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The social, political, ethical, and economic aspects of biodefense vaccines

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Abstract

Besides natural disasters and naturally occurring novel infectious diseases, nothing potentially threatens the health and stability of nations and health systems as much as the devastating threat and unfathomability of bioterrorism. Other than attempts at political solutions and interdictive attempts, only antimicrobials and vaccines offer possible means for protection. Of these, vaccines offer the most immediate and definitive of preventive solutions. Limiting the development and use of vaccines however are social, political, ethical, and economic considerations, and this article will provide a brief exploration of each of these issues and the intersection with the need for such vaccines. In this article we define bioterrorism as the deliberate use of naturally occurring or bioengineered microorganisms in order to cause harm to people, animals, or plants.

Keywords

Biodefense; Smallpox vaccine; Anthrax vaccine; Bioterrorism

1. What is the concern?

History informs valid concerns regarding bioterrorism. While a thorough discussion is beyond the scope and intent of this paper, it is clear that States, lone individuals, and political/terrorist groups have and mean to acquire and use biologic weapons in order to achieve a variety of political ends. In addition, widespread population susceptibility to these agents exists, placing the sustainability of nations at risk should a widespread bioterrorism event occur. In 2001, within the United States 22 cases of inhalational anthrax resulted from weapons-grade anthrax powder sent through the US postal system, resulting in 5 deaths. These attacks resulted in

disruption of the postal system, the Senate and Senate buildings, airlines, and multiple other entities important to national economy and political life.

Similarly, an outbreak of monkeypox in the US and concerns over use of smallpox as a weapon resulted in large scale vaccination programs against smallpox in US military forces, and attempts at implementing a similar program among civilian health care workers and first responders [1,2]. In combination with increasing global political instability and radical fundamentalism, valid concerns over the ability to protect the civilian population against agents of bioterrorism remain widespread. Recognition of this threat, and methods with which to mitigate the threat, remains at the highest levels and with much public debate.

2. Current vaccines

At the current time only a limited number of FDA-licensed vaccines against bioterrorism agents exist in the US. These are vaccines against smallpox and anthrax. A number of biodefense vaccines in IND (investigational new drug) status exist, but are only used in extremely limited, special circumstances, and are neither suitable for nor available for widespread use in the civilian populations. In addition, passive immunization utilizing hyper-immune globulin is available for smallpox. Thus, for the majority of infectious disease bioterrorism threats, we, in fact, have no useful vaccine countermeasures. The Centers for Disease Control and Prevention (CDC) lists many infectious agents of concern (Category A–C agents) that could be used as agents of bioterrorism. This, of course, does not include the possibility of bioengineered agents.

A variety of issues conspire to make the use of the currently licensed vaccines among the general public not feasible. Chief among these are cost, limited vaccine availability, and reactogenicity/adverse events. Smallpox vaccine is a live virus vaccine, and as such a large number of contraindications exist such that an estimated 30–50% of the general public would be ineligible to receive the vaccine absent a high risk of exposure or actual exposure. For example, smallpox vaccine is the most reactogenic of all currently licensed US vaccines, and can lead to death (rare) and serious or life-threatening adverse reactions [1]. An additional concern for smallpox vaccine is that of human-to-human transmission of the vaccine virus to others.

As another example, at the current time anthrax vaccine requires a series of 6 injections over 18 months, followed by yearly boosters, making administration among the public impractical, absent a quantifiable risk of exposure. While some members of the US military receive this vaccine, limited availability of the vaccine is an issue, and the vaccine is not available to citizens on a routine basis.

3. Political concerns

Political concerns play an important decision-making role in both the decision to develop and the decision to use biodefense vaccines. Due to the sizeable time and monetary costs incurred, embarking on a vaccine development program must be informed by evidence of a credible threat. The decision by one country to develop a vaccine against a bioagent implies knowledge that another country has weaponized such an agent and has the intent, will, and means to use the agent as a bioweapon. The sudden resumption of use of smallpox vaccine among one nation's military, prompts concern and use in other countries. Politically this sends an important message to neighboring or other nations. Within domestic politics concerns also exist. The development of new vaccines is expensive, and funding such a program means diverting funds from other needs. This complicates decision-making and introduces a variety of considerations difficult to reconcile among the public.

4. Ethical concerns

Bioterrorism poses real dangers and societies possess a moral obligation to mitigate that risk [3-5]. Nevertheless, discussions of biodefense preparedness can lead to political battles, involve serious questions of research ethics, challenge the boundaries of professional obligation, and require important value judgments once ready for implementation. Mistakes in any of these sensitive areas can jeopardize the integrity of healthcare professionals and public health officials and their established bond of trust with the public.

