

SMALLPOX: IS THE DEPARTMENT OF DEFENSE PREPARED?

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MASTER OF MILITARY ART AND SCIENCE

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The opinions and conclusions expressed herein are those of the student author and do not necessarily represent the views of the U.S. Army Command and General Staff College or any other governmental agency. (References to this study should include the foregoing statement.)

ABSTRACT

SMALLPOX: IS THE DEPARTMENT OF DEFENSE PREPARED? by MAJ Stephen M. Ford, 79 pages.

Biological weapons pose a clear and present danger to U.S. national security, U.S. forces, and key allies and friends. Their low cost, low visibility, high potency, accessibility, and easy delivery make BW attractive to adversaries seeking new methods of violence when current ones no longer achieve their intended effect. With a case fatality rate of 30 percent and no effective treatment smallpox is one of the most feared of all biological weapons. Thus, the central research question is: Given the asymmetric threat posed by biological weapons and recent advances in biotechnology, is the Department of Defense (DoD) prepared to counter the current smallpox threat? A comparative analysis was completed evaluating differences between smallpox and influenza preparedness. The analysis included evaluation of detection and surveillance (the components of recognition), as well as applied research, specialized infrastructure, and disease prevention and control (the elements of intervention). The analysis determined DoD is largely unprepared. Recommendations to improve response include: research and development of new vaccines and antivirals, enhanced vaccine production capacity, additional research focused at bolstering nonspecific immunity, improved clinical diagnostics and additional specialized laboratory infrastructure.

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ACRONYMS

ADRs	Adverse reactions
BSL-4	Biosafety level-4
BWC	Biological and Toxin Weapons Convention
BWs	Biological weapons
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
DoD	Department of Defense
ECTV	Ectromelia virus
ESSENCE	Electronic Surveillance System for Early Notification of Community-Based Epidemics
EV	Eczema vaccinatum
FDA	Food and Drug Administration
GV	Generalized vaccinia
HDV	Hepatitis D
HBV	Hepatitis B
IL-4	Interleukin-4
HIV	Immunodeficiency virus
IND	Investigational new drug
<i>MMWR</i>	<i>Morbidity and Mortality Weekly Report</i>
MIRV	Multiple independent reentry vehicle
PCR	Polymerase chain reaction
PV	Progressive vaccinia
RFLP	Restriction fragment length polymorphism
TK	Thymidine kinase

USAMRIID	U.S. Army Medical Research Institute of Infectious Diseases
VIG	Vaccinia immunoglobulin
WMD	Weapons of mass destruction
WHO	World Health Organization

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CHAPTER I

INTRODUCTION

The gravest danger our Nation faces lies at the crossroads of radicalism and technology. Our enemies have openly declared that they are seeking weapons of mass destruction, and evidence indicates that they are doing so with determination. The United States will not allow these efforts to succeed. . . . History will judge harshly those who saw this coming danger but failed to act. In the new world we have entered, the only path to peace and security is the path of action.

President Bush, *The National Security Strategy*

The Biological and Toxin Weapons Convention (BWC), signed in 1972 and entered into force in 1975, was the first multilateral disarmament treaty to ban an entire class of weapons of mass destruction (WMD). Article I of the BWC states:

Each State Party to this Convention undertakes never in any circumstance to develop, produce, stockpile or otherwise acquire or retain:

1. Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective, or other peaceful purposes;
2. Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflicts.

The BWC is rightly regarded as a landmark in weapons control. Unfortunately, the convention contains essentially no provisions for verification and there have been notable violations. It is now recognized that numerous state parties to the Convention including: the Soviet Union (and later Russia), Iraq, North Korea, Iran, Syria, and China continued programs of biological weapons (BW's) research and development in violation of the BWC. Rogue states, subnational groups, and terrorists now possess the capability and determination to develop and acquire BW.

The current *National Strategy to Combat Weapons of Mass Destruction* identifies BW “in the possession of hostile states and terrorists as one of the greatest security challenges facing the United States.” It is now clear that BWs, in the hands of U.S. adversaries, have the potential to cause catastrophic harm to the U.S. homeland, her military forces, and her allies. The pillars of the national strategy to combat the WMD threat include: counterproliferation measures, strengthened nonproliferation initiatives, and improved consequence management in response to WMD use.

The greatest threats to human health in the United States come from emerging and reemerging infectious agents that occur sporadically in nature (Peters 2002). Generally speaking, the population is highly susceptible to these infectious agents and there is usually an associated high rate of mortality in infected individuals. Thus an eradicated disease agent to which there is a high degree of susceptibility, for which there is a high rate of mortality among infected individuals, that can spread as an aerosol, and that can continue to spread via contagion--in effect a worst-case disease--could inflict the most casualties (National Research Council 2002). Smallpox, in essence, is a worst-case disease!

Background and Context of the Problem

The Biological Weapons Threat

Biological weapons, including smallpox, pose a clear and present danger to U.S. national security, U.S. forces, and key U.S. allies and friends. America’s military power presents an interesting paradox. Enemies recognize a conventional battle would be difficult to win so they choose unconventional or asymmetric tactics to gain the upper hand. “Asymmetric” tactics merely describe situations in which an adversary employs

weaponry or tactics in unexpected or unsanctioned ways. It also describes a situation in which the attacker is willing to use weapons and tactics that the victim is unwilling to use, possibly because they are viewed as immoral or illegal. The use of asymmetric weapons and tactics can enable an adversary to win against a more powerful enemy—an enemy that may be unable or unwilling to respond in kind (Bailey 2001).

Biological weapons pose an asymmetric threat. To rogue nations, religious zealots, terrorists, and criminal elements, BWs are another WMD to inflict harm and threaten neighbors. Bioweapons have similar lethality to a nuclear device but are much cheaper to produce and easier to obtain. Dual-use (civil and military) technologies make identifying bioweapons production facilities difficult. Equipment is available through legitimate channels and is used in the manufacture of pharmaceuticals, vaccines, even beer. In fact, until the point of weaponization all aspects of bioweapons production have a licit use.

Biotechnology

It is now recognized that the same technology leading to some of science and medicine's greatest triumphs may now be used for perverse and immoral purposes such as the development of BW. Recent scientific and technologic developments in the fields of microbiology, biotechnology, molecular biology, genetic engineering, and any applications resulting from genome studies could be used to create enhanced bioweapons. It is conceivable that making subtle genetic alterations to existing pathogens to increase their virulence or durability in the environment, or to make them harder to detect or to treat with drugs, is within the limits of today's technology (Dennis 2001).

Examples of advances in genomics and biotechnology that can be used to enhance BW include: mixing and matching traits from different microorganisms, using knowledge of pathogen genomics and human genetics to target particular ethnic groups, developing techniques of “directed molecular evolution” (accelerating the evolution of desired traits by deliberately introducing genetic variation and then applying artificial selection), deoxyribonucleic acid (DNA) shuffling (genes are broken down into smaller pieces and then shuffled during their reassembly to create “daughter genes” with new properties), deliberate hybridization of related viral strains, gene therapy, and the creation of “stealth viruses.” All these techniques have serious implications for biowarfare. Fortunately, many of these same techniques can also be used to develop BW countermeasures.

History and Potential as a Biological Weapon

Smallpox is one of the most feared of all potential biological weapons. Throughout human history smallpox has killed hundreds of millions of people. It is a disfiguring, communicable disease, with a case-fatality rate of 30 percent, for which there is no effective medical treatment.

Smallpox was probably first used as a biological weapon during the French and Indian Wars (1754-67) by British forces in North America. Soldiers distributed blankets that had been used by smallpox patients with the intent of initiating outbreaks among American Indians. Epidemics occurred, killing more than 50 percent of many affected tribes (Henderson et al. 1999). With Edward Jenner’s demonstration in 1796 that inoculation with a related cowpox virus conferred immunity to smallpox, the scourge of smallpox was gradually controlled. Despite Jenner’s discovery and the gradual uptake of

vaccination, smallpox persisted into the first half of the twentieth century due to poor vaccine quality, strong public opposition to vaccination, and waning enthusiasm among individuals effectively vaccinated in childhood who contracted the disease as adults.

In 1980, after a global vaccination campaign spearheaded by the World Health Organization (WHO), the World Health Assembly declared smallpox eradicated worldwide. Since its eradication, smallpox vaccination programs and vaccine production have ceased. The United States stopped its routine childhood vaccination program in 1972. The U.S. military continued widespread smallpox vaccinations until 1984, when vaccinations were restricted to recruits in basic training. Recruit vaccination was intermittent from 1984 to 1990 due to inadequate supplies of an antidote known as vaccinia immunoglobulin (VIG) and the introduction of serologic testing for human immunodeficiency virus (HIV). The Department of Defense (DoD) ceased routine use of smallpox vaccine in March 1990. However, on 13 December 2002, President Bush announced his orders to resume mandatory smallpox vaccinations for military personnel and on a voluntary basis for medical personnel and emergency first responders. A DoD news release indicated the department will immunize personnel based on their occupational responsibilities, with emergency response teams and hospital and clinic workers receiving the vaccine first. Next will be those individuals with “critical mission capabilities.” Therefore, excluding the military, first responders, and medical personnel vaccinated under the current national smallpox vaccination plan, the entire global population remains highly susceptible to the deliberate release of smallpox.

Since its eradication, the only remaining stocks of smallpox virus have been stored in two WHO reference laboratories--the State Research Center of Virology and

Biotechnology (the Vektor Institute), in Novosibirsk, Russia, and the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Many experts believe, however, that the smallpox virus is not confined to these two official repositories and may be in the possession of states or subnational groups pursuing active biological weapons programs. Of particular importance and concern is the legacy of the former Soviet Union's biological weapons program. It is widely known that the former Soviet Union cultivated and maintained a stockpile of twenty tons of smallpox virus in its biological weapons arsenal throughout the 1970s, and that, by 1990, they had a plant capable of producing 80 to 100 tons of smallpox virus per year (O'Toole et al. 2002). This Soviet research also included adapting its use in bombs and intercontinental ballistic missiles and in attempting to bioengineer more virulent and contagious strains of the virus. There also remains a lingering concern about the "brain drain" of unemployed former bioweapons scientists from Russia. The *New York Times* reported in December 1998 that at least five former bioweapons scientists were working in Iran, which was paying them \$5,000 a month in lieu of their previous \$100 monthly salary. Other former Soviet experts might be sharing their deadly expertise over the Internet without ever leaving home. In an interview with CBS News, Ken Abilek, a former deputy director of the Soviet Union's civilian bioweapons program, observed, "Thousands of people know how to work with the smallpox virus. Where these people are and what they're doing, of course, nobody knows. It makes me nervous" (Tucker 2001, 203).

