. (246)

Conclusion
The development of the RTS,S malaria vaccine and the efforts to ensure its implementation in the future represent the work of a large and diverse partnership representing interests from industry, nonprofits, governments and militaries, and academic institutions. Since the threat of malaria is such a significant one, it has been able to garner a broad support base and a relatively large source of funding (although many would say that far more funding is needed). Many smaller, less prevalent or well-known diseases may simply not be able to do likewise. In addition, while the pharmaceutical industry has been a cooperative player in this process, it has still done so with significant monetary support and publicity motive, reminding us that while philanthropy may be a small part of corporate motivation, profit will always reign supreme. Nonetheless, the malaria story may have a happy ending someday because so many strong and strongly vested interests will push progress forward and maintain accountability. There will be no hepatitis E story of a neglected vaccine, or hepatitis A story of a vaccine not reaching the most needy, when it comes to malaria.
Looking for Solutions

Framing the Problem

Military research has shown itself to be generally successful in achieving its research goals—perhaps even highly successful, considering the relatively limited resources it is afforded. As several case studies have shown, it could benefit from a more streamlined, actively managed process, as well as a less industry-reliant one, and many working in the system or evaluating it independently have supported this viewpoint. The combination of dependence on industry to finish the final steps of the research and approval process, to produce vaccines to meet the military’s needs, and to do this without a dynamic military system that is able to adapt to the market forces that guide industry is doomed to fail at times.

As a background to the discussion of what should be done to improve vaccine access, we must not forget that access to newly developed vaccines in the developing world is a problem hardly limited to products developed in part or in whole by the U.S. military. In recent years, vaccines for rotavirus and HPV—both of which have large applicability in both developed and developing countries—have gained widespread acceptance, but initially were used in a limited fashion in low and middle-income countries. A vaccine for Rotavirus, a diarrheal disease that affects nearly all young children and kills between 400-500,000 globally each year—almost all in Africa and Asia—became available in the United States in 2006, and is on the CDC’s vaccine schedule. (247, 248) The vaccine has been on the radar of nonprofit organizations since the early 2000s, and PATH and GAVI spearheaded a program to ensure the rapid introduction into the countries that need it most. In 2009, South Africa was the first African nation to introduce the vaccine—the only country to do so—and more rapid introduction of the vaccine has only begun in the past several years. It is now in use in 23 African countries, but more than half remain without vaccine access. In fact, of the five countries with the highest number of deaths from rotavirus—India, Nigeria, Pakistan, the Democratic Republic of the Congo, and Ethiopia—only one, Ethiopia, had a vaccine program in place as of 2013. (249)
Recognizing the universal challenge of widespread vaccine access, what steps might the military consider to improve vaccine access while still operating within its mission and its budget? Fortunately, many of the recommendations that might benefit military access to medical technology could also benefit our overseas partners and their respective public health agendas. Increased creativity in finding funding and partnerships could allow for broader use of vaccines once they are developed, and could help ensure their availability to the military. Integrating nonprofit organizations into the fold traditionally occupied by the military and industry has proven effective, and nonprofits serve both as a source of funds and as lobbying bodies to pressure industry to establish price controls and subsidies for the developing world. The current WRAIR-GSK-MVI partnership is a prime example of what nonprofits are capable of, although the fact that such collaboration developed around a disease as significant as malaria is unsurprising. Smaller scale or more regional diseases might require a more active approach to finding or building partnerships between industry, nonprofits, foreign governments and militaries, but they are far from impossible. The Thai-Sanofi Pasteur partnership is a prime example of a smaller scale relationship that has provided mutual benefits to both parties involved. And while CRADAs are intended to favor American companies, the military may even consider cooperative efforts with foreign producers, such as Thailand, which would allow us to directly support economic and health development in our partner nations. Ebola also provides a current example of the diverse partnerships possible. The collaborations between academia, smaller biotech firms, and several governments represent a unique example for a much smaller scale disease—albeit one that is so deadly that it inspires perhaps inordinate attention and occupies a unique space in the popular imagination. And even in the case of Ebola, it took a frightening epidemic for the most rapid research progress to occur.