As history teaches, when war, terrorism and fear mix, decision makers are susceptible to the influences of bias and political interests. King has argued that by framing risks of emerging very large public health problems in terms that make particular interventions (vaccines) appear necessary, logical, or practical; scientists and politicians build alliances and thereby acquire power and resources [6].

On a practical level, biodefense vaccine development and implementation raise several ethical challenges most notably in three areas: establishing informed consent during clinical testing, defining professional obligations of healthcare workers to participate in vaccine development research and fairly allocating vaccines once developed. Ethical standards of informed consent require autonomous authorization from participants with decision-making capacity informed of the risks and benefits of the research [7]. In particular, this principle must extend to all members of society and participation in studies of or receipt of experimental vaccines must not be presumed or forced upon anyone—absent exceptions codified in just law. As one challenging example, the development of biodefense vaccines could require development and testing of novel methods of delivery whose risks and benefits are largely unknown, making informed consent difficult or impossible.

Risk is the product of probability of an event multiplied by the severity of the event. For biodefense vaccines, there is considerable uncertainty about how to determine the probability of adverse events, as well as the probability of benefit, absent defined or known risks of exposure. Thus, disclosing the risks and benefits of participation in vaccine trials absent a current and tangible bioterrorism threat may be especially difficult. It is hard to image how, for instance, a healthcare worker should think about the personal risks and potential benefits of participating in a trial of a novel smallpox vaccine—the frequency and severity of a future attack is virtually incalculable, and the marginal benefits therefore are hard to conceptualize. Thus, often the risks as well as the benefits of biodefense vaccines are and will remain unknown until after their implementation. For this reason, research participation in the case of biodefense vaccines exacerbates the general challenges in research ethics related to informed consent. In such cases, we especially need to acknowledge the limitations of informed consent and insure that additional ethical safeguards beyond informed consent are in place such as the use of “best interest” standards, extensive community involvement, or additional layers of independent oversight. Each of these has been used in other circumstances where obtaining consent is not possible.

Establishing a strong professional obligation of healthcare workers to participate in vaccine development activities is also a challenging task. The fledgling attempts to get healthcare workers to accept smallpox vaccination as part of the 2002–2003 Federal plan to create smallpox response teams illustrated this struggle. The plan faced stiff opposition from individuals, institutions, and professional organizations. Even after legislation clarified liability concerns, health care professionals responded meagerly. While healthcare professionals clearly have an obligation to subject their interests and needs to that of the patients they serve, absent an actual outbreak, it is difficult to see why healthcare workers have a special duty to participate in vaccine development research. Thus, a well-founded case establishing a

professional obligation for healthcare workers to participate in such research based on national security interests has not yet been developed, given that healthcare workers signed up for patient care, not national defense. Unlike the case of routine seasonal influenza where the risks are clear and moral obligations of the healthcare provider unambiguous [8], in the setting of bioterrorism, at best professions have a general, collective responsibility to promote public health preparedness but not necessarily a specific individual obligation [9].

Once vaccines are developed, tested and are ready for implementation other tough ethical choices will need to be made [10,11]. These include deciding who gets priority in receiving first dosing of vaccines, and what freedoms can be limited for the sake of the public good. These choices may well raise serious questions about where our personal and civic obligations lay in the setting of pandemic or bioterrorism conditions [12].

It is important to notice that under conditions of scarcity, either we will make deliberate allocation decisions based on sound principles, or expedience, self-interest, and serendipity will prevail. In the case of pandemic influenza preparedness, Persad et al. have proposed a “fair lifespan” model of rationally allocating scarce vaccines. They propose that those whom families and society have invested most in should be given the greatest priority to live a full life [13]. Others would resist such a consequentialist rationale; but regardless of ones final judgment about specific allocation proposals, we must admit that without defensible and proactive allocation principles biodefense vaccine implementation is likely to exacerbate existing inequities in public health.

We would argue that these and other ethical decisions must involve public, truthful, and balanced deliberations to insure long-term public trust and sustainability of the public health objectives of biodefense preparedness. However, achieving such a standard will be no small task.

5. Social concerns

In many ways, the social concept of vaccines for biodefense has undergone two major shifts. Our only two FDA-approved vaccines, smallpox and anthrax, were not at all developed for biodefense. They were initially developed and deployed for the prevention of communicable and occupational diseases. In fact, both have been successful in protecting against those diseases. Smallpox as a communicable disease was announced as eradicated in the 1970s and routine vaccination against smallpox ended with the exception of its use in preventing harm from occupational exposure to vaccinia.

Our major defense strategies against bioweapons have been similar to our major defense strategies against chemical warfare. Organized nations agreed to conventions such as the Geneva Convention regarding the prohibition of certain types of weapons including biological and chemical warfare. The prohibition codified by these conventions were supported by a shared sense across the international community of their unacceptability with the understanding that violations of these conventions would be enforced by some form of recognition and prosecution as war crimes.