Epidemiology and Virology

Variola virus, the virus that causes smallpox, is one of a family of large, enveloped DNA poxviruses. The smallpox virus is robust and can be disseminated through the air as an aerosol. Unlike anthrax bacteria, the smallpox virus can spread from person to person by face-to-face contact primarily through respiratory droplet nuclei. Less commonly, transmission may also occur through fomites, such as infected clothing or bedding. Although smallpox is less transmissible than measles, chickenpox, or influenza, secondary attack rates among unvaccinated contacts range from 37 to 88 percent (Breman and Henderson, 2002). The incidence of smallpox is highest during the winter and early spring, because aerosolized orthopoxviruses survive longer at lower temperatures and low levels of humidity.

Smallpox Disease

There are five known classifications of smallpox. The ordinary form is most common, accounts for approximately 90 percent of cases, and has a case fatality rate of 30 percent. The flat form of the disease accounts for only 5 percent of cases but has a 97 percent case fatality rate. The hemorrhagic form accounts for less than 3 percent of cases but has a 100 percent fatality rate. The two remaining classifications of smallpox are the modified form (occurring in less than 2 percent of cases and having less than a 1 percent fatality rate) and *V. sine eruptione* (occurring in less than 1 percent of cases with no known fatalities). There are no specific strains associated with hemorrhagic disease; thus, it is believed to be a host response. Patients with hemorrhagic disease die despite postexposure vaccination.

After exposure to smallpox, the incubation period is between twelve to fourteen days (range, seven to seventeen days) which ends with sudden onset of fever, headache, and backache, usually severe enough to confine a patient to bed. Fever usually continues as the rash develops, with pain associated with pustule growth. Scabs develop and gradually separate, leaving pitted scars. The rash is the most important feature allowing for early recognition of smallpox. Smallpox is distinguishable from chickenpox by the prominent prodromal period and lesions that develop at the same pace and on any part of the body, appear identical to each other, evolve slowly, and are peripherally distributed (Whitby et al. 2002).

Laboratory diagnosis can be made by observing the characteristic brick-shaped virions in negatively stained isolates from vesicular fluid or scab preparations viewed by electron microscopy. Genus and species identification can now be made using relatively rapid polymerase chain reaction (PCR) methods available at CDC and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Additional diagnostic techniques include: tissue culture, DNA probe, and a restriction fragment length polymorphism (RFLP) assay.

The only proven effective means of controlling smallpox is vaccination, either before or within four days of exposure, which may prevent or reduce the severity of disease. Other treatment is supportive and includes: antibiotics for secondary bacterial infections, fluids, nutrition, and strict quarantine with respiratory isolation for seventeen days of all cases and direct contacts. Until late 2001, only 15 million doses of Dryvax-brand vaccinia (smallpox vaccine) were available through the CDC. This supply has now been augmented by studies supporting dilution of the Dryvax vaccine, a supply of

vaccine from Aventis Pasteur produced in the 1950s now tested and found potent, and additional vaccine produced under modern manufacturing conditions that is currently in production. In total, over 300 million doses of potent smallpox vaccine are currently available to respond to a smallpox outbreak. However, only 2.7 million doses are licensed vaccine not requiring informed consent under regulations governing the use of an investigational new drug (IND). DoD owns one million of the 2.7 million total.

U.S. military policy development in this area culminated with the publication of the *DoD Smallpox Response Plan*, version 3.1, dated 29 September 2002. This capstone document provides response planning for smallpox outbreaks on military installations and for military support to civil authorities. Modeled after the *CDC Interim Smallpox Response Plan and Guidelines*, it expands response measures and implementation guidelines to military-unique missions and responsibilities.

The Research Question

Given the threat of a deliberate smallpox attack, an analysis of current DoD preparedness to respond is clearly in order. A wide chasm often exists between available planning guidance and the military's ability to implement established policy. A smallpox attack would significantly affect military readiness. "An outbreak would degrade combat mission capability among vulnerable troops; stress military medical operations to maximum capacity; restrict military operations; limit transit of international boundaries and divert military manpower for healthcare or crowd control" (Department of Defense 2002, 6).

The purpose of this paper is to systematically analyze the following research question: Given the asymmetric threat posed by BW and advances in biotechnology, is DoD prepared to respond to the current smallpox threat?

Subordinate questions develop supporting information for analyzing the primary research question. Is the threat of a deliberate attack with smallpox valid? Will the virus be a genetically modified strain? What capabilities exist for detection, surveillance, and diagnosis of smallpox and are they adequate? What are current prevention and response measures? What are available strategic policy options for countering both the smallpox and other BW threats?

If the answers to any or all of the above questions are not positive, then what changes could DoD make to existing capabilities to enhance the U.S.'s ability to respond to a smallpox attack?

Assumptions

Two assumptions are necessary for this study. The first is that if smallpox is released as a biological weapon, it will likely be genetically modified to evade protection offered by current vaccines. The second assumption is since routine civilian vaccination ceased around 1972, that susceptibility to smallpox is universal among children and young adults, and widespread among older adults (excluding the small number of military personnel and emergency responders recently vaccinated under the provisions of the Smallpox Vaccination Program).

Key Terms

Biological Warfare Agents: Living organisms, whatever their nature, or infected material derived from them, which are used for hostile purposes and intended to cause disease or death in man, animals and plants and which depend for their efforts on the ability to multiply in the person, animal, or plant attacked.

Immunity: An inherited, acquired, or induced resistance to a particular pathogen.

Investigational New Drug (IND): A new drug or biological drug used in a clinical investigation. An authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

Smallpox: An acute, highly infectious disease caused by variola virus and initially characterized by chills, high fever, headache, and backache, with subsequent widespread eruption of pimples that eventually blister, suppurate, and form pockmarks.

Vaccinate: To inoculate with a vaccine (a live virus, in this case) so as to produce immunity to a disease.

Vaccinia Immunoglobulin: An isotonic sterile solution of the immunoglobulin fraction of plasma from persons vaccinated with vaccinia vaccine.

Limitations

There are two limitations to this study. This is an unclassified thesis. The author is limited to analyzing only unclassified data and cannot access classified information relevant to clandestine stockpiles of variola virus, bioweapon production capabilities by rogue states and subnational groups, and undocumented vaccine supplies or vaccine production capabilities.

The second limitation is no outside funds are available to support this research. This study is limited to consideration of available resources in the Combined Arms Research Library, Internet resources, and the medical and scientific literature.

Delimitations

The author has chosen to delimit this study in two areas. The first delimitation is that of time. This study deals only with materials available prior to February 2003. As this study is completed advances in the diagnosis and treatment of smallpox are under development. It is expected that research and development activities will produce new detection and diagnostic strategies in the near future. However, this study cannot be completed without limiting input to a specified time. The rationale for February 2003 is the revised draft was due at this time.

The second delimitation is that the recommendations in this study are directed only towards the military community and not civilian agencies. This is not to imply that the information contained within will not have civilian applications. However, this study is undertaken by a military officer, attending a military academic institution, and is intended for a primarily military audience. Should this study circulate beyond the military, it hopefully will serve as a useful resource for identifying available smallpox response capabilities and provide potential solutions to problems faced in preparing to respond to a smallpox attack.

Significance of the Study

Inherent to the national strategy to combat WMD is the U.S.'s ability to minimize the effects of WMD. By minimizing the potential catastrophic effects of these weapons

the U.S. deters their use by convincing enemies that their employment will not achieve intended effects. Similarly, an enemy will not generally employ those agents for which the U.S. is prepared. Smallpox remains a viable biological threat to the U.S., its deployed military forces, and key allies. To date, no systematic evaluation of DoD's preparedness to meet this potential threat is available. This study will benefit DoD, and more specifically the Army Healthcare System, because it will attempt to identify strengths and weaknesses in current smallpox response capabilities.

CHAPTER II

LITERATURE REVIEW

States like these (Iran, Iraq, and North Korea), and their terrorist allies, constitute an axis of evil, arming to threaten the peace of the world. By seeking weapons of mass destruction, these regimes pose a grave and growing danger. They could provide these arms to terrorists, giving them the means to match their hatred. They could attack our allies or attempt to blackmail the United States. In any of these cases, the price of indifference would be catastrophic.

President George W. Bush, State of the Union

The terrorist attacks on the World Trade Center and the Pentagon 11 September 2001 showed the vulnerability of the U.S. to terrorist attacks and to potential future attacks by rogue nations, state-sponsored terrorists, religious zealots, and criminal elements using asymmetric tactics. Biological weapons, employed by the U.S.'s adversaries, pose a clear and present danger to U.S. national security and military forces. Their low cost, low visibility, high potency, accessibility, and easy delivery make BW attractive to adversaries seeking new methods of violence when current ones no longer achieve their intended effect. "For them, these are not weapons of last resort, but militarily useful weapons of choice intended to overcome our nation's advantages in conventional forces and to deter us from responding to aggression against our friends and allies in regions of vital interest" (Bush 2002, 1).

This chapter will review pertinent literature related to BW proliferation, the potential use of smallpox as a BW, and mitigation of its effects. For purposes of clarity and understanding the format of presentation is the majority opinion first followed by the views of a minority (if these opposing views exist).

The Biological Weapons and Smallpox Threat

Most experts agree that the threat posed by BW is not hype and caution against ignoring their potential. Any group that wants to mount a BW attack will not face insurmountable obstacles. Knowledge and technology are readily available. The threat of germ weapons, including smallpox, is real and rising, driven by scientific discoveries and political upheavals around the world (Miller et al. 2001).

In *Biological Weapons: Limiting the Threat*, Joshua Lederberg, Ph.D., outlines shortfalls in the U.S.'s current strategic planning for BW. This work is a compilation of articles previously published in a *JAMA* theme issue (with updated information) on biological warfare. It is the author's opinion that three primary reasons exist for BW receiving low priority on the U.S. national security agenda, including: BW defense is both unfamiliar and difficult, a belief that because BW have never been used--they never will be, and finally, a sense that BW will not be used if the U.S. makes it clear that an attack would invite nuclear retaliation.

