

# **The Dangerous Decline in the US Military's Infectious-Disease Vaccine Program**

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For over 230 years, vaccines advanced by the US military research and development (R&D) community have dramatically reduced the impact of naturally acquired infections not only in America's armed forces but in society at large. In recent years, however, the military's infectious-disease vaccine program has lost considerable emphasis, funding, and mission capability. In the 1990s, with the burgeoning concern for weaponized bioagents in Iraq and North Korea, 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 of the right vaccines at the right time to optimally protect US forces from established and emerging natural infections now and in the future.<sup>1</sup>

In this paper, I 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 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; 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.<sup>2</sup>

In presenting the argument, I first make a case for why vaccines against natural infectious diseases, developed under US military R&D leadership, must remain a vital force health protection (FHP) imperative for safeguarding the war fighter and optimizing US military mission effectiveness. I then 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

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hindering infectious-disease vaccine acquisition follows, including unbalanced threat assessment and mission focus, ineffective organization, insufficient funding, and inferior priority status. Finally, I recommend ways to enhance FHP vaccine acquisition and availability that will posture the DOD and America's military forces for twenty-first-century national security success.

### **Why DOD-Led Vaccines against Naturally Acquired Infections Are Vital**

Throughout America's wars, naturally acquired infectious diseases—many preventable by vaccine—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 explains why US military R&D leadership is 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.”<sup>3</sup> These were the sentiments of Gen George Washington as thousands of troops fell ill—and hundreds died—from smallpox during the first two years of the American Revolution, resulting in campaign losses, poor morale, and sparse recruiting. Via inoculation, the Continental Army dramatically reduced smallpox mortality from 160 to 3.3 per 1,000 cases, all but eliminating the threat.<sup>4</sup> The US Civil War saw twice as many deaths from disease (65 per 1,000) as from battle (33 per 1,000).<sup>5</sup> Of the 6 million disease cases among 2.8 million enlistees on both sides, over 95,000 died and roughly 250,000 were discharged for disability.<sup>6</sup> 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.<sup>7</sup> 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.<sup>8</sup> Various diseases accounted for 95 percent of American battlefield hospital admissions in World War II, 69 percent in Vietnam, 71 percent in the Gulf War, and over 95 percent in Somalia.<sup>9</sup> Unchecked, natural infections can wreak havoc on military forces.<sup>10</sup>

## **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 requiring total life-cycle support and health maintenance.<sup>11</sup> Protecting the human weapon system, the central element of military power, 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 United States to transform its military into a lighter, leaner, and more agile force. With fewer people performing more specialized roles, it is critical 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 naïve, and healthcare support is limited. A vital part of FHP, immunization is effective in mitigating these operational hurdles.<sup>12</sup>

## **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 chemoprophylactics) and personal protection (e.g., repellents and bed nets) since it does not require knowledge of exposure; is not contingent upon an accurate and timely diagnosis; protects against severe diseases (e.g., rabies) and those for which treatment is unavailable, ineffective, or prone to cause side-effects; does not require individual compliance (e.g., antimalarials); and 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.<sup>13</sup> Furthermore, vaccines not only elicit a direct benefit to recipients, they also afford herd immunity to those in the communities with whom they live and work.<sup>14</sup> Finally, despite perceived differences between weaponized and natural pathogens, “vaccines are a unifying technology proven to effectively and efficiently defeat both of these threats.”<sup>15</sup>

## **The Case for US Military Leadership in Infectious-Disease Vaccine R&D**

Fielding a licensed vaccine is a long, complex, high-risk endeavor. It requires the synergy of expertise and resources from multiple partners spanning government, industry, academia, nonprofits, and international organizations.<sup>16</sup> 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, just as industry relies on the DOD to bring its many unique R&D capabilities to the cooperative effort.<sup>17</sup>

First is the DOD's unique experience. More than half of the routine vaccines given to service members today were codeveloped by the US military.<sup>18</sup> Beyond protection of its own forces, the military's advances also created solutions to diseases of dire importance to national and international public health. Of 15 adult vaccines licensed in the United States since 1962, the DOD played a significant role in developing eight.<sup>19</sup> Currently used worldwide, these include vaccines for influenza, meningococcal disease, hepatitis A, hepatitis B, rubella, adenovirus, typhoid, and Japanese encephalitis.<sup>20</sup> 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.<sup>21</sup> 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 are the DOD's unique facilities. The 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.<sup>22</sup> Industry actively seeks the WRAIR's in-house laboratory capabilities to conduct animal modeling studies.

