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THE DANGEROUS DECLINE IN THE UNITED STATES MILITARY'S INFECTIOUS DISEASE VACCINE PROGRAM

by

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BIOGRAPHY

Colonel Hall is currently a student at the Air War College, Maxwell Air Force Base, Alabama. Prior to the College, he served as the Commander of the 27th Special Operations Medical Group, Cannon Air Force Base, New Mexico. He has supported numerous combat operations including Operations IRAQI FREEDOM (OIF), ENDURING FREEDOM (OEF) and DESERT STORM. His other military positions include Deputy Command Surgeon and Command Public Health Officer at Headquarters Air Combat Command, Aerospace Medicine Squadron Commander, Command Public Health Officer and Health Promotion Director at Headquarters United States Air Forces in Europe, Chief of Public Health and Prevention at the Air National Guard Readiness Center, Medical Inspector at the Air Force Inspection Agency and base public health officer at stateside and overseas installations. Colonel Hall holds a bachelor's degree in biology from Virginia Tech, a doctorate in veterinary medicine from Auburn University and a master's in public health from Harvard University. He is a chief biomedical sciences corps officer and is board certified in veterinary preventive medicine.

Introduction

For over 230 years, vaccines advanced by the United States (US) military research and development (R&D) community have dramatically reduced the impact of naturally-acquired infections not only on America's armed forces but society at large. In recent years, however, the military's infectious disease vaccine program has lost considerable emphasis, funding and mission capability. With the burgeoning concern for weaponized bio-agents in Iraq and North Korea in the 1990s, Congress turned its attention to combating biological threats of deliberate origin over those of natural causes. The Department of Defense (DOD) responded by partitioning its biodefense and infectious disease vaccine acquisition programs, with biodefense vaccines holding a higher acquisition priority and receiving more robust funding than infectious disease vaccines. The result has been a significant erosion of the DOD's ability to ensure the acquisition and availability[i] of the right vaccines at the right time to optimally protect US forces from established and emerging natural infections now and in the future.

This paper will argue that the DOD needs to take swift actions to revitalize its infectious disease vaccine program and enhance the synergy between biodefense and infectious disease activities in order to resolve vaccine acquisition and availability shortfalls. Specifically, the DOD must: collectively assess and prioritize all biological threats, whether natural, accidental or deliberate in nature;[1] consolidate redundant vaccine acquisition activities; elevate the priority of infectious disease vaccines; and provide ample resources to sustain a robust vaccine acquisition capability to protect US military forces against validated and prioritized biological threats.

In presenting the argument, this paper will first make a case for why vaccines against natural infectious diseases, developed under US military R&D leadership, must remain a vital

[i] In this paper, *acquisition* is defined as DOD's process for ensuring vaccines are acquired and maintained for the protection of its forces, from needs identification, prioritization and basic research to advanced development, testing, production and procurement. *Availability* is having on hand the right vaccine for the right threat at the right time.

force health protection (FHP) imperative for safeguarding the warfighter and optimizing US military mission effectiveness. It will establish the historical impact of naturally-occurring infectious diseases on military operations, the criticality of FHP in defending the human weapon system and the superiority of vaccines among medical countermeasures. An analysis of the factors hindering infectious disease vaccine acquisition will follow, including unbalanced threat assessment and mission focus, ineffective organization, insufficient funding and inferior priority status. Finally, recommendations are advanced for enhancing FHP vaccine acquisition and availability that will posture the DOD, and America's military forces, for 21st Century national security success.

Why DOD-Led Vaccines Against Naturally-Acquired Infections Are Vital

Throughout America's wars, naturally-acquired infectious diseases--many vaccine-preventable--have eclipsed bombs and bullets as the culprits of morbidity, mortality, disability and mission degradation. This section investigates the criticality of infectious disease vaccines in protecting force health, and why US military R&D leadership is inimitably vital to their development.

Historical Impact of Infectious Diseases on US Military Readiness and Effectiveness

"Should the disorder infect the Army, in the natural way ... we should have more to dread from it than from the sword of the enemy."[2] These were the sentiments of General George Washington as thousands of troops fell ill--and hundreds died--from smallpox during the first 2 years of the American Revolution, resulting in campaign losses, poor morale and sparse

recruiting. Via inoculation,[ii] the Continental Army dramatically reduced smallpox mortality from 160 to 3.3 per 1,000 cases, all but eliminating the threat. The US Civil War saw twice as many deaths from disease (65 per 1,000) as from battle (33 per 1,000).[3] Of the 6 million all-disease cases among 2.8 million enlistees on both sides, over 95,000 died and roughly 250,000 were discharged for disability.[4] Typhoid fever, malaria and yellow fever accounted for 80 percent of US military deaths in the Spanish-American War, forcing a rapid withdrawal from Cuba soon after the end of hostilities.[5] While World War I saw--for the first time--parity between US deaths from battle (50,510) and disease (51,477), the latter's impact on combat operations was demoralizing.[6] Various diseases accounted for 95 percent of American battlefield admissions in World War II, 69 percent in Vietnam,[7] 71 percent in the Gulf War[8] and over 95 percent in Somalia.[9] Unchecked, natural infections can wreak havoc on military forces.[10]

