Preparing for Smallpox:
Bioterrorist Threat or Quixotic Delusion?

ABSTRACT: Terrorist attacks on the United States since September 11, 2001, have raised the specter of smallpox as a potential bioterrorist weapon. Although the World Health Organization proclaimed the disease eradicated in 1980, live variola virus remains in supposedly controlled, secure storage in two locations. Still, rogue states or non-state terrorist groups may have acquired enough live virus in the past to pose a direct threat to the U.S. and the global community. This essay addresses key questions: What precisely is the smallpox virus? What are its deleterious effects on victims, particularly mortality and morbidity? What kinds of effective public health preventive measures and medical treatments are available, and what are the attendant risks? How dangerous and how probable is smallpox as a geopolitical / bioterrorist threat? What are the strategic options concerning pre-event and post-event vaccination in the United States, and which offer(s) the most ethical public policy? The study concludes that the U.S. ought to (1) retain a smaller sample of live variola virus as a contingency for additional research and development of better vaccines against variola or other genetically manipulated versions that might surface, (2) continue the mandatory vaccination of all U.S. military personnel and DoD civilians deploying to southwest Asia, and (3) devise a cogent, reasonably comprehensive, and scalable plan for post-event mass vaccination of the cities or other areas directly affected by a smallpox attack rather than attempting a more refined, sophisticated, limited targeted approach.
Table of Contents

Section .................................................................................................................. Page

Purpose ................................................................. ................................................. 3

Methodology .............................................................. ........................................... 4

Historical Background .......................................................... ................................ 5

Science of Smallpox ............................................................................................. 8

Nature and Etiology of Smallpox ................................................................. 8
Deleterious Symptoms and Effects ............................................................. 10
Preventive Measures and Attendant Risks .................................................... 11
Alternative and Supplemental Medical Treatments .................................... 15

Geopolitics of Smallpox .................................................................................... 18

Strategic Policy Options .................................................................................... 24

OPTION A: Pre-Event Vaccination for Selected Military Personnel ................ 24
OPTION B: Post-Event Mass Vaccination ...................................................... 26
OPTION C: Post-Event Targeted (“Ring”) Vaccination .................................... 28
OPTION D: No Pre-Event Vaccinations ......................................................... 30
OPTION E: Destruction of All Variola Stockpiles ......................................... 32

Ethical Analysis and Policy Recommendations ............................................... 33

References ......................................................................................................... 39

Appendix A: CDC Smallpox Fact Sheet (modified) ........................................ 43

Appendix B: WHO Photos of Child with Smallpox .......................................... 44

Appendix C: Routine Progression of Skin Rash from Vaccinia ....................... 44
Today I am directing additional steps to protect the health of our nation. I’m ordering that the military and other personnel who serve America in high-risk parts of the world receive the smallpox vaccine, (sic) men and women who could be on the front lines of a biological attack must be protected. This particular vaccine does involve a small risk of serious health considerations. As Commander-in-Chief, I do not believe I can ask others to accept this risk unless I am willing to do the same. Therefore I will receive the vaccine along with our military (Bush, 2002).

Purpose

When President George W. Bush led a new round of smallpox vaccinations among the U.S. armed forces by receiving the smallpox vaccine on December 13, 2002, he was not the first U.S. Commander-in-Chief to require the military to prepare for the dreaded disease.

As commanding general of the Continental Army, the future President George Washington gave a similar order to the entire Army in 1777. He based his radical decision on circumstantial evidence that the opposing British Army may have employed smallpox as a biological weapon in Boston and Quebec in 1775 and in southern colonies, particularly Virginia, in 1776. General Washington feared that the British also planned to repeat the perfidy. In any case, the British troops were, on the whole, already immune to the disease, unlike their vulnerable American opponents. Like so many of his contemporaries, Washington had survived a bout with smallpox with a permanently pockmarked face at the age of nineteen and knew how devastating an unchecked smallpox contagion would be for his hobbled Army (Tucker, 2001, pp. 21-22; Glynn & Glynn, pp. 88, 90). Finally overcoming his initial resistance to experimental inoculation with the live virus, on January 6, 1777, General Washington wrote to Dr. William Shippen, Director General of the Hospitals West of the Hudson River: "Finding the smallpox to be spreading much and fearing that no precaution can prevent it from running through the whole of the Army, I have determined that the troops shall be inoculated. Should the disorder infect the Army in the natural way and rage with its usual virulence, we should have more to dread from it than from the sword
of the enemy.’” When the systematic inoculation of the entire Continental Army concluded during the winter of 1778, the death rate from smallpox had declined from 160/1,000 to 3/1,000 (Military Medical History, n.d.). Smallpox thus presented a direct threat to the nascent American nation as a bioweapon and may pose an even more egregious bioterrorist threat to the United States in the post-Nine Eleven era.

This essay will explore both the science and the politics of smallpox as a potential threat to the armed forces and people of the United States and propose, in response to the threat assessment, an informed, evidence-based, ethical public policy. Key questions will frame the analysis. What precisely is the smallpox virus? What are its deleterious effects on victims, particularly mortality and morbidity? What kinds of effective public health preventive measures and medical treatments are available, and what are the attendant risks? How dangerous and how probable is smallpox as a geopolitical / bioterrorist threat? What are the strategic options concerning pre-event and post-event vaccination, and which offer(s) the most ethical public policy?

**Methodology**

The research plan for this essay encompassed peer-reviewed scholarly articles on smallpox, bioterrorism, and biodefense accessed through the Washington Research Library Consortium website and the George Mason University Libraries E-Journals website; exploration of the websites of the Centers for Disease Control and Prevention (CDC), the Center for Biosecurity at the University of Pittsburgh, MILVAX (the U.S. Department of Defense Smallpox Vaccination Program), GeoVax, Global.Security.org, and the Federation of American Scientists (FAS); keyword searches on google.com for news articles and editorials in the major media including as the Wall Street Journal, USA Today, BBC, and CBS News; full-length monographs such as Ken Alibek’s *Biohazard*, as well as more comprehensive books on public health and the history of
medicine; and a personal interview with Lisa G. Kaplowitz, MD, MSHA, Deputy Assistant Secretary for Policy, U.S. Department of Health and Human Services. In view of the dynamic state of biological threats, particularly bioterrorism, since the decisive terrorist attacks on the American homeland on Nine Eleven and the virtually coterminous anthrax scare in 2001, the database, online, and library searches focused, though not exclusively, on the last decade.

Although the present study does not provide new data or fresh quantitative analysis, many of the published articles referenced below do report such statistical surveys or present computational models or evidence-based analysis. The diversity of scientific conclusions and conflicting policy recommendations are striking but not so daunting as to preclude a reasonable practical and ethical choice in the concluding section of this paper.

**Historical Background**

An official announcement by the World Health Organization (WHO) in May 1980 marked the extinction of smallpox as an active infectious disease in the natural world. It was and remains “a triumph of modern medicine,” as well as a singular achievement by public health professionals who employed “the time-honoured methods of case tracking, isolation, and mass vaccinations of populations at risk” (Bynum, p. 141).

But the origins of this uniquely lethal human scourge, which has taken a toll in human life in the hundreds of millions—as well as one-tenth of the entire human race since its inception either dead, blinded, disfigured, or otherwise seriously disabled, are shrouded in uncertainty. It may have arisen in ancient Egypt (Pharaoh Ramses V’s mummy evidences yellow pustules akin to smallpox), moved to India circa 1500 BC, and arrived in China ca. 1100 BC. But the first solid indications in the Western world point to plagues from a “pustular disease” in the Roman Empire of the 2nd century AD (Tucker, 2001, pp. 6-7; Block, p. 34; Belongia et al., p. 87; Alibek, p. 109). There is even a patron saint for smallpox victims in the early Church. A tenth century manuscript
includes a prayer of blessing for a pendant to ward off smallpox that invokes the intercessions of St. Nicaise, Bishop of Rheims (France), martyred ca. 451 AD (Hopkins, p. 101). The Latin term that, fittingly, gave rise to the scientific name for the primary strain of the smallpox virus—*variola major*—within the genus of orthopoxviruses (or “true pox” viruses) was either *varius* (“spotted”) or *varus* (“pimple”). The English appellation derives from an apt fifteenth century description of the most prominent symptom of the disease: “small pockes” (Tucker, 2001, pp. 2, 5, 7).

