Terrorist attacks highlight the need for exotic new shots; development has lagged, thanks to a lack of commercial interest and management snafus

Vaccines for Biodefense: A System in Distress

Two months before the 11 September terrorist attacks, the U.S. Department of Defense (DOD) sent Congress a report that attracted little attention at the time but has suddenly been catapulted into prominence. An unsparing and sometimes scathing critique by an independent panel of experts, the report bluntly concludes that the military's system for developing vaccines to protect troops from anthrax, smallpox, and other exotic bioweapons "is insufficient and will fail."

The document has become a hot topic in Washington, D.C.—from the White House on down. It has been seized upon by scientists who have long been arguing that the United States is ill prepared to defend against bioterrorism, and it helps answer a question that has become pressing in the wake of last week's anthrax scare (see p. 490): Why, several years after experts began issuing dire warnings about bioterrorism, are there no new vaccines against some of the most worrisome potential agents and scant supplies of existing vaccines?

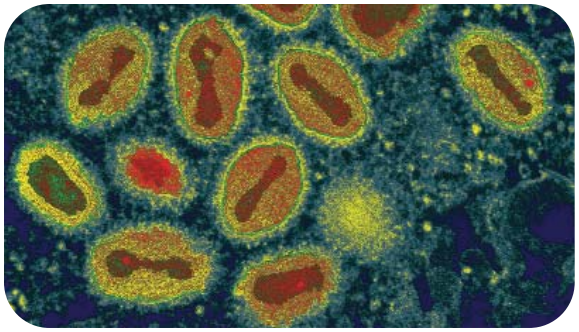
The report, sources tell *Science*, may lead to a sweeping overhaul of how the federal government develops vaccines to protect both the military and civilians from bioweapons. But the problems are not just logistical: Developing a new suite of vaccines presents difficult scientific challenges, and testing the safety and effectiveness of preparations against lethal diseases that aren't already widespread will be problematic. "In light of the events of September 11, [the issue] takes on a new sense of urgency," says Anna Johnson-Winegar, a microbiologist who oversees and coordinates DOD's biological and chemical defense program.

Vaccines form the cornerstone of DOD's extensive program to defend against biological attack (see table on p. 499). Industry has little financial incentive to develop such vaccines, so the Pentagon, until recently, has been virtually alone in funding their development. In the mid-1990s, DOD tried to move things along by creating the Joint Vaccine Acquisition Program (JVAP). It takes promising biodefense leads from military researchers and hands them to an outside contractor, which then farms out vaccine production to other contractors. Currently, JVAP has targeted eight vaccines against bioweapons.

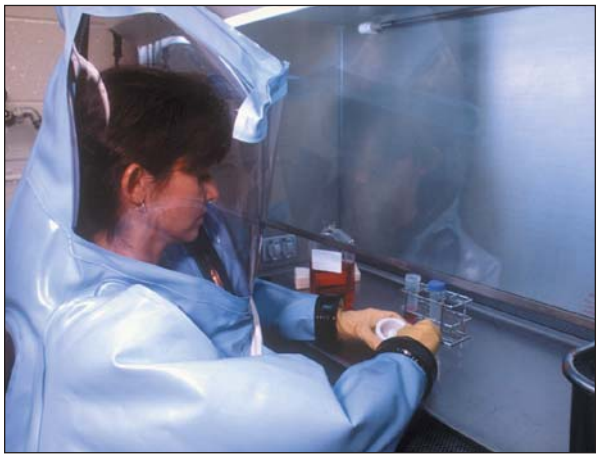
The independent panel called this arrangement cumbersome and poorly coordinated, noting that the number of organizations involved "seems unnecessary and counterproductive." The report "was not pretty to write," says the panel's chair, Franklin Top, who previously served as the commander of the Walter Reed Army Institute of Research (WRAIR) and now is an executive at MedImmune, a biotechnology company in Gaithersburg, Maryland. Top and the four other panelists recommended a radical gold-plated solution: Scrap JVAP and replace it with a $3.2 billion military program that would produce its own vaccines in a government-owned production plant.

Outside researchers applaud the idea to scrap JVAP. "It really is a terrible operation," says epidemiologist D. A. Henderson, who formerly headed the World Health Organization's (WHO's) smallpox eradication program and now directs the Center for Civilian Biodefense Studies at Johns Hopkins University. Maj. Gen. Philip Russell (retired), another former head of WRAIR, uses even stronger language: "It's a disaster."