Criticality of Force Health Protection in Defending the Human Weapon System

The DOD's FHP doctrine characterizes every service member as a human weapon system[11] requiring total life cycle support and health maintenance.[12,13] As the central element of military power, protecting the human weapon system is pivotal. Absent "craniums at the controls," "boots on the ground" and "hands on deck," wars cannot be won. Strained budgets, emerging technologies and evolving threats have pressed the US to transform its military to a lighter, leaner and more agile force. Fewer people performing more specialized roles mark the critical need for each military member to remain healthy, fit and effective. Such is the challenge, as DOD personnel are often placed in austere locations, on short notice and under stressful conditions, where naturally-acquired infectious threats are abundant, immune systems are naive

[ii] Specifically, this was *variolation*, an obsolete process of inoculating a susceptible person with material taken from a vesicle of a person who has smallpox. (http://wordnetweb.princeton.edu/perl/webwn?s=variolation).

and healthcare support is limited. A vital part of FHP,[14] immunization is effective in mitigating these operational hurdles.

Superiority of Immunization Among Medical Countermeasures

In defeating health threats, primary prevention--action prior to exposure--reigns supreme. Immunization affords the lowest risk, highest efficacy and most cost-effective protection to vaccine recipients. Immunization is superior to therapeutics (e.g., antibiotics and chemo-prophylactics) and personal protection (e.g., repellents and bed nets) since it does not require knowledge of exposure, it is not contingent upon an accurate and timely diagnosis, it protects against severe diseases (e.g., rabies) and those for which a treatment is unavailable, ineffective or side-effects prone, it does not require individual compliance (e.g., antimalarials), and it neither contributes to nor is fazed by microbial resistance. As well, immunization can notably reduce the medical logistical footprint in theater since for every casualty, five personnel are required in the evacuation and treatment support chain.[15] Furthermore, vaccines not only elicit a direct benefit to recipients, they afford herd immunity to those in the communities with whom they live and work.[16] Finally, despite perceived differences between weaponized and natural pathogens, "vaccines are a unifying technology proven to effectively and efficiently defeat both of these threats."[17]

The Case for US Military Infectious Disease Vaccine R&D Leadership

Fielding a licensed vaccine is a long, complex and high-risk endeavor. It requires the synergy of expertise and resources from multiple partners spanning government, industry, academia, nonprofits and international organizations.[18] Cooperation is essential to manage the substantial scientific and financial risks. In general, no partner is capable of developing and producing a vaccine countermeasure alone. The DOD, for instance, must rely on industry for

scale-up production,[19] just as industry relies on the DOD to bring its many unique R&D capabilities to the cooperative effort.

First is the DOD's unique experience. More than half of the routine vaccines given to service members today were co-developed by the US military.[20] Beyond protection of its own forces, military advances also created solutions to diseases of dire importance to national and international public health. Of 15 adult vaccines licensed in the US since 1962,[iii] the DOD played a significant role in developing eight.[21] Currently used worldwide, these include vaccines for influenza, meningococcal disease, hepatitis A, hepatitis B, rubella, adenovirus, typhoid and Japanese encephalitis.[22] In addition, development of licensed vaccines for yellow fever, mumps, measles, varicella and oral polio was supervised by investigators who began their careers at US military R&D centers.[23] In the high-risk business of vaccine production, experience breeds proficiency and efficiency, and curbs scientific, regulatory and financial risk that can stifle product development.

Second is the DOD's unique facilities. Walter Reed Army Institute of Research (WRAIR) is currently home to one of the nation's three pilot facilities dedicated to the production of a variety of investigational vaccines for use in clinical trials.[24] Industry actively seeks WRAIR's in-house laboratory capabilities to conduct animal modeling studies.

Third is the DOD's unique intellectual property (IP) sharing.[iv] Highly sought after by industry,[25] companies are drawn to DOD partnerships when they are allowed to retain IP rights for use in lucrative civilian markets.[26]

[iii] In 1962, the Federal Food, Drug and Cosmetic Act was amended to require manufacturers to prove the efficacy and safety of their drugs (including vaccines) prior to FDA approval. (http://vm.cfsan.fda.gov/~lrd/histor1b.html).
[iv] Intellectual Property (IP) is the group of legal rights to things people create or invent. IP rights typically include patent, copyright, trademark and trade secret rights. (http://www.sitepoint.com/glossary.php).

Fourth is the DOD's unique R&D networks.[27] Because the Food and Drug Administration (FDA) requires pivotal clinical trials[v] of products in people living in areas endemic for infectious diseases, the DOD's overseas laboratories[vi] serve as bases for conducting clinical trials that attract industry partnerships. Due to its enduring presence, strong host-nation relationships and professional development of host-nation scientists, the DOD has been able to successfully execute complex clinical trials with industry and international partners.[28]