Third is the DOD's unique intellectual property (IP) sharing.<sup>23</sup> Highly sought after by industry, DOD partnerships attract companies by allowing them to retain IP rights for use in lucrative civilian markets.<sup>24</sup>

Fourth is the DOD's unique R&D networks.<sup>25</sup> Because the Food and Drug Administration (FDA) requires pivotal clinical trials of products in people living in areas where infectious diseases are endemic, the DOD's overseas laboratories serve as bases for conducting clinical trials that attract industry partnerships.<sup>26</sup> Because of 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.<sup>27</sup>

Fifth, and most importantly, is the DOD's focus on the often unique needs of the war fighter. 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 underdeveloped countries. The goal of the DOD's program, on the other hand, is to prevent the war fighter 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, any drug or vaccine used to protect US war fighters 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 military-relevant products through early development, FDA licensure, and eventual use by the US military.<sup>28</sup>

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."<sup>29</sup> Infectious diseases contribute significantly to social unrest and conflict in these scenarios. Infections not only ravage the local civilian populace, but also can decimate the strength of their national militaries. The prevalence of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) in Africa provides a persuasive example. Of 33 million people living with HIV worldwide, two-thirds reside in sub-Saharan Africa.<sup>30</sup> 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.<sup>31</sup> 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 hegemony cannot send peacekeepers, contribute to growth and stability, or guarantee their own internal stability, US security interests in the continent . . . are severely threatened.<sup>32</sup>

This situation demonstrates the powerful potential impact that vaccines for endemic diseases could have on geopolitical stability.<sup>33</sup> An

effective HIV vaccine could remarkably strengthen foreign militaries, secure vulnerable families and communities, bolster international public health, and reinforce US national security.<sup>34</sup>

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 (influenza A virus or “swine flu”) constantly emerging, infectious diseases will remain a formidable national security threat indefinitely.<sup>35</sup> The expeditionary nature of military missions, the effects of climate change, and the interconnectedness of an increasingly globalized planet accentuate the risks. Worldwide, 14.7 million people die each year from known and preventable contagions.<sup>36</sup> Even in industrialized nations, 46 percent of all deaths result from infectious causes.<sup>37</sup> Emerging infections have been discovered at the rate of one per year since the late 1980s.<sup>38</sup> Pathogens adapt, persist, and emerge; this pattern will continue.<sup>39</sup>

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 backseat to countering the bioterrorism threat since the mid-1990s. Beginning with its stand-up of the Joint Program Office for Biological Defense in 1993 and formalized requirements for biodefense vaccines in 1995, the DOD—with a push from Congress—justifiably turned a focused eye to biodefense.<sup>40</sup> By 1998 the DOD had established the Joint Vaccine Acquisition Program (JVAP) and significantly increased funding for advanced biodefense vaccine development, while core funding for infectious-disease vaccine R&D declined.<sup>41</sup> Because of the post-9/11 anthrax letters, fears of state-sponsored weapons-of-mass-destruction proliferation by Iraq,

and the express interest in bioagents by al-Qaeda, the nation perceived an urgent vulnerability to biological attack.<sup>42</sup> The DOD responded with wholesale investments in biodefense as infectious-disease R&D funding remained level.<sup>43</sup>

Reportedly, about a dozen states and multiple nonstate actors possess or are pursuing biological weapons.<sup>44</sup> Their potential use clearly poses a level of danger to US forces in the contemporary battlespace, 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 have been reported in deployed US forces since 1998.<sup>45</sup> While the potential threat is duly noted, bioterrorism 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 link to either state sponsors or nonstate actors.<sup>46</sup>

In contrast, by 2008 West Nile virus had sickened 28,961 Americans—claiming 1,131 lives—since its arrival on US soil in 1999.<sup>47</sup> The emergence of severe acute respiratory syndrome (SARS) in 2003, H5N1 (influenza A virus or “bird flu”) in 2006, and H1N1 in 2009 further underscores the clear and present danger posed by natural infectious diseases. Also, to some experts, the emergence of a novel strain of adenovirus among military recruits in 2007 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.”<sup>48</sup>

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

### **Natural Pathogens: An Operational Reality Check**

All the while, natural-origin infectious diseases have continued to pose real challenges to US military commanders in lost manpower-days, reduced effectiveness, increased medical visits, and frequent medical evacuations.<sup>49</sup> 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, 69 percent suffered one or more episodes of acute respiratory illness, and “one-quarter believed that combat unit effectiveness had been negatively affected by these common illnesses.”<sup>50</sup> 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.<sup>51</sup>

Table 1 summarizes the incidence of the four leading—and potentially vaccine-preventable—infectious diseases in deployed US forces between 1998 and 2009.<sup>52</sup> Of 3,386 total cases, leishmaniasis, malaria, and Lyme disease accounted for 95.8 percent of the disease burden. Through 2004, leishmaniasis prompted 4.4 percent of the monthly medical evacuations during OIF.<sup>53</sup> The occurrence of 126 cases of meningococcal disease reflects the absence of an effective vaccine for subtype B of this 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.

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

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

*Data from* Armed Forces Health Surveillance Center (AFHSC), “Defense Medical Surveillance System,” 10 December 2009.

### **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.<sup>54</sup> 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.

