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The Anthrax Vaccine Controversy
Questions about its Efficacy, Safety and Strategy

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ABSTRACT Although all U.S. Armed Forces personnel have been ordered to receive the anthrax vaccine, questions remain concerning its efficacy and safety and its intended use to counter a biological weapons threat. Since published data on the anthrax vaccine are scarce, it is difficult if not impossible to evaluate claims on its effectiveness and safety. In addition, questions concerning its safety have been raised, based on reports that associate the anthrax vaccine with high frequencies of adverse reactions and chronic illnesses. The chronic signs and symptoms associated with anthrax vaccination are similar to those found in Gulf War Illness patients, suggesting that at least some of the chronic illnesses suffered by veterans of the 1991 Gulf War may have been caused by vaccines. Commercial vaccines are often contaminated with microorganisms, such as *Mycoplasma* species, and this type of microbe has been found in the blood of a sizable subset of Gulf War Illness patients along with antibodies against an unapproved vaccine adjuvant. With concerns about safety and efficacy of the military's vaccines, the strategy of using multiple vaccines to protect against biological warfare agents must be re-evaluated in the context of integrated warfare and the potential simultaneous exposure of forces to chemical, biological and radiological agents along with conventional warfare environmental (smoke, chemicals, etc.) exposures.

Introduction—Anthrax Biological Warfare

To counter an increasing threat that anthrax spores could be used as a biological warfare (BW) agent all U.S. Armed Forces personnel, including reserve and National Guard members, were ordered to receive anthrax vaccine. This decision has resulted in disciplinary hearings among U.S. Armed Forces personnel who have refused, based on safety considerations, the anthrax vaccine.[1] Although rarely found in North America, *Bacillus anthracis* is a relatively common spore-forming, infectious soil bacterium in some areas of the world, and exposure to a lethal dose can cause death within one week of exposure. [2,3] Spore-forming bacteria like *Bacillus anthracis* fulfill the most important criteria for a BW agent—their spores are highly infectious, very pathogenic and stable in the air and environment for effective dissemination and infection by inhalation. Spores are relatively inactive metabolically and are much more resistant to sunlight, heat, dryness and chemicals than the replicating microorganism and are thus more effective as BW agents.[4]

Bacillus anthracis is one of dozens of lethal and incapacitating (causing nonlethal sicknesses) agents that have been produced for BW,[2] and it is one of the few BW agents for which a vaccine exists that is capable of preventing some (but not all) lethal infections.[3,4] Although weaponized (with enhanced survival and pathogenicity over naturally occurring strains) bacterial, viral, fungal and toxin BW agents have been produced by several countries,[2] *Bacillus anthracis* is considered one of the greatest threats because of the ease of its production, storage and dissemination as airborne spores.[2,4]

Three methods exist to counter microbial BW: (1) prophylactic administration of antibiotics or antivirals, (2) passive immunization using immune sera or monoclonal antibodies and (3) active immunization using vaccines.[1,3,4] Antibiotics and antivirals must be administered shortly before or after exposure to known BW agents to be effective, and in the case of anthrax BW, they cannot prevent a lethal infection once signs of illness have appeared.[4] Passive immunoprophylaxis requires quantities of immune sera or monoclonal antibodies not currently available, and their administration must usually occur in a monitored, hospital setting.[3] In contrast, active immunity can be effective if the vaccines are administered in an appropriate sequence, some for up to years before exposure, and if immunity is maintained.[1,3] Thus vaccines can be effective as long as enough immunity exists to neutralize BW agents like *Bacillus anthracis* before it starts rapidly replicating *en masse* from its inactive spore form and producing lethal toxins.[3] From a practical standpoint, only antibiotics, antivirals and vaccines can protect the large numbers of people who could be exposed in a BW attack. Antibiotics and antivirals are more effective when the BW agents and their antibiotic/antiviral sensitivities are known so the appropriate drug(s) and dose(s) can be used. Similarly, active and passive immunity require some immunochemical knowledge about the BW agent.[1,3]

