Smallpox Biodefense: A Multifactoral Analysis

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ABSTRACT

An integrated analysis of the multiple factors involved in smallpox biodefense planning indicates that pre-attack voluntary, controlled smallpox vaccination would provide the most viable defense. The essential factors include the historical virulence and infectivity of smallpox, the contemporary lack of herd immunity, current response capabilities, vaccine risk, the likelihood and progression of a smallpox bioterror attack, the potential for global spread, psychosocial factors, and political factors.

Historical Virulence

The virulence of smallpox has been well known for thousands of years. In the 20th century alone, smallpox was responsible for 300 million deaths worldwide, despite the existence of a very effective vaccine for more than 100 years before the start of that century.[1] This huge death toll is even more striking in view of the fact that the disease was essentially nonexistent for the latter third of that century. The World Health Organization (WHO) declared it to be completely eradicated in 1980.[2] The devastation occurred despite significant herd immunity to the disease. A third of those who were exposed to the disease contracted it, and a third of those who contracted the disease died.[1]

The effect on a world without any significant herd immunity would undoubtedly be much greater, as occurred when the Native American population first encountered the smallpox virus. Many tribes lost a majority of their members to the disease.[3] The universal susceptibility to the disease is shown by the fact that even in populations with herd immunity in the 18th century, almost the entire population contracted smallpox before reaching adulthood, [4] and the scars of smallpox marked most of the population.[5] Today, the probability that an unvaccinated individual who encountered the virus would contract smallpox is likely much greater than one-third, and may approach 90 percent. The risk is magnified by increasing numbers of those with immunodeficiency and other disorders that would increase individual susceptibility, morbidity, and mortality.

Infectivity

There is a well-known significant level of infectivity of the smallpox virus, with well-documented examples such as those seen in Europe during the 1970s. In Germany in 1970, a single case of smallpox admitted through the emergency room of a hospital led to 19 additional cases on multiple floors of the hospital via airborne transmission, including a case in a person who had visited the hospital (not the infected patient) for only 15 minutes.[6] In Yugoslavia in 1972, a single case of smallpox transferred multiple times before the diagnosis was made, initially infecting 11 others, who in turn infected 138 more people, leading to the isolation of 10,000 people and the vaccination of 20 million.[7] It is of note that this high transmission rate is far in excess of the single-digit rate usually attributed to smallpox. Also note that these events occurred in an era of relatively high herd immunity. The former Soviet Union's biological warfare planners recognized the infectivity of aerosolized spread of smallpox as so great that they considered it the only biological weapon that could be successfully delivered by intercontinental ballistic missile (ICBM), and special warheads were developed for this purpose.[8]

Current Response Capabilities

Current response plans focus on trying to isolate any cases of smallpox, and rapidly implementing mass vaccinations after a case has been confirmed, by vaccinating around the index case(s) ("ring" vaccination), and then beyond to the rest of the population.[9] The development of such plans has relied heavily on the Third World experiences of WHO's smallpox eradication program of the mid-20th century, but these experiences are not as relevant to modern American biodefense, because of such factors as the rapid and extensive travel of the American population,[10] and absence of any significant herd immunity. By the time a single case of smallpox is diagnosed anywhere in the United States, it would mean that the entire nation has potentially been exposed, and that the whole world is at risk.

In contemporary America, isolation and rapid mass vaccination programs will have great difficulty in interrupting the spread of the disease from beyond those initially infected. Even very limited tests of such programs have required very large public health and volunteer efforts[11,12] that could not reasonably be scaled up and sustained to the level necessary to keep bioterrorist-caused smallpox from spreading beyond the cases expected in the first two epidemiologic cycles of the disease.

Vaccine Risk

There is a relatively low risk to controlled vaccination of the U.S. population before a smallpox outbreak, compared to the risk inherent in rapid mass vaccination. In 1968, the last year of universal vaccination in the United States, 14.2 million people were vaccinated, with only nine deaths attributed to vaccination-related complications.[1]

Contemporary risks of smallpox vaccination have been reduced through recent medical advances, such as a better ability to assess immunocompromise in potential vaccinees, the use of transpirational occlusive dressings (e.g. Tegaderm or OpSite) for vaccination sites,[13] greatly improved supportive care, availability of vaccine immune globulin (VIG),[14] and the development of cidofovir for the treatment of vaccinia complications.[15]

Recent experiences with vaccinations of military personnel, and with limited vaccination of U.S. medical workers in 2003, confirm the lessened risks of modern vaccination practices.[16,17] The risks, however, would undoubtedly increase greatly in the confusion of a panicked rapid mass vaccination because of resultant less careful assessment of the immunologic status of potential vaccinees, suboptimal dressings for vaccination sites, and less chance for individualized attention after vaccination.