The most instructive example is the DOD’s loss of adenovirus vaccine. Because of crowding and various stressors, adenovirus is a frequent cause of acute respiratory disease in unvaccinated military recruits.<sup>55</sup> 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.<sup>56</sup> Outbreaks stressed medical services, eroded

**Table 2. Previously licensed and IND-only infectious-disease vaccine shortfalls**

	<i>Vaccine</i>
Previously licensed but unavailable	Adenovirus, types 4 and 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

*Data from Stanley M. Lemon, Susan Thaul, Salem Fisseha, and Heather C. O'Maonaigh, eds., Protecting Our Forces: Improving Vaccine Acquisition and Availability in the US Military (Washington, DC: Institute of Medicine of the National Academies, National Academies Press, 2002).*

training effectiveness, and sometimes stalled the training pipeline altogether.<sup>57</sup> During 25 years of use, the adenovirus vaccine provided to recruits on day one of training virtually eliminated the disease.<sup>58</sup> 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, prevaccination 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.<sup>59</sup> 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, and the disease continues to sicken trainees, burden medical systems, and disrupt training.<sup>60</sup> For the 12 months prior to December 2009, over 4,400 military recruits with febrile respiratory illness tested positive for adenovirus.<sup>61</sup> Not all who became ill were tested; the actual number of cases was higher.<sup>62</sup> 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.<sup>63</sup> Another study projected the related annual medical and training costs at \$26.4 million for the US Army alone.<sup>64</sup>

The loss of the adenovirus vaccine “sounds a warning for the fragile system supporting other vaccines of military and public health importance.”<sup>65</sup> 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 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.

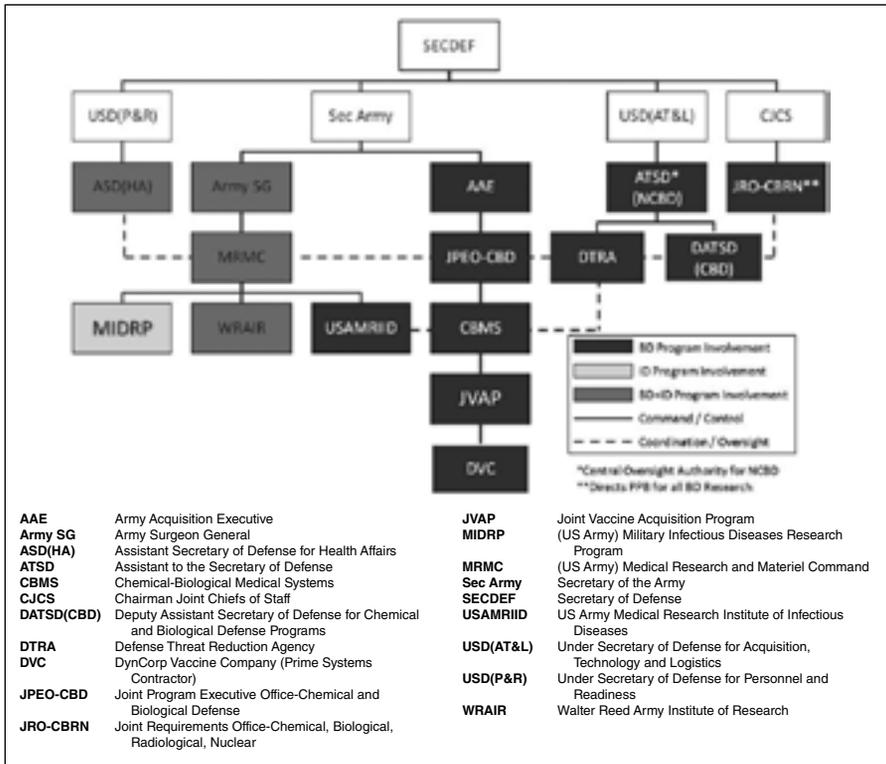
### **Disparate Organizations, Disproportionate Funding, Dissimilar Priority**

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 Military 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.<sup>66</sup> The JVAP exists to “develop, produce and stockpile FDA-licensed vaccine systems to protect the warfighter from biological agents.”<sup>67</sup> Figure 1, a simplified organizational chart, highlights these agencies’ disparate command and control relationships.<sup>68</sup> 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.<sup>69</sup> In retrospect, however, separating the acquisition of infectious-disease and biodefense vaccines was ill-advised for multiple reasons.

First, separate acquisition precludes a unified approach to the identification and prioritization of vaccine solutions based primarily



**Figure 1. Simplified organizational chart depicting DOD infectious-disease and biodefense vaccine programs.** (Adapted from LTC Coleen K. Martinez, “Biodefense Research Supporting the DOD: A New Strategic Vision,” Research Report no. 1-58487-288-8 [Carlisle Barracks, PA: US Army War College, 2007]; Rudolph Kupperts, USMRMC/MIDRP, to the author, e-mail, 11 December 2009; and COL Charles Hoke, retired, MD, USAMRIID, to the author, e-mail, 24 January 2010.)

on operational risk rather than the 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.<sup>70</sup> The National Select Agent Registry (NSAR), utilized for monitoring the possession and use of 48 pathogens and toxins that pose a severe threat to human health, contains 13 bioweapons that are also natural infections for which vaccines have been, or currently are, in some stage of development by the MIDRP.<sup>71</sup>

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 pro-

duction 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. Also, 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; to sustain a fielded product costs millions more. Separation curbs professional and budgetary synergy.<sup>72</sup>

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."<sup>73</sup> The Joint Program Executive Office for Chemical and Biological Defense (JPEO-CBD) leads the TLCSM of biodefense vaccines.<sup>74</sup> To date, no single locus of TLCSM authority, responsibility, and accountability exists for infectious-disease vaccine products.<sup>75</sup> Separation undermines infectious-disease vaccine acquisition and precludes enterprise-wide vaccine TLCSM collaboration.