Although currently the method of choice to protect against BW, vaccines—like the anthrax vaccine—may not be a reliable method of protection. For example, although vaccines can protect against accidental exposure of relatively small doses of anthrax spores infecting skin wounds, such as encountered occasionally in meat processing, it remains unproven whether the anthrax vaccine will protect against a lethal aerosol dose of inhaled weaponized anthrax spores.[3-6] This problem may be compounded if mixtures of BW agents are used instead of single agents.[1,3]

Safety Concerns—The Anthrax Vaccine

There are valid questions about the safety of the anthrax vaccine. It remains unproven in its ability to stop a lethal dose of weaponized *Bacillus anthracis* spores, and there are serious safety questions about the vaccine.[1,3,7] Although the anthrax vaccine used by the U.S. military was determined to be safe, and adverse reactions were originally found to occur at a rate of 1/50,000 doses, the rate of chronic health problems after receiving the anthrax vaccine may be 7-10% or higher.[8] The difference is that the official rates are for acute reactions only, and vaccine chronic reactions are claimed not to exist.

Assessing anthrax vaccine safety is dependent on how vaccine adverse effects are reported.[1] Often individuals suffering from adverse anthrax vaccine effects, especially in the military, are reluctant to seek medical care, because they have seen their colleagues' concerns dismissed as due to depression or stress. There have also been losses in assignment duties because of undiagnosed illnesses that began after receiving anthrax vaccinations. Officially the anthrax vaccine can produce adverse effects, such as soreness, redness, itching, swelling, and lumps at the injection site, but these are claimed to last only a short time. In addition, from 5-35% of people report muscle aches, joint aches, headaches, rash, chills, fever, nausea, loss of appetite, malaise, or related symptoms. More importantly, there have been no completed studies of the long-term side effects of anthrax vaccine using active surveillance.[8]

The difference between the official reports about adverse anthrax vaccine reactions and the complaints of vaccinated subjects appears to be based on whether it is accepted that vaccines can cause chronic illnesses beyond the initial reporting period of vaccine adverse effects. These chronic health problems include: polyarthralgias, polymyalgias, cognitive problems, weakness and numbness, fever, vomiting, diarrhea, splenic tenderness, among others, and these problems can occur well after the usual reporting period.[8] Patients with preexisting autoimmune illnesses such as rheumatoid arthritis, lupus, multiple sclerosis and other conditions, appear to be more likely to suffer a serious adverse reaction, as are those with neurologic diseases, such as childhood illness

caused by polio or other viral infections. Some anthrax vaccine recipients report seizures, loss of consciousness, respiratory distress and other pulmonary illnesses. Few of those reporting illness have been subjected to an intensive medical evaluation, including immunological testing, and thus the mechanisms by which anthrax vaccine may be causing chronic signs and symptoms have not been elucidated. The entire supply of anthrax vaccine is owned by the Department of Defense (DoD), and it has not been made available for independent testing.

Source of the Anthrax Vaccine

Specific information on the anthrax vaccine and its safety have proven elusive. Most U.S. military vaccines are FDA-approved and from sole-source manufacturers that must fulfill strict production, efficacy and safety requirements. However, the anthrax vaccine apparently does not meet these requirements. The sole licensee and producer of the anthrax vaccine was originally state-owned Michigan Biologic Products, Inc. (MBPI), who obtained approval for the vaccine from the NIH Bureau of Biologics in 1970, two years before efficacy data and approval were required by the FDA. Long-term safety data were not supplied with the license application, and evidently none have been supplied to the FDA. Moreover, the vaccine preparation procedures may be different from the original approved vaccine, and this usually requires that the vaccine and its altered preparation procedures are re-approved. The FDA has apparently not examined or approved modifications made to the current anthrax vaccine.[4]

