

# BIOTERRORISM



# WATCH

Preparing for and responding to biological,  
chemical and nuclear disasters

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## Bioengineering smallpox: Rethinking the unthinkable

*Widespread immunization urged — but would it make a difference?*

While the United States has taken steps to prepare for smallpox bioterrorism event, the nation remains starkly vulnerable to a genetically engineered strain of the deadly virus. Indeed, if a smallpox attack occurs, a genetically altered strain that could be more virulent or elude the current vaccine actually may be the most likely choice of weapons, the author of a provocative new report argues.

“Most of the literature treats smallpox as a natural disease,” says **Martin Weiss, MD**, professor of medicine at the University of California, Los Angeles. “We have to consider any new smallpox event as being man-made and therefore essentially being a weapon. It will be improved upon because man tends to improve on his weapons. It will not be a natural event. It will be an unnatural, man-made event. We have to assume that someone will try to expand the transmissibility of smallpox.”

The former Soviet Union was known to have engaged in an active program to aerosolize bioweapons, including smallpox, Weiss and co-authors of the report note.<sup>1</sup> If modified or attached to the appropriate carrier, modified variola virus possibly could remain suspended and infectious for a much longer period than wild smallpox.

“The concern is that [the virus] could be bioengineered so that it could evade our vaccines,” Weiss tells *Bioterrorism Watch*. “Another concern is that it could be made more virulent. Either way would be a problem.” He acknowledges the threat may not be immediate, noting that the smallpox genome is complex and its DNA requires the activity of associated proteins to be infectious. However, “it may not be long in coming,” Weiss adds.

Indeed, not only is bioengineering possible with smallpox, it apparently is moving from heresy to accepted science. Recently, an advisory committee to the World Health Organization (WHO) recommended scientists be approved to insert genetic markers in the virus to expedite the search for effective drug treatments. The marker would glow under florescent light if a trial drug were ineffective

against the pox virus. Weiss says he backs the recommendation, but reaction in the scientific community has been decidedly mixed.

According to published reports, **Ken Alibek**, MD, PhD, DSc, a former researcher in the Soviet Union's biological weapons program who defected to the United States in 1992, called it "absolutely the right decision. The bad guys already know how to do it. Why prohibit legitimate researchers to do research for protection."<sup>2</sup>

Others were aghast at the implications. "We have seen no evidence of a threat that would justify this research," says **Sujatha Byravan**, executive director of the Council for Responsible Genetics in Boston. "A decade ago, the WHO was planning to

destroy the world's last remaining samples. Today, it is proposing to tinker with the virus in ways that could produce an even more lethal smallpox strain. This is a devastating step backward."

### **Likelihood vs. plausibility**

But as Weiss points out, such genetic engineering of pox viruses already is occurring. Australian researchers increased mousepox virulence by splicing a mouse gene into a laboratory strain.<sup>3</sup> Similar constructions might be assembled using human smallpox virus or another pox virus (e.g., monkeypox virus) and human genes.

"We tend to underestimate our enemies," he adds. "It could be an aerosolized virus, a bioengineered virus that we have no vaccine for, or there could be several attacks at once. I don't want to be overly pessimistic, but I think we should be prepared for any eventuality. If the question is one of likelihood, it is probably unlikely. But the issue is not one of likelihood, it is plausibility. Is such an attack plausible? If it is, the common-sense thing to do is try to [reduce] the risk as much as possible."

Yet Weiss casts a critical eye on many of the assumptions that have guided the nation's smallpox preparations. Such considerations could prove to be overly optimistic because they do not take into account the many uncertainties regarding transmission and infectivity of the smallpox virus. For example, another misnomer in current thinking on smallpox is that the virus is not a highly infectious disease, he notes. Indeed, review of outbreaks in India and Pakistan in the 1960s showed that each case of smallpox gave rise to not more than three new cases, he found. However, a factor not emphasized in those reports is the extent of existing immunity in the affected population.