When we consider military-specific process improvements, an active intention to consider open access to intellectual property for partners would be an important step. Senior researchers have commented in an independent fashion on the importance of supporting our partners, and we have already discussed the fact that this support might benefit the U.S. military’s strategies goals in our consideration of hepatitis E; however, the organization as a whole has not moved in this direction. In the civilian world, a movement for open access to technology, particularly that developed by academic institutions, has gained strength in the past decade. Much like the
military, universities often partner with or license their innovations to industry, and although these innovations were developed with university funds and resources and often with public research funding (such as NIH grants), historically there has been little appreciation of the fact that universities might have an obligation to ensure that their innovations are used for the common good. Open access, particularly for vaccines (like hepatitis A) with a large market in the developed world, could allow countries like Thailand to produce generic drugs at costs that make them available in their economy.

A complete rethinking of the government’s role in vaccine development may also be a valid approach, and this could be coupled with increased integration with other government agencies. Historically, military researchers and the NIH have often worked on similar projects and frequently collaborated. This type of partnership could be enhanced, and given the geographic relationship of the NIH, Walter Reed, and WRAIR, this would be far from difficult. In addition, while the military currently has the Pilot Bioproduction Facility for small-scale production, the NIH has looked at expanding their own similar capability from pilot scale to full production capacity. This decision was based on several factors, including the expense, difficulty, and time involved in transferring technology to outside manufacturers. (250) The impetus for this change was the recognition after the 9/11 attacks that having the ability to fast-track vaccine production might be necessary to mitigate bioterrorism threats, and that industry partnerships simply could not respond quickly enough to an evolving bioterrorism situation. Following the NIH’s lead or working with them to utilize their facility might be a highly effective way for the military to adopt a vaccine production mission. While funding for such a significant undertaking would undoubtedly be hard to come by initially, we should not forget that the U.S. government is one of the world’s largest contributors to global health initiatives of all kinds. In fact, in early 2015, the government announced its plans to contribute $1 billion to GAVI, the Vaccine Alliance, over the next four years. (251) This very money will likely come back, indirectly, to support projects and products developed by the U.S. government (via the NIH) or the U.S. military. If $1 billion in funds are available to support nonprofits that work for vaccine access, it seems that funds could be found to develop a government facility for producing vaccines that could be provided, at cost, here and abroad.
This paper has mentioned three potential approaches to improving military partner access: more diverse and intentional partnerships, open licensing of technology to low-income partners, and expanding the military’s production role. We will now examine open-licensing more thoroughly, which is an approach that has never been used by the military and which would represent the most fundamental philosophical change in the approach to vaccine research. We will conclude with a brief review of several of the military’s highest profile, ongoing vaccine projects—Ebola, HIV and Dengue. These serve as a reminder of the importance of the projects the military contributes to.

The Open Licensing Movement

Although its research efforts have obvious implications for global health, the Department of Defense does not currently abide by provisions for generic production or tiered pricing in the licensing of vaccines or drugs developed in its laboratories. In fact, although such policies are relatively new for research institutions in general, gaining momentum primarily in the past decade, the idea of the government maintaining control of the technologies it funded is not entirely new. Prior to 1980, federally funded research patents were maintained by the government; in that year, with the passage of the Bayh-Dole Act, companies gained the ability to exclusively license technology, increasing their inventive to develop and produce these technologies. (252) At the time, the Bayh-Dole addressed an important problem of low technology uptake by industry; however, one could argue that the pendulum has now swung in the opposite direction, with industry exerting inordinate control over technology at the expense of access and to the detriment public health interests in certain cases. The open-licensing movement might be seen as a backlash to this pendulum swing.