“These modes of thought are dangerously inappropriate. While it is often said that familiarity breeds contempt, no national security establishment can let unfamiliarity breed neglect” (Danzig and Berkowsky 1999, 11). The United Nations Special Commission inspections of Iraq after the Gulf War should serve as a wake-up call in this regard. In addition to revelations provided by a high-level defector who had responsibility for Iraq's unconventional weapons programs, these inspections revealed large-scale biological production and weaponization programs which had largely been undetected by the West.

The assumption that BW will not be used in the future since they have not been used in the past is an error of fact. History is filled with examples of BW use, including: in the Middle Ages, diseased cadavers were catapulted over the walls of European cities and castles; in the French and Indian Wars, the British supplied the Indians with smallpox infected blankets; and in World War II, the Japanese conducted BW experiments on prisoners-of-war in Manchuria resulting in more than 1,000 deaths.

In evaluating the nuclear deterrent many point to Saddam Hussein's unwillingness to employ his biological weapons arsenal during the Gulf War as validating the primacy of the nuclear deterrent. "However, nations are not the only potential users of BW. If one of the most likely scenarios entails their use by non-state actors, small groups, or individuals, a nuclear deterrent may be ineffective" (Danzig and Berkowsky 1999, 11). Secondly, a nuclear retaliatory threat may be flawed since rapid attribution of the source of a biological attack would be difficult.

Kanatjan Alibekov (a.k.a. Ken Alibek), former First Deputy Director of Biopreparat (the Soviet Union's offensive biological weapons research facilities), chronicles his career in research directed at the manufacture and delivery of biological agents via weapons (aerosols, dry powders, and ballistic missiles) in *Biohazard*. As a high-level defector, it is clear from his accounts that the Soviet Union (and later Russia), despite being a signatory state party to the BWC, had a prolific BW research and development program into the early 1990s which probably continues today. Alibek describes research efforts which focused on biological agents for which there was no known cure. This feature, unique to the Soviet program, is unlike the U.S. offensive BW program (ended in 1969 by then President Nixon) which restricted research to developing

armaments that could be countered by antibiotics or vaccines out of concern for protecting troops and civilians from potential accidents. “Launched by a secret Brezhnev decree in 1973, the program aimed to modernize existing BW and to develop genetically altered pathogens, resistant to antibiotics and vaccines, which could be turned into powerful weapons for use in intercontinental warfare” (Alibek and Handelman 1999, 41).

The Soviets viewed BW as strategic rather than tactical weapons. Incubation periods (sometimes weeks) limited their utility as tactical weapons. U.S. countermeasures (biodefense) are directed towards creating vaccines and immunizing vulnerable troops/people. This countermeasure is proven impractical in situations where vaccine is limited since perpetrators will focus attacks on those not vaccinated. This strategy fails as well, if citizens choose not to be vaccinated as is the early indication with pre-exposure smallpox vaccination efforts.

It is clear from *Biohazard* that the Soviet Union conducted smallpox research. Ken Alibek speculates that attempts were made to genetically modify variola to create a more virulent strain. After eradication, “where other governments saw a medical victory, the Kremlin perceived a military opportunity. A world no longer protected from smallpox was a world newly vulnerable to the disease” (Alibek and Handelman 1999, 111).

Through years of trial and error, the smallpox program was clever enough to master production techniques (capable of producing tons of smallpox per year), weaponize the virus, and conduct research directed toward developing genetically altered strains.

Scourge: The Once and Future Threat of Smallpox provides a complete history of smallpox disease and analyzes its threat as a potential BW (Tucker 2001). Tucker, like Alibek, chronicles the legacy of the Soviet BW program. His research indicates that the

Soviet program to produce a genetically engineered smallpox was broken into subtasks which included: development of new strains resistant to vaccines; development of more lethal forms of smallpox by inserting foreign genes into the variola DNA (including those coding for small protein toxins); and efforts to clone fragments of India-1 (a more virulent strain of smallpox) in bacteria so the viral DNA would be available to Soviet researchers even after stocks of live variola virus were destroyed--perhaps making it possible to reconstitute the virus in the laboratory.

Another goal of the Soviet program was to produce chimeric viruses (splice genes from one virus into another). It is known that they achieved success with a mousepox/Venezuelan equine encephalitis construct in an animal model where infected mice manifested symptoms of both diseases. One of the goals of this research was to create a smallpox-based weapon with virulence genes for Ebola hemorrhagic fever--a potential doomsday weapon.

Also of importance is Tucker's description of terrorists seeking BW. "After the nerve gas attack on the Tokyo subway, a Japanese police investigation revealed that members of Aum Shinrikyo had released two biowarfare agents, anthrax bacteria and botulinum toxin, in downtown Tokyo on nine occasions in 1990 and 1993 with the intent of inflicting mass casualties" (Tucker 2001, 191). While Tucker believes the threat of terrorists obtaining smallpox is low it cannot be discounted with absolute certainty. Identified potential obstacles include: obtaining the variola virus, obtaining sufficient quantities of vaccine to protect scientists, growing the virus in eggs or tissue culture, and dispersing the virus.

The Demon in the Freezer by Richard Preston describes U.S. efforts to counter the current smallpox threat largely through research currently conducted at the USAMRIID. It documents the difficulties in developing drugs for the treatment of smallpox, a uniquely human disease, where no animal model exists given Food and Drug Administration licensing requirements.

Preston again documents the clandestine offensive bioweapons program in the former Soviet Union. Vladimir Pasechnik, another Russian scientist defector (also of Biopreparat), describes vast supplies of frozen plague and smallpox that could be loaded into weapons. More importantly, he explained that the warhead material had been genetically engineered. He was afraid that a genetically engineered virus or germ could escape from the weapons program and said that genetic engineering was why he defected. He describes a program where tonnage amounts of weapons-grade smallpox were produced using new manufacturing processes. The author provides additional information regarding weaponization of smallpox recounting the ability to deliver the virus via an intercontinental ballistic missile with a massive multiple independent reentry vehicle (MIRV) payload. The biowarheads could be filled with dry powder or liquid smallpox. Each MIRV bus had ten warheads, and each warhead had ten grapefruit-sized bomblets inside it. Floating down on parachutes, these warheads released their bomblets which subsequently blew out a mist of variola. One MIRV missile could deliver forty-five pounds of smallpox mist into a city.

The smallpox contained in these warheads is the India-1 strain. It is believed that Soviet scientists chose India-1 for weaponization after comparing it to other strains for its resistance to current vaccine. India-1 may be exceptionally virulent in humans.

Unfortunately, the Russian government has refused to share the India-1 strain with any scientists outside Russia, and so its characteristics and the means to defend against it remain uncertain.

Most importantly, Preston's work documents the potential existence of interleukin-4 (IL-4)-smallpox (smallpox with the human IL-4 gene spliced into it). By genetically modifying smallpox through the addition of the human IL-4 gene, researchers potentially created a superlethal, vaccine-resistant pox of humans. It is believed that the primary obstacle standing between the human species and the creation of superviruses is a sense of responsibility among individual biologists. Given human nature and the record of history it is very possible that someone may be manipulating the genes of smallpox right now.

In *Germes: Biological Weapons and America's Secret War* authors Judith Miller, Stephen Engelberg, and William Broad, through meticulous research, provide a telling history of offensive BW programs and discuss potential future risks posed by BW. Shortly after the attack on the World Trade Center and the Pentagon came the anthrax scare. This episode emphasized the fact that biological warfare is not only thinkable, it is, to some minds, a cost-effective means of conducting war. Biological weapons are usually less expensive than conventional weaponry to manufacture and cause less damage to infrastructure when employed. Infectious agents can be designed to incapacitate rather than kill a targeted population. Therefore, some rogue states, subnational groups, or terrorists may view biological weapons as more humane than conventional or nuclear weapons.

This work retells the story of a domestic terrorist incident in 1984 involving the use of a biological agent. Followers of Bhagwan Shree Rajneesh, a religious cult in Oregon, poisoned over 100 people in the local community by contaminating salad bars at local restaurants. The book then traces the development of biological weapons during the United State's offensive program and discusses rumored use of these capabilities in the Vietnam War and an attempted invasion of Cuba.

Despite the prohibitions set forth in the BWC, the Soviet Union and Iraq continued research and development of BW weapons. The authors report that, by 1990, Iraq had purchased enough microbial media for the production of 74 billion lethal doses of botulinum toxin. The descriptions of the secret laboratories and weapons supplies in these countries are sobering.

Also described is Project Bacchus, initiated by the Defense Threat Reduction Agency in 1998, a venture to see if a BW production facility could be built with commercially available materials. Armed with \$1.6 million and commercial catalogs of lab equipment, the team was able to build a functioning BW production facility. The project had proven its point--a nation or terrorist with the requisite expertise could easily assemble a BW factory from off-the-shelf materials. Of greater concern, none of the overseas purchases were detected, meaning a small-scale laboratory could be constructed without intelligence agencies' knowledge.

The authors conclude that the threat of germ weapons is real and rising, driven by scientific discoveries and political upheaval around the world. They define biological weapons as "the poor man's atomic bomb." They believe that the emergence of the United States as the world's most powerful nation has made biological attack more likely.

Adversaries that resent America's global dominance, envy its wealth, or fear its overwhelming military power can fight back most effectively with unconventional weapons. "In the coming years, those willing to die for their cause may well choose instead to become smallpox carriers or Marburg martyrs" (Miller et al. 2001, 316). The pace of scientific advance has also intensified the germ threat. Genetic manipulations can now be exploited to confuse, maim, and kill. While it is impossible to predict the recombinant future, the most likely danger is that classic agents will be turned into custom pathogens capable of defeating available drugs, antidotes, and vaccines.

D. A. Henderson's *Smallpox as a Biological Weapon: Medical and Public Health Management* provides specific recommendations for smallpox vaccination, treatment, post-exposure isolation and infection control, hospital epidemiology and infection control, home care, and decontamination of the environment. In the event of an actual smallpox outbreak and resultant epidemic, early detection, isolation of infected individuals, surveillance of contacts, and a focused selective vaccination program are recommended to control disease spread.

A recent *Washington Post* article "Four Nations Thought to Possess Smallpox" (5 November 2002) provides evidence from a Bush administration intelligence review that concluded four nations--including Iraq and North Korea--possess covert stocks of the smallpox pathogen. "Records and operations manuals captured this year in Afghanistan and elsewhere, also disclosed that Osama bin Laden devoted money and personnel to pursue smallpox, among other biological weapons" (Gellman 2002). The Central Intelligence Agency report now assesses that four nations—Iraq, North Korea, Russia, and France--have undeclared samples of smallpox virus. Though the quality of its

information varied from “very high” to “medium,” the report covered only nations for which there was “good evidence.”