Fifth, and most importantly, is the DOD's focus on the often unique needs of the warfighter. This mission distinguishes its infectious disease activities from other organizations conducting what may appear to be similar R&D. The global effort to develop antimalarial countermeasures provides one example. Outside of the DOD, this effort is focused on drug therapies to attenuate lethal disease in children and pregnant women in under-developed countries. The goal of the DOD's program, on the other hand, is to prevent the warfighter from ever contracting the debilitating illness in the first place. To that end, DOD research has focused on developing prophylactic drugs and, more recently, a malaria vaccine solution. Additionally, in order to use any drug or vaccine to protect US warfighters, it must be FDA licensed. Because many companies are reluctant to independently take on this costly risk, the DOD's R&D community plays a key role in moving potential militarily-relevant products through early development, FDA licensure and eventual use by the US military.[29]

Also compelling is the potential impact of infectious disease vaccines on the military's increasing role in stability operations, which the DOD recently designated as "a core US military mission that [it] should be prepared to conduct with proficiency equivalent to combat operations."[30] Infectious diseases contribute significantly to social unrest and conflict in these

[v] A pivotal clinical trial must: be controlled; have a double-blinded design when practical and ethical; be randomized; and be of adequate size. (http://www.adisinsight.com/aClientServiceinfo/CTI%20Appendix.pdf).
[vi] DOD overseas labs are located in Thailand, Peru, Kenya, Egypt and Indonesia. (Email communication, Hoke).

scenarios. Infections not only ravage the local civilian populous, they can decimate the strength of their national militaries. The prevalence of human immunodeficiency virus (HIV) infection and Acquired Immune Deficiency Syndrome (AIDS) in Africa provides a persuasive example. Of 33 million people living with HIV worldwide, two-thirds reside in sub-Saharan Africa.[31] Armed forces in this region experience HIV infection rates two to three times those of the civilian population, further eroding local, national and regional prospects for stability.[32] The significance of this US national security concern is well summarized in the following excerpt from a 2002 report by the Center for Strategic and International Studies:

> In Africa, HIV/AIDS is spreading fastest in the Horn of Africa, where the US already has deep concerns about lawlessness and extremism. In both Ethiopia and Kenya, potentially important regional hubs in the violent and volatile East African sub-region, adult HIV-prevalence rates are over 10 percent. Nigeria, an essential guarantor of security and economic growth in the West African region, has more than 3 million citizens living with HIV or AIDS. The adult prevalence rate in South Africa, which plays a similar economic and security role in the southern African region, is 20 percent. If these two regional hegemons cannot send peacekeepers, contribute to growth and stability, or guarantee their own internal stability, US security interests in the continent ... are severely threatened.[33]

This situation demonstrates the powerful potential impact that vaccines for endemic diseases could have on geopolitical stability.[34] An effective HIV vaccine could remarkably strengthen foreign militaries, secure vulnerable families and communities, bolster international public health and reinforce US national security.[vii]

Natural infections will continue to challenge the US military and its R&D community. With 1,500 known human pathogens continuously lurking and novel agents like H1N1 (swine flu) constantly emerging,[35] infectious diseases will remain a formidable national security threat

[vii] In June 2009, a US Army-led Phase III community-based trial of a candidate HIV vaccine was completed, yielding encouraging preliminary results but requiring further research. (Email communication, Hoke).

indefinitely.[36] The expeditionary nature of military missions, the effects of climate change[viii] and the interconnectedness of an increasingly globalized planet accentuate the risks. Worldwide, 14.7 million people die each year from known and preventable contagions.[37,38,ix] Even in industrialized nations, 46 percent of all deaths result from infectious causes.[39] Emerging infections have been discovered at the rate of one per year since the late 1980s.[40] Pathogens adapt, persist and emerge; this pattern will continue.[41]

Keeping pace with the evolving threat requires a robust US military infectious disease vaccine program with the venerable experience, proven track record and unique attributes that no other agency can bring to bear--one that can continually improve upon its unparalleled protection of America's warriors, and in the process, her citizens and global neighbors.

The DOD's Unbalanced Biological Threat Assessment and Mission Focus

Since the Cold War's end, the DOD has become fixated on combating biological threats of deliberate origin over those of natural causes. This section examines the DOD's lopsided focus on notional bio-weapons while natural infections continue to plague military operations.

Weaponized Pathogens: A Matter of National Insecurity

Despite its remarkable history, the US military infectious disease vaccine program has taken a back seat to countering the bio-terrorism threat since the mid-1990s. Beginning with its standup of the Joint Program Office for Biological Defense in 1993 and formalized requirements for biodefense vaccines in 1995,[42] the DOD--with a push from Congress--justifiably turned a focused eye to biodefense. By 1998, it had established the Joint Vaccine Acquisition Program (JVAP) and significantly raised funding for advanced biodefense vaccine development,[43] while

[viii] Arguably, climate change is resulting in significant changes in weather patterns and disruption in ecosystems leading to emergence of new niches for infectious disease pathogens and vectors. (Email communication, Lynch).
[ix] The top five infectious disease killers include HIV/AIDS, pneumonia, diarrhea, malaria and tuberculosis. (WHO).

core funding for infectious disease vaccine R&D declined.[44,x] Since the post-"9/11" anthrax letters, fears of state-sponsored weapons of mass destruction proliferation by Iraq and the express interest in bio-agents by al-Qaeda,[45] the nation perceived an urgent vulnerability to biological attack.[46] The DOD responded with wholesale investments in biodefense as infectious disease R&D funding remained level.[47]