As if the natural course of the disease were not deadly enough, nefarious human beings perceived in smallpox a powerful type of what we now term “bioweapons” in the prosecution of biological warfare against enemies. Such weapons have been called “the poor man’s atom bomb” (Block, p. 33) and “public health in reverse” (Tucker, 2001, p. 250). The British historian Thomas Macaulay dubbed smallpox, in particular, “the most terrible of all the ministers of death” (Glynn & Glynn, p. 2), and Steven Block has accorded it similar respect as “the bête noire of bioweapons” (Block, p. 34). The early form of inoculation was variolation or “engrafting” matter from the pustule of one smallpox victim into an exposed wound of a healthy person to engender a milder form of the disease as a preventive measure, which Lady Montague, wife of the British ambassador observed in Ottoman Turkey in 1717 AD and later introduced to England. That concept may have been perverted by British military officers to generate an outbreak of smallpox among American Indians besieging Fort Pitt in 1763 during the French and Indian War through the seemingly innocuous distribution of smallpox-infected blankets (Glynn & Glynn, pp. 44-45; Tucker, 2001, pp. 19-20).

Ironically, the decision to employ bioweapons may backfire and prove self-defeating for the aggressor. During the decisive Battle of Stalingrad in 1942, the Soviet Union reportedly attempted to infect invading German Panzer troops with tularemia, but the deadly infectious disease eventually spread to both sides and took 100,000 lives (Block, p. 30). Bioweapons,
including smallpox, are much more unpredictable and uncontrollable than others, such as chemical munitions and nuclear bombs, commonly designated as weapons of mass destruction (WMDs): hence their potential popularity among rogue states and especially non-state actors such as Islamist terrorists in the present era for whom sheer terror, even at the risk of their own destruction and perhaps that of the human race, is a premium.

Here is a series of additional milestones to conclude this quick historical survey of smallpox as both a disease and a weapon of choice and to frame the subsequent discussion of the science and politics of smallpox in the post-Nine Eleven context:

- The ill-fated King Louis XVI of France provides a royal stamp of approval on the public health procedure when he is successfully inoculated in 1774 after his father Louis XV dies from smallpox (Bynum, p. 73).

- Dr. Edward Jenner of England introduces vaccination (from the Latin word vacca for cow) in lieu of variolation in AD 1796, when he takes some fluid from a cowpox lesion on the hand of a healthy milkmaid and injects it into the arm of a young boy who had not previously contracted smallpox; when Jenner inoculates the boy six weeks later with the usual smallpox matter, the boy proves to be immune to smallpox.

- A devastating smallpox epidemic occurs in Boston, Massachusetts, from 1901 to 1903, spanning 1596 reported cases and 270 deaths (for a case fatality rate of 17%); according to one epidemiological study, patients at Boston City Hospital with previous vaccinations “were more likely to develop the relatively mild varioloid form of the disease and had a higher probability of survival compared with patients who were not vaccinated” (Albert et al., pp. 993, 998).

- In 1939 a British scientist concludes that “vaccinia,” an orthopoxvirus not found in nature, had displaced the cowpox that Jenner had introduced, probably as a result of decades of experiments with various vaccine strains by vaccinators seeking one that had fewer side-effects (Tucker, 2001, p. 37).

- Around the same time, the so-called Ankara strain of vaccinia, a modified version later known as “modified vaccinia Ankara” (MVA), develops in a horse in Turkey: in the twenty-first century, MVA becomes the focus of a renewed research and development program for a less onerous smallpox vaccine than vaccinia.

- The “modern vaccine” is created in the 1950s by means of a centrifuge to create the virus in suspension, freeze-dries it in heat-stable ampoules (small sealed glass vials), and allows for storage without the need for refrigeration (Belongia et al, p. 88).
• The last endemic case of smallpox in the United States occurs in 1949, and the first large scale attempt to eradicate smallpox globally begins in the Western Hemisphere in the 1950s; Bangladesh experiences the last case of natural variola major in 1975, and the last natural case of the less virulent strain (variola minor) occurs in Somalia in 1977.

• The Centers for Disease Control in Atlanta play a key international role in the elimination of the scourge of smallpox through its “eradication escalation” approach (surveillance and targeted large-scale vaccinations) at a cost of only $32 million (Turnock, p. 200).

• President Richard M. Nixon announces on November 25, 1969, that the United States will unilaterally renounce all biological weapons research, development, production, and stockpiling; by May 1972 all such stockpiles are destroyed.

• The Biological and Toxin Weapons Convention (BWC) bans all biological and chemical weapons, but the international treaty signed initially on April 10, 1972—currently including among the signatories 160 nations (including the U.S., Russian Federation, China, Iraq, Iran, Libya, and North Korea)—lacks investigative and enforcement authority (Block, p. 31).

• Although the Soviet Union, according to Ken Alibek, Deputy Director of Biopreparat, a pharmaceutical front organization, inspired the global campaign to eradicate smallpox at the WHO meeting in 1958, for the two decades between 1972 and 1992 the Soviet Union maintains a comprehensive but clandestine bioweapons program in direct violation of the BWC—with the world now defenseless against possible smallpox attack, for which there is, since 1972, “no prevention and no cure” (Alibek, pp. 110-111; Block, p. 31).

• In June 1999 a blue-ribbon panel of scientists with the CDC includes smallpox along with five other disease-causing biological agents in Category A: the highest priority—for agents that post a serious risk to national security.

• President George W. Bush announces a new smallpox vaccination campaign in December 2002 to include 500,000 members of the U.S. armed forces, as well as, on a strictly voluntary basis, 500,000 health workers and perhaps 10 million emergency responders considered essential personnel for the purpose; organized resistance among the latter reduces the final numbers to fewer than 40,000 vaccinations among health workers and emergency responders (Levy & Sidel, p. 148).

**Science of Smallpox**

*Nature and Etiology of Smallpox*

What precisely is the smallpox virus? The most fascinating preliminary scientific question about viruses as a class is whether they are, in fact, living organisms. Glynn & Glynn (2004)
concede that it is “entirely a matter of definition” (p. 179). Viruses are simpler and much smaller than bacteria and consist of “a protein shell, a sequence of DNA or RNA, and sometimes a lipid membrane,” but they cannot move, metabolize, or procreate without a living host that possesses the requisite cell structure and nutrients. In Ken Alibek’s apt phrasing, “Viruses come to life inside the nucleus or cytoplasm of their host cells, fusing with them and ultimately hijacking their functions,” quickly multiplying and thereby disabling the living host (Alibek, pp. 107-108). Suitable hosts for these parasites include bacteria, blue-green algae, fungi, plants, invertebrates, and vertebrates, particularly human beings.

The variola major virus, the most common and lethal of the smallpox viruses, is brick or biscuit shaped with a diameter of approximately 200 nm. The CDC Smallpox Fact Sheet lists four types: “ordinary (the most frequent type, accounting for 90% or more of cases); modified (mild and occurring in previously vaccinated persons); flat; and hemorrhagic (both rare and very severe).” The case fatality rate (CFR) for victims of variola major ranges historically from 10% to 30%, but flat and hemorrhagic smallpox are predictably fatal in all but a few cases. The less common version of the virus, variola minor, has historically engendered the more mild illness known as alastrim with a CFR of 1% or less. Despite similar symptoms, the disparate lethali ties of the major and minor forms defy scientific explanation (Tucker, 2001, p. 2).

The internal spread and external transmission of the smallpox virus is a perverse marvel. After receiving an infectious dose of as little as a few virions (particles) with implantation on the oropharyngeal or respiratory mucosa (i.e., back of the throat or most of the nasal cavity), the human host suffers a migration to and proliferation of the virus in the regional lymph nodes, and from there to the spleen, bone marrow, blood vessels, and adjacent cells. Unlike the other types of the genus orthopoxvirus (monkeypox, vaccinia, and cowpox), which can also cause lesions on human skin, only smallpox may be transmitted accidentally between human beings (Henderson et
al., p. 2129). The CDC Smallpox Fact Sheet notes that, as a rule, “direct and fairly prolonged face-to-face contact is required,” but that other modes of transmission include “direct contact with infected bodily fluids or contaminated objects such as bedding or clothing.” Though not easily transmitted, smallpox may be contracted through inhalation of aerosol droplets (from coughing, for example) or direct contact on cuts or exposed subcutaneous skin. Historical studies indicate that “high population densities are required to sustain transmission,” which is, however, not a serious impediment in an increasingly urbanized America (Belongia et al, p. 87). Especially pernicious is the long incubation period following exposure to the virus—seven to seventeen days—when the victim, though not contagious, displays no symptoms, feels quite healthy, and may not even know that he or she is a carrier. Meanwhile, the carrier might spread the disease unwittingly to dozens or even hundreds of additional victims.