Biotechnology

The threat posed by recent advances in life sciences and how these changed the nature and scope of the BW threat was addressed by a JASON Group study with a review published in *The New Terror: Facing the Threat of Biological and Chemical Weapons*. The Jason Group is a collection of primarily academic scientists (biologists, physicians, mathematicians, physicists, computer scientists, and engineers) who dedicate a portion of their time to addressing problems of national interest. They concluded that “progress in biomedical science also has a dark side and potentiates the development of an entirely new WMD: genetically engineered pathogens” (Block 1999, 40). It also was concluded that the twenty-first century danger of these weapons is real and pose extraordinary challenges for “detection, mitigation, and remediation.”

The “hype” over BW proliferation is indeed warranted concludes the Jason Group. Modern science has developed many tools for manipulating genes. These tools hold both keys to revolutions in medical treatment but also hold the same potential to create weapons of unprecedented destruction. An example is given to illustrate this potential. Pre-World War II conventional bombs carried up to approximately twenty tons of TNT explosive. With the advent of the atom bomb in 1945, explosions unleashed 1,000-fold more power (12-23 kilotons). Within a decade, fusion devices, such as the hydrogen bomb, released explosive power equivalent to fifteen megatons of TNT which is 1000-fold more than atomic bombs and 1,000,000-fold more than conventional weapons. Each scientific advance produced three orders of magnitude increases in

destructiveness. “The type of biological weaponry made possible by genetic engineering may conceivably produce an analogous increase in virulence over conventional biologic agents, which in turn, have greater destructive potential than natural outbreaks” (Block 1999).

Six examples of the spectrum of agents which pose a threat in the twenty-first century include: binary BW, designer genes and life forms, gene therapy as a weapon, stealth viruses, host swapping diseases, and designer diseases. What follows is a brief explanation of each. Binary BW, much like binary chemical weapons, would keep the toxic components separate (making them safe to handle) until just prior to use when combining the components result in a lethal mixture. A satellite virus, such as Hepatitis D (HDV), is an example. Hepatitis D cannot replicate in host cells on its own. It needs to coinfect a host with another virus hepatitis B (HBV) which codes for key proteins that the helper requires for its propagation. Coinfection with both HBV and HDV greatly increases the severity of disease caused by HBV.

Designer genes and life forms pose a threat since the possibility of developing (in increasing order of possibility) synthetic genes, synthetic viruses, and even synthetic organisms is not beyond the scope of today’s technology. It is now possible to mix and match known components of genes or subtly alter surface properties of major antigens so a virus retains virulence but evades recognition by the immune system. A natural example of these capabilities is the influenza virus which can rapidly change its susceptibility to a previous year’s antibodies by mutating and swapping genes creating variant forms.

The science of gene therapy is first to get the desired gene into cells and then for this transmitted gene to stably be expressed. A crippled virus is used as the genetic vector. This vector lacks the critical genes that lead to disease. The genes of choice are then introduced along with control elements designed to function once the vector reaches its target. Genes can be introduced for both good and evil and can induce disease as well as cure it.

A “stealth virus” is based on the realization that humans already carry a substantial and silent viral load. “The basic idea is to produce a tightly regulated cryptic viral infection, using a vector that can enter and spread in human cells, remaining resident in human cells for long periods without causing harm. However, once triggered by an appropriate external (or internal) signal, the cryptic virus is activated and causes disease” (Block 1999, 63). A natural example is the herpes simplex type I virus. It remains dormant in cells throughout life and in a minority of infected individuals is periodically reactivated by ultraviolet light, stress, and infections with other organisms.

Host-swapping diseases are created by introducing specific viral mutations with resultant escape of the virus from its natural host (nonhuman) capable of infecting and causing disease in humans. Lastly, technology exists to potentially create designer diseases. Theoretically, our understanding of cellular and molecular biology has evolved to the point where one can study a disease, then construct a pathogen to produce it. These designer diseases may work through a number of differing mechanisms including: targeting the immune response, activating normally dormant genes which wreak havoc in cells, and mechanisms which may simply instruct cells to commit suicide often referred to as apoptosis, or programmed cell death.

Two additional publications in the scientific literature echo the potential threats posed above. Carina Dennis published an article, “The Bugs of War,” in the journal *Nature* which provides evidence of the power of microbial genomics and genetic engineering skills in creating enhanced BW. His views are echoed in an article by Claire M. Fraser and Malcolm R. Dando published in the journal *Nature Genetics* which determines that the revolutions in biology have great potential to be misused in offensive BW programs. In both articles, they discuss the relevant trends in genomics research and development, and discuss how these capabilities might be misused in the design of new BW.

The use of genetic engineering to potentially create BW that surpass the destructive potential of natural pathogens is exemplified by the accidental findings of Jackson and colleagues in “Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox” published in the *Journal of Virology* (2001). Researchers were investigating a way to control mice (a common pest in Australia) by creating a contraceptive vaccine through manipulation of mousepox virus genes. Inadvertently, however, the project created an unusually virulent strain of mousepox. “We have observed that thymidine kinase (TK)-positive recombinant ectromelia virus (ECTV) expressing mouse IL-4 are highly virulent and that infection of mice with these viruses suppresses natural killer and cytotoxic T lymphocyte cytolytic activity and interferon gamma expression by CD8+ T cells. Suppression of cellular immunity in both mousepox resistant mice and ECTV-immune mice resulted in acute mousepox with high mortality”

(Jackson et al. 2001, 1206). It is feared that a similar genetic manipulation applied to smallpox could make this feared disease even more dangerous.

Richard Preston in *Demons in the Freezer* discusses attempts by Mark Buller, a researcher at St. Louis University School of Medicine, and his team to duplicate the work of Jackson and Ramshaw. He and his group began testing IL-4 mousepox on vaccinia (smallpox) vaccinated mice and got strange results. They were not able to completely duplicate the Jackson-Ramshaw experiment. “They discovered that immunized mice with natural smallpox became completely immune to IL-4 mousepox--it did not break through their immunity after all. That was encouraging and contradicted part of the Jackson-Ramshaw experiment” (Preston 2002, 226).

“But in doing preliminary experiments with the smallpox vaccine they began to see something more troubling (experiment in progress). It seemed that IL-4 mousepox could crash through the smallpox vaccine, killing the mice if they had been vaccinated some time previously. But if their vaccinia vaccines were fresh, they were protected against the engineered pox” (Preston 2002, 226). What these preliminary findings suggest is engineered IL-4 smallpox might be able to break through people’s immunity unless recently vaccinated (perhaps within weeks of exposure).

Biological Agent Detection and Warning

Janes’s *Chemical-Biological Defense Guidebook* provides an excellent review of available biodetection technology. Detection techniques can be classified according to their specificity and sensitivity. “In a biological context, specificity is the identification of the agent that is being tested for, while sensitivity refers to the detection limit of an analytical technique” (Janes Information Group 2000, 2). Unfortunately, most of today’s

technology is highly specific looking for a characteristic unique to a specific pathogen. An ideal system would be one which not only detected all potentially dangerous agents (not very specific) but also was sensitive enough to detect these agents at minute concentrations. There are huge efforts underway to advance the capability of detection systems using available science and technology.

Examples of existing technologies, albeit not all contained in one system and field ready, include: immunoassays, bioassays, genetic analysis, gas liquefied chromatography, and mass spectrometers. While an in-depth discussion of each technology is beyond the limits of this paper, a short summary of technology important to this review follows.

Immunoassays take advantage of responses by the immune system to invasion by a foreign pathogen. The immune reaction produces antibodies specific for combating that specific invading pathogen. This host response (pathogen-antibody) can then be exploited in the laboratory where organisms are 'tagged' to allow them to be tracked and identified biologically. Tags are generally colored (colorimetric), emit light (chemi- or bioluminescent), fluoresce when illuminated by a source, or radioactive. Examples of immunoassays include: radioimmunoassay and enzyme-linked immunosorbent assay.

Bioassays involve tests (biochemical, physiological, and morphological) on deliberately cultured microorganisms.

Most viruses and bacteria contain sections of DNA with unique base sequences. Taking advantage of this fact, DNA probes (shorter sequences of DNA) can be used to detect a specific microorganism. Each microorganism has a specific DNA probe which can be tagged and when paired with DNA from a sample microorganism reveals its identity. Polymerase chain reaction, a technique which rapidly amplifies DNA sequences,

greatly enhances this capability and infectious disease detection. This highly specific test can also detect genetically modified organisms. Additionally, an improved method was developed combining the benefits of PCR with immunoassay known as Immuno-PCR. This technique allows for the detection of minute concentrations of a microorganism but is limited by the fact that there must be adequate knowledge of an unknown organism for this to be useful in detection.

RFLP analysis is highly useful in detection of biological agents. Frequently referred to as “genetic fingerprinting,” this technique uses special restriction enzymes which cut DNA at specific sites creating DNA fragments of varying sizes. When then separated on a gel, the resulting pattern of spots can be used to compare the genetic makeup of a biological agent to existing data from a microbial pathogen library. RFLP analysis can therefore provide sufficient information to identify a microorganism and determine whether it has been genetically modified in a laboratory.

Surveillance

The Electronic Surveillance System for Early Notification of Community-based Epidemics (ESSENCE) is a DoD system which scans computerized outpatient treatment information from more than 300 military hospitals and clinics worldwide to detect both naturally-occurring outbreaks of disease and potential bioterrorism attacks. Information on the system was highlighted in an Armed Forces Information News article: “DoD Database Provides Global Tripwire for Bio-Terror” dated 17 December 2002. Army Dr. (Colonel) Patrick W. Kelley, an epidemiologist at Walter Reed Army Institute of Research, stated: “ESSENCE is on the front line of defense in the war on global terrorism.” Its worldwide reach is important, he emphasized, because “infectious diseases

have no borders . . . and attack on one country with a bio-terrorist agent could well be an attack on the globe. The insidious nature of many diseases (like smallpox and anthrax), which often present with flu-like symptoms early in the disease, makes this system critically important in detecting potential outbreaks.” ESSENCE functions to record abnormal disease incidence which then prompts an alert to public health officials who investigate the situation further. Dr. Kelley also noted that DoD maintains a companion database, ESSENCE II, in cooperation with Johns Hopkins Applied Physics Laboratory and other groups which monitors civilian hospitals, school absenteeism data, and veterinary facilities for similar purposes.