"The smallpox [transmissibility] studies were on populations that already had, in effect, herd immunity," Weiss says.

Though emerging data indicate smallpox immunity may last many years after vaccination, those never immunized would be strikingly vulnerable to infection. The immune status of never-vaccinated people (generally younger than 37) probably resembles that of the New World populations that were devastated by smallpox. "The younger population is naive to this virus," he warns. "It would be much like the Aztecs or the American Indians among people under age 36 or 37."

According to U.S. Census Bureau data for 2000, there are some 140 million people younger than 35 in the United States. Though almost 40,000

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#### **Editorial Questions**

For questions or comments, call **Gary Evans** at (706) 742-2515.

health care workers have been immunized in recent years, Weiss says the health system could not deal with a competent smallpox attack.

"I think it would be overwhelmed," he says. "If it was natural smallpox, we could probably handle it. But if it is going to be an unnatural event that is amplified by man, I don't think [the health care system] could handle it."

### **More vaccinations needed**

A great unknown is what level of protection the existing vaccine would afford against a smallpox virus designed to elude it. Nevertheless, the bottom line to many pro-vaccine advocates is that widespread smallpox vaccination of the public and health care community would yield more benefit than risk. The thinking, in part, is that it certainly would protect against wild virus and may at least minimize the impact of a bioengineered strain.

"We would like more widespread vaccination," Weiss says. "I don't think it should be imposed on the public. There is a long history of people of being resistant to vaccinations. It would create a big political turmoil that is unnecessary. It should be voluntary for people who would like the vaccine. They could judge for themselves, and they can choose if they want it or not."

The risk of side effects and deaths is real, but adverse reactions were relatively few in the recent round of vaccinations among the military and health care workers. In recent data from an ongoing Department of Defense (DoD) study, there was one case of encephalitis reported among 623,244 vaccinations.<sup>4</sup> The patient recovered. Fifty cases of contact transfer of vaccinia occurred, primarily in spouses and adult intimate contacts. The lower-than-expected incidence of adverse events may reflect more-careful screening of vaccination candidates, the generally healthy status of the population being vaccinated, the previous vaccination in up to two-thirds of vaccine recipients, and covering of the vaccination site to reduce inadvertent inoculation, Weiss theorizes. Still, there were unexpected coronary problems during the recent round of smallpox vaccinations in both the civilian and military populations.

Ongoing research to improve smallpox vaccine could mitigate the risk, but mass inoculation inevitably would result in fatalities. Depending on the percentage of the population vaccinated, the number of deaths is estimated to be in the range of 125 to 500, Weiss reports.<sup>5-7</sup>

In addition, a long-forgotten smallpox drug called methisazone should be back on the radar screen given the current threat of bioterrorism, he emphasizes. The agent fell into disuse with the eradication of smallpox, but could be used as prophylaxis to reduce the incidence of smallpox by 30% to 40%.

"It would be better than nothing. I suspect it would be very inexpensive to produce. They used it in India in the 1960s, so it can't be that expensive. It has no patent protection; it's in the public domain. I don't know how expensive it would be to produce it, but it can't be very much. It would be like a backup insurance policy. In case disaster struck, we would have something available."

On a chillingly practical note, Weiss also recommends stockpiling respirators so that society could continue to function in the aftermath of a smallpox attack. The smallpox virus is 200-300 nm in size, meaning \$7 N-100 respirators would be very efficient in preventing inhalation, he notes. The N-95 respirators commonly used in health care settings would be less effective, but still provide some protection. If masks were distributed to the public, it might lessen paralysis of cities and allow continuation of essential services.

"I don't want to overplay that, because if there is a smallpox attack, no one is probably going to be aware of it for seven or eight days," he says. "So a mask isn't going to prevent the initial consequences of attack. But once the attack is recognized, if people are wearing masks, they can go out in public with some relative degree of assurance and plus, they would be able to take care of the people who are sick."