A saving grace may be the evolutionary stability of the smallpox virus. Unlike the flu viruses with which most Americans are familiar annually, the smallpox virus does not mutate: immunity to the variola major virus is still good from year to year, rendering smallpox vulnerable to aggressive measures (Glynn & Glynn, p. 180). In addition, the disease has no known vectors or reservoirs besides human beings, so it could, unlike influenza, which has many reservoirs in the animal kingdom, be eradicated once again by vaccination.

**Deleterious Symptoms and Effects**

The morbidity rate for smallpox without vaccination or medical treatment is 60% to 90%, a veritable “life sentence” of pockmarked scarring or even blindness (Alibek, p. 114). Jonathan Tucker’s eloquent description of the course of the disease without vaccination pre- or post-event should give pause to anyone who might downplay its deleterious effects:

> [V]ariola major once rampaged through the human species and caused the most feared of deadly scourges. After a two-week incubation period, smallpox racked the body
with high fever, headache, backache, and nausea, and then peppered the face, trunk, limbs, mouth, and throat with hideous, pus-filled boils. Patients with the infection were in agony—their skin felt as if it was being consumed by fire, and although they were tormented by thirst, lesions in the mouth and throat made it excruciating to swallow. The odor of a smallpox ward was oppressive: The rash gave off a sweetish, pungent smell reminiscent of rotting flesh. For those who survived, the disease ran its course in a few weeks. Pustule formation concluded on days eight to ten of the illness, after which the boils scabbed over and were gradually reabsorbed. On days fifteen to twenty, the crusty dry scabs separated and fell off, leaving depigmented areas of skin that later turned into ugly, pitted scars (Tucker, 2001, p. 2).

A modified version of the CDC’s detailed chart of the smallpox disease phases appears in Appendix A to this paper. If death does not result during the second week of illness from toxemia connected with soluble variola antigens, encephalitis (life-threatening inflammation of the brain) may ensue. But the most distinctive characteristic of the disease is the initial lesions that ulcerate in the mouth and pharynx and the progress of a hideous skin rash from macules to papules to vesicles to pustules to lesions with scabs. Appendix B to this essay displays a series of photographs from the World Health Organization that illustrates iconically the typical devastation of smallpox upon a child at days 3, 5, and 7, respectively, of the rash phase.

**Preventive Measures and Attendant Risks**

The scientific insights of the ancients—East and West—as well as modern physicians like Dr. Edward Jenner continue to be validated through the best means of preventing smallpox and curtailing its deleterious effects after infection: vaccination. Mostly to augment the previous supply of some 15 million doses of the vaccinia strain (Dryvax) produced primarily by Wyeth Laboratories in Pennsylvania until 1982 and the 85 million doses of another old vaccine given to the U.S. by Aventis Pasteur, a French-German pharmaceutical company, the U.S. federal government quickly spent $1.8 billion toward a renewed biodefense program after Nine Eleven and now has in excess of 300 million doses of vaccine in the Strategic National Stockpile (McKay, 2011; Belongia et al, p. 89; Cohen and Enserink, p. 2314). A newer vaccine known as
ACAM2000 manufactured by Acambis Inc. displaced Dryvax in the U.S. in March 2008 (MILVAX, 2008). The new combined arsenal would enable the vaccination of every person in the nation before or after a smallpox event. The vaccinia virus effectively induces the human immune system to manufacture antibodies and aggressive T-cells that identify proteins from the vaccinia virus as if they were from the similar variola virus; immunization with vaccinia therefore leads to immunization to smallpox (Glynn & Glynn, p. 243). If a person is vaccinated before the onset of smallpox or within, at most, four days of exposure, immunity is almost certain. The vaccine will “prevent or significantly ameliorate subsequent illness” (Henderson et al, p. 2132). That’s the good news.

The less happy news is that vaccinia routinely causes temporary uncomfortable and even painful side effects and sometimes permanent morbidity. A trifold brochure on smallpox vaccination distributed to soldiers by the U.S. Department of Defense (MILVAX, 2007) gently warns recipients that a successful vaccination will display these symptoms in sequence: “[A] red and itchy bump forms at the vaccination site in 2 to 4 days. Over the next few days, the bump becomes a blister and fills with pus. During the second week, the blister dries up and a scab forms. The scab falls off after 2 to 4 weeks, leaving a scar.” Recipients also ought to expect the following “mild” reactions, which “usually peak 3 to 12 days after vaccination and rarely last more than 30 days”:

- Itching at the vaccination site.
- Swollen and/or sore lymph nodes.
- The arm for the vaccination site may become sore and red.
- Fever, headache, and body aches.
- Fatigue.
The brochure neglects to mention nausea, the severity of soreness at the vaccination site, and formation of satellite lesions. Appendix C to this essay includes photographs of the usual progression of the skin lesions at days 5, 8, 10, and 14 after “primary,” or first-time, vaccination. In addition, a clinical trial in 2002 disclosed that more than one-third of recipients were absent from work or school owing to those “mild” symptoms (Belongia et al., p. 89). A recent clinical study of 1,006 CDC laboratory workers and smallpox response team members who were vaccinated from October 2001 through December 2001 focused on the “mild-to-moderate” adverse effects that were heretofore neglected. The study found that “itching at the vaccination site” was most commonly reported along with eleven additional symptoms including those listed above. What the research team did not expect was reports of joint pain, abdominal pain, backache, and difficulty breathing, all of which warranted additional study (Baggs et al., p. 1133, 1135, 1139). Any or all of those side-effects is probably the best result for which one may hope after smallpox vaccination at present.

In what the CDC assures the public is a “small minority” of cases, primary vaccination with vaccinia may result in death (one or two out of 1 million persons) or severe adverse reactions short of death (49 to 935 per million) (Cohen & Enserink, p. 2313, 2315). Such complications are daunting and encompass at least the seven following health risks (Lane et al., pp. 489-490; Henderson et al., pp. 2134-2135; Belongia et al., pp. 89-90; Rinaggio & Glick, pp. 455-457):

1. **Cardiac ischemia and myo/pericarditis** have a “questionable” connection to smallpox vaccination, but they seem to have deterred most health care professionals from cooperating with President Bush’s program announced on December 13, 2002. In a large-scale vaccination campaign for 489,000 persons through June 2003, 37 military personnel and 21 civilians developed myo/pericarditis as evidenced through chest pain, electrocardiographic and heart alterations, dyspnea, and increased serum levels of cardiac enzymes. Medical treatment
emphasized non-steroid anti-inflammatory drugs and optional analgesics, and most patients recovered. Though statistically small, the number of reported cases was sufficient for the CDC to recommend that persons with similar cardiovascular histories or who demonstrate three or more possible causes of heart disease such as hypertension, diabetes, or smoking refrain from smallpox vaccination.

2. **Progressive vaccinia** is, if untreated medically, a grave, frequently fatal reaction among recipients with immune deficiency disorders such as HIV/ AIDS. Also known as vaccinia gangrenosum, this uncontrolled replication of the virus may occur when the vaccinial lesion expands and spreads instead of healing naturally in fifteen days, displaying central cratering vulnerable to secondary bacterial infection and leading to a progressive necrosis of the surrounding tissue including adjacent skin, bones, and internal organs.

3. **Post-vaccinial encephalitis** is rare and the cause is unclear, but the CFR typically ranges from 15% to 25%, particularly among infants and young children. Patients may lapse into coma, display seizures, or endure decreased mental function, and 10% to 25% of survivors suffer from long-term neurologic deficits including paralysis. There is no effective medical treatment.

4. **Eczema vaccinatum** is an expansion of smallpox lesions to areas of the skin of recipients affected by eczema or a history of atopic dermatitis. Most often mild and self-limited, this reaction may become severe and even fatal, particularly in young children; recorded CFRs have reached 40% when compounded with secondary infection on the dry skin, sepsis, and dehydration.

5. **Fetal vaccinia** is a rare but serious complication that may result if a pregnant woman receives the smallpox vaccination. The few cases present with scars or pock marks, but the CFRs approach 90%. Universal medical practice prohibits pregnant women from receiving live virus vaccines for good reason.
6. **Generalized vaccinia** suggests that the virus has entered the vascular system and has spread throughout the body via the blood. An eruption of vesicles in a generalized rash may occur six to nine days following vaccination, but it is usually self-limited and vanishes without therapy and with no lingering effects.

7. **Inadvertent inoculation**, the most common adverse effect of the volatile smallpox vaccination, occurs when the recipient unintentionally spreads the vaccinia virus to other parts of his or her body simply by touching the uncovered vaccination site and then, without washing the hands immediately and thoroughly, touching, most commonly, the face, mouth, eyelids, anus, or genitals. Vaccinia also may be transmitted sexually within 21 days after vaccination. Most of the new lesions eventually vanish untreated without serious morbidity, but some difficult lesions may respond to therapy such as the vaccinia immune globulin (VIG) to be discussed below.