Reportedly, about a dozen states and multiple non-state actors possess or are pursuing biological weapons.[48,49] Their potential use clearly poses a level of danger to US forces in the contemporary battle space, as do established and emerging natural infections. To date, the DOD has yet to incur a single case of weaponized disease while some 3,400 cases of natural-origin and vaccine-preventable infectious diseases were reported in deployed US forces since 1998.[50] While the potential threat is duly noted, bio-terrorism against US interests has been limited to 22 American citizens sickened by anthrax-tainted letters in 2001, of whom five tragically died. Allegedly, this may have been the work of a lone American researcher, with no association to either state sponsors or non-state actors.[51]

In contrast, by 2008 West Nile virus had sickened 28,961 Americans--claiming 1,131 lives--since its arrival on US soil in 1999.[52] The emergence of Severe Acute Respiratory Syndrome in 2003, H5N1 (bird flu) in 2006 and H1N1 in 2009 further underscore the clear and present danger posed by natural infectious diseases. As well, to some experts, the emergence of a novel strain of adenovirus among military recruits in 2007[xi] served to "remind us that we are at least equally likely ... to soon experience large-scale morbidity through epidemics of emergent pathogens as we are to experience a biological weapons attack."[53,54]

[x] Compares 1997 and 1999 MIDRP funding. (Email communication, Kuppers).
[xi] In 2007, 23 trainees at Lackland Air Force Base, hospitalized for pneumonia, were found to be infected with a variant strain (type 14) of adenovirus; one of the trainees died. (Adalja, "Adenovirus 14: An Emerging Threat").

Although it is undoubtedly a national security imperative for the US to prepare its public and military against the intentional use of biological agents, vigilance for natural infections warrants at least the same level of emphasis.

Natural Pathogens: An Operational Reality Check

All the while, natural-origin infectious diseases continued to pose real challenges to US military commanders in lost person-days, reduced effectiveness, increased medical visits and frequent medical evacuations.[55] In one tri-service study, of 15,459 Operation IRAQI FREEDOM (OIF) and Operation ENDURING FREEDOM (OEF) deployers surveyed, 75 percent reported having at least one bout of diarrhea,[xii] 69 percent suffered one or more episodes of acute respiratory illness[xiii] and "one-quarter believed that combat unit effectiveness had been negatively affected by these common illnesses."[56] Roughly 13 percent of ground forces missed at least one patrol, 12 percent of air forces were grounded, 25 percent required intravenous fluids and over 10 percent were hospitalized.[57] In addition, Table 1 summarizes the incidence of the four leading--and potentially vaccine preventable--infectious diseases in deployed US forces between 1998 and 2009.[58] Of 3,386 total cases, leishmaniasis, malaria and Lyme disease

Table 1. Summary of the major potentially vaccine-preventable infectious diseases incurred by deployed US military forces, 1998-2009.

	Leishmaniasis	Malaria	Lyme Disease	Meningococcal Disease
Active	771	990	551	106
Reserve	420	68	445	20
TOTAL	1,191	1,058	996	126

accounted for 95.8 percent of the disease burden. Through 2004, leishmaniasis prompted 4.4 percent of the monthly medical evacuations during OIF.[59] The occurrence of 126 cases of meningococcal disease reflects the absence of an effective vaccine for subtype B of this

[xii] *Campylobacter*, *Shigella*, *Escherichia coli* and Norovirus have been the most commonly reported diarrheal infections in deployed forces. (Defense Medical Surveillance System).
[xiii] Rhinovirus, Coronovirus, Parainfluenza virus and Adenovirus have been the most commonly reported causes of acute respiratory infections in deployed forces. (Defense Medical Surveillance System).

potentially lethal pathogen. Each of these operational experiences emphasizes the current threat from naturally-acquired pathogens, and urges continued development of vaccine solutions for the mission-crippling diseases they cause.

Signs of a Program in Serious Decline: Loss of Adenovirus Vaccine

While its emphasis was shifting to biodefense, the DOD was losing ground in its portfolio of infectious disease vaccines. Table 2 depicts the major vaccine shortfalls, which resulted from a variety of economic, regulatory, scientific and legal pressures the existing DOD vaccine acquisition apparatus was unable to mitigate.[60] Previously-licensed vaccines for Lyme disease, cholera and plague are currently unavailable. Ten Investigational New Drug (IND) vaccines are no longer produced and have limited availability.

Table 2. Previously Licensed and IND-Only Infectious Disease Vaccine Shortfalls.