The new owner of the anthrax vaccine license is Bioport, Inc., owned by investors lead by Admiral William Crowe, Jr., former head of the Joint Chiefs of Staff, DoD, and Faud El-Hibri, a German citizen (now naturalized American) of Lebanese descent. The facility was sold to Bioport after the DoD decided to vaccinate all of its forces against anthrax.[1] Recently Bioport ran into financial problems and negotiated changes in its DoD contract that increased by three-fold the per dose price of the anthrax vaccine.[8] The financial relationship between DoD and the new owners of Bioport have been questioned.[1]

The FDA and Anthrax Vaccine Safety

Problems with the anthrax vaccine have raised questions about previous military vaccine programs. Unlicensed anthrax vaccines were used on DoD personnel before the Gulf War,[9] but there is, of course, no record of safety available for unlicensed vaccines. Even for the anthrax vaccine there were no published studies of safety or efficacy until very recently, well after the decision was made to vaccinate. Although some safety information about the anthrax vaccine has been provided, it refers to previously unpublished data that are not available for evaluation.[10]

The FDA must review adverse reactions from approved vaccines through the Vaccine Adverse Event Reporting System (VAERS). Adverse events are usually recorded independently by a FDA-approved contractor, which then sends its data to the FDA, where upon the FDA assembles a committee that evaluates adverse events for the likelihood that the vaccine might have caused them and can then recommend further studies.[11] However, in the case of the DoD's anthrax vaccine, military physicians were instructed that only certain adverse effects could be vaccine-related (classic immediate allergic reactions), and others, such as polyarthralgias, polymyalgias, cognitive disturbances, etc. were not vaccine-related. Unfortunately, physicians treating these patients had no access to published data on anthrax vaccine adverse effects. The package insert for the vaccine is based on data collected from an earlier anthrax vaccine, and it does not list the possible reactions that could occur.[12] None of the vaccine's long-term chronic effects were reported until recently. Only reactions that resulted in hospitalization or immediate loss of 24 h duty time were reported to a military clearing-house for vaccine reactions.[13] This has now been changed, and it appears that adverse vaccine effects will be entered in patients' medical records, but it remains questionable whether they will always be reported to the FDA. Traditional and accepted means of FDA vaccine evaluation must be implemented for the DoD's vaccines, just as they are required for commercial

vaccines. The anthrax vaccine must be treated like other commercial vaccines and not given special waivers or treatment in the evaluation process.[1]

Quality of the Anthrax Vaccine

For years the FDA warned MBPI of intent to revoke their license to produce vaccines because of violations in vaccine production and testing. MBPI received formal written notification that they had not complied with FDA-mandated requirements, but since MBPI was the only manufacturer of anthrax vaccine, they were given a waiver and allowed to remain open, pending FDA compliance.[14] However, vaccine lots continued to be distributed to the DoD, and in 1998 some of these vaccine lots were retested, and only 6/31 lots passed initial supplemental testing.[15] Most of the retested vaccine lots had expired or had been redated for an additional 3-year period once or even twice.

Were expired or failed vaccine lots used for vaccinating DoD personnel during the Gulf War? Since supplemental testing on anthrax vaccines used in the Gulf War was not undertaken, and some of these lots apparently had previously expired and had been redated, some DoD personnel could have received out-of-date or contaminated vaccines. Information is not available on whether U.S. forces received contaminated vaccines. Thus some of the health problems associated with the Gulf War could be related to possible vaccine contamination.[1]

Vaccines and Operation Desert Shield/Storm

Before military personnel were deployed to Desert Shield/Storm, they had to pass physical examinations and be fit for active duty. Those that passed received several vaccinations, mostly with commercial vaccines. In the Persian Gulf theater this was usually done by administering as many as two dozen vaccine doses within a few days,[16] even if they were normally required to be given over a course of several months to over a year. In contrast to previous wars, DoD personnel were not allowed to keep a record of these vaccinations, and the shot records of hundreds of thousands of deployed personnel have since disappeared. Although some soldiers became sick after receiving the vaccines, medical personnel were not allowed to report vaccine adverse effects, unless hospitalization occurred.[4] Most personnel had to return to active duty, even if they suffered adverse effects directly attributable to the vaccines.