In short, to minimize adverse complications, the following “special risk groups” ought not to be vaccinated except *in extremis*: pregnant women; persons with HIV infection, hereditary immunodeficiency disorders, organ transplants, eczema or other significant skin conditions, leukemia, or lymphoma; and those receiving radiation treatments or large doses of corticosteroids.

*Alternative and Supplemental Medical Treatments*

An alternative smallpox vaccine that minimizes the complications of vaccinia may be in the offing. Modified vaccinia Ankara (MVA), a weakened “third generation” strain of the vaccinia virus developed by researchers at the University of Munich in the early 1960s as a vaccine for recipients with compromised immunity systems, lacks the genes that enable vaccinia to replicate in human beings, while retaining the genes involved in the immune response to smallpox. By 1978 its German creators reported that 120,000 persons had been vaccinated with MVA without serious complications. Clinical trials with non-human primates concluded by Dr.
Bernard Moss at the National Institutes of Health (NIH) in 2004 suggested its effectiveness in combating smallpox. Since 2005 the Danish corporation Bavarian Nordic has conducted trials with hundreds of patients, including the elderly and those with HIV or eczema, with none of the undesirable side effects of vaccinia. The vaccine is administered through injection, so there’s no need to scratch the skin to deposit a drop of vaccine (as many as fifteen times for repeat vaccinations), which also causes scarring on the patient. The MVA strain in production by the GeoVax corporation is also intended to be dual use: to combat smallpox and AIDS. So far, however, MVA has not been applied to a real-world outbreak of smallpox, so its utility, though quite promising, is hypothetical. Nonetheless, the U.S. federal government has contracted with Bavarian Nordic for 20 million doses—an adequate supply for 10 million persons—with an option to purchase an additional 40 million doses. Pending more clinical trials with human beings and demonstrated clinical efficacy, MVA remains an experimental product for immediate use only in an extreme emergency and for HIV/AIDS victims (Sternberg, 2010; Cohen & Enserink, p. 2314; GeoVax website; Kaplowitz interview).

Public health professionals already have at their disposal one post vaccination medication to counteract the effects of the vaccine. Vaccinia immune globulin (VIG) is a “solution of antibodies prepared from the blood plasma of normal recently vaccinated subjects” (Glynn & Glynn, p. 240n). It is intended only to respond to complications resulting from vaccination, particularly patients with eczema who lack the natural antibodies to vaccinia, and it is administered in large doses by injection intra-mucularly. Since the supply is very limited, its use, arguably, ought to be confined to the most serious cases (Henderson et al., pp. 2135-2136; Tucker, 2011, p. 61; Rinaggio & Glick, p. 457).

Meanwhile, the U.S. Food and Drug Administration (FDA) has approved provisionally three antiviral drugs as candidates in the campaign against smallpox. Previously used routinely to
treat an eye disease caused by a herpes virus, **cidofovir** shows promise for prophylaxis against poxvirus infections, but only if it is administered at the same time as vaccinia or no later than three days. Since it must be injected intravenously and may cause serious kidney toxicity with dialysis as a possible outcome, the CDC prefers to reserve it for situations where the VIG stockpiles are exhausted and has restricted it to patients who do not respond to VIG or may be at risk of death due to post-vaccination complications. A more recent modified version of the drug labeled **CMX001** may be taken orally and demonstrates in test-tube experiments an improved effectiveness against variola virus by a factor of 100. However, some trials with animals raise a note of caution: this potential wonder drug may metabolize too quickly for use against smallpox (Tucker, 2001, p. 61; Weiss et al., p. 1671; Rinaggio & Glick, p. 457; Glynn & Glynn, p. 238).

A third antiviral product, **ST-246**, is a new compound that prevents infected cells from transmitting poxvirus to other tissues or organs of the host. Several studies indicate that ST-246 protects lower primates against infection with either monkeypox virus or variola virus, acts effectively also if administered soon after the appearance of skin lesions, and appears to be stable and nontoxic in human beings. ST-246 also promises the bonus of significantly lower rates of inadvertent inoculation during the initial phase of infection (Tucker, 2001, p. 61).

Another antiviral drug deserves honorable mention in view of the current international terrorist environment. A clinical trial of **methiazone** with more than 5,000 patients in India in the 1960s yielded a 96% reduction in the incidence of smallpox. A panel of smallpox authorities subsequently concluded that it promised a much more modest benefit (only 30% to 40% reductions), but at least one scientific team proposes continued research with methiazone: “In the event of a smallpox attack with an engineered virus, even such modest efficacy could prove critical” (Weiss et al., p. 1671).
Geopolitics of Smallpox

The sobering discussion above of the mortality and morbidity of smallpox as a disease in the state of nature, as well as the imperfect solutions that science and technology offer to counteract it, requires serious attention to a fundamentally political question: How dangerous and how probable is smallpox as a geopolitical / bioterrorist threat today?

In the happy aftermath of the eradication of smallpox in 1980, the only way that the disease might pose a threat to human beings would be through intentional human activity, almost certainly an act of bioterrorism. An apt definition of bioterrorism appears on a Public Broadcasting System (PBS) website: “The employment of living agents such as viruses, bacteria, and other biological toxins to attack or intimidate societies or governments, often for political or ideological reasons” (PBS website). Smallpox falls under Category A in the CDC’s classification of bioterrorism agents along with anthrax, botulism, plague (as in “bubonic,” or *Yersinia pestis*), tularemia, and viral hemorrhagic fevers (CDC Bioterrorism Overview). What makes that roster of microscopic killers the highest priority for the CDC is the threat they pose to the American public and our national security. Category A agents

- Can be spread or transmitted easily and efficiently from person to person.
- Produce high death rates and serious long-term morbidity.
- Might cause widespread panic and social disruption.
- Require special, uniquely demanding public health preparedness and actions.

Professor Stephen Block of Stanford University is reluctant to label “most current forms” of biological and chemical agents as “weapons of mass destruction” (WMDs) (Block, p. 28), and Ken Alibek’s caveat may be technically correct: “Unlike nuclear weapons, which pulverize everything in their target area, biological weapons leave buildings, transportation systems, and other infrastructure intact. They should properly be called mass casualty weapons, not weapons of
mass destruction” (Alibek, p. 22). However, in the case of smallpox attack by terrorists, the consequences of a widespread diffusion of the virus in the entire human biosphere could be as devastating as some nuclear, radiological, or high-yield explosive detonations.

It is no state secret that the only official locations of live variola virus since the eradication of the disease are (1) a high-security CDC laboratory in Atlanta, where 451 smallpox “samples” are maintained frozen in liquid nitrogen, and (2) the Russian State Research Center for Virology and Biotechnology in Koltsovo, Siberia, known as “Vector,” which has 120 “samples” also under supposedly very tight security. The WHO conducts periodic inspections of those facilities as a political insurance policy (McKay, 2011).

But that is not to say “samples” from Vector have not already wended their way to certain rogue states or radical non-state elements such as Islamic terrorist groups. In 2001 Block put in print what many political experts suggest in whispered tones: namely, “the disturbing likelihood that their [Soviet] bioweapons experts will be forced to seek employment elsewhere, resulting in unwelcome proliferation” (Block, p. 31). Another scenario envisions “samples” of variola virus, along with other WMDs from Soviet-turned-Russian stockpiles, bartered in the interests of Soviet foreign policy before the collapse of the Soviet Union in 1991 or purloined and sold on the black market to nefarious elements since that demise. Tucker raises serious questions about the biosecurity of labs and repositories of deadly pathogens such as Vector in Russia (Tucker, 2003). Block points specifically to the biological weapons programs and production in Saddam Hussein’s Iraq in the 1980s, and mentions that “it’s expected that more than a dozen sovereign nations possess some form of offensive bioweapons program, assuming one includes some republics of the former Soviet Union” (Block, p. 32). Another prime candidate for smallpox bioweapon proliferation is North Korea (Flight, 2010; Global Security website).
Ironically, the Russian Federation, home of Vector, may still pose a potential smallpox threat to the world, though obviously not through a terrorist act per se. Ken Alibek’s book titled *Biohazard* is a treasure trove of information about the Soviet bioweapons program, particularly the “new” smallpox weapon whose creation as a “special item” he was assigned to supervise in December 1987 during the regime of Mikhail Gorbachev. Alibek concedes that a “large body of Western scientific opinion considers *Variola major* an unlikely weapon, despite its contagiousness.” But that did not phase the Soviets, who had established their first smallpox weapons factory in 1947 near Zagorsk, only forty minutes away from Moscow. The Soviets considered viruses to be especially valuable assets in their arsenal during the Cold War for their capability “to infect vast numbers of people with an infinitesimal number of particles.” Alibek’s scientific team at Vector tested a new aerosol smallpox weapon in December 1990, long after the Soviet Union had signed the BWC of 1972, which, he calculates, could yield 80 to 100 tons of weapon-ready smallpox per annum.