In late 2009, seven institutions signed a Statement of Principles and Strategies for the Equitable Dissemination of Medical Technologies. This agreement, which has since gained an additional 19 signatories (including the National Institutes of Health and the Centers for Disease Control), articulates a basic set of principles surrounding the concept of global access to technology, namely that member organizations “are committed to implementing effective technology transfer strategies that promote the availability of health-related technologies in developing countries for essential medical care.” The document not only focuses on ensuring that signatories seriously
consider the opportunity to promote global generic rights that is presented during the licensing process, but also encourages organizations to make a concerted effort to conduct research into neglected and under-researched diseases. (253) In the latter area, the military is already a leader; in the former, we believe that it could quickly become one.

The open-licensing movement that culminated in the 2009 Statement of Principles started as a result of the frustration of scientists with the failure of their work to reach the people who needed it most; in that case, difficulty in the humanitarian organization Médecins Sans Frontières (MSF)/Doctors Without Borders’ efforts to expand antiretroviral treatment for HIV in Sub-Saharan Africa. Stavudine, an early and much-prescribed antiretroviral drug, was originally developed and patented by Yale University, then licensed to Bristol-Meyers Squibb. In 2001, MSF approached Yale University seeking rights to develop generic stavudine for use in South Africa, where at the time over 10% of the entire national population and 25% of pregnant women were infected with HIV. (254, 255) When William Prusoff, co-inventor of stavudine, learned about the availability issues surrounding his drug he wrote in a New York Times editorial:

I once helped create a drug that could enable millions of people to lead better and longer lives. At Yale University's pharmacology laboratory, my late colleague Dr. Tai-shun Lin and I developed d4T, an antiretroviral drug that now forms part of a 'cocktail' used by people with H.I.V. and AIDS. The patent was held by Yale, which licensed it to Bristol-Myers Squibb for development. At great expense, Bristol-Myers took d4T through the necessary trials, then brought the drug to market under the name Zerit. More recently, it became apparent that the drug Dr. Lin and I had developed was not reaching millions of desperately suffering people because they lacked the money to purchase it (256)

Researchers and students pushed Yale University to use its power as the stavudine patent holder to pressure Bristol-Meyers to allow the drug to be made more available in developing nations. Almost immediately, the company reduced the drug's price from $2.23 per daily dose to $0.15, a 93% decrease, and removed restrictions on generic versions in developing countries. (257) This series of events also resulted in the development of Universities Allied for Essential Medicines
(UAEM), an international student organization focused on promoting global access to medicines as a way of advancing public health. Since 2001, UAEM has brought attention to issues surrounding drug access, and has forced universities around the country to examine how the medical technology developed in their laboratories is cost prohibitive for many patients. Because of UAEM's activism, many universities, academic medical centers, and other research organizations, including both the National Institutes of Health and the Centers for Disease Control, have promised to partner with pharmaceutical companies on drug development in a way that will allow for essential technologies to be available in developing nations and to work according to the principles espoused in the Statement of Principles and Strategies.

**Open Licensing and the Military – A Way Forward?**

The U.S. military stands in a unique position to promote global health and the interests of the government by considering participation in the open-licensing movement. Unlike many universities, the military conducts focused research into a variety of infectious diseases—many of them so-called “neglected diseases”—with the intent of producing a vaccine or treatment that will ultimately support military readiness by promoting the health and wellbeing of service members. They also share a common motivation with the greater U.S. government to promote global health for the purposes of national security and defense, and since 2001 this has been an area of particular focus. From funding priorities to repeated mention in the official National Security Strategy, public health is now and is likely to remain an important consideration for American policy makers. (258) Finally, the military and government devote vast resources to biomedical research, drug and vaccine production and purchase, and contributions to global health, many of which are redundant. A commitment to open-licensing might have the power to reduce costs not only for patients in developing countries, but also for American taxpayers, who fund government efforts in research and public health.