Treatment

Numerous reviews on the diagnosis and management of smallpox are available in the medical literature, medical texts, and through internet resources (CDC, Infectious Disease Society of America, and others). There is currently no effective treatment for smallpox. Treatment is supportive and includes: maintaining adequate fluid intake, reducing pain and fever, and keeping skin lesions clean to protect from bacterial superinfection. A number of antiviral medications (cidofovir, adefovir dipivoxil, cyclic cidofovir, and ribavirin) show in vitro activity against variola virus and are undergoing further testing.

Smallpox Vaccination

The capstone document for information governing smallpox vaccination is found in *MMWR* (2001; 50; No.RR-10) “Vaccinia (Smallpox) Vaccine: Recommendations of the Advisory Committee on Immunization Practices (ACIP).” The recommendations are

based upon the assumption that the threat of a deliberate smallpox attack is low. Therefore, preexposure vaccination is not recommended for any group (excluding laboratory and medical professionals working with Orthopoxviruses), since the benefits of vaccination do not outweigh the risks of vaccine complications. Post-exposure vaccination is recommended for: persons who were exposed to the initial release of the virus; persons who had face-to-face, household, or close-proximity contact (<6.5 feet) with a confirmed or suspected smallpox patient at any time from the onset of the patient's fever until all scabs have separated; personnel involved in the direct medical or public health evaluation, care, or transportation of confirmed or suspected smallpox patients; laboratory personnel involved in the collection or processing of clinical specimens from confirmed or suspected smallpox patients; and other persons who have an increased likelihood of contact with infectious materials from a smallpox patient (e.g., personnel responsible for medical waste disposal, linen disposal or disinfection, and room disinfection in a facility where smallpox patients are present). Further post-exposure recommendations include vaccination for other groups "whose unhindered function is deemed essential to the support of response activities (e.g., selected law enforcement, emergency response, or military personnel) and who are not otherwise engaged in patient care activities but who have a reasonable probability of contact with smallpox patients or infectious materials." Vaccination within three to four days after exposure to smallpox virus can prevent or decrease the severity of clinical disease.

Smallpox adverse reactions are discussed in a related *MMWR* article entitled "Smallpox Vaccination and Adverse Reactions: Guidance for Clinicians." This is a comprehensive review of all reported adverse reactions (ADRs) following vaccination

and recommended medical interventions for serious and life-threatening ADRs. Many ADRs are self-limiting and require no treatment. However, a number of serious events including: inadvertent inoculation, generalized vaccinia, eczema vaccinatum, progressive vaccinia, fetal vaccinia and postvaccinial central nervous system disease may require further treatment including VIG or cidofovir.

Dose Related Effects of Smallpox Vaccine (Frey 2002) provides data from a dilution study of Dryvax™ vaccine. This study documents the continued efficacy of smallpox vaccine when diluted to titers as low as 107.0 plaque-forming units in previously unvaccinated individuals. This study's findings are extremely important since licensed supplies of available smallpox vaccine are insufficient to vaccinate all U.S. residents with the recommended quantity of virus. A limit of this study, and an area of ongoing research, is determining whether the same dilutions are effective in previously immunized individuals.

Response to a Smallpox Attack

The *DoD Smallpox Response Plan* describes required actions in the event of a smallpox attack. This document amplifies and implements the *Smallpox Response Plan and Guidelines* published by the CDC. The DoD plan provides for response to smallpox outbreaks on military installations around the world as well as military support to civil authorities. This document provides specific detail for planning, implementation, and execution of military actions in the event of an outbreak of smallpox.

The document *Large Scale Quarantine Following Bioterrorism in the United States* defines quarantine and isolation and provides historical examples of problems encountered by public health officials during previous quarantines--specifically civil

disturbances and violence against public health officials. It provides key considerations in future quarantine scenarios: potential transmission from person-to-person, availability of resources to enforce confinement, potential benefits of quarantine versus adverse consequences, and feasibility of large-scale quarantine.

Shining Light on “Dark Winter” (O’Toole, Mair, and Inglesby 2002) documents the challenges faced by senior level leaders after a simulated bioterrorist attack that initiated outbreaks of smallpox. The most important lesson learned from this exercise is the U.S. health care system lacks the surge capacity to deal with mass casualties. Secondly, the lack of sufficient vaccine or drugs to prevent the spread of disease severely limits management options. Lastly, it was apparent from this exercise that the individual actions of U.S. citizens will be critical to ending the spread of contagious disease; leaders must gain the trust and sustained cooperation of the American people.

This literature review clearly documents the threat posed by BW, specifically smallpox, and advances in biotechnology. Preexposure vaccination remains the only effective treatment for smallpox and is limited by potentially life-threatening adverse effects. More sobering, is the specter of a genetically modified virus capable of evading the protection offered by current vaccination.

CHAPTER III

RESEARCH METHODOLOGY

Biological weapons are living organisms or toxins secreted by living organisms, which can be used against people, livestock, or crops. In considering response planning, it is logical to approach the BW threat as one would an emerging or reemerging infectious disease. An emerging infection is defined as a new, reemerging or drug-resistant infection whose occurrence in humans has increased within the past two decades or whose incidence will likely increase in the near future (Institute of Medicine 1992). In the broadest sense, a deliberate attack with smallpox (an eradicated disease) and its subsequent reemergence meets this definition.

In terms of response planning, public health systems are charged with the tasks of disease recognition and intervention. Recognition, simply stated, is the ability to detect or monitor emerging infections through available surveillance systems. Intervention involves the integration of applied research (efforts by scientists to answer questions about a disease's causes, transmission, diagnosis, prevention, and control), specialized infrastructure (supports and equips public health workers and laboratories and links them in national and global communication), and disease prevention and control (the application of the most effective tools and technologies to strengthen personal and national defenses against infectious diseases) to prepare for the unexpected (Center for Disease Control and Prevention 1998).

The methods used in conducting this analysis employ the same criteria for combating emerging infections to evaluate preparedness for response to a deliberate

smallpox attack. The criteria include detection and surveillance (the components of recognition), as well as applied research, specialized infrastructure, and disease prevention and control (the elements of intervention). To strengthen the analysis comparison will be made to response planning currently in place for influenza, another viral disease.

Influenza is a natural example of a genetically modified viral disease. It is an illness that public health officials fear most (despite the misconception that it is nothing more than a bad cold), because it is the only disease that results in what epidemiologists call “excess mortality.” Influenza is not caused by a single organism, but by a group of related viruses which are constantly changing. Because the viruses vary so much from year to year, a new vaccine must be developed for each winter season. By constantly changing, the flu virus mocks our annual attempts to protect ourselves with vaccination and may be the cleverest, most agile microorganism known (Drexler 2002).

Looming over the yearly routine of preparing for each flu season is the threat that a pandemic strain might emerge--a virulent new type of flu that can span the globe in months and decimate the world’s population--the same kind that killed 20 million people in 1918-1919. Such a lethal virus can sweep the world without warning (Center for Disease Control and Prevention 1998). Given the highly mutable nature of the influenza virus and its pandemic potential, it appears an appropriate comparator for an engineered smallpox virus employed as a BW. Like smallpox, influenza virus spreads from person-to-person via respiratory droplets and like the high susceptibility of the general population to smallpox today during pandemics no human possesses even partial immunity to influenza.

An ordinal approach will be utilized for evaluation of each criterion. Using an ordinal scale, each response will be graded (met, partially met, and not met) with no arithmetic relationship existing between the responses. Met is defined as evidence of a significant capability with no major deficiencies; partially met identifies a capability with one major deficiency; and not met equates to multiple major deficiencies within a given criterion. For purposes of comparison the disease for which a higher number of criteria are met would be considered the disease threat we are most prepared for.

In evaluating the threat posed by smallpox as a BW and in assessing the impact of advances in biotechnology (increasing or limiting this threat), a simple analysis of available evidence is used. By presenting factual information with accompanying analysis the researcher adds to existing knowledge and advances new theories based upon recently published intelligence and research information. Analysis, using this qualitative technique, clarifies or advances existing knowledge of the smallpox threat given advances in biotechnology and the life sciences.

CHAPTER IV

ANALYSIS

A Threat Assessment

A deliberate smallpox attack poses a clear and present danger to the U.S. homeland, armed forces, and key allies. Intelligence reports indicate that Russia, Iraq, North Korea, and France have undeclared samples of smallpox virus. In addition, reports and operations manuals captured last year in Afghanistan and elsewhere, disclose that Osama Bin Laden devoted money and personnel to pursue smallpox, among other BW (Gellman 2002). High-level Soviet defectors, including Ken Alibek and Sergei Popov, confirm that the Russian offensive BW program was successful in weaponizing smallpox. More importantly, with the dissolution of the former Soviet Union, many Soviet researchers, whose salaries had not been paid for months, left Russia and could have taken smallpox to Iran, Iraq, Libya, Syria, North Korea, India, Israel, and Pakistan (Harris and Paxman 2002).

America's recognized military dominance forces her enemies to choose unconventional or asymmetric tactics to gain the upper hand. The asymmetric threat posed by a deliberate smallpox attack is real and its lethality may exceed that of a nuclear weapon. Smallpox is, in effect, a worst-case disease. The world population is highly susceptible; there is a high rate of mortality among infected individuals (30 percent). It spreads as an aerosol and continues to spread via person-to-person contact. Advances in biotechnology, specifically genetic engineering, may conceivably produce smallpox variants which have greater destructive potential than natural outbreaks.

Smallpox in the hands of “stateless” terrorists, like Al Qaeda, also poses a significant threat. Groups, like Al Qaeda, believe that acts of violence are not only politically but also morally justified giving them a strong incentive for any type of terrorist attack. The belief that one is rewarded in the afterlife for violence perpetrated against the United States encourages undertaking high-risk and high-casualty attacks.

A similar threat is posed by terrorist groups that have the sponsorship of a foreign government since they could easily be provided with the necessary training, resources, and weapons. The state sponsor would have to decide that a smallpox attack by a terrorist group would accomplish the foreign government’s objectives and not be traced back to the state sponsor. Since rapid attribution of the source of the smallpox attack in this scenario would be difficult a deterrent nuclear retaliatory threat is neutralized.

Finally, the “invisibility” of smallpox production facilities increases its potential threat. As the Defense Threat Reduction Agency’s Project Bacchus confirms, a BW production facility could easily be built by a nation or terrorist group with commercially available off-the-shelf materials. Of greater concern, none of the overseas purchases were detected, meaning a small-scale laboratory could be constructed without intelligence agencies’ knowledge.