The idea for a huge government-run vaccine production operation surfaced after the Persian Gulf War, but Congress and DOD rejected it as too expensive. 11 September changed all that. Now, it's being considered for producing vaccines to protect not just troops but civilians as well. "It's being discussed in a manner of seriousness that I haven't seen before," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), who says he personally likes the idea. "Sometimes you've just got to take things into your own hands and go for it," says Fauci. "There's a real and present danger of bioterrorism. The government needs to say enough is enough … we're going to make sure these things get made."



Worst nightmare. Experts worry about a bioattack with smallpox virus (variola) on an unprotected population.



Hot bugs. U.S. Army scientists conduct lead research on candidate vaccines in high-containment facilities.

DOD's independent panel did not discuss problems with specific products, but *Science* looked closely at DOD's efforts to develop vaccines against three of the most feared bioweapons: smallpox, anthrax, and botulinum. Each illustrates why, in the words of vaccine researcher Leonard Smith of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland, officials at the Office of the Secretary of Defense "are pulling their hair out trying to think what they can do."

Smallpox

Once the scourge of humankind, smallpox has been so well controlled by vaccination that WHO declared in 1980 that it had

CREDITS: (LEFT TO RIGHT) U.S. ARMY; EYE OF SCIENCE/PHOTO RESEARCHERS INC.

been eradicated. The only known remaining samples of the virus are secured in scientific freezers at the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and at the State Research Center of Virology and Biotechnology in Novosibirsk, Siberia. Because smallpox vaccination itself carries some risk, countries also decided to end routine vaccination. But after the Soviet Union collapsed, fears that terrorists might get their hands on some of the Novosibirsk smallpox led some experts to urge the stockpiling of smallpox vaccines.

The United States has 15 million doses of aging smallpox vaccine—too few to provide adequate military and civilian protection, according to most experts. So in 1997, DOD's JVAP contracted with DynPort Vaccine Co., a British-U.S. joint venture based in Frederick, Maryland, to make 300,000 doses of a new smallpox vaccine for the military. At about the same time, President Bill Clinton became interested in stockpiling smallpox vaccine to protect the public as well.

Scientists wanted to develop something better than the old-fashioned smallpox vaccine, made by scraping vaccinia, a viral cousin of cowpox and smallpox (variola), onto the bellies of calves and harvesting the pustules that formed. Researchers at USAMRIID, the lead military lab dedicated to developing defenses against biological weapons, decided to grow vaccinia in tissue cultures for greater purity—and quickly hit a barrier.

Although Wyeth Laboratories was the last manufacturer to produce smallpox vaccine, USAMRIID researchers, for reasons that no one can now recall, turned to another company, Connaught, for vaccinia. From an array of vaccinia in the old preparation, they selected clones that were less "reactogenic" (produced fewer harsh reactions) in rabbits. But researcher Peter Jahrling, a USAMRIID virologist, acknowledges that researchers do not yet have evidence that the new vaccine will be less reactogenic in humans. Reactogenicity "is going to be a problem," predicts Top, who thinks the vaccine may cause side effects similar to those of the old one. Although rare, the side effects can be severe, including brain swelling, aggressive eczema, and—in people who suffer from immune damage such as those infected with HIV—a dangerous pox infection.

Jahrling had practical concerns as well: It was taking too long. USAMRIID had sent the tissue-grown vaccinia to JVAP in 1995, but DynPort started working on the project only in 1998. "There was a lot of hand wringing and gnashing of teeth about how vaccine will be made," says Jahrling. DynPort's president, Terry Irgens—a former commander of the Naval Medical Logistics Command at Fort Detrick—declined to discuss the smallpox vaccine, saying "we've been strictly forbidden" to talk about it.

The slow pace of vaccine development frustrated government officials and researchers alike, say both Henderson and Jahrling. Richard Clark, the national counterterrorism czar under Clinton, became involved. Jahrling says Clark wanted DynPort to provide vaccines for the Department of Health and Human Services (HHS) for civilian use, as well as for DOD. "Clark said, 'Listen, damn it, we are not going to have two vaccines; we're going to have one,' " recalls Jahrling. A big sticking point, say both Henderson and Jahrling, was the cost: DOD was paying DynPort about $75 per dose of vaccine, whereas HHS wanted to pay only about $1. In the end, HHS decided to select its own manufacturer: Last September, CDC awarded a 20-year, $343 million contract to OraVax, a Cambridge, Massachusetts, biotech. The price: $1.38 per dose. Both DynPort and OraVax subcontracted with yet another outfit, BioReliance of Rockville, Maryland, for help.