These issues have contributed to significant vaccine availability problems, such as the loss of the adenovirus vaccine as previously described. They also signify the level of commitment required by the DOD not only to bring militarily important vaccines on line but to keep them available.<sup>76</sup> 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."<sup>77</sup>

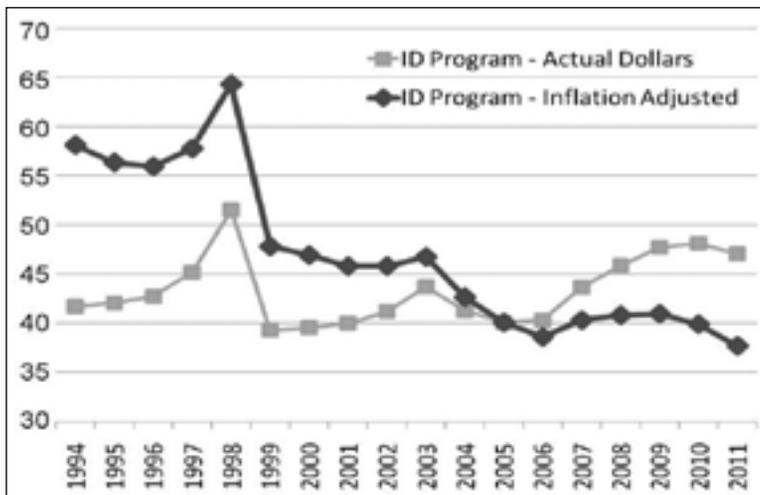
### **Disproportionate Funding**

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.<sup>78</sup> By 1998 funding levels rose to \$25 million per year.<sup>79</sup> Between fiscal year (FY) 2001 and FY 2008, the US government annually allocated \$57 billion to biodefense, with the DOD receiving nearly \$12 billion.<sup>80</sup> In FY 2009 government-wide allocations jumped by 39 percent to \$8.97 billion; the DOD share was \$1.72 billion.<sup>81</sup> Billions were allocated to the Department of Health and Human Services and the DOD to develop, produce, procure, and stock-

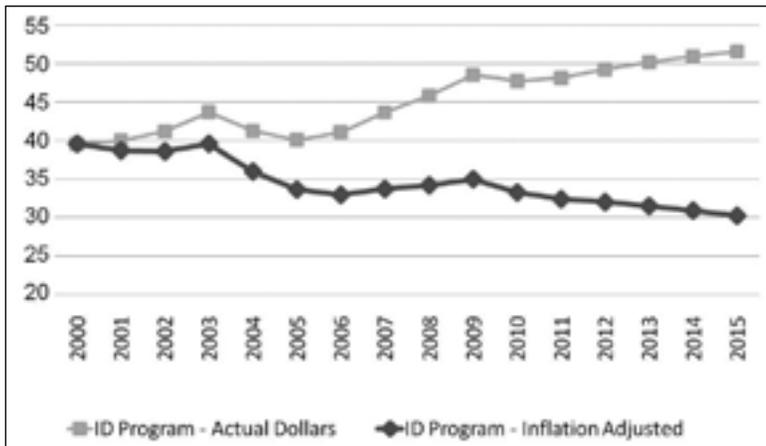
pile vaccine countermeasures against weaponized pathogens.<sup>82</sup> Since FY 1997 the annual US budget for biological defense has increased over 47-fold, from \$137 million to \$6.5 billion by FY 2008.<sup>83</sup>

Figure 2 shows MIDRP funding for its core research over the past 15 years, with projections to FY 2011.<sup>84</sup> Several points must be made. First, biodefense vaccine management transitioned from the MIDRP to the JVAP in 1998, accounting for the associated funding spike and then dip. Second, there is a relative budget flatline in actual-year dollars over the period. In FY 1994 the MIDRP's annual budget was \$42 million. By FY 2009 it had increased only to \$47 million. Third, when adjusted for inflation to FY 2005 dollars, the buying power of the FY 2009 budget was only \$41 million, less than that of 15 years earlier. Fourth, the inflationary gap is widening. By FY 2011 the MIDRP's \$46 million annual budget will be worth, in effect, only \$37 million in FY 2005 dollars.

Figure 3 depicts the mounting impact of inflation on the MIDRP budget through FY 2015.<sup>85</sup> With projected funding levels, the MIDRP cannot keep pace with inflation. This 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.<sup>86</sup> Also, clinical trials to assess a vaccine's safety and efficacy in human subjects are very expensive. In the past five years, these costs have



**Figure 2. US Army MIDRP funding for infectious diseases core research with inflation adjusted to FY 2005, in millions of dollars (does not include HIV program).** (Adapted from Rudolph Koppers, USMRMC/MIDRP, to the author, e-mail, 11 December 2009.)