Like the NIH and CDC, the DOD is funded by federal money, and has thus invested taxpayer dollars into the initial discovery, development, and often clinical trials of various vaccines and drugs before licensing them to corporations. These corporations, which may fund the culmination of research efforts—in the case of military research, they often complete clinical trials, secure FDA approval, then manufacture a product—do contribute substantially to the
development of a drug, but also receive countless millions in free research from government labs and scientists. Additionally, since 1981 the Research and Experimentation Tax Credit has provided pharmaceutical companies the ability to receive up to a 20% tax credit for the resources that they spend on the development of drugs or vaccines. (259) In these ways, the federal government can pay for a substantial portion of the research a private corporation needs to bring a drug or vaccine to market, and this represents a major investment by the taxpayer (who, through direct payment or insurance premiums, will often be a consumer of the same products they have helped to fund). Since licensing of military technology to private corporations is usually conducted to ensure that a drug or vaccine is manufactured for military use, the government often ends up being the direct purchaser of the drugs it has helped to develop. Indirectly, the government also pays corporations for drugs it helped to develop when it funds other organizations that buy drugs for the developing world. In 2013, the U.S. government gave $227,421,000 to UNICEF; UNICEF has traditionally been the largest purchaser of vaccines in the world, spending $493,000,000 in 2006. (260, 261) USAID gave $78,000,000 to the Global Alliance for Vaccines and Immunizations (GAVI) in 2010. That same year GAVI spent $506,000,000 on new and underused vaccine programs. In addition, in 2015 the U.S. owed $66,486,090 to the Pan American Health Organization and in 2010 gave over $400,000,000 to the World Health Organization. (262, 263) And, as previously mentioned, the U.S. recently committed $1 billion to GAVI. This results in the U.S. Government paying multiple times for the vaccines that its scientists and funding have helped to develop.

To complete the illustration, we will return to the case of malaria, on which the military and GSK have partnered for over 25 years with the intent of developing a vaccine. Based in large part on the substantial funding provided by MVI, GlaxoSmithKline recently announced that it will not seek to make a profit off any sales of the RTS,S malaria vaccine. Instead, it plans to sell the vaccines at a price that will allow it to cover the $300 million that it cites as its costs in developing the vaccine, plus 5% overage that it intends to reinvest into additional research projects. (239) This situation provides an excellent example of how a non-profit and pharmaceutical company can work together on a goal of critical importance to global health, and it also demonstrates the close alignment of military research interests and global health. However, care should always be taken when relying on a private corporation to sell a product “at
cost,” particularly when there is no oversight authority to confirm the cost calculation, when “at cost” sale of a malaria vaccine makes for excellent free publicity, and when comparative profit expectations for many other drugs are so incredibly high as to make reduced profit seem like generosity. Additionally, it is far from clear whether GSK's cost calculation includes administrative costs and overhead, or whether tax benefits associated with research are deducted from the cost calculation. As Oxfam and MSF noted in a recent report on vaccine access:

“in exchange [for $200 million in funding from MVI], GSK has agreed to an undisclosed set of volume-dependent price ceilings. It is difficult to know if these prices are substantially different from the prices GSK would have asked if it had developed the vaccine without help from MVI,” and that “MVI's role in the development of RTS,S has been primarily to subsidize clinical development by GSK. Although it is impossible to know for sure what path the vaccine would have taken without this subsidy, it is likely that development would have been abandoned or greatly slowed: GSK had apparently terminated work on RTS,S until MVI began to share costs.” (264)

Perhaps more interestingly, it has been noted that much of the difficulty of establishing a malaria vaccine, and presumably much associated funding, came from the challenge of developing and testing an adjuvant for the vaccine. This is technology that could theoretically be used by GSK in the development of a future HIV vaccine, for which there would undoubtedly be a significant profit margin. (265)