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# Instant hospital aims to meet bioterror surge

*Portable hospitals from the ground up*

From a large-scale bioterror attack to extreme natural disasters, we're constantly reminded of looming safety threats and the U.S. infrastructure's need to respond. And perhaps no industry has taken the threat more seriously than health care.

Doing its part, Blu-Med Response Systems in Kirkland, WA, has developed an advanced-care instant hospital structure that can be quickly deployed at various sites in the event of a large-scale disaster or bioterror attack exceeding a hospital's normal surge capacity.

Blu-Med is a division of Alaska Structures of Seattle, which has 25 years of experience developing similar structures for military use. The U.S. military currently uses the company's portable hospital buildings throughout the world, including Afghanistan, Iraq, and Kuwait.

"These shelters have really served the military well as portable hospitals, and people have wanted to know if we would make a civilian model of that," says **Gerrit Boyle**, executive vice president for Blu-Med and Alaska Structures. "We have taken the proven concepts for military use and adapted them for homeland security and other disaster-response scenarios."

Each hospital complex is composed of six interconnected shelters to create a 50-bed, 4,000-square-foot facility. The structures are Quonset hut-shaped, with a lightweight aluminum frame, and covered with a tension vinyl cover system. The units come complete with floors, windows, doors, heat, and air conditioning and electrical systems. To differentiate the civilian model from military applications, the buildings have been altered slightly to come in bright safety colors, such as a combination of blue, white, and orange.

The first organization to purchase one of these temporary hospitals was the Nevada Hospital Association (NHA) in Reno, which recently conducted the first assembly demonstration of its new system.

The association has purchased multiple units, according to **Christopher Lake**, PhD, director of hospital preparedness for NHA.

He says components for these instant hospitals would be stored with the air-conditioning units,

hardware, and electrical equipment in a warehouse in a rapidly deployable manner.

"Essentially, if a disaster was declared, and it was recognized as a biological terrorism event where hospitals needed immediate surge capacity capabilities, we will be able to get these facilities anywhere in the state of Nevada, on the ground, set up and operational, with personnel and equipment in 24 hours," Lake explains.

The units can be configured to fit different needs, including triage, emergency department, surgery, intensive care, and other isolation requirements. He says the warehouses are geographically located so the temporary facilities can be deployed anywhere in Nevada in five or six hours. "The concept really is a 50-bed hospital, where and when [it is] needed," Lake adds.

The recent demonstration was the first test to see how long it would take to assemble one of the structures, with all components, using an uninitiated crew of people. "We needed a facility that was very easy to set up because you never know who will be available in a disaster," he explains. Lake said response from medical personnel has been very positive.

"One of the concepts with any event — pandemic disease, bioterrorism, nuclear explosion or natural event — is these patients are going to be long-term," he says, explaining why NHA chose the Blu-Med system as opposed to other alternatives. "We needed something for large numbers of patients who will not be able to be simply treated and then moved."

The No. 1 factor was that the facility needed to be able to last, Lake says. "We needed surge capacity not for two, three, or four days. We needed it for months or a year."

A nonmilitary look and feel also was important, because the public must know where the facilities are and how to reach them, he adds. In addition, because the structures have been tested for fire, heat, snow, wind, and other extreme weather, they can provide a controlled, clean environment.

"We looked all over — including other structures such as tractor-trailers and basic tents," Lake says. "This is a better long-term solution."

Boyle said Blu-Med is in the process of talking to other states and hospital associations about its new product. Each basic 50-bed unit — configured similarly to Nevada's — costs roughly \$350,000. And Blue-Med is able to accommodate clients, based on need, such as the level of equipment required, medical supplies, and other hardware, he adds.

Nevada's program is supported through funding from the National Hospital Bioterrorism Preparedness Program. ■

## Bioterror mail threats continue to be reported

*Feds outline action steps for local response*

Public health and law enforcement officials recently declassified a report that reveals ongoing biological threats through the mail. A large number of potentially suspicious letters and packages continue to be reported to federal, state, and local law enforcement and emergency response agencies nationwide, the Nov. 2, 2004, report states. In some instances, these letters or packages may include powders, liquids, or other materials.