**Figure 3. US Army MIDRP budget, FY 2000–15, in millions of dollars** (does not include HIV program). (Adapted from Rudolph Kuppers, USMRMC/MIDRP, to the author, e-mail, 11 December 2009.)

risen from \$15,000 to as much as \$26,000 per enrollee.<sup>87</sup> 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 rules of the Defense Acquisition Management System govern the acquisition of military vaccines. Acquisition categories (ACAT I, II, and III) are used to assign priority and determine the level of DOD review, decision authority, and milestones that apply to a given project.<sup>88</sup> 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.<sup>89</sup> Biodefense vaccines, on the other hand, are developed by the JVAP as an ACAT II “major system” program under the JPEO-CBD.<sup>90</sup> The ACAT II designation affords biodefense vaccines not only a higher priority for acquisition funding but also higher visibility than 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, the inferior priority of infectious-disease vaccines makes their funding vulnerable to becoming offsets for higher ACAT programs.

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

### **Redesign the Biological-Threat Assessment Process**

Concurrently consider all biothreats regardless of origin. Then prioritize them based on a balanced assessment of notional and experiential risks to war fighters independent of the nature of the threat.<sup>91</sup> To facilitate this process, a standardized cost-benefit computation should be instituted for candidate vaccines and strategies, where solutions to natural or weaponized biothreats with the most compelling calculations garner the highest priority for funding.<sup>92</sup>

### **Merge Infectious-Disease and Biodefense Vaccine Management**

A single DOD program is required to unify needs identification, prioritization, basic and advanced research, production, procurement, and ongoing product management.<sup>93</sup> Program leadership must be vested in a single agent with the authority, responsibility, and accountability for ensuring effective TLCSM of all vaccines that protect war fighters against natural and weaponized pathogens. Combining programs will facilitate the 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 biothreats. 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.

### **Elevate the Acquisition Priority of Infectious-Disease Vaccines**

Like those intended for biodefense, vaccines to counter natural infections should be managed at the ACAT II major-system level (or higher). This is in alignment with the first recommendation above to

consider all biological threats—regardless of origin—of equal threat potential to war fighters. This will ensure appropriate visibility and emphasis of both infectious-disease and biodefense vaccine acquisition within the DOD.

### **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.<sup>94</sup> 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.<sup>95</sup> This kind of overlap should become the rallying cry of DOD vaccine prioritization and resource allocation. A successful biothreat vaccine program 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."<sup>96</sup> To meet his intent, the DOD needs to reorganize its current infectious-disease and biodefense vaccine acquisition stovepipes and establish a unified program to effectively assess, prioritize, develop, and procure vaccines to protect war fighters against threats from all causes.

Staying ahead of the changing threat requires the DOD to refocus on the full range of biothreats 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.

### **Notes**

1. In this paper, *acquisition* is defined as the DOD's process for ensuring that 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.

2. National Security Council, *National Strategy for Countering Biological Threats*, November 2009, [http://www.whitehouse.gov/sites/default/files/National\\_Strategy\\_for\\_Countering\\_BioThreats.pdf](http://www.whitehouse.gov/sites/default/files/National_Strategy_for_Countering_BioThreats.pdf) (accessed 15 January 2010).
3. Stanhope Bayne-Jones, *The Evolution of Preventive Medicine in the United States Army, 1607–1939* (Washington, DC: Office of the Surgeon General, Department of the Army, 1968), 52, <http://history.amedd.army.mil/booksdocs/misc/evprev/default.html> (accessed 28 October 2009).
4. Specifically, this was *variolation*, an “obsolete process of inoculating a susceptible person with material taken from a vesicle of a person who has smallpox.” Princeton University, WordNet, <http://wordnetweb.princeton.edu/perl/webwn?s=variolation>.
5. Bayne-Jones, *Evolution of Preventive Medicine in the US Army*, 99.
6. *Ibid.*
7. *Ibid.*, 124.
8. *Ibid.*, 151.
9. Mark S. Riddle et al., “Past Trends and Current Status of Self-Reported Incidence and Impact of Disease and Nonbattle Injury in Military Operations in Southwest Asia and the Middle East,” *American Journal of Public Health* 98, no. 12 (2008): 2199; and Stanley M. Lemon et al., *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the US Military* (Washington, DC: Institute of Medicine of the National Academies, National Academies Press, 2002), 10.
10. John W. Sanders et al., “Impact of Illness and Non-Combat Injury during Operations Iraqi Freedom and Enduring Freedom (Afghanistan),” *American Journal of Tropical Medicine and Hygiene* 73, no. 4 (2005): 713–19.
11. Joint Publication (JP) 4-02, *Doctrine for Health Services Support in Joint Operations*, 31 October 2006, GL-14; Anthony P. Tvaryanas, Lex Brown, and Nita L. Miller, “Managing the Human Weapon System: A Vision for an Air Force Human-Performance Doctrine,” *Air and Space Power Journal* 23, no. 2 (Summer 2009): 34–41; and Joint Chiefs of Staff (JCS), *Force Health Protection Capstone Document* (Washington, DC: JCS, 2000), 2.
12. JP 4-02, *Doctrine for Health Services Support*, IV-5.
13. Richard D. Nidel, JVAP Office Video, <http://www.jpocbd.osd.mil/packs/DocHandler.ashx?DocId=4711> (accessed 5 December 2009).
14. John D. Grabenstein, “Immunization to Protect the US Armed Forces: Heritage, Current Practice, Prospects,” *Epidemiologic Reviews* 28, no. 1 (2006): 10.
15. DOD, *Report on Biological Warfare Defense Vaccine Research & Development Programs* (Washington, DC: DOD, July 2001), 7.
16. Rudolph Koppers, USMRMC/MIDRP, to the author, e-mail, 11 December 2009.
17. *Ibid.*
18. *Ibid.*
19. Military Infectious Diseases Research Program (MIDRP), “History and Achievements,” <https://midrp.amedd.army.mil/info/HAchieve.html> (accessed 5 January 2010).
20. *Ibid.*
21. *Ibid.*
22. The Quantic Group, “CBRN Medical Countermeasures (MCM) Manufacturing Capabilities Analysis of Alternatives Report,” 15 June 2009, 10.
23. Intellectual property is “the group of legal rights to things people create or invent. Intellectual property rights typically include patent, copyright, trademark and trade secret rights.” Sitepoint, <http://www.sitepoint.com/glossary.php>.
24. Koppers to the author, e-mail; and Lemon, *Protecting Our Forces*, 87.
25. COL Charles Hoke, retired, MD, USAMRIID, to the author, e-mail, 24 January 2010.