While it is important to acknowledge that GSK has made great steps towards improving access to their drugs and vaccines, it should also be recognized that corporations must always consider self-interest and profit in their decisions; moreover, a corporate decision to support greater access to its products is frequently a move motivated by outside pressure, and exploited for positive publicity. Open licensing, in contrast, would provide a much greater guarantee of competitive pricing in developing countries. On this topic, the U.S. State Department has reported to Congress that “[I]n every case generics prices present an opportunity for cost savings; in some cases, the branded price per pack of a drug is up to 11 times the cost of the approved generic
version,” and that “since sales of the patented, brand-name versions of such medicines are minimal or non-existent in many impoverished regions of the world, allowing generic versions of those medicines will have minimal impact on the sales of brand-name, patented versions in such regions, or the licensing revenues of publicly funded research institutions, while saving an untold number of lives.” (266)

Some might argue that committing to open licensing will only add to what is sometimes a difficult task for the military—finding a private licensing partner to manufacture necessary drugs and vaccines for military use. As has already been demonstrated, a number of military vaccines have fallen out of production because of concerns about cost-effectiveness and profit on the part of a private manufacturer, and in the case of the RTS,S vaccine, substantial philanthropic funding was necessary to entice a private company to continue research and development. If such intervention is necessary for a disease that kills some 800,000 people per year, it is easy to see why diseases that are much more limited in their impact might present an even greater challenge. (233) Nonetheless, the model of RTS,S malaria vaccine development provides a powerful possibility for other diseases—the potential for collaboration between the military, private corporations, and humanitarian or philanthropic organizations. By seeking out partners that might share the military's interest in certain infectious diseases because of global health applications, the military could gain additional support, and potentially funding, that could be used to find a manufacturer to develop and produce a drug or vaccine. By publicizing its commitment to open-licensing, the military would not only promote its status as a leader both in infectious disease research and in equality of access, it may gain new partners interested in accessing the same drugs and vaccines the military seeks for its own use.
Conclusions

Vaccines have changed the way we think about infectious diseases—in many cases, they have completely removed our fear of diseases that were once scourges. Several case studies have shown us how infectious diseases have come to the attention of the military, how military research contributed to understanding them and to developing vaccines for them, and what effect this work has had subsequently. These cases have also shown how inconsistently the military’s partners have benefited from their support of our research. The examples thusfar have focused primarily on stories that are complete; this diminishes that fact that major projects are still underway, and the policy critiques and recommendations made in the previous chapter could still have very real implications for diseases affecting millions of people, most of them outside the military and the United States.

Present Research

Briefly, we will now examine the ongoing vaccine projects in the military in order to help gain perspective on the magnitude of the threat from infectious diseases and reflect on how our understanding of public health might change with the completion of these vaccines. Although many of these diseases do not touch the lives of the average American on a daily basis, they nonetheless have a remarkable effect on the lives of billions of people worldwide. The military’s ongoing projects are also a reminder of how significant the issue of public access to publicly developed medical technology remains.

HIV

In 1986, recognizing the potential impact of HIV-1 on military readiness and national security, Congress directed the creation of the organization now known as the U.S Military HIV Research Program with the goal of conducting research on the newly discovered virus. From its beginnings at the Walter Reed Army Institute of Research (WRAIR), the program now works from six countries. In the mid-2000s, the program gained publicity for its work on the RV-144 HIV-1 vaccine, a vaccine that is primarily the result of military research. Conducted in Thailand, trials on 16,000 human volunteers found that vaccination conferred a modest protective effect against HIV-1 infection, the first accomplishment of its kind in HIV research. (267, 268)
results of this trial were announced in 2009 and since then, additional trials have been carried out to investigate RV-144. There are also several other vaccine candidates in various stages of testing.