The administration of multiple vaccines all at once can result in immune-depression and susceptibility to opportunistic infections.[16] To be effective, the vaccines used in the Gulf War should have been given in several steps, over months to over a year to maximize immunity. Since this could not be done, they were given within a short time period. If given all at once, these vaccines are more likely to cause adverse reactions and produce diminished immunity.[1,4]

Vaccines and Gulf War Illnesses

Gulf War Illnesses (GWI) are characterized by complex, multi-organ chronic signs and symptoms, including chronic fatigue, headaches cognitive problems, nausea, gastrointestinal problems, vomiting, diarrhea, polyarthralgias, fever, splenic tenderness, polymyalgias, among other signs and symptoms.[17,18] Often these patients show the appearance of rheumatic and other autoimmune signs and symptoms. The signs and symptoms of GWI overlap with Chronic Fatigue Syndrome (CFS) or Myalgic Encephalomyelitis (ME),[17] and often they meet the criteria for diagnosis of CFS/ME or a related sydnrome, Fibromyalgia syndrome (FMS). Often included in this complex clinical picture are increased sensitivities to various environmental agents and enhanced allergic responses.[18] There are other clinical problems in these patients, including impaired cardiac function, increases in spontaneous abortions and other chronic signs. Importantly, the signs and symptoms reported by many anthrax vaccine recipients overlap with those that characterize GWI.[1]

In some cases GWI has apparently spread to immediate family members, suggesting an infectious nature. Although incomplete, a U.S. Senate committee found that ~77% of spouses and ~65% of children born after the war developed the chronic signs and symptoms of GWI,[19] indicating that at least a subset of GWI patients have a an illness that is being transmitted to spouses and children. These GWI cases cannot be explained solely on the basis of chemical or radiological exposures, or battlefield stress leading to Post Traumatic Stress Disorder.[16] Although stress can induce some illness, the link between stress and GWI has not been established.[20] Of course, stress can exacerbate chronic illness, and in the absence of physical or laboratory tests that could identify possible origins of GWI, many physicians accepted that stress was the cause of GWI or that it was caused by combinations of chemical exposure and stress. However, a recent psychiatric study indicates that patients with GWI do not fit the classical picture of a stress-related illness.[21]

If stress, chemical, biological and other toxic exposures are added to multiple vaccines given at once, then immune suppression and opportunistic infections could be a likely outcome in at least a subset of GWI patients. This would also explain in some cases the apparent transmission of illness to immediate family members and the occurrence of GWI in some vaccinated forces that were not deployed.[1]

Vaccine Contamination and Gulf War Illnesses

Contamination can and does occur in commercial vaccines.[22] Common commercial vaccine contaminants are *Mycoplasma* species, small cell wall-deficient bacteria lacking many of the genes involved in macromolecular and lipid synthesis. Mycoplasmas have now been implicated in a variety of chronic illnesses, including CFS/ME, FMS, Rheumatoid Arthritis, GWI, respiratory diseases, among others.[23] When we examined GWI patients for blood mycoplasmal infections, we found them in about one-half of GWI cases. One species in particular, *Mycoplasma fermentans*, was found at high incidence.[24,25] *M. fermentans* has been examined for its role in causing a progressive, non-HIV AIDS-like fatal disease that has many of the hallmarks of GWI.[26] In addition, the presence of antibodies to an unlicensed vaccine adjuvant in over 90% of the GWI patients evaluated strongly suggests that experimental vaccines were used in the Gulf War.[27] Experimental vaccines are unapproved vaccines without available safety and efficacy data.