But the wild card in this already clandestine scheme was Alibek’s discovery that another team of Soviet scientists had genetically manipulated samples of vaccinia in an attempt to create a “chimera virus”—a composite “animal” resulting from the insertion into the vaccinia virus of genetic material from Venezuelan equine encephalitis (VEE), a virus that attacks the human brain. The intent was to create a “double agent” that reproduces both VEE cells and the vaccinia itself—“a superweapon capable of triggering both diseases at once.” According to Alibek, the same team of scientists (now post-Soviet Russians) reported in a Russian-language journal in 1997 “that they had successfully inserted a gene of Ebola into the genome of vaccinia.” Such genetic engineering raises collateral issues concerning what Professor Steven Block and others have nicknamed “black biology”—a kind of Frankensteinian attempt to develop bacterial and viral microbes as bioweapon agents with resistance to antibiotics or other medical treatments and “unprecedented power to
destroy” (Block, p. 35). The consequences for the biosphere, not merely circumscribed geographic areas, would be incalculable. For his part, Alibek dutifully reports that “our stockpiles of plague, tularemia, and smallpox have been destroyed,” but also notes cryptically that “there is persistent evidence that Russia continues to place a high value on its old biological warfare infrastructure.” He wrote that in 1999 (Alibek, pp. 111, 113, 115, 117-118, 120-122, 258-261, 264). Alibek also claimed in a BBC interview in 2002 that the Soviets developed delivery systems for smallpox virus through aerial bombs and ballistic missile warheads (Flight, 2010). Twelve years after his blockbuster book the unanswered question is whether the Russian Federation still has such interests, its protestations to the contrary notwithstanding.

What then are the gravity of the threat of smallpox attack by bioterrorists and the probability of such an event in the United States? First, together with Martin M. Weiss et al., we must ask three technical questions: (1) Can smallpox virus be inflicted as an aerosol? (2) If so, then how long would it remain viable and what is the predictable geographic range? (3) How infectious would smallpox virus be through that method? The Weiss team provides its own answers: (1) Smallpox virus can indeed be aerosolized. (2) Studies of vaccinia suggest that, by extrapolation, variola virus in aerosol form protected from ultraviolet (UV) light can survive for 24 hours. (3) With an appropriate vehicle, deadly variola virus could remain in suspension and retain its potency to infect “for a considerable period” of time. There is a caveat, however. The minimum infective dose of variola virus remains uncertain, and release of smallpox into the air might compromise its potency owing to UV light, wind, heat, humidity, or precipitation (Weiss et al., p. 1670).

Professor Steven Block posits two similar hurdles concerning efficacy. First, terrorists must obtain or generate “stable quantities” of a potent agent such as the variola virus. Second, terrorists must be able to utilize an effective means of delivery of the agent to the designated target,
which raises the issue of dispersal. Block’s caveat militates in favor of the bioweapon’s potential utility. But, he avers, dispersal is not a critical issue, “because bioweapons terror attacks are highly leveraged.” Only a few cases of smallpox disease in a bioterrorist event would, potentially, cause enough public fear, demands on the public health and medical infrastructure, and social disruption as to accomplish the diabolical mission. Thus Block concludes—ironically, early in 2001 before the Nine Eleven attacks—that “the terrorist threat is very real and it’s about to get worse.” Bioweapons attacks, like a theoretical nuclear war, are fundamentally “low probability, high consequence” events (Block, p. 34).

Computational modeling and high-level role-playing in hypothetical smallpox events offer educated guesses about the gravity of the threat and ways of counteracting it. For example, the CDC published a case study in 2003 focusing on the economic impact of a smallpox attack. One scenario envisions terrorists releasing smallpox virus in the domestic terminals of the ten largest airports in the U.S. The computational model employed by a team headed by Samuel A. Bozzette projects 5,000 to 200,000 infections among those in the terminals at the time of release with deaths from the variola virus itself numbering in the 2,000s irrespective of the vaccination strategy (CDC Case Study). “Atlantic Storm,” an extraordinary table-top exercise in January 2005 under the direction of Dr. Tara O’Toole, CEO of the Center for Biosecurity at the University of Pittsburgh, gathered more than a dozen distinguished international government leaders and diplomats in a simulated summit meeting to respond to a coordinated terrorist smallpox attack in six cities: Rotterdam, Warsaw, Frankfurt, Istanbul, New York, and Los Angeles. Within only four and a half hours after the covert attacks on transportation hubs and commercial centers, 3,320 cases of infection were reported with projections of 666,000 cases throughout the world in less than a month. The stunned participants concluded that thorough preparedness for such
bioweapons attacks “is one of the great global security challenges in the 21st century” (Center for Biosecurity website).

Another potential threat with profound consequences could result from scientific research gone awry. The now infamous case of the mousepox experiment in Australia in 2000 provides a cautionary tale of good intentions paving the way to a hellish destination. Two scientists tried to reduce the reproductive ability of the mouse population as vectors of some diseases by infecting mice with a genetically re-engineered virus that usually causes mousepox. The idea was that “the mice would contract an attenuated case of the disease and present an immune response to the virus that would extend to the mouse egg protein. This extended immune response would lead to anti-ZP3 antibodies attacking the mouse’s own eggs, causing sterility.” However, the experiment backfired when the genetic tinkering generated a new, potent mousepox strain that led to suppression of the immune response system of the mice to mousepox virus and the subsequent deaths of all ten of the mouse subjects in the experiment. Critics of the experiment fear that it shows how “the simple insertion of the IL-4 gene into the smallpox virus could conceivably render these precautions and the vaccine stockpile useless.” In addition, despite the highest biosafety levels of some laboratories, “genetically modified pathogens could be accidentally released” for which there is no vaccination, prophylaxis, or post-event medical treatment (Federation of American Scientists “Mousepox Case Study”). Incredible as it may seem, another scientific team at St. Louis University in Missouri attempted three years later to duplicate the Australian experiment with mousepox by creating a super virus to learn how to defeat it as part of the U.S. biodefense program. This time the infected mice recovered after treatment with a combination of antiviral drugs (Arak, 2003).

Therefore, potential smallpox threats abound from terrorist groups and rogue states that may have acquired some form and quantity of variola virus. Even if the probability of an attack
with variola virus, much less a non-conventional strain of the poxvirus, within the continental U.S. is generally acknowledged to be low, especially compared to other terrorist actions, the consequences of a sophisticated smallpox bioterrorist event could be so devastating as to rend the social fabric of the nation. Still worse is the potential impact on the entire human biosphere. As Tucker notes in a handy comparison of the characteristics of fissile materials (nuclear) and biological pathogens, since the latter are living organisms or entities that reproduce, “inventory control is unreliable” (Tucker, 2003). That is rather muted language for potentially uncontrollable and unstoppable once released or, in the case of smallpox since its eradication last century, re-released upon a world generally not ready for it. Alison Pease frames the policy and ethical challenge succinctly: “[T]he government must find a balance between being prepared for a potential attack and dealing with the financial and logistical costs involved in preparation” (Pease, 2010).

**Strategic Policy Options**

Four strategic policy options for the utilization of smallpox vaccination and a fifth policy option concerning the destruction of variola stockpiles arise from the scholarly literature on the subject and public discussions in the popular media. We shall consider each briefly in turn, focusing on one or two exemplary arguments for each.

**OPTION A: Pre-Event Vaccination for Selected Military Personnel**

This is the current policy of the U.S. federal government since President George W. Bush inaugurated it on December 13, 2002. (See the last bullet above on p. 8.) The military component of the precautionary selected vaccination program known as MILVAX has proceeded apace, with every uniformed member of the U.S. armed forces and DoD civilians deploying for the first time to southwest Asia, particularly Afghanistan or Iraq, required to receive the vaccinia injection
unless recently vaccinated or exempt because of disqualifying conditions such as eczema or other forms of atopic dermatitis. More than two million troops have received the vaccine to date, the first large-scale vaccination regime since the eradication of smallpox in the 1970s. According to the MILVAX website, the initial round of 500,000 vaccinations through December 2003 led to few serious complications: “Some first-time vaccinees had chest pain due to myo-pericarditis [inflammation in or around the heart]. These cases ranged from mild to serious. One case of lupus-like illness may have been triggered by vaccination.” Pursuant to several heart attack cases in 2003 that may have been connected to the smallpox vaccination, DoD and the CDC recommended that persons with known cardiac disease or even three of the conventional indicators of potential heart problems not receive smallpox vaccination.