Dengue

The military is a collaborator in the Pediatric Dengue Vaccine Initiative, a continuation of decades of military research and development into Dengue fever vaccination that has resulted in a number of vaccine trials and collaboration with the pharmaceutical industry. (269, 270) Dengue appeared in the Caribbean in 1963 with a major outbreak in Puerto Rico; prior to that, the last outbreak had occurred during the Second World War. Six years later after the Puerto Rico outbreak, the Caribbean experienced another major outbreak. The spread of dengue into this hemisphere raised red flags in the public health community. Rates of dengue and hemorrhagic fever in Central America rose rapidly through the 1990s and 2000s. Texas had its first case in 1980, and experienced an epidemic in 2005. Florida began to report cases in the last 2000s. Outbreaks were simultaneously increasing in frequency in Asia. (164, 271) Given the geographic range of the aedes aegypti mosquito and hence dengue endemicity, the U.S. military has had extensive experience with the disease during foreign deployments in the Philippines, World War II and Vietnam. More recently, smaller American operations in Somalia and Haiti have resulted in small numbers of hospitalized troops, and Special Operations members, many of whom are deployed to Central and South America and Asia, show a sero-prevalence rate of approximately 10%. (271)

Through a partnership established in 1994 with researchers at several American universities and Thai research institutes, researchers at AFRIMS contributed significantly to research on the pathogenesis of dengue. (41) AFRMIS also worked on research into the epidemiology of dengue. (179) Military research institutes are involved in development of at least three vaccines against dengue, including one that is a collaboration with GSK and completed Phase II clinical trials in 2010. (272) That vaccine was subsequently modified and is currently undergoing Phase I trials. A vaccine by Sanofi-Pasteur may be the first to complete Phase III trials and enter the marketplace, although it has limited efficacy (topping out at 60%), so there remains significant room for a next generation vaccine to take its place. (273)
Ebola

The recent West Africa Ebola outbreak has also drawn attention to a major area of military research, Ebola, which is one of a number of emerging or reemerging infectious diseases of interest to the military. Since 1976, when the first cases of Ebola were reported, the military began research into the virus and possible treatment options. Although the military has never experienced a case, since 2001 in particular Ebola has been recognized as a potential bioterrorism threat, and in 2014, the U.S. Army made a large deployment of troops to help fight the West Africa Ebola outbreak, heightening the sense that a protective vaccine is necessary for the military in war and peace. The current outbreak has also sped along the research process, and there are now two vaccines undergoing clinical trials, both of which were developed through collaborative efforts including USAMRIID scientists. There are also a number of experimental drugs in various stages of progress, many of which have been developed with military support, either financial support to biotech companies or within military labs.

The ChAd3 (GSK/NIAID) Ebola vaccine was developed by NIAID scientists in collaboration with USAMRIID and industry and received significant media attention in August 2014 as it became the first Ebola vaccine to enter clinical trials. Early results were released in November and show that it is safe and well-tolerated by recipients and that it did instigate an immune response. An additional trial was also conducted in Europe, and simultaneously GSK produced an additional 10,000 additional vaccine doses for future trials in Africa. This trial was tentatively planned for Mali and the Gambia owing to established infrastructure in those countries, but as of late January 2015, GSK had shipped these additional doses of its vaccine to Liberia in hopes of starting a 30,000 person clinical trial in the setting of the ongoing Ebola outbreak in that country. (49, 274-276)

The rVSV vaccine followed the GSK/NIAID vaccine into clinical trials at the Walter Reed Army Institute of Research in fall 2014. The technology behind the vaccine was originally developed by the Canadian government, and in 2010 it was licensed to an American biotech firm with the intent of modifying the vaccine for human use. The company, BioProduction Systems, has worked in conjunction with and has received financial support from the Department of Defense.
The phase I clinical trial, which began in October 2014, was conducted at WRAIR. (277) Although movement towards trials has been swift, there have been some contentions that it has not been swift enough, and many have blamed disputes over intellectual property rights and hitches in the collaboration between the various players participating. One WHO expert did suggest that the speed with which the GSK-NIAID vaccine was able to enter trials was “due to the fact that the partnership behind [the GSK vaccine] is more experienced.” (278)