Microorganisms like *M. fermentans* in commercial and experimental vaccines could be involved in the transmission of GWI to immediate family members. When tested for the presence of mycoplasmal infections in their blood, sick family members were found to have the same species of mycoplasma as found in the related veteran. In addition, most of these patients responded to the appropriate antibiotics and eventually recovered from their illness, albeit slowly, similar to CFS/ME, FMS and Rheumatoid Arthritis patients with mycoplasmal infections. When recovered patients were retested for mycoplasmal blood infections, they were no longer positive, suggesting that mycoplasmal infections could be causing at least some if not most of the signs and symptoms of GWI.[25]

Were the [experimental] vaccines or anthrax vaccine used in the Gulf War the source of the mycoplasmas found in veterans' blood? Although listed as our number one possible source of the chronic infections found in GWI patients, vaccines were not the only possible source. The Iraqis were known to have extensive stockpiles of BW agents and the potential to deliver these weapons offensively, at short range in modified Italian-made biological sprayers and at long range in modified SCUD-B (SS-1) missiles with 'airburst' warheads or sprayers carried by aircraft. Many of the storage and factory facilities where BW agents were stored were destroyed immediately up to, during and after the Desert Storm ground offensive, releasing plumes that could have caused 'blow-back' exposures.[16] These and other possible mechanisms of potential exposure must be carefully examined.

Protection Against BW Attacks

If BW agents are ever deployed in war or terrorist attacks, many times the lethal (human) dose could be encountered in an aerosolized BW-chemical mixture (Russian Doll Cocktails) designed to inhibit and overwhelm the body's defensive abilities. The pulmonary immune system, particularly the pulmonary macrophage, is the first level of defense against inhaled foreign microorganisms and its suppression could result in systemic infection. Future BW use will likely involve multiple BW agents and chemical mixtures to heighten virulence and confuse the diagnosis and treatment of casualties. BW can be developed and produced at a fraction of the cost of other weapons of mass destruction, making it likely that future terrorists will choose BW agents over other weapons.

Our defensive strategy against BW agents is prior immunization using multiple vaccines. This can only be successful if the exact agent(s) likely to be encountered is known in great detail and for some time in advance of exposure. Obviously, this strategy requires advance knowledge of the threat and careful long-term preparation. To prepare for new threats that arise requires time, possibly years or over a decade. Recent reports indicate that the Russians have developed anthrax strains for which it is claimed protective vaccines do not exist. This poses a problem for our vaccines if they will not protect against all known anthrax strains.[6]

Strategies other than the vaccine approach to BW defense exist and have been used successfully. During the Gulf War the French forces did not to use vaccines as a primary defense against Iraqi BW and not to use anti-nerve agents as a defense against Iraqi Chemical Warfare agents. Instead, they used prophylactic antibiotics to counter BW agents, and they depended on protective suits to counter chemicals. The French Armed Forces were the only nation in the Coalition Forces that did not report any or only a few cases of GWI, nor were there any illnesses reported in the immediate families of French veterans. Interestingly, certain U.S. units were issued antibiotics like ciprofloxacin and doxycycline, and these antibiotics would be expected to be effective in preventing infections of at least two of the agents identified in veterans with Gulf War Illness (*Mycoplasma fermentans* and *Brucella spp.*). Examination of deployments and types of casualties and their diagnoses in the units administered antibiotics before and during the Gulf War could tell us if this approach was more effective than administering multiple vaccines to prevent BW casualties.[16]

If prophylactic antibiotic or antiviral agents are used for BW defense, can these be defeated? Certainly—BW agents can be modified or constructed that possess antibiotic- or antiviral-resistance genes. Similar to the engineering of more lethal BW agents to circumvent known vaccines, such microorganisms can be engineered to resist specific antibiotic or antiviral agents.[1]

Vaccines and Disease

What assurances do we have that future vaccines will be free of microbial contamination that could cause disease? The purity and safety of vaccines depend on their ability to remain free of contamination by microorganisms.[22] FDA-mandated vaccine preparation methods are generally considered adequate to prevent this possibility, but unless each lot of vaccine is routinely tested for possible contamination, including animal testing, there remains a possibility that vaccines could be contaminated.

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