Since there often is an articulated threat, it is likely the substance was intentionally introduced into the package in an effort to validate that threat. An articulated threat itself (with or without the presence of a suspicious substance) is a federal crime and also may constitute a violation under state and local statutes.

According to the report, these are some of the key steps to take for a letter/container with unknown powderlike substance and a threatening communication (with or without illness in the recipient):

- **Request the assistance of the nearest certified hazardous materials response team** to conduct risk assessments, field safety screening, sample (evidence) collection, decontamination, and other mitigation activities. Any sample (evidence) collection must be coordinated with law enforcement.
- **Notify appropriate law enforcement when a potential threat is identified.** Do not touch, move, or open any suspicious package until an initial hazard risk assessment of the package can be performed in coordination with HAZMAT personnel and law enforcement.
- **Contact your local public health department** (who should in turn notify state authorities and the Centers for Disease Control and Prevention) if there is a threat of public health exposure or environmental contamination exists.
- **In coordination with law enforcement, always notify the U.S. Postal Inspection Service,** whenever it appears the threat was delivered

through the U.S. mail. Assist with ensuring the origin and tracking information is obtained from the package (ideally, photographs of the front and back).

- **Treat the scene as a crime scene.** Preserve evidence in coordination with law enforcement and ensure materials are packaged safely. Take steps to retain enough suspicious material for laboratory analysis and forensic examination of criminal evidence, regardless of whether the threat ultimately is determined to be accompanied by a hazardous material.
- **Transfer custody of evidence to a law enforcement officer as soon as possible.** Maintain chain of custody by obtaining a record of names and signatures every time custody of a suspicious material or sample for laboratory analysis changes hands.
- **In coordination with public health and law enforcement, identify and list names and contact information for anyone who may have been exposed to the suspicious substance** so they may be contacted when the lab test results are available or if there is other additional information. If positive results are obtained, state and local public health departments will need to contact those potentially exposed as soon as possible to provide appropriate assistance (e.g., antibiotics, education, additional testing, vaccination, and surveillance/symptom reporting). ■

## New bioterror vaccines are getting in the pipeline

*All aimed at 'Category A' agents*

The federal government has awarded \$232 million to fund research and development of new vaccines against three potential agents of bioterrorism: smallpox, plague, and tularemia. The National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), will administer the contracts.

The funding responds to a key objective of the NIAID biodefense research agenda, which emphasizes the development of new and improved medical products against "Category A" agents — those considered by the Centers for Disease Control and Prevention (CDC) to pose the greatest threat to national security.

The smallpox awards continue advanced development work that began in February 2003 on two modified vaccinia Ankara (MVA) vaccine candidates. These contracts will support larger scale manufacturing of the vaccines as well as further safety and effectiveness studies in animals and humans. The tularemia and plague awards will fund early-stage product development of the respective vaccines, which will include dosage formulation, pilot batch production, and initial clinical assessment. All four contracts are for purchases of vaccine lots intended for research use. Any future purchases of additional vaccines for stockpiling in the event of an emergency will depend on the results of the research currently under way.

NIAID awarded two contracts totaling up to \$177 million for advanced development of MVA vaccines against smallpox. The three-year contracts were awarded to Bavarian Nordic A/S of Copenhagen, Denmark, and Acambis Inc. of Cambridge, MA, and Cambridge, England. MVA is a highly weakened form of the vaccinia virus that cannot replicate in human cells.

Previous NIAID research has demonstrated that MVA is nearly as effective as the standard smallpox vaccine, making it a promising candidate for use in children and pregnant women as well as people with weakened immune systems or skin conditions such as eczema. The new contracts will allow the companies to continue the work they began under contracts awarded in February 2003.