In such a situation, resources to deal with vaccinia complications would be limited, as the nation attempts to develop a surge capacity to vaccinate large numbers of people within a short time. Many vaccinia reactions would occur simultaneously across the nation, at the same time that the nation would be coping with a smallpox outbreak. There would be a shortage of inpatient and intensive care facilities, isolation facilities, VIG, and cidofovir. Vaccinia reactions might be difficult to distinguish from smallpox infections. Any potential complications of smallpox vaccination would be much better handled in the calm situation of controlled vaccination over an extended period, rather than within the crisis of a bioterror attack.

Consequences of a Bioterror Attack

Given the contagiousness of smallpox, it is reasonable and conservative to expect that one infected person would on average infect three others in the time between an initial bioterrorist attack and the time that smallpox is first diagnosed. It is easy to envision a bioterrorist initially exposing 1,000 people to the disease in a covert attack. Such an attack could involve a group of self-sacrificing terrorists who become infected with smallpox prior to entering the United States and then disperse themselves across the country during the incubation period. Aerosolized dissemination of the virus might theoretically be another means of viral spread[18] that would expose terrorists to less risk, and their command structure to less exposure.

Assuming the traditionally accepted likelihood that a third of those exposed contract the disease, then at least 300 people would become infected. It might be conservatively, and optimistically, hoped that the disease will be diagnosed during that first epidemiologic cycle of exposure. We might also hope that increased awareness would decrease the average number of others to whom an infected person might pass the disease, and that the average would be only one person after the first epidemiologic cycle. This would mean that in the second epidemiologic cycle, there would be at least 300 new cases expected, which would total at least 600 cases in the first two cycles.

Further assuming the traditionally accepted likelihood that a third of those who contract the disease would die, then at least 200 deaths would result from the first two epidemiologic cycles in such a conservative scenario. So, the number of initial deaths resulting from a bioterror attack that exposes 1,000 people to the smallpox virus exceeds the number of deaths expected if the 1968 vaccinia reaction data is extrapolated to the contemporary American population. Such numbers would increase if the disease is not diagnosed early in the first epidemiologic cycle, or if more than 1,000 people are initially exposed to the virus. A larger attack or several simultaneous attacks can be easily envisioned.

Likelihood of Biowarfare

It is vital to consider the likelihood that smallpox could be used as a biological weapon. It has already been used in biowarfare in each of the previous three centuries. During the French and Indian War in the 1750s, the British purposely supplied Native Americans with smallpox-infected blankets.[19] During the War Between the States in the 1860s, Confederate sympathizers purposely sold smallpox-infected clothing to Union troops,[20] and during the 1930s the Japanese experimented with smallpox in Manchuria.[21]

There is a strong possibility that smallpox could be similarly used in this century. After proposing the resolution for declaring the global eradication of smallpox to the 19th World Health Assembly in 1966,[22] the former Soviet Union produced large quantities of the virus as part of its biological weapons program. It is unknown how much of this production is unaccounted for.[8] Fears were heightened by revelations that sources of the smallpox virus exist outside of the two WHO-designated repositories in the United States and Russia.[23] France may have surreptitiously held a smallpox virus cache,[24] and the U.S. government has reported that "rogue nations" such as Iran and North Korea also have stocks of the smallpox virus.[25] Ominously, in 1998 North Korean military defectors were found to have been recently vaccinated against smallpox.[26] The availability of the smallpox virus, along with the ideological orientation of potential terrorists, makes the probability of a smallpox outbreak within our current generation very high.

Global Risk

The United States is probably the most likely target for a bioterrorist attack, but the effects of such an attack would not be limited to this country alone. Given the availability of rapid international travel, an infectious bioterror outbreak could quickly spread throughout the world.[27] Such concerns would not deter committed terrorists, who have shown little regard for collateral casualties. Third World nations stand at the greatest risk of collateral spread of smallpox because of their relative lack of resources to combat an outbreak. Thus, the vulnerability of the U.S. to the smallpox virus places the poorer nations of the world at the greatest risk. This is especially true of those underdeveloped African nations that concurrently suffer from high rates of infection with the acquired immune deficiency syndrome (AIDS) virus.

Psychosocial Factors

Poor understanding of the nature of terrorism hampers America's ability to take decisive action against this threat. There is a tendency to view each new war from the mindset of the last war.

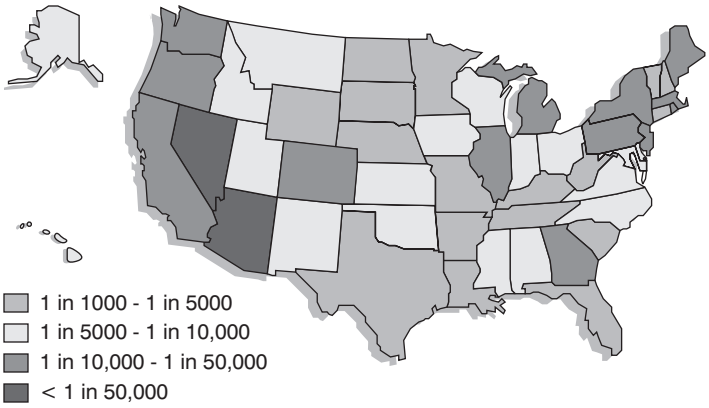

Figure 1. A Biodefense Failure: the National Smallpox Vaccination Program One Year Later. Prepared by Democratic Members of the House Select Committee on Homeland Security. January, 2004.