Biotechnology

Most BW experts and scientists agree that recent advances in biomedical science have a dark side which could accelerate the development of an entirely new WMD: genetically engineered pathogens. Modern science has developed many tools for manipulating genes. These tools hold both the keys to revolutions in medical treatment but also hold the same potential to create weapons of unprecedented destruction.

The use of genetic engineering to potentially create BW that surpasses the destructive potential of natural pathogens is exemplified in the accidental findings of Jackson and colleagues who inadvertently created an unusually virulent strain of mousepox (a related poxvirus). By creating a recombinant IL-4-mousepox construct normal cell mediated immunity in resistant mice was suppressed resulting in acute mousepox with high mortality. It is feared that creating a similar IL-4-smallpox construct could make natural smallpox even more dangerous--possibly able to breakthrough immunity provided by vaccination.

Similar concern is raised over research conducted by Ariella Rosengard and colleagues at the University of Pennsylvania and recently published in the *Proceedings of the National Academy of Sciences*. Using molecular engineering techniques, Rosengard created a protein from the smallpox virus to help her study the virus' ability to evade the human immune system. She was investigating ways to reduce the rejection of transplanted organs, but her research gained more attention for different reasons: She had built and used a part of the virus that arguably has caused more deaths than any other disease in human history. While many experts feel Rosengard's findings are far more likely to result in advances in vaccinology and viral therapy than threaten national security, its potential use in enhancing a smallpox weapon cannot be overlooked. The same techniques could be employed in creating a more virulent smallpox virus with an even greater potential to evade the human immune system and cause unparalleled harm.

Evidence indicates, like the research just discussed, that the Soviet program actively pursued research in evading the immune response to smallpox. The program to develop genetically engineered smallpox was divided into three subtasks. The first was to

develop new strains of variola resistant to vaccines. The general approach was to identify the proteins responsible for inducing immunity to variola and vaccinia, and then genetically engineer strains containing modified viral proteins which the human immune system could not recognize or defend against. Second, the program attempted to develop more lethal forms of smallpox by inserting foreign genes into variola DNA, including those coding for small protein toxins. Lastly, the Soviets attempted to clone fragments of India-1 in bacteria so the viral DNA would be available to researchers even after live variola stocks were destroyed. An unexplained outbreak of smallpox near an open-air test site may prove this research, at least in part, was successful.

A 1971 outbreak of smallpox in the city of Aralsk, Kazakhstan, may be evidence that the former Soviet Union's secret bioweapons program was successful in both aerosolizing smallpox and in creating a more virulent strain. Of the ten people affected, three unvaccinated patients developed fatal hemorrhagic smallpox, which in previous outbreaks occurred in less than 2 percent of cases. All the others (all previously vaccinated) developed the classical form of smallpox. The strain appeared to be unusually infectious, because three of 25 people who were vaccinated against smallpox and were close to vaccinated patients got sick, an unusually high percentage (Institute of Medicine 2002).

An Assessment of Preparedness

Detection and Surveillance

Accurate intelligence is required to develop an effective defense against biological warfare. Once an agent has been dispersed, detection of the biological aerosol prior to its arrival over the target, in time for personnel to don protective equipment, is the best way to minimize or prevent casualties. However, interim

systems for detecting biological agents are just now being fielded in limited numbers. Until reliable detectors are available in sufficient numbers, usually the first indication of a biological attack in unprotected soldiers will be the ill soldier. (2001, 82)

USAMRIID, *Medical Management of Biological Casualties Handbook*

Smallpox

Analysis: Criteria Partially Met

The principal difficulty in detecting biological agent aerosols is developing a system which can differentiate a BW agent cloud from background organic matter in the atmosphere. Detector systems are evolving and represent an area of intense research and development. However, limited capability currently exists. Fielded systems include the Biological Integrated Detection System, Joint Portal Shield, Joint Biological Point Detection System, and the Navy's Interim Biological Agent Detector. Unfortunately, current numbers of biological detection devices are insufficient to meet major theater war requirements (DoD Chemical and Biological Detection Program April 2002). There are currently no real-time BW detection systems available. While there are systems that provide the ability to detect respirable aerosols in near real time, the best available systems today take fifteen-to-forty-five minutes to identify a specific biological agent. Thus, these detectors do not render warnings quickly enough to allow donning of protective equipment before exposure to the virus. Available systems would also be ineffective in detecting genetically modified smallpox since current technology matches the detected agent against a previously identified strain.

Since limited detection capabilities exist, surveillance (detecting changes in disease occurrence) appears to be the most important tool for identifying a deliberate

smallpox attack. To improve surveillance, DoD recently fielded the Electronic Surveillance System for Early Notification of Community-based Epidemics (ESSENCE). This system scans computerized outpatient treatment information from more than 300 military hospitals and clinics worldwide to detect both naturally occurring outbreaks of disease and potential bioterrorism attack. The insidious nature of many diseases (like smallpox and anthrax), which often present with flu-like symptoms early in the disease, makes this system critically important in detecting potential outbreaks. ESSENCE functions to record abnormal disease incidence which then prompts an alert to public health officials who investigate the situation further. Unfortunately, no information is available as to whether this system is integrated with deployable medical systems.

Recognition of a smallpox outbreak, like the recognition of almost all emerging infections--both naturally occurring and intentional--depends in large part on an astute clinician suspecting an unusual serious illness and contacting a public health agency (civilian) or preventive medicine service (military). Unfortunately, this system depends on the training of physicians and other health care providers in both disease awareness and in the reporting system. Since most clinicians lack experience in recognizing smallpox, detection by this means would likely be delayed. Given its long incubation period (two weeks) and its ability to spread via contagion delays in detection could realistically have disastrous effects.

Influenza

Analysis: Criteria Met

By comparison there exists a robust system for influenza detection and surveillance. While no military-style detector system exists (for obvious reasons), a number of rapid diagnostic tests are available for point-of-care influenza diagnosis. During a respiratory illness outbreak rapid testing for influenza can be very helpful in determining if influenza is the cause of the outbreak. No similar test is available for smallpox. The results of these rapid tests are usually available within thirty minutes and are extremely useful in making treatment decisions.

The CDC manages an extensive national influenza surveillance program. The four components of this program are: World Health Organization and National Respiratory and Enteric Virus Surveillance System Laboratories (a system of 125 participating laboratories located throughout the U.S. which report each week the number of respiratory specimens tested and number positive for influenza), U.S. Influenza Sentinel Physicians Surveillance Network (650 physicians across the U.S. who report each week the total number of patients seen and those seen for influenza-like illness by age group), 122 Cities Mortality Reporting System (vital statistics offices for 122 cities report total number of death certificates and the number which listed pneumonia or influenza as the cause of death; percentage is then compared to baseline and epidemic threshold calculated for each week) , and lastly, State and Territorial Epidemiologists Reports (state health departments report the estimated level of flu activity each week). The components of this system provide a national picture of flu activity. This surveillance program provides information on where, when, and what flu strains are circulating. This

information can also be used to determine if flu activity is increasing or decreasing and alert health care providers of outbreaks and epidemics.

Applied Research

Smallpox

Analysis: Criteria Not Met

A number of technical barriers exist to pursuing applied research activities with variola virus. First, restricted stocks of live virus (limited to CDC in the U.S.) prevent all but a limited number of experiments with variola virus. Second, there exist a number of logistical difficulties with the necessity to work with variola virus in a high-containment (BSL-4) laboratory. Lastly, research into vaccines and antivirals is severely limited by the lack of an appropriate animal model. All of the above barriers generally restrict research activities to related poxvirus viruses.

Variola virus is the only uniquely human orthopoxvirus. It exhibits a complex and well-adapted ability to evade the human immune system. “Research using variola virus therefore offers the potential to contribute to mankind’s knowledge of the human body’s uniquely evolved system of defense against infection” (Institute of Medicine 1999, 1). However, because research on live variola virus is restricted to maximum containment facilities (CDC in Atlanta and the Vektor Institute in Russia), little research has occurred with live virus since eradication. Also, variola virus interacts with humans in a unique way which cannot be mimicked by other poxviruses. Therefore, research on related poxviruses may not yield data on immune evasion applicable to variola virus.

Vaccine research and development efforts are lacking largely due to the military vaccine market being too small and uncertain to encourage industry to make large investments in research, development, and manufacturing of new products. There also remains insufficient production capacity among the four major vaccine manufacturers to meet military requirements. This is an unfortunate reality since vaccines not only afford the best protection against infectious disease but may serve as a strong deterrent as well. Also important to note here is the fact that it generally takes between eight-to-ten-years to develop a new vaccine whereas it is estimated to take only between two-to-three years to develop a BW. This lag in vaccine development obviates the need for research into additional countermeasures.

Currently there is no effective treatment for smallpox. Most countermeasure research and development efforts are focused on antiviral medications. Thus far, in vitro testing has shown the drug cidofovir to have activity against variola virus and makes it the leading antiviral candidate. However, cidofovir is not approved for the treatment of smallpox. Unfortunately, cidofovir must be administered intravenously and is highly nephrotoxic, which probably makes it unsuitable for mass casualty use. Additional research must be directed at identifying more suitable antiviral drugs and in identifying other therapeutics such as immunomodulators.

Lack of an animal model further complicates antiviral drug development. A major goal of current research is to define an animal model that dependably replicates human smallpox. This animal model would be extremely valuable in evaluating potential antiviral drugs, in developing diagnostic assays, and in furthering existing knowledge of the pathogenesis of smallpox.

Influenza

Analysis: Criteria Met

The biology of influenza is much better understood than is that of smallpox. There are two major types of influenza virus--A and B. Influenza B mostly infects children and causes mild respiratory illness. Influenza A, on the other hand, is the virus responsible for serious epidemics and deadly pandemics. Influenza A is further divided into subtypes on the basis of two surface antigens: hemagglutinin and neuraminidase. New influenza virus variants result from frequent changes in the hemagglutinin and neuraminidase antigens resulting from point mutations that occur during viral replication. Identification of these antigenic targets has resulted in a number of therapeutic options for treatment. Applied research efforts to date developed an inactivated (killed virus) vaccine, influenza-specific antiviral drugs used to prevent or treat influenza, and rapid diagnostic tests used in making treatment decisions. A new intranasally administered live, attenuated, influenza vaccine is in the late stages of vaccine development and may be marketed as early as the upcoming flu season.