	Vaccine
Previously Licensed but Unavailable	Adenovirus, Types 4 & 7
	Lyme Disease
	Cholera
	Plague
IND Product No Longer Produced and of Limited Availability	Argentine Hemorrhagic Fever
	Chikungunya Virus
	Eastern Equine Encephalitis
	Q Fever
	Rift Valley Fever
	Tularemia
	Venezuelan Equine Encephalitis
	Western Equine Encephalitis
	Botulinum Toxoid
	Tickborne Encephalitis

The most instructive example is the DOD's loss of adenovirus vaccine. Due to crowding and various stressors, adenovirus is a frequent cause of acute respiratory disease in unvaccinated military recruits.[61] Prior to routine immunization in 1971, adenoviral outbreaks in DOD basic training units were common. Infection rates approached 50 percent, hospitalizations reached 10

percent and occasionally trainees died.[62] Outbreaks stressed medical services, eroded training effectiveness and sometimes stalled the training pipeline altogether.[63] During 25 years of use, adenovirus vaccine[xiv] provided to recruits on day one of training virtually eliminated the disease. In the mid-1990s, however, negotiations between the DOD and the sole adenovirus vaccine manufacturer failed to produce a financial agreement concerning upgrades to the production facility required by the FDA. In 1996, the manufacturer could no longer afford to produce the vaccine. As supplies waned across the DOD, pre-vaccination program morbidity returned, with unvaccinated trainees 28 times more likely than vaccinated trainees to be positive for the types of adenovirus covered by the vaccine.[64] All stocks were depleted by 1999, and by the end of 2000, seven basic military training centers had experienced adenoviral epidemics.

Today, the DOD remains without an adenovirus vaccine,[65,xv] and the disease continues to sicken trainees, burden medical systems and disrupt training. For the 12 months prior to December 2009, over 4,400 military recruits with febrile respiratory illness tested positive for adenovirus.[66] Not all who became ill were tested; the actual number of cases was higher.[67] One DOD study estimated the loss of adenovirus vaccine to be responsible for 10,650 preventable infections, 4,260 medical clinic visits, and 852 hospitalizations among the roughly 213,000 active duty and reserve trainees enrolled in basic training each year.[68] Another study projected the related annual medical and training costs at $26.4 million for the US Army alone.[69]

The loss of adenovirus vaccine "sounds a warning for the fragile system supporting other vaccines of military and public health importance."[70] To stay in business, vaccine manufacturers need to realize a profit. To do so, they must weigh what it costs to manufacture a product, how

[xiv] Referred to as a single entity in this paper, two adenovirus vaccines were actually lost, types 4 and 7.
[xv] The DOD is pursuing an adenovirus vaccine from a new manufacturer with the assistance of WRAIR. That product was successfully tested in a phase III efficacy study conducted by military investigators in 2008. Licensure is currently pending FDA review, with a response expected in summer 2010. (Email communication, Lynch).

much of it they can sell at what price, and what they could be making if they used their production capacity on a different product. The economic pressures brought on by evolving regulatory requirements caused this sole-source manufacturer to abandon its production of a limited market, mainly military-use vaccine. Competing priorities and the lack of a single agent with the authority and budget to preserve adenovirus vaccine availability were significant DOD shortcomings.

Disparate Organizations, Disproportionate Funding, Dissimilar Priority

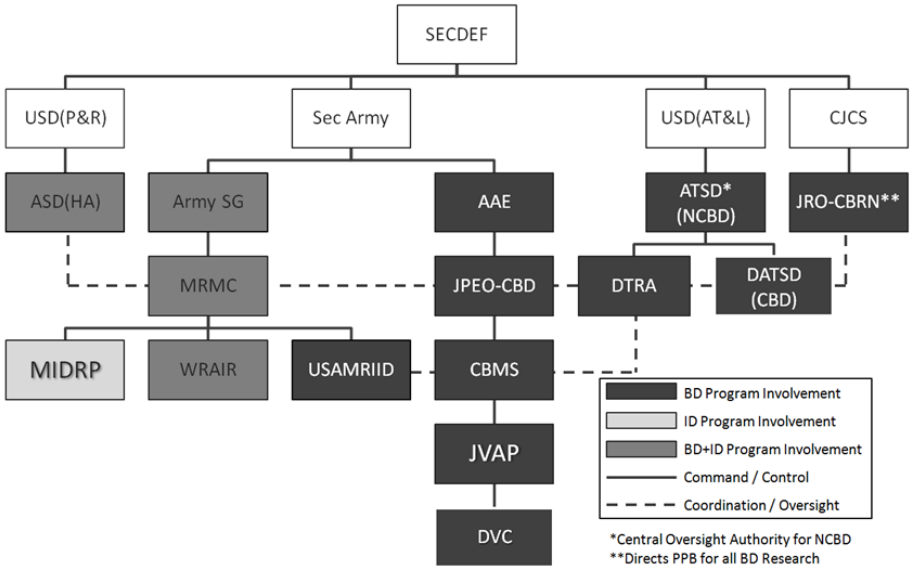
Despite overlapping missions, the DOD maintains separate organizations for infectious disease and biodefense vaccine development, procurement and product management. Each has exclusive budgetary authority and product-line responsibility. This section investigates the negative impacts from the DOD's decision to decouple its vaccine programs while granting preferential funding and priority to its biodefense efforts.

Disparate Organizations

The Medical Infectious Diseases Research Program (MIDRP) mission is to "protect the US military against naturally-occurring infectious diseases via the development of FDA-approved vaccines" and other protection systems.[71] The JVAP exists to "develop, produce and stockpile FDA-licensed vaccine systems to protect the warfighter from biological agents."[72] Figure 1, a simplified organizational chart, highlights these agencies' disparate command and control relationships.[73,74,75] In reality, the number of players and interactions is much more complex, indicative of the fragmented and diffuse organization that encumbers acquisition. Congress directed the split management scheme to raise the visibility of biodefense and

streamline acquisition procedures.[76] In retrospect, however, separating the acquisition of infectious disease and biodefense vaccines was ill-advised for multiple reasons.

