

Military vaccines in today's environment

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The US military has a long and highly distinguished record of developing effective vaccines against pathogens that threaten the armed forces. Many of these vaccines have also been of significant benefit to civilian populations around the world. The current requirements for force protection include vaccines against endemic disease threats as well as against biological warfare or bioterrorism agents, to include novel or genetically engineered threats. The cost of vaccine development and the modern regulatory requirements for licensing vaccines have strained the ability of the program to maintain this broad mission. Without innovative vaccine technologies, streamlined regulatory strategies, and coordinating efforts for use in civilian populations where appropriate, the military vaccine development program is in jeopardy.

Historical Perspective

The number of military personnel admitted to US Army hospitals as the result of infectious diseases was much higher than admissions due to wounds or other injuries incurred in WWII or the wars in Korea, Vietnam or the Persian Gulf.¹ It is not surprising; therefore, that since George Washington first ordered mandatory variolation of new recruits to the Continental Army to prevent smallpox in 1777, vaccination of military personnel has been a crucial component of deployments (reviewed in refs. 2 and 3). Because of the large number of diverse endemic disease pathogens encountered by military personnel around the world, it is also not surprising that the US Department of Defense (DoD) has historically maintained an extensive vaccine research and

development program, and that those vaccines have been important for civilian as well as military populations. For example, military sponsored research contributed to the Food and Drug Administration (FDA) licensure of 10 vaccines between 1945 and 1995, to include vaccines for anthrax, plague, influenza, rubella, adenoviruses, meningococci, hepatitis B, typhoid, Japanese encephalitis, and hepatitis A (reviewed in refs. 2 and 3), all of which have been widely used and have provided enormous benefits in both civilian and military settings. Other licensed vaccines for naturally occurring diseases, such as those for yellow fever, mumps, measles, chickenpox and polio, were developed with the guidance of former military researchers. In addition to these FDA-licensed vaccines, several vaccines; for example, against malaria, tularemia, Dengue, HIV-AIDS, Chikungunya, Rift Valley fever, Argentinian hemorrhagic fever, and hemorrhagic fever with renal syndrome (HFRS), have been developed and tested in clinical studies by the military but have not yet been, or never will be, licensed.

Not only are endemic diseases of concern for the military, so are potential exposures to agents deliberately introduced into the environment through biological warfare (BW) or bioterrorism, to include toxins such as ricin, botulinum toxin, Staphylococcus enterotoxin B, and pathogens causing anthrax, plague, tularemia, glanders, smallpox, Ebola and Marburg hemorrhagic fevers or Venezuelan, eastern or western equine encephalitis. Further, genetically engineered novel threats are now a possibility, which has expanded the scope of military vaccine research and development.

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Because it is recognized that some of these same BW or endemic disease agents are also potential threats to civilians, significant funds have been programmed for the Biomedical Advanced Research and Development Authority (BARDA) to stockpile vaccines against a few of the most likely pandemic disease threats or bioterrorism agents, such as pandemic influenza, anthrax and smallpox. Although there is overlap in the missions of BARDA and DoD, their ultimate goals differ in that BARDA focuses on countermeasures for treating the population after exposure to a bioterrorism agent or in response to a pandemic, whereas the DoD aims to provide protective immunity to the armed forces prior to exposure. Today, however, while vaccination of deployed troops remains a matter of national security, the cost of vaccine development has increased to the point where, without innovation and renewed commitment, the current scope of military vaccine development efforts is not sustainable.

The Cost of Licensing Military Vaccines

The overall expense associated with a single new FDA-licensed vaccine has been estimated to average between \$600 million and \$1 billion dollars.⁴ Nevertheless, unless extraordinary conditions call for special measures, only licensed vaccines are routinely given to military personnel. In rare situations, vaccines with Investigational New Drug (IND) status have been used. For instance, a European tick-borne encephalitis virus vaccine was offered to military personnel deployed to Bosnia in 1996 (reviewed in ref. 1). In such circumstances, the FDA requires that informed consent is documented. As it is extremely difficult to maintain adequate records under combat conditions, this is not really a practical solution to a vaccination requirement and is not consistent with the goal of using only the most effective and safest products in troops.

The other special situation in which vaccines developed by the military are used under IND status with informed consent is in the Special Immunizations Program (SIP) located at USAMRIID. The vaccines given in the SIP are intended

to provide added protection to individuals with an occupational risk of exposure to pathogens (e.g., laboratory scientists, animal caretakers, facilities and equipment maintenance staff, etc). Numerous problems with the SIP have been recognized in recent years, and are well described in a 2011 National Academies Publication "Protecting the Frontline of Biodefense Research: The Special Immunizations Program." Among the issues highlighted are the limited remaining supplies and age of the vaccines (mostly developed in the 1970s and 1980s under different regulatory standards), and arguably the most important issue, the cost of maintaining the SIP (approximately \$6 million per year) with no dedicated funding source. The NAS committee emphasized the worth of the SIP, and recommended that the cost of the program be supported by all users and that the vaccines be replaced with newer licensed or IND vaccines as they become available. Both are absolutely critical if vaccination of personnel who deal with these dangerous pathogens is to continue, and if these vaccines or other military vaccines developed through IND status are to remain an option for additional use in emergencies.