The military has had a part in a vaccine called VesiculoVax and a number of Ebola drugs as well. TKM-Ebola, an experimental Ebola drug that was developed through a collaboration between USAMRIID, Boston University and Vancouver-based biotechnology firm Tekmira, is currently undergoing Phase I clinical trials. (279) Zmapp, which was famously used to treat several American patients with Ebola, is intended to grant patients passive immunity to Ebola through a combination of three antibodies, one of which was developed at USAMRIID. The biotech firm developing the drug, Mapp Pharmaceuticals, is supported by a 3 year, $10 million contract with the DOD. (280)

**Looking Ahead – Future Research and an HIV Vaccine**

Colonel Samuel Martin, commander of the U.S. Army Medical Research Unit in Kenya, presented a realistic picture of how military leaders and researchers view their work when he said:

> We are as interested in these diseases as the local people and institutions with which we partner. For us, these diseases are a threat to our deployed military; for our partners, they cause major public health problems. We need our partners as much as they need us: You can’t do that final step of testing the efficacy of new drugs, new vaccines, unless you are somewhere where the disease occurs at a high-enough prevalence. We are not an aid agency. We’re here because we need those products…Discoveries we make go a long way toward helping Kenyans and civilian populations in many places. (281)

As this quote makes clear, the DOD's first focus in any endeavor is military readiness, and research to support the health of troops is no exception. This focus may sometimes come at the
expense of focus on the question of how military research and technology might be best employed to assist partner nations and international communities, although Colonel Martin also makes it clear that these partners are essential to the research and development progress. Their access should therefore not be an afterthought given the resources and focus the U.S. government spends on public health and stability. Consideration of access to military-developed products need not be more difficult than a reexamination of the technology licensing process, and adopting one of the several approaches, some of which have already proven effective for past vaccines—collaboration with nonprofits or foreign producers, adoption of open-licensing principles, or even expanding to take on a production role, which would benefit the military, the nation, and our foreign partners.

While the DOD's main focus is and should be the national security of the country and the protection of its soldiers from disease, it falls short of being a leader in the greater medical community and of protecting national interests when it ignores how its technology is used after licensing. It also limits its ability to meet its own medical needs by failing to recognize potential partners outside of industry, and failing to see linkages between its interests and the interests of the remainder of the U.S. government. Moreover, if it appreciates the significant of these points but fails to put concrete policy measures and procedures into place, access for the neediest populations still cannot be ensured. Relying on the goodwill of private corporations to ensure that licensed drugs and vaccines are made available is simply not good policy. While it appears that, in the case of malaria, a vaccine will be sold at a reasonable cost due largely to the efforts of MVI, there is no guarantee that this will be the case in the future. If the military contributes to developing a vaccine for HIV-1—a vaccine that would undoubtedly garner large profits in the developed world—but does not defend generic competition in low and middle-income countries during any ensuing licensing process, millions of people stand to lose an incredible opportunity to protect their health. Likewise, the military will have lost a valuable and unique opportunity to build ties with humanitarian organizations, allied governments, and to promote national security. As former Chairman of the Joint Chiefs of Staff and Secretary of State Colin Powell stated in 2002:
AIDS is not just a compelling moral issue, it is not just a humanitarian issue; it is far more than just a health issue. It is a security issue. It is a destroyer of nations. It is a destroyer of societies. It has the potential to destabilize regions, perhaps even entire continents. It can tear social fabric apart within any nation. It can rob young democracies of citizens they need to build freer, better futures for themselves and for their children. HIV/AIDS is an economic issue, leaving nations without human resources to grow and develop, ultimately sapping global well-being. (282)

The same is true for most of the diseases the military has contributed its money, manpower, and innovative spirit to. Security, international relations, and health are all intimately intertwined, and the military, through its impressive history of medical research, has already acknowledged this. It need only recognize its power not just to innovate in research, but also its power to provide innovative medicines to its allies around the world.
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