Civilian advocate. D. A. Henderson heads Johns Hopkins's biodefense center.

When OraVax asked JVAP for the seed vaccinia, however, DOD balked, claiming liability concerns. (OraVax, which in December 2000 changed its name to Acambis, declined comment, saying CDC forbids the company from discussing its smallpox vaccine program; CDC denied *Science*'s request to speak with the agency's leading expert about smallpox.) One person close to the negotiations says that OraVax's lawyers offered to indemnify DynPort, but JVAP still refused to provide the seed vaccinia. Subsequently, the company obtained seed vaccinia from Wyeth.

Today, DynPort and Acambis are making smallpox vaccines that are essentially the same—both with help from BioReliance. Critics suggest that DOD should simply

Federal Biodefense Research, Fiscal Years 2000 and 2001 ($ millions)

Department or agency	FY 2000	FY 2001	Sample activities
U.S. Agricultural Research Service	0	$0.5	Detection of biological agents
Department of Energy	$35.5	$39.6	Improving detection technologies
Department of Health and Human Services			
Centers for Disease Control and Prevention	$48.2	$46.6	Researching smallpox and anthrax therapeutics
Food and Drug Administration	$8.8	$9.1	Licensing anthrax and smallpox vaccines
National Institutes of Health	$43.0	$49.7	Developing new techniques for smallpox virus and antigen detection
Office of Emergency Preparedness	0	$4.6	Emergency response studies
Department of Justice			
Office of Justice Programs	$0.7	$4.6	Detecting biological agents
Federal Bureau of Investigation	0	$1.1	Detecting and characterizing biological materials
Department of the Treasury: Secret Service	0	$0.5	Improving detection of biological agents
Environmental Protection Agency	0	$0.5	Detecting biological agents
USAMRIID Biodefense	$40.6	$43.5	Researching and developing vaccines and therapeutics
DARPA Biological Weapons Defense	$124.3	$166.8	Developing biosensors, protective gear, and futuristic treatment and prevention

CREDITS: (TOP TO BOTTOM) COURTESY D. A. HENDERSON; SOURCES: GAO AND DOE

Blocking Smallpox: A Second Defense

Variola, the virus that causes smallpox, was destined for obliteration 6 years ago when a select group of researchers took a new interest in it. The team, spearheaded by Peter Jahrling and John Huggins of the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Maryland, extensively studied a promising antiviral treatment for variola infection that might be useful in containing an outbreak. They also demonstrated for the first time that the virus can cause fulminant disease in a species other than humans. But their work has been controversial, in part because it raises a question about the World Health Organization (WHO) plan to destroy all known stocks of variola.

For security reasons, the experiments took place in Atlanta at the Centers for Disease Control and Prevention's (CDC's) biosafety level 4 laboratory, which has special air filters that allow researchers to handle the most lethal viruses on Earth. "It's kind of a thrill to be working with [variola]," says Jahrling. "It's an awesome responsibility."

In 1995, Huggins and his co-workers, including James Leduc of the CDC, decided to pursue an antiviral lead from Erik De Clercq and Johan Neyts of the Rega Institute for Medical Research in Leuven, Belgium. Two years earlier, the Belgian researchers had reported that in mouse experiments, a drug known as cidofovir—made by Gilead Sciences of Foster City, California—could thwart vaccinia virus, a tame vaccine strain. In test tube experiments, Huggins and colleagues found that cidofovir worked remarkably well against 31 different strains of variola, too. They also showed that cidofovir can protect monkeys exposed to a close relative of variola, monkeypox. And they identified 10 compounds that appeared even more potent than cidofovir.

Donald Smee, a virologist at Utah State University in Logan who has collaborated with the USAMRIID researchers, notes that cidofovir has two attractive features: It works with a single dose, and it already has been licensed (although for a different use) by the U.S. Food and Drug Administration. If used in conjunction with vaccine during a smallpox outbreak, says Smee, "the damage could be certainly contained more quickly."

Cidofovir does have a downside: It must be given intravenously. "If you had a biological attack where a lot of people had to be treated, IV [would] become a pain," says Smee, who, along with De Clercq, notes that it might be relatively easy to make an aerosolized form of the drug. Epidemiologist D. A. Henderson, the former head of WHO's smallpox eradication program, says he's "very doubtful" that an antiviral drug would prove effective against symptomatic smallpox. Nor does he think it would be preferable to a vaccine during the window of time between infection and disease, when the vaccine could still help. Henderson says, however, that antivirals like cidofovir could play a useful role in treating problems such as infection of immunocompromised people caused by the renewal of vaccinations with the vaccinia virus (see main text).