To be sure, the public health and emergency responder communities largely declined voluntary vaccination because of the serious attendant risks (see pp. 13-15 above), a widespread belief that they were unlikely to contract the disease, increased possibility of unintentionally transmitting the infection to hospital patients in a weakened condition, lost work days during the initial recovery period, and a lack of federal compensation (until April 2003) for side-effects resulting from the smallpox vaccination (Cohen & Enserink, p. 2312; Gray, 2003).

In March 2005 the Armed Forces Epidemiological Board (AFEB) reviewed the biological threat and the MILVAX program and recommended that the Department of Defense “expand research efforts to identify intrinsic risk factors for cardiac complications associated with the smallpox vaccine.” The AFEB encouraged DoD also “to consider the threat posed by influenza as an agent of biowarfare and bioterrorism.” Most important, however, was the AFEB’s refusal to endorse expansion of the vaccination programs for smallpox and anthrax to the entire military force “under the current threat conditions” (DoD AFEB, 2005).
At least one controlled study has provided scientific validation of the MILVAX program. Les R. Folio and Eveline F. Yao, two senior U.S. Air Force (USAF) medical officers and faculty on the Uniformed Services University of Health Services, conducted a “retrospective cohort study of duty-restriction rates” among C-17 aircrews at three of the eleven USAF Air Mobility Command (AMC) bases from January 2002 to May 2002 (before smallpox vaccination) and again from January to May 2003 (post-vaccination). Based on sophisticated statistical analysis of reported side-effects leading to “duties not to include flying” (DNIFs), they conclude that (1) the smallpox vaccination program “did not impose operational constraints or adversely affect aircrew preparedness in the USAF AMC,” and (2) the overall safety of the program was successfully demonstrated and may serve as a reference for future occupational medicine and immunization programs” (Folio & Yao, pp. 547, 552). So far, however, no other segments of the U.S. population have elected to pursue pre-event smallpox vaccination in significant numbers.

**OPTION B: Post-Event Mass Vaccination**

A descriptive study of the initial phase of the MILVAX program published in the *Journal of the American Medical Association* (JAMA) in June 2003 anticipated the findings of Folio and Yao two years later. John B. Grabenstein and William Winkenwerder, JR., both with the Military Vaccine Agency in northern Virginia, reviewed the rates of symptoms and complications against the numbers of vaccinations and vaccination exemptions. They found that most “adverse events occurred at rates below historical rates”—for example, one case of encephalitis and 37 cases of myopericarditis, with full recovery of all victims—and they found “no cases of transmission of vaccinia from [health] worker to patient, no cases of eczema vaccinatum or progressive vaccinia, and no attributed deaths.” Such a surpassing safety record moved the research team to suggest that “broad smallpox vaccination programs may be implemented with fewer serious adverse
events than previously believed” (Grabenstein & Winkenwerder, p. 3278). That study, and several others, led Mary E. Wright and Anthony E. Fauci in the same issue of JAMA to dub the conclusion “a critically important piece of new information” for a “21st-century population” (Wright & Fauci, p. 3307).

An unequivocal case for post-event mass smallpox vaccination appears in Edward H. Kaplan et al.’s presentation of their application of “a disease transmission model of a smallpox attack in a large urban center” in the August 6, 2002, issue of the Proceedings of the National Academy of Scientists (PNAS) (Kaplan et al., pp. 10935, 10938). They compare the CDC’s preferred interim response plan for targeted vaccination and quarantine (TV) (see the next option) to mass vaccination of the entire population (MV) following a hypothetical attack that infects 1,000 persons initially. Their computational model of projected fatalities results, somewhat counter-intuitively, in fewer deaths “over a wide range of scenarios” under the MV option compared to the TV option. The TV strategy is rooted in the celebrated “surveillance-containment” policy in the 1960s and 1970s that enabled the WHO to eradicate smallpox by 1980, but that previously successful strategy is dependent on drastically limited surveillance and vaccination resources in the 21st century. The Kaplan team’s model has TV actually slowing the overall vaccination rate in pursuit of possible close contacts of infected persons, while effectively quarantining those infected. The “queuing delays” allow the infection to continue to spread as a function of the mass panic and accelerated demand for vaccination that would probably ensue in the aftermath of a bioterrorist attack. As a result, many victims miss the maximum four-day window of opportunity for effective post-event vaccination. By contrast, planning for and implementing the MV strategy immediately after an outbreak of smallpox instead of waiting until the TV strategy reaches critical failure reduces significantly the number of smallpox fatalities.
Kaplan et al. recommend, therefore, that an MV strategy replace the current CDC policy, at least for smallpox attacks in large urban centers.

**OPTION C: Post-Event Targeted ("Ring") Vaccination**

Two strong arguments against mass evacuation and in favor of the CDC’s preferred targeted or “ring” strategy emerge from the scientific / policy literature on smallpox as a bioterrorist threat. The “ring” nickname derives from the process of quickly identifying, immunizing, and isolating infected persons as well as quickly identifying, immunizing, and monitoring the “ring” of persons around each infected individual, particularly his or her personal contacts.

First, in 2002 (before the MILVAX program initiated by President George W. Bush) a team at Emory University’s School of Public Health led by M. Elizabeth Halloran conducted a “discrete-time, stochastic simulation model of smallpox spread within a structured community.” Their model for a demographically representative community of 2,000 persons statistically projects the probability of sequential infection based in particular on each person’s vaccination status. A worst-case scenario assumes that persons vaccinated against smallpox before 1972 have no residual immunity, and an alternate scenario assumes that they had immunity equivalent to 50% of a fresh vaccination. The team also considers policies of mass vaccination pre-event and mass vaccination over the course of ten days after a smallpox outbreak. The key to the team’s findings is whether adults vaccinated before 1972 retain residual immunity. Targeted or “ring” vaccination fares better in the study than mass vaccination among those with residual immunity if the program is implemented immediately as measured by two metrics: number of smallpox cases prevented per dose and number of vaccine-related deaths (the latter owing to the fewer doses administered compared to the mass vaccination alternative). To be sure, if previous vaccination does not confer
even 50% immunity at present, then “timely mass vaccination” might be more effective than the targeting strategy: in either scenario, “rapid response can make the difference” (Halloran et al., pp. 1432, 1434-1435).

Second, in 2002 (again before the MILVAX program initiated by President Bush) the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP) issued a detailed policy statement that gave a ringing endorsement to the CDC’s recommended strategy of targeted smallpox vaccination. The AAP was persuaded that such a post-event response could control “a localized outbreak with minimal exposure of vulnerable populations to the complications of immunization,” while preventing “disease severity if given within 3 or 4 days of initial exposure” and decreasing “symptoms if given within the first week of exposure.” The AAP cites seven specific reasons in their argument (AAP, pp. 843-845):

1. The same strategy of surveillance and containment proved remarkably successful in the final push to eradicate smallpox in the 1960s and 1970s.

2. A mass vaccination campaign would probably incur much higher adverse reactions, since many persons with contraindications (e.g., skin conditions or immunosuppressive disorders such as HIV) might be undiagnosed or unidentified during the hasty rush to vaccinate the entire population.

3. Current supplies of VIG are not adequate for treating the predictably high number of patients with serious post-vaccination complications.

4. The elderly could be even more vulnerable to complications than young children—the focus of attention prior to 1972: there is scant clinical evidence concerning the deterioration of the immune system with aging.

5. Mass vaccination would rapidly exhaust the current supply of smallpox vaccine [a point soon rendered moot after the initiatives of the Bush administration].

6. Mass pre-event vaccination would demand high numbers of health care and public health professionals to conduct the program and monitor complications.

7. A post-event mass vaccination regime might detract from “other essential outbreak control measures, such as careful surveillance, contact tracing, and isolation of cases.”
As a hedge, however, the AAP also concurs with the CDC’s recommendation to vaccinate and train 10,000 to 20,000 “carefully screened” health care professionals at the national, state, and local levels as soon as possible in the hope that persons infected during a smallpox outbreak would receive care from immunized persons.