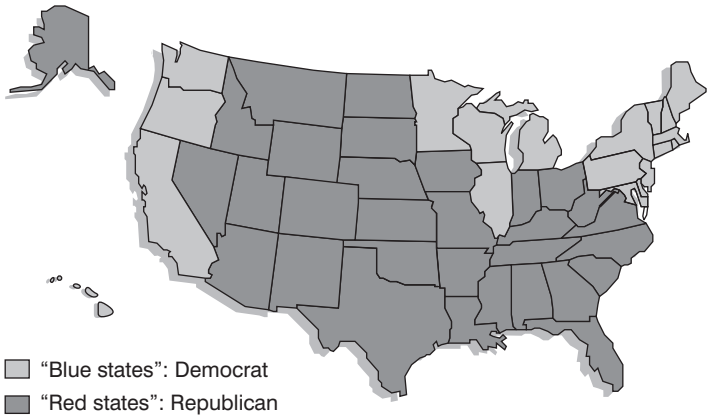

Figure 2. Election 2004 National Results Prepared by Yahoo! News, November 8, 2004. Available at: http://news.yahoo.com/electionresults.

Thus, Americans tend to view the current threat of bioterrorism in the same light as they viewed the nuclear weapons of mass destruction (WMD) threat of the Cold War. Under the mutual assured destruction (MAD) concept, both sides viewed the consequences of a nuclear war as being too devastating to risk starting one. Thus, because the results of an attack with smallpox appear so horrific to Americans, there is a tendency to view the probable incidence of such an attack as low. The MAD mentality, however, is not shared by non-state terrorists who use such tactics as suicide hijackings and suicide bombings.

This perception of low smallpox risk is the reason that current planning seems overly risk-averse to vaccination, as is exemplified by the emphasis on vaccine complications,[28] vaccine medical-legal concerns,[29] and worker compensation concerns for those medical workers who were considering vaccination in 2003.[30] All such concerns would be expected to vanish in the event of a smallpox outbreak, in much the same way that the anthrax vaccine concerns of the 1990s[31] vanished after the anthrax letter attacks of 2001.[32]

Political Factors

Immunization policy in the United States is highly politicized, as shown by the political polarization surrounding the influenza immunization shortage in 2004.[33] There is an interesting correlation between acceptance of smallpox immunization by medical workers in 2003 (Figure 1) and the state-by-state outcome of the 2004 Presidential election (Figure 2). While the reasons that medical workers declined smallpox vaccination in 2003 are many and varied, and included such considerations as liability issues, vaccine complications, and the potential of transmission of vaccinia to patients or family, political factors may have contributed. Would the map of per-capita smallpox vaccination have been different if a different political party had held the Presidency at the time, or had the issue not been perceived as intertwined with election-year politics?

Decision Making

Because decisions related to biowarfare defense are national and multifactoral, they can only be made at the Presidential level, but must be, and appear, nonpartisan and in the interest of all. If the decision were made to vaccinate the U.S. population in advance of a smallpox outbreak, it would be best announced jointly, with all state governors, in conjunction with bipartisan legislative leadership support, and it should be timed to avoid election-cycle concerns. For instance, such a decision could ideally be made before the end of 2007 by the current Presidential administration, which is not eligible for reelection. Only a voluntary immunization plan would be accepted in advance of a smallpox outbreak, and its announcement must include not only medical information on the disease and the risks of immunization, but also information on geopolitical risk, current response limitations, and contemporary psychosocial influences, so that consent would be fully informed. The Department of Health and Human Services should provide leadership as an "honest broker" of an immunization plan that must include private and local physicians and medical workers, as well as hospitals and departments of public health.

Conclusion

There is no question about the necessity of immunization as a defense against smallpox if the virus is used as a biological weapon. The controversy concerns timing. Should we wait for an outbreak? Or should we institute a voluntary program in advance of a potential outbreak? I believe that medical, geopolitical, and psychosocial factors determine that fewer disease casualties and vaccine complications would occur with preemptive vaccination than with mass vaccination after an outbreak, and that reliance on the "ring" vaccination concept alone is almost certain to fail in the absence of herd immunity and the presence of rapid international travel.

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Acknowledgement: I would like to thank the staff of the Preston Medical Library at the University of Tennessee Medical Center for their assistance in research for this paper.

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