Figure 1. Simplified Organizational Chart Depicting DOD Infectious Disease and Biodefense Vaccine Programs.



AAE, Army Acquisition Executive; **Army SG**, Army Surgeon General; **ASD(HA)**, Assistant Secretary of Defense for Health Affairs; **ATSD**, Assistant to the Secretary of Defense; **CBMS**, Chemical-Biological Medical Systems; **CJCS**, Chairman Joint Chiefs of Staff; **DATSD(CBD)**, Deputy Assistant Secretary of Defense for Chemical and Biological Defense Programs; **DTRA**, Defense Threat Reduction Agency; **DVC**, Dyncorp Vaccine Company (Prime Systems Contractor); **JPEO-CBD**, Joint Program Executive Office-Chemical and Biological Defense; **JRO-CBRN**, Joint Requirements Office-Chemical, Biological, Radiological, Nuclear; **JVAP**, Joint Vaccine Acquisition Program; **MIDRP**, (US Army) Medical Infectious Diseases Research Program; **MRMC**, (US Army) Medical Research and Materiel Command; **Sec Army**, Secretary of the Army; **SECDEF**, Secretary of Defense; **USAMRIID**, US Army Medical Research Institute of Infectious Diseases; **USD(AT&L)**, Under Secretary of Defense for Acquisition, Technology and Logistics; **USD(P&R)**, Under Secretary of Defense for Personnel and Readiness; **WRAIR**, Walter Reed Army Institute of Research.

First, separate acquisition precludes a unified approach to the identification and prioritization of vaccine solutions based primarily on operational risk rather than nature of the threat. Similarly, it impedes a united approach to the acquisition of "dual-use" vaccines, those which could counter both a natural and a weaponized threat to military personnel.[77] The National Registry of Select Agents, utilized for monitoring the possession and use of 48

pathogens and toxins that pose a severe threat to human health,[78,xvi] contains 13 bio-weapons that are also natural infections for which vaccines have been, or currently are, in some stage of development by the MIDRP.[79]

Second, separate acquisition fosters programmatic redundancy. There are many more similarities than differences between the pathogens, science, technology and business processes for vaccines against natural and weaponized agents. Their development and production follow like pathways, encounter similar difficulties and present comparable developmental and financial risks.

Third, separate acquisition dilutes limited expertise and splits budgetary power. Because vaccine development is so complex, highly skilled and experienced professionals are required in all facets, from scientists to administrators. As well, the industry-average cost to bring a new vaccine through the development process from concept to licensure ranges from $800 million to $1.6 billion over 14 years;[80] to sustain a fielded product costs millions more. Separation curbs professional and budgetary synergy.

Fourth, separate acquisition hinders the Total Life Cycle Systems Management (TLCSM) of vaccine products--"the implementation, management, and oversight, by a single accountable authority, of all activities associated with the acquisition, development, production, fielding and sustainment of a DOD system across its life cycle."[81] The Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) leads the TLCSM of biodefense vaccines.[82] To date, no single locus of TLCSM authority, responsibility and accountability exists for infectious disease vaccine products.[83] Separation under-serves infectious disease vaccine acquisition and precludes enterprise-wide vaccine TLCSM collaboration.

[xvi] The National Select Agent Registry currently requires registration of facilities including government agencies, universities, research institutions, and commercial entities that possess, use or transfer biological agents and toxins. (http://www.selectagents.gov/).

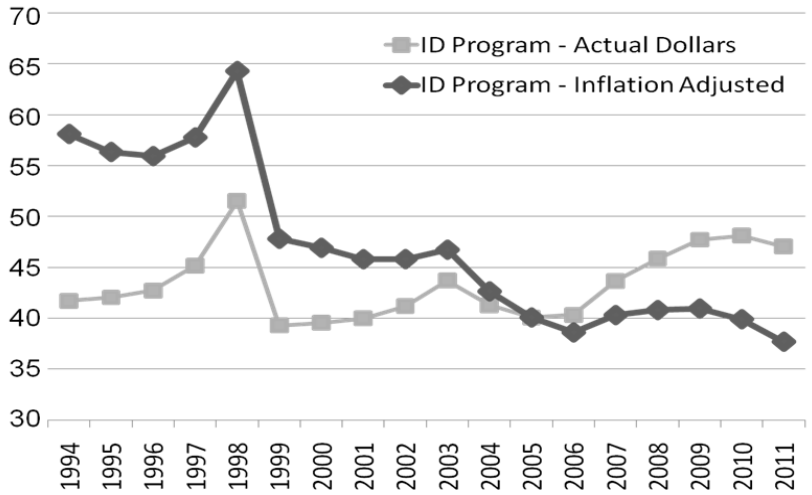
These issues have contributed to significant vaccine availability problems, such as the loss of adenovirus vaccine as previously described. They also signify the level of commitment required by the DOD to not only bring militarily-important vaccines on line but to keep them available.[84] In its 2002 report to the DOD, the Institute of Medicine was "convinced that disjointed authority ... within DOD contributed significantly to the lack of additional investment required for continued production of [adenovirus] vaccine." [85]