**OPTION D: No Pre-Event Vaccinations**

A peer-reviewed “commentary” article by Hillel W. Cohen et al. in an October 2004 issue of the *American Journal of Public Health* presented a politically-charged, ostensibly ethical argument against any smallpox preparedness programs (which will receive more attention in the final section of this essay). From a practical policy perspective, however, the authors, through their argument by assertion, do manage nonetheless to raise serious questions about the efficacy of pre-event vaccinations for anyone in the 21st century. First, the revived smallpox vaccination program since 2002 “has been linked to fatalities and other serious adverse events, although evidence of risk of exposure to smallpox has been minimal,” and that program “may cause substantial harm to the public health if allowed to proceed.” Second, pre-event vaccinations divert “essential public health personnel, facilities, and other resources from urgent, real public health needs.” Third, the post-Nine Eleven biodefense program includes new “secret” research facilities that store and manipulate dangerous materials, “thus increasing the risk of accidental release or purposeful diversion” and possibly fostering a “global ‘biodefense race’ that would likely spur proliferation of offensive biowarfare capabilities” (Cohen et al., 2003, pp. 1667, 1669).

More sanguine and measured are the epidemiological studies in 2003 by Martin Eichner of the University of Tubingen. In one project Eichner, together with Klaus Dietz, assess historical data for a smallpox epidemic in 1967 in Abakaliki, Nigeria, a commercial town with a population of 31,200. Only 32 persons contracted the disease of whom 30 belonged to Faith Tabernacle
Church, a religious community that eschewed vaccinations and medical treatment. Despite the relatively small number of infections, the smallpox outbreak warranted international attention. Abakaliki was the central venue of a pilot project of the WHO’s smallpox eradication program, which had successfully vaccinated 88.5% of the population only a few months before the latest outbreak. Focusing on how the contagion spread to close and remote contacts, especially during the incipient pre-rash fever phase, the research team found that “smallpox spread slowly, mainly among close contacts, and that infectivity before the onset of rash was negligible.” Despite the rather small study sample, they conclude that “smallpox could even be controlled by isolation alone,” and concur with a previous study in 1988 that, short of a total breakdown of public health services, “reserve stocks of vaccine . . . would ensure the containment of any outbreak that followed a deliberate release of variola” (Eichner & Dietz, pp. 110-112, 116).

In a single-author project shortly afterward, Eichner provides supporting evidence that militates against pre-event vaccination. To assess the residual protection of prior smallpox vaccination, Eichner analyzes historical epidemiological data from two smallpox outbreaks: (1) 943 reported vaccinated smallpox cases and 220 unvaccinated cases during an epidemic in Liverpool, England, from 1902 to 1903, and (2) 680 cases of smallpox, including 109 fatalities, in the wake of renewed smallpox epidemics in Europe from 1950 to 1971. Eichner discovered that the “probability of mild disease is much higher for vaccinated cases than unvaccinated cases . . . and the probability of fatal disease is much lower . . . even if vaccination occurred decades before infection.” Computational models suggest that “protection against infection is lost about 20 – 40 years after primary vaccination,” and that “residual protection against death from smallpox may even be lifelong for the majority of vaccinees.” Ironically, Eichner also notes a concurrent risk that at least some pre-vaccinated persons who contract milder forms of the disease might, while yet undiagnosed, spread the infection unwittingly among their contacts (Eichner, 2003, pp. 717-721).
OPTION E: Destruction of All Variola Stockpiles

When it meets later this month, the World Health Assembly (WHA) is expected to decide whether to set a firm deadline for the destruction of all remaining samples of the variola virus. Of course, that means the U.S. supply in storage at the CDC in Atlanta and the Russian supply at Vector; any rogue nations or non-state terrorist groups that may have obtained their own supplies would hardly heed anything the WHA decrees. But ought the U.S. to abide by such a deadline?

In a science op-ed published in the British Medical Journal on April 12, 2007, Edward Hammond, director of the now defunct Sunshine Project advocacy organization, argues strenuously that both the U.S. and Russia ought to destroy their smallpox stocks (Hammond, 2007). Simply put, “the risks far outweigh the potential benefits” of retaining the live virus. Other WHO member nations insist that the stocks ought to be destroyed. The WHO’s experts concluded in 2006 that scientific research no longer required the samples. The variola virus now has ample “sequence information” as well as adequate detection and diagnostic systems. New antiviral drugs are unnecessary, because “existing vaccines are effective and diagnostic tests are rapid and accurate”; in any case, dual-use antiviral research could utilize the safer alternative of monkeypox virus. Hammond also claims that no “credible evidence” exists that any terrorist group possesses smallpox virus in any quantity. Resistance by the U.S. or Russia to a firm WHA deadline might lead to a renewed smallpox virus proliferation among other nations who may wish to acquire the virus and conduct similar research. Hammond goes so far as to recommend that possession of the variola virus be considered “a crime against humanity”!

But the ever prudent Jonathan B. Tucker takes a more measured approach in the March 2011 issue of the journal, Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science. He attempts to mediate between “destructionists”—primarily public health professionals
who downplay the threat of smallpox bioterrorism and stress the biosafety risks of ongoing research with live variola virus—and “retentionists,” virologists and national security professionals who highlight the potential bioterrorist threat of smallpox and the corresponding need to improve the medical counter-measures. Tucker’s compromise recommendation has multiple parts, but the gist is this: If the U.S. cannot, for any number of political or geopolitical reasons, accept a deadline for destruction by the end of 2012, then it ought, at least, to broker a “grand bargain” with three key features:

1. Partial destruction of the variola stocks, perhaps a reduction to ten representative strains at both CDC and Vector.

2. Specific steps by the WHA to prevent de novo synthesis of variola virus.

3. Equitable sharing of all benefits from smallpox research with WHO member states.

Although decision time concerning this second-order policy issue is almost upon us, resolution of the debate is less urgent and profound than the primary question about vaccination.

**Ethical Analysis and Policy Recommendations**

To prepare and respond most effectively and ethically for a possible smallpox terrorist event the U.S. federal government ought to consider how the usual American values (“virtues” would be a more apt term) of justice, fairness, compassion, individual personal worth, and practicality shape the issue.

For example, confronted by such a potentially devastating disease as smallpox, the primary objective would be, of course, to preserve individual lives as “virtual absolutes” and to minimize the morbidity attendant upon either infection by the smallpox variola virus itself or vaccination with vaccinia. But how might the quality of our collective social or cultural life be diminished by a national campaign to immunize the entire population prior to or even pursuant to a smallpox outbreak? Americans have, historically, disdained living in fear of enemies and have insisted on
bold risk-taking to preserve a material way of life to which we have become accustomed. At the same time, however, Americans cherish youth, health, and fitness (if only through lip service) and have come to rely on a multilayered health care system for medical care even to the breaking point.

Similarly, stakeholders in the formation of public health and defense policy have to weigh the practical demand of ensuring the survival of the healthy majority (or the “strongest”) against a more compassionate emphasis on care for the most vulnerable and/or medically needy. A team of physicians at the U.S. Department of Veterans Affairs opts for the former when they propose that the historic practice of battlefield or emergency triage be applied to a large-scale public health emergency (such as a smallpox attack) (Kuschner et al., 2007). In contrast, a special committee of the Institute of Medicine would focus in disaster situations on “vulnerable populations and those with medical special needs, including pediatrics, geriatrics, and persons with disabilities” (IOM, 2009). To put the conflict in more stark utilitarian terms, the public policymakers may have to weigh the interests of the “many” against those of the “few.”

Another key factor is at once ethical and prudential: the predictable opportunity cost in dollars of a robust policy of smallpox preparedness and response compared to other public health and national security priorities. Not well known is the rather puny size of the entire biodefense portion of the U.S. federal budget for fiscal year 2011: $6.48 billion compared to $500+ billion for Medicare, $375+ billion for Medicaid, and $27+ billion for HIV / AIDS research and medical treatment. That biodefense sum is spread over seven federal agencies—most notably Health and Human Services (67%), the Department of Homeland Security (18%), and DoD (11%)—and includes numerous “dual use” expenditures for enhanced disease surveillance, increased hospital surge capacities, and improved responses to natural epidemics. It is quite obvious that, even if the probability of a bioterrorist smallpox attack on the U.S. is low, as most geopolitical and scientific experts seem to agree, the opportunity cost in dollars of any of the vaccination policy options
considered above would be relatively meager. And yet some opponents of pre-event smallpox vaccination (policy OPTION D above) seem determined to perpetuate a series of myths. Hillel Cohen et al., for example ground their immoderate, even shrill rejection of any smallpox preparedness policy as “irrational and dysfunctional” on dubious, unsupported assertions about needless “diversion” of public health personnel and resources, the illusion of the “dual use” rationale, “inexcusable” deaths and other serious complications as a result of the limited vaccination campaign since December 2002, and an inordinate risk of “accidental release or purposeful diversion” of pathogens at “a number of new secret research facilities” (Cohen et al., 2004, pp. 1667, 1669). Contrary to those claims, none of the smallpox vaccination options amounts to a significant financial diversion of public funds in pursuit of a quixotic delusion. Conversely, considering the unique ramifications of a terrorist-inflicted smallpox epidemic upon the entire human biosphere, the stakes could not be higher for a failure to prepare adequately for such a “low probability, high consequence” disaster.