Indeed, the rise of terrorism in the 21st century, combined with the actual use of anthrax as a biological weapon, has created a second social shift in the consideration of vaccines for biodefense. We now struggle with the conceptualization of a threat or enemy that is nationless and borderless, an enemy who will not agree to certain conventions in war and peace, and an enemy who often lacks even a commitment to self-preservation and survival of its people in pursuit of its ideology.

These concerns have developed during a time when science and technology have developed to the point of containing and controlling biological agents effectively as bioweapons. Simultaneously the ability to travel safely and rapidly to deploy those bioweapons internationally is easier than ever. Mass communication, with rapid and better broadcast than ever, equips terrorists with the ability to publish their threats and demands, leaving large populations feeling vulnerable to further attacks.

Thus we have witnessed the emergence of a global need for biodefense against bioterrorism that goes beyond conventions and treaties and the jurisdiction of war tribunals. Thus, on a social level, our need for biodefense vaccines is different now than it has been before. Just as nations before recognized a need to agree to prohibit the use of bioweapons in times of peace and wars, nations now might agree for a need to collaborate internationally to develop vaccines against bioterrorism.

There are other social implications of biodefense vaccines. In our discussion of ethics, we considered the issues of product rationing. We must also consider other social issues in the development and deployment of such vaccines such as managing non-compliance, overseeing testing, and controlling the means of production. As noted above, the scarcity of biodefense vaccines raises questions regarding the rationing of the distribution of those vaccines in times of need. The biodefense vaccines that are currently licensed (e.g., anthrax and smallpox vaccines) remain in the near exclusive use of the military, but we would need to consider civilian distribution in times of imminent threat and of course post-exposure. In preparation for potential bioterrorist use of smallpox in 2003 and 2004, public health officials gave consideration to a number of strategies including ring vaccination of those in direct contact with diagnosed smallpox patients in the event of an attack, preparatory vaccination of first responders, and voluntary population vaccination [1].

In recent years, the military had to deal with personnel refusing anthrax vaccinations despite the vaccine's licensure and track record of safety [14]. Similarly, following presumed exposures in October 2001, postal workers and other civilians likewise refused anthrax vaccine when offered. Furthermore, during the execution of the National Smallpox Vaccination Program, healthcare workers refused smallpox vaccination [15]. Since some bioweapons result in contagion, refusal of vaccination affects more than personal risk. As we have during epidemics, we may need to require vaccination regardless of personal considerations for certain categories of individuals where society has a vital interest [2].

We also need to address the clinical testing necessary for safe and effective use of biodefense vaccines. At a minimum we will need to conduct pre-exposure and post-exposure studies of new biodefense vaccines, as well as studies of older vaccines that currently lack data supporting their use in specific populations including children, pregnant women, the elderly, pregnant women, and others. Testing biodefense vaccines in children remains ethically problematic. After an extensive review by empanelled experts and consideration of public comment, the Secretary of the Department of Health and Human Services and the Commission of the Food and Drug Administration disapproved a study of smallpox vaccination in children 2–5 years of age [16,17].

Issues also arise in regard to the production of biodefense vaccines. Should the government depend upon commercial interests to produce sufficient quantities of safe and effective vaccines? [18]. Can we permit private companies to manufacture and distribute such vaccines freely? What steps should society take to prevent sales to those who might use the bioweapons and benefit from the immunity due to the vaccine? What is our basis for restricting their availability? Such challenges require further debate and rational decision-making.

6. Economic concerns and challenges

The development and effective deployment of biodefense vaccines in the US are limited by several economic factors. From industry's perspective, critical economic issues include the costs of vaccine development, costs associated with potential product liability, and indeterminate market size [19,20]. Bringing a new biodefense vaccine to market may involve 10 or even 20 years of research and investments of hundreds of millions of dollars. The federal government through the Biomedical Advanced Research Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services, the Department of Defense, and other federal agencies has facilitated biodefense vaccine development through increased spending for biodefense vaccine research grants and contracts, but this investment has not been sufficient to move the biodefense industry much beyond a nascent stage [19], and we still have just two FDA-approved biodefense vaccines available, anthrax and smallpox vaccines.

The Public Readiness and Emergency Preparedness (PREP) Act of 2005 provides for immunity from tort suits on designated products for those involved with the development, production, and distribution of biodefense countermeasures and has addressed many of industry's liability concerns—as well as concerns of government planners and those involved with the distribution and administration of biodefense vaccines [20,21]. However, concerns remain about whether our current laws provide the right balance of legal protections while also providing for adequate compensation mechanisms for persons suffering adverse events [21,22].