Disproportionate Funding

While discrete programs with no single oversight authority are problematic, the pivotal issue in separating the acquisition of infectious disease and biodefense vaccines is budgetary. In 1993, the DOD's annual budget for the advanced development of biodefense vaccines was $1 million.[86] By 1998, funding levels rose to $25 million per year.[87] Between FY2001 and FY2008, the US government annually allocated $57 billion to biodefense, with the DOD receiving nearly $12 billion.[88] In FY2009, government-wide allocations jumped by 39 percent to $8.97 billion; the DOD share was $1.72 billion.[89] Billions were allocated to the Department of Health and Human Services and the DOD to develop, produce, procure and stockpile vaccine countermeasures against weaponized pathogens.[90] Since FY1997, the US annual budget for biological defense has increased over 47 fold, from $137 million[91] to $6.5 billion by FY2008.[92]

Figure 2 shows MIDRP funding for its core research over the past 15 years, with projections to FY2011.[93] Several points must be made. First, biodefense vaccine management transitioned from the MIDRP to the JVAP in 1998, accounting for the associated funding spike then dip. Second, there is a relative budget flat-line in actual-year dollars over the period. In FY1994, the MIDRP's annual budget was $42 million. By FY2009, it had only increased to $47 million. Third, when adjusted for inflation to FY2005 dollars, the buying power of the FY2009

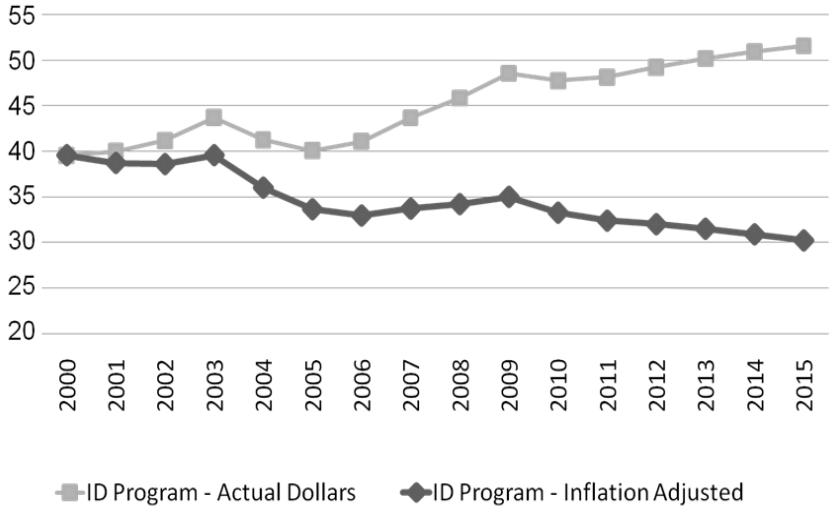
Figure 2. US Army MIDRP Funding for Infectious Diseases Core Research with inflation adjusted to FY2005 (in $Ms) (Does not include HIV Program)



budget was only $41million, less than that of 15 years earlier. Fourth, the inflationary gap is widening. By FY2011, the MIDRP's $46 million annual budget will be worth, in effect, only $37 million in FY2005 dollars.

Figure 3 depicts the mounting impact of inflation on the MIDRP budget through FY2015.[94] With projected funding levels, the MIDRP cannot keep pace with inflation. This

Figure 3. US Army MIDRP Budget, FY2000-15 (in $Ms) (Does not include HIV Program)



dismal scenario is exacerbated by the rising cost of advanced product development and clinical trials, which accounts for roughly 75 percent of total development outlays.[95] As well, clinical trials, to assess the vaccine's safety and efficacy in human subjects, are very expensive. In the past 5 years, these costs have risen from $15,000 to as much as $26,000 per enrollee.[96,97] With static funding and less buying power, the MIDRP's ability to develop vaccine products is, and will remain, seriously constrained.

Dissimilar Priority

To make the best use of limited resources, the acquisition of military vaccines is bound by the rules of the Defense Acquisition Management System. Acquisition Categories (ACAT I, II or III) are used to assign priority and determine the level of DOD review, decision authority and milestones that apply to a given project.[98] The MIDRP's infectious disease vaccines are now managed as an ACAT III "less than major" program, the lowest priority level, with each vaccine managed as a separate acquisition project.[99] Biodefense vaccines, on the other hand, are developed by the JVAP as an ACAT II "major system" program[xvii] under the JPEO-CBD.[100] The ACAT II designation affords biodefense vaccines not only a higher priority for acquisition funding but higher visibility compared with vaccines against infections of natural origin. The lack of emphasis on these natural infectious disease countermeasures has contributed to the loss of licensed vaccines (e.g., adenovirus, plague and cholera) and the inability to advance IND products (e.g., tick-borne encephalitis, Rift Valley fever and Eastern Equine Encephalitis vaccines) to full licensure. Additionally, inferior priority of infectious disease vaccines makes their funding vulnerable to becoming offsets for higher ACAT programs.