Hard cases make for bad laws, as the legal saying goes, and worst-case scenarios ordinarily do not drive good public policy. However, in the case of bioterrorist smallpox attack, the “worst case” is so unthinkable as to render more optimistic public policies irresponsible. The historic scientific evidence of the deleterious effects of the variola smallpox virus on humanity before its eradication, particularly the steep 30% CFR and the extreme morbidity that afflicts up to 90% of survivors, requires a robust program of prevention and treatment that trumps other considerations. This is no raw utilitarian calculus. The greater good of the entire populace—not only of the U.S. but perhaps the entire planet—and, at once, a decent respect for the most vulnerable and medically needy mandates such preparedness and response. No individual or demographic group may, in good conscience, be subjected to a preventable risk of contracting smallpox, even in view of the
sometimes serious complications attendant upon vaccination with vaccinia or, we may hope, MVA, or other less risky next-generation vaccines.

Therefore, the most ethical public policy for smallpox preparedness would seem to be a combination of several of the five options described above.

First, OPTION E (destruction of all variola stockpiles) is a fool’s errand in a very volatile world beset by bad international actors. At the risk of incurring the wrath of the WHA and other respectable international organizations, the U.S. (and Russia, too, if it so desires) ought to adopt Jonathan Tucker’s “grand bargain” and retain a smaller sample of variola virus as a contingency for additional research and development of better vaccines against variola or other genetically manipulated versions that might surface. With so much at stake concerning a re-introduction of smallpox into the human biosphere, U.S. public policymakers would be both prudent and ethical to regard U.S. national interest as a better servant of humanity than the preferences of the international community of nations.

Second, OPTION A is worth continuing for U.S. military personnel and DoD civilians deploying to southwest Asia, where, as targets of opportunity in uncommonly large concentrations in closer proximity to the most likely terrorist perpetrators, they are most susceptible to smallpox attack. The encouraging findings of the early epidemiological studies remain unchallenged, so the risk of serious complications from vaccination through the MILVAX program is both negligible and a signal to the wider population (minus the identified special at risk demographic groups such as pregnant women and those with skin diseases or immunodeficiency disorders) that post-event smallpox vaccination is feasible, worthwhile, and necessary. This is yet another case of the U.S. armed forces serving in the vanguard of national defense, particularly since Nine Eleven.¹

¹ Full disclosure: the author of this essay was exempt during five consecutive years of short deployments as a U.S. Army chaplain due to rosacea.
Finally, OPTION B (post-event mass vaccination) promises a better outcome in extremis than OPTION C (post-event targeted vaccination). The evidence-based scientific studies for either option lack sufficient population databases; the various computational models build on dubious assumptions (such as Halloran et al.’s 50% residual immunity from previous smallpox vaccination even decades later); and the sweeping conclusions seem supported by dubious reasoning (such as Kaplan et al.’s “queuing effect”). So we must navigate parallel seas of uncertainty.

Without a compelling case for either mass or targeted vaccination post-event, perhaps the most persuasive ethical argument in miniature for post-event mass vaccination is Rosemary Quigley’s serendipitous focus on children. Referring to a controversial decision in 2002 by the American Academy of Pediatrics in favor of a clinical trial of smallpox vaccine including forty children, Quigley suggests that those children, far from a merely expedient means to a good end even with parental permission, would assume a minimal risk for the greater good of all children. Further, not to do so would place a greater burden of risk upon the 70 million children who would have to receive untested vaccine in the aftermath of a smallpox attack (Quigley, p. 945). From that argument one may extrapolate a broader ethical principle concerning the ethical duty of some to assume a special risk of heroic sacrifice for the many.

In the horrific event of a bioterrorist smallpox attack within the borders of the U.S., the exigencies of time, geography, and resources would mitigate the success of, perhaps even cripple, a strategy of targeted or ring vaccination. That approach managed to eradicate smallpox in the 1960s and 1970s, but there was little geopolitical pressure then, and every child born in the United States was vaccinated in what was tantamount to a pre-event mass vaccination program. What seems most ethical and most prudent in the post-Nine Eleven era is for the U.S. to devise a cogent, reasonably comprehensive, and scalable plan for mass vaccination of the cities or other areas directly affected by a smallpox attack rather than attempting the more refined, sophisticated,
limited targeted approach. That would also entail sparing no effort to identify the special at risk populations for post-vaccination medical treatment with VIG, cidofovir, or even experimental antiviral drugs under extreme emergency conditions. Those persons, in the aggregate, would probably fare worse without vaccination than with it, although the risk might still be agonizing. Even the most unfavorable results among at risk groups would comport with the philosophical principle of “double effect,” which requires a “teleological” proportionality of means and ends.\(^2\) The vaccination itself is a good, or at least morally neutral, and necessary means to a good end—namely, the deliverance of human beings from a deadly disease. Any fatalities or side effects caused by vaccination would be clearly unintended; they would not serve as a direct means to the desired good end, since all persons, if necessary, would be subject to the same procedure; nor would the adverse consequences, however tragic, be disproportionate to the considerably positive outcome for the vast majority of the people of the United States. Post-event mass vaccination would, therefore, be the most ethical option both for those who survive unscathed and for those who do not survive their ennobling act of voluntary sacrifice.

The operative term here is scalable. As a bioterrorist smallpox epidemic expands from venue to venue, so, too, would the mass vaccination regime in response. Vigorous epidemiological surveillance of outbreaks of the disease and on-going training of health personnel to diagnose specific cases would have to keep pace. Fortunately, the national pharmaceutical stockpile has just enough smallpox vaccine for every American according to the 2010 census. That may be the only science-based assurance that the American landscape need not resemble an apocalyptic scene straight out of a science fiction novel.

References


Kaplowitz, L. G. (2011, April 26). Deputy Assistant Secretary for Policy, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services [Personal Interview].


Appendix A: CDC Smallpox Fact Sheet (modified)
(http://www.bt.cdc.gov/agent/smallpox/overview/disease-facts.asp)

<table>
<thead>
<tr>
<th>Smallpox Disease</th>
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<tbody>
<tr>
<td><strong>Incubation Period</strong></td>
</tr>
<tr>
<td>(Duration: 7 to 17 days)</td>
</tr>
<tr>
<td><strong>Not contagious</strong></td>
</tr>
<tr>
<td><strong>Initial Symptoms</strong></td>
</tr>
<tr>
<td><em>(Prodrome)</em></td>
</tr>
<tr>
<td>(Duration: 2 to 4 days)</td>
</tr>
<tr>
<td><strong>Sometimes contagious</strong></td>
</tr>
<tr>
<td><strong>Early Rash</strong></td>
</tr>
<tr>
<td>(Duration: about 4 days)</td>
</tr>
<tr>
<td><strong>Most contagious</strong></td>
</tr>
<tr>
<td><strong>Pustular Rash</strong></td>
</tr>
<tr>
<td>(Duration: about 5 days)</td>
</tr>
<tr>
<td><strong>Contagious</strong></td>
</tr>
<tr>
<td><strong>Pustules and Scabs</strong></td>
</tr>
<tr>
<td>(Duration: about 5 days)</td>
</tr>
<tr>
<td><strong>Contagious</strong></td>
</tr>
<tr>
<td><strong>Resolving Scabs</strong></td>
</tr>
<tr>
<td>(Duration: about 6 days)</td>
</tr>
<tr>
<td><strong>Contagious</strong></td>
</tr>
<tr>
<td><strong>Scabs resolved</strong></td>
</tr>
<tr>
<td><em>(Not contagious)</em></td>
</tr>
<tr>
<td><strong>Not contagious</strong></td>
</tr>
</tbody>
</table>

* Smallpox may be contagious during the prodrome phase, but is most infectious during the first 7 to 10 days following rash onset.
Appendix B: WHO Photos of Child with Smallpox
(Source: Henderson et al., p. 2130)

Appendix C: Routine Progression of Skin Rash from Vaccinia
(Source: ADAM2000 [Acambis] Package Insert:
http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM142572.pdf)

Figure 1: Progression of major cutaneous reaction after primary vaccination

Day 5 Day 8

Day 10 Day 14