Supply and demand issues remain as considerable issues. How shall large numbers of doses of these vaccines be supplied in a short time period during an actual event? The US government has worked with vaccine manufacturers to guarantee purchase of minimum numbers of doses for pre-event use or for stockpiling for possible post-event use. However, issues of shelf-life longevity further impact stockpiling and supply/demand decisions. Nevertheless, the ultimate number of doses that might be sold for pre-event or post-event use is uncertain and/or relatively small, and delays in obtaining contracts for guaranteed purchase can leave vaccine manufacturers in vulnerable economic positions [19].

From the individual's perspective, economic considerations are particularly relevant with regard to possible adverse events associated with vaccination. Biodefense vaccines may have unknown or even relatively high risk benefit ratios, especially for pre-event vaccination. Individuals experiencing adverse reactions to biodefense vaccines may become ill, incur health care costs, miss work, or even die. Recent experience with the phase I civilian smallpox vaccination program initiated in 2002–2003 illustrates some of these challenges for individuals. Even with a no-fault compensation program (Smallpox Vaccine Injury Compensation Program created by the Emergency Protection Personnel Act of 2003), compensation for adverse events associated with smallpox vaccination was limited by caps on awards, compensation for lost employment, and survivor benefits and complicated by reliance on other primary sources of compensation like paid sick leave and workers' compensation [22]. The no-fault compensation scheme provided by the PREP Act of 2005 still has limitations with the resulting risk of inadequate compensation for persons who experience adverse events [21].

From the societal perspective, the costs associated with use of biodefense vaccines can be substantial. The existing public/private infrastructure that might be used for mass vaccination programs may be inadequate and underfunded and would have to be substantially expanded for timely administration of vaccine. Some of the costs associated with this infrastructure expansion and vaccine delivery may not be covered by federal or other sources of reimbursement. For example, with the phase I civilian smallpox vaccination program, estimates of the cost of vaccine administration varied by more than 100-fold, with state public health

departments and hospitals being underfinanced for their final direct costs [22]. Concerns among many implementers about insufficient resources were recognized as barriers to program implementation [23]. Society also bears substantial direct and indirect costs associated with potential serious adverse events following vaccination. A recent analysis of cardiac adverse events associated with smallpox vaccination highlights the potential burden associated with adverse events with mass vaccination. For every million smallpox vaccinees, there would be >3000 cardiac adverse events that would require a sizeable amount of medical resource utilization including nearly 8000 healthcare visits, over 15,000 medical tests, and hundreds of hospitalization days. Worker productivity would also be reduced by nearly 16,000 work days [24]. Thus, economic barriers at the manufacturing, distribution, individual, and societal levels continue to conspire against the rapid development and use of new biodefense vaccines.

7. Conclusion

The development and deployment of vaccines against bioterrorism threats have multiple concerns not usually associated with vaccine development against standard infectious disease threats. These include political, ethical, social, and economic concerns not normally present for standard vaccines. A practical concern also exists—that of an inadequate base within the next generation of investigators and clinicians skilled in the diagnosis and prevention of the diseases of concern. For many of these diseases, it is doubtful that current or future clinicians will have expertise in the recognition and treatment of these diseases. Similarly, experts who have worked in the lab with these agents and who can develop vaccines and therapeutics against these diseases remain few in number. In toto, these concerns form sizeable barriers to vaccine and therapeutics development. In the US, only two FDA-licensed vaccines, smallpox, and anthrax, are available as bioterrorism vaccine countermeasures. Many more vaccines are either in preclinical development or at the IND stage. Whether the factors discussed above will prove to be “no-go” barriers to licensure, and hence availability for use, remains an open question. New programs such as BARDA should, in part, accelerate private sector interest in developing such vaccines. Nonetheless, in a current global era of unusually constrained and insufficient resources, it remains unclear how to weigh the tremendous costs of vaccine development against the intangible risks of bioterrorism. The calculus may just be too unclear at this point in history, yet this is a situation that invites innovation in vaccine development and deployment. Achieving solutions to this dilemma will require cooperation between nations, industry, academia, and others. This will be difficult, iterative work, and further requires public discourse and education in order to make sustainable and informed decisions. Nonetheless, doing nothing or continuing on the current path, is both untenable and unresponsive to the concerns, needs, and fears of governments and the populace. We believe that there may be utility in addressing these common issues, and developing lower cost, rapid methods of vaccine development, testing, and deployment; in the context of a multidisciplinary, multinational forum, jointly funded by interested nations who understand the values associated with joint vaccine development and production. Whether traction for such an idea can be generated prior to a significant bioterrorism event is unknown, but it will take political will, resources, and wisdom.

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