26. A pivotal clinical trial must be controlled, have a double-blinded design when practical and ethical, be randomized, and be of adequate size. AdisInsight, <http://www.adisinsight.com/aClientServiceinfo/CTI%20Appendix.pdf>. DOD overseas labs are located in Thailand, Peru, Kenya, Egypt, and Indonesia. Hoke to the author, e-mail.

27. COL Julia Lynch, USMRMC/MIDRP, to the author, e-mail, 18 January 2010.

28. Kupperts to the author, e-mail.

29. Department of Defense Instruction (DODI) 3000.05, *Stability Operations*, 16 September 2009, 2.

30. World Health Organization (WHO), *Towards Universal Access: Scaling Up Priority HIV/AIDS Interventions in the Health Sector, Progress Report 2009* (Geneva, Switzerland: WHO Press, 2009), 7, [http://whqlibdoc.who.int/publications/2009/9789241598750\\_eng.pdf](http://whqlibdoc.who.int/publications/2009/9789241598750_eng.pdf) (accessed 9 January 2010).

31. Mark Schneider and Michael Moodie, *The Destabilizing Impacts of HIV/AIDS* (Washington, DC: Center for Strategic and International Studies, May 2002), 2.

32. *Ibid.*, 4.

33. Kupperts to the author, e-mail.

34. 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. Hoke to the author, e-mail.

35. Lynch to the author, e-mail; and W. Neal Burnette et al., "Infectious Diseases Investment Decision Evaluation Algorithm: A Quantitative Algorithm for Prioritization of Naturally Occurring Infectious Disease Threats to the US Military," *Military Medicine* 173 (February 2008): 174–81.

36. Arguably, climate change is resulting in significant changes in weather patterns and disruptions in ecosystems leading to the emergence of new niches for infectious disease pathogens and vectors. Lynch to the author, e-mail. On the death rate from contagions, see Sara E. Davies, "Securitizing Infectious Disease," *International Affairs* 84, no. 2 (2008): 295–313; and WHO, "The Top Ten Causes of Death," fact sheet, February 2007, <http://www.who.int/mediacentre/factsheets/fs310.pdf> (accessed 15 January 2010). The top five infectious disease killers include HIV/AIDS, pneumonia, diarrhea, malaria, and tuberculosis.

37. Burnette et al., "Infectious Diseases Investment," 174.

38. Davies, "Securitizing Infectious Disease," 298.

39. Hoke to the author, e-mail.

40. Edward T. Clayson, JVAP Product Management Office, JVAP overview presentation slides, 30 May 2003, slide 5.

41. *Ibid.*; and Kupperts to the author, e-mail (compares 1997 and 1999 MIDRP funding).

42. US Senate, *Testimony for the Senate Foreign Relations Committee by Amy Sands, PhD, Deputy Director, Center for Non-Proliferation Studies, Monterey Institute of International Studies, before the US Senate Foreign Relations Committee*, 19 March 2002, <http://cns.miis.edu/pubs/reports/asands.htm> (accessed 7 January 2010); and LTC Coleen K. Martinez, "Biodefense Research Supporting the DOD: A New Strategic Vision," Research Report no. 1-58487-288-8 (Carlisle Barracks, PA: US Army War College, 2007), 23.