For the plague vaccine, NIAID awarded a contract to Avecia Biotechnology Ltd. of Manchester, England. The three-year, \$50.7 million contract covers the manufacture of a new plague vaccine as well as animal testing and initial human trials. There currently is no licensed plague vaccine, and the pneumonic form of the disease, which infects the lungs and can spread from person to person through the air, is nearly always fatal unless antibiotic treatment is started within 24 hours of infection.

NIAID also modified an existing contract with DynPort Vaccine Company LLC of Frederick, MD, to include the manufacture of a pilot batch of live, attenuated tularemia vaccine. The three-year, \$4.5 million contract modification also covers stability testing of the vaccine. Tularemia is a highly infectious bacterial disease most often transmitted by ticks and insects.

In humans, illness is characterized by intermittent fever, headache, and swelling of the lymph

nodes. This live, attenuated vaccine contains a weakened form of the tularemia bacterium, enabling the immune system to recognize and produce neutralizing antibodies against the bacterium if it is encountered again. ■

## Anthrax vaccination policy dropped after court ruling

*Court rules against forced military vaccinations*

The Department of Defense (DoD) has halted mandatory anthrax vaccinations of military personnel after a ruling by the U.S. District Court for the District of Columbia. The injunction cited a congressional "prohibition on forced inoculations with investigational drugs" in issuing a permanent injunction.

Until the Food and Drug Administration (FDA) certifies that the vaccine is safe and effective, the DoD "may no longer subject military personnel to involuntary anthrax vaccinations absent informed consent," the court ruled. Six plaintiffs, known as John and Jane Doe No. 1 through No. 6, brought the action to challenge the lawfulness of the government's anthrax vaccination program.

They all are military personnel and civilian contract employees of the DoD who have submitted or have been instructed to submit to anthrax vaccinations without their consent. The ruling also cited an expert panel on finding that "no meaningful assessment of the [the vaccine's] value against inhalation anthrax is possible."

Moreover, interested parties who originally were invited to comment on the vaccine in 1985 "could not have anticipated that FDA would permit the vaccine to be used for inhalation anthrax as a result of exposure through a biological attack," the court found. "Now for the first time, 18 years later, FDA's Final Rule and Order asserts the FDA 'does not agree with the panel report,' and believes that 'the vaccine is indicated for active immunization against [anthrax], independent of the route of exposure,' and that the vaccine will 'protect humans against . . . inhalation anthrax.'"

The court ruled that the FDA position was a significant post-comment expansion of the scope of the original inquiry and it deprived the public of a meaningful opportunity to submit comments and participate in the administrative process mandated by law.

In a press release, the DoD pointed out that the ruling does not question the safety and effectiveness of the anthrax vaccine.

"The injunction centered on FDA procedural issues stating that additional public comment should have been sought before the FDA issued its final rule in December of 2003," the DoD stated. "DoD remains convinced that the anthrax immunization program complies with all the legal requirements and that the anthrax vaccine is safe and effective." ■



## ***B. cereus* mimics anthrax infection**

*Could be used to confound attack response*

**Synopsis:** A patient with a disease resembling anthrax led to the identification of anthraxlike virulence factors in an isolate of *Bacillus cereus*.

**Source:** Hoffmaster AR, et al. **Identification of anthrax toxin genes in a *Bacillus cereus* associated with an illness resembling inhalation anthrax.** *Proc Natl Acad Sci USA* 2004; 101:8,449-8,454.

A previously healthy patient presented with a two-day history of nausea, vomiting, hemoptysis, shortness of breath, and fever. His chest X-ray was abnormal, and his WBC on admission was 12,000/mm<sup>3</sup>, subsequently rising to a peak of 22,400/mm<sup>3</sup>.

Cultures of sputum and of blood yielded a gram-positive bacillus identified using traditional phenotypic characteristics, including biochemical reactions, as *Bacillus cereus*. The patient required mechanical ventilation for 44 days but eventually recovered.