Specialized Infrastructure

Smallpox

Analysis: Criteria Partially Met

The laboratory response network (LRN) is the best example of specialized infrastructure developed for smallpox response. Since all testing of specimens from patients considered at high risk for smallpox must be performed in maximum containment laboratories (CDC and USAMRIID only) the LRN was developed to

coordinate clinical diagnostic testing for bioterrorism events. This system essentially links local clinical laboratories to CDC or USAMRIID through state public health laboratories. The network is organized into four laboratory levels (A, B, C, and D) with the level of sophistication increasing from very limited identification capabilities (Level A) to diagnostics capable of specific characterization of the involved biological agent (Level D).

Smallpox response teams represent a second example. Vaccinated preexposure, these healthcare workers provide local response and support to local responders during potential outbreaks. These specially trained epidemiologic investigation teams (Epi-Teams) augment existing capabilities at medical treatment facilities and travel to these sites to confirm the diagnosis, trace contacts, and assist with local control measures. These teams can be further augmented with vaccination teams and treatment teams if necessary.

The DoD's ESSENCE surveillance system represents specialized infrastructure since it enhances the communication of public health information and assists in identifying unusual disease outbreaks. This system scans computerized outpatient treatment information from more than 300 military hospitals and clinics worldwide to detect both naturally occurring outbreaks of disease and potential bioterrorism attack. While not specific for smallpox, information gathered by this system may be the first evidence of a smallpox attack.

Influenza

Analysis: Criteria Met

Significant specialized infrastructure exists for influenza because of its yearly occurrence and its global reach. Most prominent is the WHO global surveillance network which comprises 110 treatment centers in 83 different countries. They record the local incidence of influenzalike illness via an internet database (FluNet), culture, and type 175,000 isolates of influenza each year and send a representative 6,500 of those to one of four major research centers in London, Tokyo, Atlanta, and Melbourne for more detailed characterization. Data is gathered throughout the year and is used in making recommendations for strains to be included in the following season's vaccine (Owens 2001). This recommendation is passed on to vaccine manufacturers together with provided stocks which are then used in vaccine production.

The CDC's national surveillance network, described earlier, also meets this criterion. The components of this system (World Health Organization and National Respiratory and Enteric Virus Surveillance System Laboratories, U.S. Influenza Sentinel Physicians Surveillance Network, 122 Cities Mortality Reporting System, and the State and Territorial Epidemiologists Reports) provide a national picture of flu activity. This surveillance program provides information on where, when, and what flu strains are circulating. This information can also be used to determine if flu activity is increasing or decreasing and alert health care providers of outbreaks and epidemics.

CDC's influenza branch (epidemiology section) directs response teams charged with the tasks of identifying where an influenza outbreak started, how it spread, and how it can be contained if an epidemic occurs in the United States. If a pandemic were to erupt

anywhere in the world, these same teams, along with members of the CDC's Epidemic Intelligence Service, would be dispatched to provide their expertise in answering scientific questions and in managing emergency response. These teams, much like the smallpox response teams previously discussed, provide support and advice to local medical authorities in containing a potential epidemic or pandemic.

Prevention and Control

Smallpox

Analysis: Criteria Not Met

At this writing there is insufficient licensed smallpox vaccine to immunize everyone in the United States. Only 2.7 million doses of licensed vaccine are currently available with approximately 500,000 doses earmarked for the military vaccination program and an equal number committed to vaccination of healthcare workers and emergency responders. Similarly, there remains an inadequate supply of vaccinia immunoglobulin necessary for treating the expected adverse reactions should an attempt be made to vaccinate the entire U.S. population. It also remains unclear as to whether the current vaccine would protect against aerosol exposure of the type and magnitude that would be expected during a deliberate attack.

Complicating the limited vaccine supply further is the potential for serious adverse effects following vaccination. Potential serious adverse effects include: inadvertent inoculation, generalized vaccinia (GV), eczema vaccinatum (EV), progressive vaccinia (PV), postvaccinial central nervous system disease (encephalitis/encephalomyelitis), and fetal vaccinia. Two primary sources are available

for information related to adverse reactions: the 1968 U.S. national survey and the 1968 ten-state survey. Serious but not life-threatening reactions (inadvertent inoculation, GV, and erythema multiforme) occurred in 48.8 and 935.3 (number per million) primary vaccinees in the two surveys respectively. Life-threatening reactions (PV, EV, and postvaccinial encephalitis/encephalomyelitis) occurred in 14.2 per million primary vaccinees in the U.S. national survey and in 52.3 per million in the ten-state survey (CDC 2003, 9). It is estimated that adverse reaction rates in the U.S. today would probably be higher than previously reported since the number of individuals at risk for adverse events is higher.

The potential for serious adverse reactions from the smallpox vaccine complicates vaccination policy since the potential threat of a deliberate attack is uncertain and the risk-benefit information is difficult to assess. Understanding that vaccines are administered to healthy individuals to prevent disease the risk of serious adverse events must be offset by the potential threat of infection and morbidity/mortality from disease. For the current smallpox vaccine experts believe the risk from vaccination far outweighs the potential threat of smallpox and vaccination of civilians is not recommended.

Limited local laboratory diagnostics further hampers response to a smallpox outbreak. Currently only two laboratories in the U.S. are equipped to conduct confirmatory tests on high-risk specimens (CDC and USAMRIID). The only validated diagnostic test for variola virus remains viral culture. Additional techniques may be useful in detecting poxviruses but are not variola-specific or are experimental and include: direct examination of vesicle or pustular material (via light or electron microscopy), tissue culture, PCR-based methods, DNA probes, and a RFLP assay.

Smallpox treatment options remain inadequate. There is currently no effective treatment for smallpox. Excluding postexposure vaccination (within four days) treatment remains supportive and includes: maintaining adequate hydration and nutrition, antibiotics for secondary infections, and the topical antiviral idoxuridine for eye infections.

Isolation and quarantine with “ring-vaccination” (surveillance containment) of expected contacts is the current smallpox response strategy. This strategy may be flawed since certain types of smallpox may elude early detection and considering the existing high susceptibility to smallpox. The question becomes whether to vaccinate just the right people (ring strategy) or to protect everyone as quickly as possible (postattack mass vaccination). Given the limited resources available for tracing, locating, and vaccinating what seem to be the “right” people, it is much more efficient in all but the smallest attacks to mass vaccinate and bring the population to herd immunity levels as rapidly as possible (Kaplan et al. 2002).

Quarantine may also be difficult. Despite quarantine being recognized as an effective public health tool for managing infectious disease outbreaks no large scale human quarantine has been implemented within U.S. borders for more than eighty years. Therefore, public health and professional medical familiarity with quarantine is limited. Quarantine may also cause harm. Disease may spread disproportionately among those quarantined. Civilian noncompliance with public health efforts may compromise the action and lead to organized civil disobedience and violence. Lastly, quarantine may restrict commerce and transportation to and from the quarantine area and result in

shortages of food, fuel, medicines and medical supplies, essential personnel, and social services, such as sanitation (Barbera et al. 2001).

Influenza

Analysis: Criteria Partially Met

Prevention and control measures for influenza are widely available when compared to smallpox. Influenza vaccine is highly effective, even in immunocompromised persons and young children, and displays a positive risk-benefit profile. The most frequent side effect of the influenza vaccine is soreness at the injection site. This and other local reactions are mild and rarely interfere with a person's daily activities. Systemic reactions (fever, malaise, and muscle aches) occur less frequently and are usually self-limiting.

Four antiviral medications are available for either chemoprophylaxis or treatment of influenza and include: amantadine, rimantadine, zanamivir, and oseltamivir. Amantadine and oseltamivir are approved for the treatment of uncomplicated influenza infections in adults and children as young as one year of age. The four drugs differ in side effects, dosages, routes of administration, approved age groups, and cost; but all have been proven effective and are generally well tolerated. Most importantly, these antivirals when used for chemoprophylaxis can prevent illness while permitting subclinical infection and the development of protective antibody against circulating influenza virus (CDC 2002, 16). This property of chemoprophylaxis is vitally important during pandemic influenza. These drugs could be taken each day for the duration of influenza activity to limit the impact of the outbreak.

A number of tests are available for the diagnosis of influenza. During a respiratory illness outbreak, testing for influenza can be very helpful in determining if influenza is the cause of the outbreak. Rapid influenza tests provide results in as little as thirty minutes and viral culture results are available in three to ten days. Rapid tests with confirmatory viral culture provide both rapid diagnosis and determine influenza subtypes and specific strains causing illness. Additional diagnostic tests for influenza include: serology, immunofluorescence, enzyme immunoassay, and reverse transcriptase-PCR.

Pandemic influenza, however, may present unique challenges to the existing influenza treatment system. Expected vaccine and drug shortages would create difficult public health questions, such as who should receive preferential treatment in light of vaccine and drug shortages. Also, existing public health and treatment infrastructures are probably inadequate for prompt mass prophylaxis and do not have the capacity to care for mass casualties. Most public health experts agree that the stockpiling of antiviral is currently the best available defense for pandemic influenza.

Analysis Summary

Table 1 summarizes the findings of this analysis.

Table 1. Analysis Summary

Detection and Surveillance			
	Met	Partially Met	Not Met
Smallpox		X	
Influenza	X		
Applied Research			
	Met	Partially Met	Not Met
Smallpox			X
Influenza	X		
Specialized Infrastructure			
	Met	Partially Met	Not Met
Smallpox		X	
Influenza	X		
Prevention and Control			
	Met	Partially Met	Not Met
Smallpox			X
Influenza		X	

CHAPTER V

CONCLUSIONS AND RECOMMENDATIONS

The recent bioterrorist attacks using anthrax-laden letters, sent through the U.S. postal system, increased awareness that biological agents are truly weapons of mass destruction. Unlike anthrax, smallpox is a contagious disease with fairly high rates of human-to-human transmission. As such, the use of smallpox as a biological agent is considered to pose an even greater threat than anthrax. The anthrax attack exemplifies the danger these weapons pose and the extraordinary challenges they create for detection, mitigation, and remediation.

Hailed as one of medicine's greatest triumphs, the eradication of smallpox and subsequent elimination of compulsory vaccination now leaves the general population uniquely vulnerable to a deliberate attack. With a case-fatality rate of 30 percent (ordinary smallpox) and the potential for much higher rates (up to 50 percent) in highly susceptible populations a deliberate attack may well cause casualties exceeding that of a nuclear device. Smallpox, because of its high mortality in a susceptible population, its ability to spread as an aerosol, and its ability to continue to spread by human-to-human transmission, is in effect, a worst-case biological agent.