43. Kupperts to the author, e-mail.

44. US Senate, *Statement by Assistant Secretary of State for Intelligence and Research Carl W. Ford, Jr. before the US Senate Committee on Foreign Relations Hearing on Reducing the Threat of Chemical and Biological Weapons*, 19 March 2002, <http://www.fas.org/bwc/news/testimony/CT2002March19Ford.htm> (accessed 7 January 2010); and US Senate, *Testimony by Amy Sands*.

45. Armed Forces Health Surveillance Center (AFHSC), "Defense Medical Surveillance System," <http://www.afhsc.mil/dmss> (accessed 10 December 2009).
46. Federal Bureau of Investigation, "Amerithrax Investigation," <http://www.fbi.gov/anthrax/amerithraxlinks.htm> (accessed 28 January 2010).
47. Centers for Disease Control and Prevention (CDC), "West Nile Virus: Statistics, Surveillance, and Control," [http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount99\\_detailed.htm](http://www.cdc.gov/ncidod/dvbid/westnile/surv&controlCaseCount99_detailed.htm) (accessed 22 December 2009).
48. Amesh A. Adalja, "Adenovirus 14," quoting Gregory C. Gray and Margaret L. Chorazy, "Human Adenovirus 14a: A New Epidemic Threat," *Journal of Infectious Disease* 199 (2009): 1413, <http://www.journals.uchicago.edu/doi/full/10.1086/598522> (accessed 5 November 2009). In 2007, 23 trainees at Lackland AFB, Texas, hospitalized for pneumonia, were found to be infected with a variant strain (type 14) of adenovirus; one of the trainees died. Amesh A. Adalja, "Adenovirus 14: An Emerging Threat," 17 April 2009. Clinician's Biosecurity Network, [http://www.upmc-cbn.org/report\\_archive/2009/04\\_April\\_2009/cbnreport\\_04172009.html](http://www.upmc-cbn.org/report_archive/2009/04_April_2009/cbnreport_04172009.html) (accessed 27 November 2009).
49. Sanders et al., "Impact of Illness and Non-Combat Injury."
50. Ibid., 714. *Campylobacter, Shigella, Escherichia coli* and norovirus have been the most commonly reported diarrheal infections in deployed forces. *Rhinovirus, Coronavirus*, parainfluenza virus, and adenovirus have been the most commonly reported causes of acute respiratory infections in deployed forces. AFHSC, "Defense Medical Surveillance System."
51. Sanders et al., "Impact of Illness and Non-Combat Injury," 716.
52. AFHSC, "Defense Medical Surveillance System."
53. C. G. Hawley-Bowland, *Casualty Analysis: Health Policy and Services* (Washington, DC: US Army Medical Command, 2004).
54. Lemon et al., *Protecting Our Forces*, 44–45.
55. James Chin, ed. *Control of Communicable Diseases Manual*, 17th ed. (Washington, DC: American Public Health Association, 2000), 428.
56. Grabenstein, "Immunization to Protect the US Armed Forces," 13.
57. Gregory C. Gray et al., "Adult Adenovirus Infections: Loss of Orphaned Vaccines Precipitates Military Respiratory Disease Epidemics," *Clinical Infectious Disease* 31, no. 3 (September 2000): 663–70.
58. Although referred to as a single entity in this paper, two adenovirus vaccines were actually lost, types 4 and 7.
59. Sanders et al., "Impact of Illness and Non-Combat Injury," 663.
60. Lynch to the author, e-mail. The DOD is pursuing an adenovirus vaccine from a new manufacturer with the assistance of the 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.
61. Naval Health Research Center, Department of Respiratory Diseases Research, "Febrile Respiratory Illness (FRI) Surveillance Update," week ending 16 January 2010, <http://www.med.navy.mil/sites/nhrc/geis/Documents/FRIUpdate.pdf> (accessed 25 January 2010).
62. Ibid.
63. Gray et al., "Adult Adenovirus Infections," 668.
64. M. René Howell et al., "Prevention of Adenoviral Acute Respiratory Disease in Army Recruits: Cost-Effectiveness of a Military Vaccination Policy," *American Journal of Preventive Medicine* 14, no. 3 (April 1998): 168.
65. Gray and Chorazy, "Human Adenovirus 14a," 1414.
66. MIDRP, "MIDRP Overview," <https://midrp.amedd.army.mil/login.jsp> (accessed 27 December 2009).

67. David Williams and Calvin Carpenter, "Medical Systems: Advanced Planning Briefing to Industry," briefing slides, Joint Program Management-Chemical Biological Medical Systems (JPM-CBMS), 7 May 2009, slide 8.

68. Martinez, "Biodefense Research Supporting the DOD," 11; Kupperts to the author, e-mail; and Hoke to the author, e-mail.

69. Lemon et al., *Protecting Our Forces*, 64.

70. Ibid.

71. *Possession, Use, and Transfer of Select Agents and Toxins, Interim Final Rule*. Code of Federal Regulations, title 42, pt. 73, <http://www.cdc.gov/od/sap/docs/42cfr73.pdf> (accessed 4 November 2009); and Lemon et al., *Protecting Our Forces*, 40–41. The NSAR "currently requires registration of facilities, including government agencies, universities, research institutions, and commercial entities, that possess, use, or transfer biological agents and toxins." See the NSAR Web site, "Overview," <http://www.selectagents.gov> (accessed 19 July 2010).

72. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics* 22, no. 2 (2003): 180.

73. Office of the Assistant Deputy Undersecretary of Defense for Logistics Plans and Programs, *Total Life Cycle System Management: Plan of Action and Milestones*, [http://www.acq.osd.mil/log/sci/exec\\_info/sm\\_milestone\\_plan010603.pdf](http://www.acq.osd.mil/log/sci/exec_info/sm_milestone_plan010603.pdf) (accessed 31 January 2010), 2.

74. Government Contract & Bid, "Joint Vaccine Acquisition Program (JVAP) Storage, Distribution, and Testing of Government Owned/Regulated Chemical Biological Defense," <http://www.govcb.com/H-Joint-Vaccine-Acquisition-Program-ADP11981138560001613.htm> (accessed 31 January 2010).

75. Hoke to the author, e-mail.

76. Ibid.

77. Lemon et al., *Protecting Our Forces*, 59.

78. Clayson, JVAP Overview, slide 5.

79. Ibid.

80. Center for Arms Control and Non-Proliferation, *Federal Funding for Biological Weapons Prevention and Defense, Fiscal Years 2001 to 2009*, 15 April 2008, [http://www.armscontrolcenter.org/media/fy2009\\_bw\\_budgetv2.pdf](http://www.armscontrolcenter.org/media/fy2009_bw_budgetv2.pdf).

81. Ibid.

82. Ibid.

83. D. R. Franz, "Ways Ahead: USG Biodefense Program from 2010 to 2020," Biodefense Way Ahead Project Workshop, Defense Threat Reduction Agency, Washington, DC, 16 September 2009, 2; and Center for Arms Control and Non-Proliferation, *Federal Funding for Biological Weapons Prevention*.

84. Kupperts to the author, e-mail.

85. Ibid.

86. Lemon et al., *Protecting Our Forces*, 52.

87. Kupperts to the author, e-mail; and LifeSciencesWorld, "Phase 3 Clinical Trial Costs Exceed \$26,000 per Patient," 13 October 2006, <http://www.lifesciencesworld.com/news/view/11080> (accessed 31 January 2010).

88. DODI 5000.02, *Operation of the Defense Acquisition System*, 8 December 2008.

89. Lemon et al., *Protecting Our Forces*, 33.

90. The DOD estimates that major systems will require an eventual total expenditure for research, development, test, and evaluation of more than 140 million in FY 2000 constant dollars or for procurement more than 600 million dollars. Department of the Army, *US Army Weapon Systems 2010*, 2009; and Office of the Deputy Assistant Secretary of Defense for Chemical and Biological Defense, *Department of Defense*

*Chemical and Biological Defense Program Annual Report to Congress*, March 2005, E-38, <http://handle.dtic.mil/100.2/ADA435936> (accessed 14 July 2010).

91. Burnette et al., "Infectious Diseases Investment Decision Evaluation Algorithm," 174.

92. Hoke to the author, e-mail. Burnette et al. provide a viable algorithm for conducting this type of (annually recurring) prioritization.

93. No fewer than five separate studies have previously made this recommendation: DOD, *Report on Biological Warfare Defense Vaccine*, ii; DOD, *Quadrennial Defense Review Report*, 30 September 2001, 52; General Accounting Office (GAO), *Defense Acquisitions: DOD Faces Challenges in Implementing Best Practices*, Testimony before the Subcommittee on Readiness and Management Support, Committee on Armed Services, US Senate, GAO-02-469T (Washington, DC: GAO, 27 February 2002), 3; Lemon et al., *Protecting Our Forces*, 58; and University of Pittsburgh Medical Center, *Ensuring Biologics Advanced Development and Manufacturing Capability for the United States Government: A Summary of Key Findings and Conclusions*, final report for cooperative agreement research study with Defense Advanced Research Projects Agency, 6 October 2009, 66.

94. Ibid.

95. Franz, "Ways Ahead," 2.

96. National Security Council, *National Strategy for Countering Biological Threats*, 3.

## ***Abbreviations***

ACAT	acquisition category
AIDS	acquired immune deficiency syndrome
AWC	Air War College
CBRN	chemical, biological, radiological, and nuclear
CDC	Centers for Disease Control and Prevention
DOD	Department of Defense
FDA	Food and Drug Administration
FHP	force health protection
FY	fiscal year
H1N1	influenza A virus or “swine flu”
H5N1	influenza A virus or “bird flu”
HIV	human immunodeficiency virus
IND	investigational new drug
IP	intellectual property
JCS	Joint Chiefs of Staff
JPEO-CBD	Joint Program Executive Office for Chemical and Biological Defense
JVAP	Joint Vaccine Acquisition Program
MIDRP	Military Infectious Diseases Research Program
NSAR	National Select Agent Registry
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
R&D	research and development
SARS	severe acute respiratory syndrome
TLCSM	Total Life-Cycle Systems Management
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research