[xvii] Major Systems are estimated by the DOD to require an eventual total expenditure for Research Development Test & Evaluation of more than $140 million in FY2000 constant dollars, or for procurement of more than $600 million. (US Army Weapon Systems 2010).

Recommendations and Conclusion

This section recommends four imperatives for ensuring the DOD's ongoing ability to produce vaccines against natural infections, and provides final thoughts on reversing the dangerous decline in US military infectious disease R&D capability.

Recommendations

While the challenges are formidable, the DOD can return its ailing infectious disease vaccine program to the world's premier force health defender. Here is what needs to be done:

1. *Redesign the biological threat assessment process*. Consider, concurrently, all bio-threats regardless of origin. Then, prioritize them based on a balanced assessment of notional and experiential risks to warfighters independent of the nature of the threat.[101] To facilitate this process, a standardized cost-benefit computation should be instituted for candidate vaccines and strategies, where solutions to natural or weaponized bio-threats with the most compelling calculations garner the highest priority for funding.[102,xviii]
2. *Merge infectious disease and biodefense vaccine management*.[xix] A single DOD program is required to unify needs identification, prioritization, basic and advanced research, production, procurement and ongoing product management. Program leadership must be vested in a single agent with the authority, responsibility and accountability for ensuring effective TLCSM of all vaccines that protect warfighters against natural and weaponized pathogens. Combining programs will: facilitate the

[xviii] Burnette et al provide a viable algorithm for conducting this type of (annually-recurring) prioritization.
[xix] No less than five separate studies have previously made this recommendation: (1) Top, FH Jr, "Report on Biological Warfare Defense Vaccine Research & Development Programs," 2001, p *ii*; (2) DOD, "Quadrennial Defense Review Report," 2001, p52; (3) GAO, "Testimony Before Congress," 27 Feb 02, p 3; (4) Institute of Medicine, "Protecting Our Forces," 2002, p 58; (5) DARPA/University of Pittsburgh," Ensuring Biologics Advanced Development and Manufacturing Capability for the US Government," 2009, p 66.

synergistic sharing of ideas, expertise and resources; incentivize cohesive thinking on vaccine solutions of mutual benefit to infectious disease prevention, biodefense and public health; and underpin the maintenance of a robust, adaptable technology base that can flex to conduct timely research on the moving target of natural and weaponized bio-threats. In addition, a unified program champion will provide the strongest advocacy for infectious disease vaccines to balance against the government's proclivity for biodefense countermeasures.

3. *Elevate the acquisition priority of infectious disease vaccines*. Like those intended for biodefense, vaccines to counter natural infections should also be managed at the ACAT II, "major system" level (or higher). This is on par with Recommendation 1 in considering all biological threats--regardless of origin--of equal threat potential to warfighters. This will ensure appropriate visibility and emphasis of both infectious disease and biodefense vaccine acquisition within the DOD.
4. *Increase funding for infectious disease vaccine research, development and procurement*. In addition to raising overall program funding, each infectious disease vaccine should be funded as a separate line item in the Future Years Defense Program to ensure TLCSM.[103] These are the most important actions the DOD must take. To be clear, what is needed is not a zero-sum realignment of biodefense and infectious disease vaccine resources. Biodefense vaccines should remain fully funded, with relative parity achieved for infectious disease vaccine development. Currently, at least half of national biodefense funding serves both biodefense and public health ends.[104] This kind of overlap should become the rallying cry of DOD vaccine prioritization and resource allocation. In the final analysis, it is about cooperation, not competition.

Conclusion

The President's 2009 National Strategy For Countering Biological Threats calls for "a comprehensive and integrated approach to prevent the full spectrum of biological threats ... whether natural, accidental or deliberate in nature."[105] To meet his intent, the DOD needs to re-organize its current infectious disease and biodefense vaccine acquisition stovepipes, and establish a unified program to effectively assess, prioritize, develop and procure vaccines to protect warfighters against all-cause threats.

Staying ahead of the changing threat requires the DOD's willingness to refocus on the full range of bio-threats and commit ample resources for the sustained development of infectious disease--as well as biodefense--vaccines. Anything less places force health, combat readiness and operational effectiveness at serious risk.

GLOSSARY

ACAT	Acquisition Category
AIDS	Acquired Immune Deficiency Syndrome
BD	Biodefense
DOD	Department of Defense
DTRA	Defense Threat Reduction Agency
DVC	Dyncorp Vaccine Company
FDA	Food and Drug Administration
FHP	Force Health Protection
FYDP	Future Years Defense Program
FY	Fiscal Year
IND	Investigational New Drug
ID	Infectious Disease
IP	Intellectual Property
H1N1	Influenza A Virus known as "Swine Flu"
H5N1	Influenza A Virus known as "Bird Flu"
HIV	Human Immunodeficiency Virus
JPEO-CBD	Joint Program Executive Office for Chemical-Biological Defense
JVAP	Joint Vaccine Acquisition Program
MIDRP	Military Infectious Diseases Research Program
NCBD	Nuclear, Chemical and Biological Defense
OEF	Operation ENDURING FREEDOM
OIF	Operation IRAQI FREEDOM
PPB	Planning, Programming and Budgeting
R&D	Research and Development
TLCSM	Total Life Cycle Systems Management
US	United States
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

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