There are no effective treatments for smallpox. Little research into the pathogenesis of smallpox and its unique ability to evade the human immune system was conducted after eradication. During that time, scientific knowledge about the molecular pathogenesis of viral infections has become considerably more sophisticated. Smallpox is a uniquely human disease and as such represents a "missed research opportunity."

Applied research on variola virus had the potential to contribute greatly to our understanding of the human body's sophisticated system of defending against infection. More importantly, these research efforts may have provided breakthroughs necessary for developing antiviral drugs, an improved vaccine, or other therapeutics. More alarming however, is the now clear evidence of "black research" with variola.

The Former Soviet Union, and later Russia, conducted extensive clandestine research with variola virus. Efforts were directed at weaponizing smallpox, increasing its virulence, and in developing more lethal engineered forms of the virus. Most sobering was their attempt to produce chimeric viruses by splicing genes from one virus into another, with the goal of creating a smallpox-based weapon containing virulence genes for Ebola hemorrhagic fever. High-level Soviet defectors report success in many of these research efforts.

Soviet research with variola is a glaring example of how advances in biotechnology, if left unchecked, can be used to create microbiologic agents of unprecedented destructive potential. Modern science has developed many tools for manipulating genes. These techniques hold great promise for revolutionary medical advances but also have the same potential to create weapons conceivably with virulence factors orders of magnitude above conventional biological agents.

Terrorists, and their use of asymmetric tactics, also increase the threat of a deliberate smallpox attack. Groups, like Al Qaeda, believe that acts of violence are not only politically but also morally justified giving them a strong incentive for any type of terrorist attack. Their belief that one is rewarded in the afterlife for violence perpetrated here on earth encourages undertaking high-risk and high-casualty attacks. Biological

weapons therefore, with their low visibility, high potency, accessibility, and easy delivery (crop dusters, backpack sprayers, and even perfume atomizers), have aptly been described as the “poor man’s atomic bomb.” Reports and operations manuals captured last year in Afghanistan and elsewhere, disclose that Osama Bin Laden devoted money and personnel to pursue smallpox, among other BW.

Intelligence reports indicate that Russia, Iraq, North Korea, and France have undeclared samples of smallpox virus. It is known as well that with the dissolution of the former Soviet Union, many Soviet researchers left Russia and may have taken smallpox to Iran, Iraq, Libya, Syria, North Korea, India, Israel, and Pakistan. A smallpox weapon in North Korea destabilizes Northeastern Asia and threatens South Korea, China, and Japan. Possession by Libya, Syria, Iran, and Iraq destabilizes North Africa and the Middle East and is a threat to U.S. interests abroad and her allies. Possession by terrorists or religious zealots threatens the U.S. homeland and other key U.S. interests. Therefore, it is concluded that smallpox (and other biological agents) pose a clear and present danger to U.S. national security, deployed U.S. forces, and U.S. key allies and friends.

Given the potential threat of a deliberate smallpox attack, questions arise as to whether DoD is prepared to respond. The analysis presented in an earlier chapter indicates the answer is largely--no. Detection of smallpox remains difficult and depends largely on the observations of astute physicians suspecting an unusual illness and contacting public health officials. No real-time detection systems exist. While there are systems that provide the ability to detect respirable aerosols in near real-time the best available systems today take fifteen to forty-five minutes to identify a specific biological

agent. Thus, these detectors do not render warnings quickly enough to allow donning of protective equipment before exposure to the virus.

Applied research efforts with smallpox have lagged behind those of other viral diseases and face numerous technical barriers including: (1) restricted stocks of live virus (limited to CDC in the U.S. and the Vektor Institute in Russia) preventing all but a limited number of experiments with variola virus; (2) a number of logistical difficulties with the necessity to work with variola virus in a high-containment (BSL-4) laboratory; and (3) research into vaccines and antivirals is severely limited by the lack of an appropriate nonhuman primate animal model. The resultant effect is a limited understanding of the pathogenesis of smallpox disease, limited diagnostic capabilities, an antiquated vaccine, and no effective treatment.

DoD recently initiated a smallpox vaccination program for soldiers deploying to high threat areas. However, the long incubation period of smallpox (up to fourteen days) limits its use as a tactical weapon. Given the short vaccine supply, this program may leave the most vulnerable individuals without access to licensed vaccine in the event of an attack. Recognition that troops are protected forces adversaries to focus attacks on those not vaccinated. This problem becomes most apparent if smallpox is employed against a strategic target, such as a civilian population center. Complicating this scenario further is the current smallpox response strategy of ring vaccination which may be flawed. Since smallpox may elude early detection and since limited resources exist for tracing, locating, and vaccinating people, the appropriate response may be mass vaccination in all but the smallest attacks.

Vaccines currently represent the U.S.'s best protection against infectious disease. However, limited funding of research and development programs for military-unique vaccines leaves DoD largely unprepared to meet the threats posed by BW, including smallpox. Limited production capacity among the four major vaccine manufacturers, plus even greater limitations on surge capacity, makes production of sufficient stockpiles of military-unique vaccines all but impossible.

Current medical treatment infrastructure is probably inadequate for prompt mass prophylaxis and does not have the capacity to care for mass casualties in the event of a smallpox attack--despite the existence of the National Disaster Medical System. The health care system today is designed for efficient use of available resources to deal with predictable health problems, but lacks the excess capacity to deal with large-scale outbreaks or those that may result from a deliberate attack with smallpox. Most hospital emergency rooms are already at their maximum utilization capacity and probably lack sufficient surge capacity to accommodate a sudden influx of patients after a deliberate attack. Available hospital bed space is also reduced resulting from recent trends to provide the majority of healthcare on an outpatient basis. This trend limits the availability of inpatient treatment resources and similarly lacks sufficient surge capacity to respond to sudden influxes of patients requiring hospitalization and treatment. Lastly, hospital morgues probably lack sufficient capacity to expeditiously handle remains to prevent public health threats while avoiding mortuary practices seen as dehumanizing, such as mass graves.

The question now becomes what can be done to improve preparedness for smallpox and other biological threats. First and foremost, since vaccines represent the

U.S.'s best defense against infectious diseases, greater emphasis must be placed on research in vaccinology. Since attacks might involve engineered variants new research must provide a means to quickly develop and deploy a vaccine to protect against a novel agent. DNA-based vaccines hold great promise for this purpose and must be more fully investigated. This approach uses DNA to translate and express the antigenic protein in transfected cells and stimulates an immune response. Similar to live attenuated vaccines, DNA vaccines stimulate both cellular and humoral immune responses. DNA vaccines represent a potential quick pathway from determination of a pathogen's genomic sequence to the availability of a vaccine.

Unfortunately, no matter how successful research and development activities are, unless vaccine production capacity expands, significant vaccine shortages will continue to exist. The fragility of the vaccine supply is exemplified by recent shortages of routine vaccines used in the civilian population. The U.S. military has no large-scale manufacturing capability and therefore must rely on current vaccine manufacturers to meet its requirements. However, a number of factors lead manufacturers to avoid developing military-specific vaccines including: lower profits, higher risk, limited resources, complex regulatory and statutory requirements, and finally indemnification issues. In order to overcome these production obstacles, DoD must partner with industry and make continuing, long-term funding commitments, invest in infrastructure, and commit to purchasing a predictable volume of vaccine over time. Since there is no profitable commercial market for military-specific vaccines in the civilian sector, the federal government must reimburse manufacturers for opportunity costs (what it would cost industry to develop a product wanted by the military in terms of a reduction in a

manufacturer's ability to pursue other, potentially more profitable products). Lastly, the federal government must provide manufacturers with indemnification or product liability insurance against non-negligent adverse drug reactions and related litigation.

An alternative proposal is for the federal government to subsidize the construction of vaccine production facilities that the manufacturer could use to produce other vaccines when the facility was not in use for production of vaccines for the U.S. military (Institute of Medicine 2002). In this model the contractor would provide dedicated staff and could operate with flexibility, which are not possible using government personnel and budget rules. The contractor would bear the burden of operations and management costs and makes this more attractive than the costly proposal of a government-owned and contractor-operated facility.

In the near term, nothing will replace the protection provided by vaccines but additional research is necessary to bolster nonspecific immunity which may provide at least temporary protection against pathogens. Biological response modifiers (BRM) or immunomodulators are biomolecules with the ability to enhance or diminish the immune response of the body. Examples of BRMs include interferons and interleukins. When injected, these enhance the immune response to a given antigen (virus or bacterium) and reduce the likelihood that exposure to a biological or toxic agent will result in disease or death.

Despite the existing technical barriers to variola research a commitment must be made to developing effective antivirals. The deciphering of all available variola strain genomes and the analysis of their function through bioinformatics will reveal potential new drug targets. Most importantly, this research will identify targets present only in

variola virus and not human cells whereby antivirals with broad activity but limited toxicity to the human host can be developed.

Investments must be made in improving laboratory infrastructure necessary for smallpox diagnosis, developing rapid diagnostic tests, and in validating existing methods and techniques. The existence of only two laboratories with high containment facilities and the necessary sophistication for laboratory diagnosis of smallpox is grossly inadequate. The construction of regional BSL-4 laboratory facilities would greatly enhance the existing capability. These laboratories could serve as regional referral laboratories and conduct diagnostic tests of high-risk specimens using broad range methods including tests for suspected biological agents, including smallpox. Rapid assays specific for variola in the primary care setting as well as clinical laboratories would greatly enhance disease detection and speed tracing, locating, and vaccination of those potentially exposed.

In summary, DoD remains largely unprepared to respond to a deliberate smallpox attack. In evaluating a deliberate smallpox attack as a reemerging infectious disease, an analysis of current detection and surveillance technologies, applied research efforts, specialized infrastructure, and prevention and control measures confirm that the military health care system currently has limited capabilities to respond. Inadequate supplies of licensed vaccine and potential serious or life-threatening vaccine side effects make preexposure mass vaccination untenable. The existing high susceptibility to smallpox and limited public health resources for tracing, locating, and vaccinating people makes a ring vaccination strategy effective in only the smallest of attacks. Beyond vaccination, there remains no effective treatment for smallpox. Recommendations to improve response

include: research and development of new vaccines and antivirals, enhanced vaccine production capacity, additional research focused at bolstering nonspecific immunity, improved clinical diagnostics and additional specialized laboratory infrastructure.

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