Sequencing of the organism's 16S rRNA confirmed its identity as *B. cereus* while multilocus

### CE/CME questions

1. Some of the concerns about bioengineering smallpox virus included the possibilities of making the pathogen:
  - A. capable of spreading in a suspended aerosol
  - B. impervious to current vaccines
  - C. more virulent
  - D. all of the above
2. An advisory committee to the World Health Organization recommended that scientists be approved to insert genetic markers in smallpox to expedite the search for:
  - A. transmission enhancers
  - B. effective drug treatments
  - C. ways to render it noninfectious
  - D. rapidly conferred immunity
3. The so-called "instant hospital" complex is composed of six interconnected shelters to create a 50-bed, 4,000-square-foot facility.
  - A. true
  - B. false
4. During an investigation of a letter containing a suspicious powder and a threatening note, whose names and contact information should be collected on a list?
  - A. likely suspects
  - B. customers, patients who were turned away due to the incident
  - C. anyone who may have been exposed to the suspicious substance
  - D. all of the above

**Answer Key:** 1. D; 2. B; 3. A; 4. C

sequence typing found that it was closely related to, but distinct from, *Bacillus anthracis*.

The patient's isolate, however, contained a circular plasmid, named by Hoffmaster and colleagues as pBCXO1, that had 99.6% similarity with the *B. anthracis* toxin-encoding plasmid, pXO1.

In addition, a polysaccharide capsule cluster was encoded on a second plasmid, pBX218, thus providing an analog to the *B. anthracis* capsule genes encoded on its other plasmid, pXO2.

### COMING IN FUTURE MONTHS

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■ Ill wind revisited: The Sverdlovsk anthrax outbreak of 1979

■ Public Health Emergency Response Guide

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The virulence of the patient isolate was confirmed by mouse inoculation experiments.

**Comment by Stan Deresinski, MD, associate chief of infectious diseases, Santa Clara Valley (CA) Medical Center.**

*B. cereus*, a cause of food poisoning, is an uncommon cause of invasive infection. These infections mostly occur in immunocompromised patients, and have included post-traumatic or post-cataract surgery endophthalmitis, prosthetic valve endocarditis, native valve endocarditis in injection drug users, and meningitis in neonates and hematopoietic stem-cell recipients.<sup>1</sup> Other reported infections include those of cerebrospinal fluid shunts and of vascular access. *B. anthracis*, on the other hand, is a highly virulent organism that causes potentially fatal disease regardless of precipitating events or immunocompromise.

The virulence is the consequence of the presence of the expression of genes carried by 2 plasmids, pXO1 and pXO2, which encode the lethal toxin complex and the poly-g-D-glutamic acid capsule, respectively. The virulent *B. cereus*, isolated from the patient had acquired a plasmid encoding the anthrax toxins and a second plasmid capable of encoding polysaccharide capsular material.

As indicated by Hoffmaster, et al, in a comment on the evolutionary plasticity of the microbial world, "depending on the number extent of lateral gene transfer, nature could produce an unlimited number of variations and combinations." Thus, when using standard clinical laboratory techniques, notions such as "anthrax bad, cereus not so bad" potentially are dangerous over simplifications that may have a number of important clinical and other implications, and that potentially apply to other organisms.

Thus, in some instances, the identification of an isolate such as *B. cereus* may lead to its being inappropriately disregarded as a contaminant.

The lack of association of severe virulence with such an isolate may lead to unnecessary searches for other etiologies of a patient's perilous clinical state. Finally, an engineered bioterrorism agent that clinical laboratories identify simply as *B. cereus* could lead to significant delay in the identification of a sinister attack.

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To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this semester's activity, you must complete the evaluation form that will be provided and return it in the reply envelope to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you. ■

## CE/CME objectives

After reading each issue of *Bioterrorism Watch*, the infection control professional will be able to do the following:

- identify the particular clinical, legal or educational issue related to bioterrorism;
- describe how the issue affects health care providers, hospitals, or the health care industry in general;
- cite solutions to the problems associated with bioterrorism, based on guidelines from the federal Centers for Disease Control and Prevention or other authorities, and/or based on independent recommendations from clinicians and bioterrorism experts. ■