The value of maintaining such vaccines that have already been tested under IND was illustrated most recently when a vaccine against the mosquito-borne Chikungunya virus, which was developed by the Army in the 1970s, was transferred to French scientists for further study after an explosive outbreak of Chikungunya in the Indian Ocean Islands in 2006.^{5,6} The live-attenuated Chikungunya vaccine was previously evaluated through phase 2 clinical studies by the military, with very promising results; i.e., 57 out of 58 vaccinees developed neutralizing antibodies by day 28, and 85% were still seropositive a year later.⁷ Lack of funding was the overriding reason for the termination of the Chikungunya vaccine development effort by the DoD at that time, in that there was no commercial partner interested in pursuing the vaccine, and there was no clear path toward licensure due to the unpredictability of outbreaks.

The same funding obstacles exist today with a number of vaccines that the military is developing. For example, a vaccine

under development for HFRS caused by hantavirus infections is currently in Phase 1 clinical testing, (ref. 8 and unpublished information). If the vaccine is shown to be safe and immunogenic in early clinical studies, as encountered with the Chikungunya vaccine, it might be difficult to find a commercial partner or a field testing site with sufficient disease to support FDA-licensure. Even in regions, where a phase 3 trial might be possible; that is, areas of China, Russia and possibly Finland,^{9,10} without a commercial partner, the cost would probably be prohibitive in that thousands of volunteers would need to be enrolled, and the cost of such a study would likely be well over \$100 million.^{11,12} Given issues such as these, if military vaccines for diseases like HFRS and several others are going to be licensed and available for use in the armed forces and in civilian populations, significant government or industry investments and innovative paths to licensure will be required.

Alternative Licensing Strategies and Incentives

In cases where it isn't possible to do human studies (cost not currently being an acceptable reason), an alternative licensing strategy must be pursued. Specifically, the recently defined "animal rule," allows licensure based on efficacy results of studies performed in well-defined animal models that reflect the human disease (reviewed in ref. 13). Safety studies in humans would still be required. This pathway to licensure is not necessarily easier or quicker than a traditional path, given that it is very difficult to correlate animal disease with human disease, and in some cases there are no animal models of disease (e.g., in the case of HFRS). In that situation, another unconventional strategy that the FDA has outlined involves the use of surrogate endpoints obtained in well controlled clinical studies that are shown to be reasonably likely to predict clinical benefit (USFDA 21CFR314.510). If marketing approval is granted using these criteria, then post-marketing studies would also be required to verify and describe the clinical benefit. For example, if neutralizing antibodies could be established as a surrogate marker of protection, then

it might be possible to obtain marketing approval from the FDA without a traditional phase 3 study, but efficacy as well as safety measurements would be included in the follow-up study.

Incentives for commercial development of vaccines with limited expected profitability also exist already and include the designation of Orphan Drug Status, which the FDA can grant for vaccines that will be administered to less than 200,000 people per year in the US. This incentive is particularly attractive to Pharma, in that developers receive a 50% tax credit for qualified clinical research expenses, a waiver of fees for the Biologics License Application (BLA), and a 7-year marketing exclusivity period (USFDA 21CFR316, Orphan Drug Act). Even more attractive to a commercial partner is the possibility of obtaining a "Priority Review Voucher," which can be awarded by the FDA when a Biological Licensing Agreement (BLA) is filed for a vaccine against a neglected disease. This process is intended to shorten the normal FDA review time by at least six months, and importantly, the vaccine developer can save this voucher to use for priority review of a more lucrative product, or they can even transfer or sell it to another company. Other means of shortening the review process would also very likely be attractive to commercial partners if they were available.

Innovations

Novel vaccine design and delivery methods are being intensely pursued by researchers in Government, Academia and Industry. Development of broad spectrum platforms that are suitable for "plug and play" types of vaccines could provide a means to generate multiagent vaccines that would both reduce the time to availability and also the shot burden for military personnel (and civilians). The platform that has so far come closest to this goal is plasmid DNA vaccines, which involves delivery of DNA plasmids engineered to express one or more genes of interest. To date, DNA vaccines have been tested in numerous phase 1 and phase 2 clinical studies, both for prophylactic and therapeutic purposes (reviewed in refs. 14 and 15). Overall, the potential of DNA vaccines has been

limited mostly by the need for better delivery methods, which will result in sufficient immune responses in humans. A similar concept, but with synthetic RNA instead of DNA, is in early developmental stages by several companies, and could offer the same plug and play advantages as DNA, but would avoid the need for delivery to host cell nuclei for gene expression.

Other platforms that might be suitable for many different types of vaccines are also under development, including virus-like particles displaying immunogenic proteins, nanoparticle vaccines produced by trapping proteins or nucleic acids in particulate substances (some with inherent adjuvanting properties), or even platforms that can modulate host immune responses. It is doubtful that a single platform will answer all vaccine needs, and to date, none of the innovative platforms have resulted in a licensed vaccine, although DNA vaccines have been approved for veterinary use.

Conclusion: What Should the Modern Military Vaccine Program Encompass?

Protecting the health of military personnel is clearly in the best interest of the US, and vaccination is the best way to prevent endemic and BW disease threats. The question, therefore, is how to pay for the numerous vaccines that would need to be developed to accomplish this goal. One answer might be for the military to just fund all of the efforts required. Many comparisons of the cost of medical countermeasures vs. the cost of fighter jets, tanks, etc. have been made, and while it is true that the DoD medical research program is small compared with the acquisition of artillery and vehicles, such comparisons are not really helpful, as the requirement for one does not negate the requirement for the other. Realistically, the chances of major increases in the DoD budget to pay for vaccines are not good. Consequently, it will be necessary to either reduce the scope of the effort to only a few high impact diseases, or to develop novel vaccine platforms and innovative (and shortened) licensing strategies to meet the need to protect deployed troops, and for spillover benefits to the civilian community.

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