It will be difficult to prove that cidofovir works against smallpox, however, because the disease was declared eradicated in 1980. This is where Jahrling's monkey studies could be critical. Jahrling and his colleague Lisa Hensley last year found a strain of variola that could infect and cause severe disease in cynomologous monkeys—a first. "They had vesicular lesions that looked just like smallpox," says Jahrling. In all, 11 of these 12 monkeys died within a week to 10 days. This is much "hotter" than human variola, which takes a few weeks to cause disease, and Jahrling now is attempting to refine the model. But Henderson calls the monkey model "ridiculous," because he is not convinced that it represents human smallpox. "There's a great desire on the part of [the Department of Defense] to justify retaining the smallpox virus," says Henderson. "And that's what it all boils down to." Henderson is referring to the fierce debate about whether the remaining stocks of variola should be destroyed. If a monkey variola model proves valid, it could alter the decision. Jahrling plans to present his data this December at a WHO meeting about variola destruction; unless the plan changes, variola will be snuffed out in December 2002. **–J.C.**

abandon its plan to have DynPort make 300,000 doses—an amount that both Jahrling and Henderson say is inadequate to protect U.S. troops—and purchase the cheaper vaccine from Acambis.

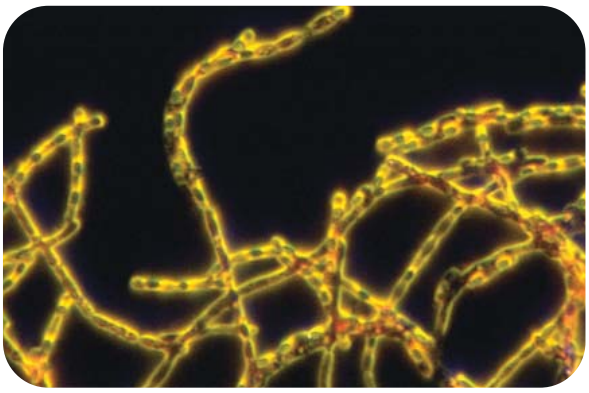
After 11 September, Acambis, at CDC's request, said it could step up its production schedule and have vaccine ready by summer 2002. Plans are also under way to have the company make tens of millions of doses more than scheduled.

In the meantime, Fauci says NIAID scientists will soon launch studies to see how much they can dilute the 15 million doses of old Wyeth vaccine in the stockpile without reducing the ability to stimulate a robust immune response. "There's the potential to go from 15 million doses to 150 million," Fauci says. NIAID also expects to help CDC with clinical testing needed to win approval from the Food and Drug Administration (FDA) for the new Acambis vaccine. And sources tell *Science* that officials are considering compelling large pharmaceutical companies to manufacture up to 300 million doses of smallpox vaccine and make them available within a few months as an unlicensed "investigational new drug."

Anthrax

Unlike smallpox, anthrax has become a real and present bioterror threat. But the good news is that the FDA has already licensed a vaccine, and animal tests have shown that it protects against the worst infections: those caused by inhaled spores. The bad news, however, is that only one company makes the vaccine, BioPort of Lansing, Michigan, and BioPort's production line has been down since 1998.

Before the company changed hands that year, FDA inspected its facilities and found them deficient. Production was suspended while renovations were begun, but according to testimony from a BioPort executive in the House of Representatives last year, the new owners found that the required improvements were more costly than they had anticipated. Even after DOD agreed to double the contract price of the vaccine, the company was struggling to survive.



Infamous. This form of anthrax produces deadly infectious spores.

CREDIT: MICHAEL ABBEY/PHOTO RESEARCHERS INC.

Before it stopped production, BioPort had accumulated more than 2 million doses of vaccine. All have been spoken for. Some were quarantined on FDA's orders. About 1.8 million were used by the Pentagon during the Clinton Administration for a mass vaccination of troops, and the remaining 24,000 doses "are dedicated to the military," says Lt. Col. John Grabenstein, deputy director of DOD's Anthrax Vaccine Immunization Program. Vaccinations are being given only to "special mission units and researchers" in high-risk labs, he says. BioPort is sub-

mitting an application this month to FDA to resume production, and an agency spokesperson says the review will be conducted soon, because "we're not handling this as a routine inspection."

BioPort's vaccine is a complex broth of proteins filtered from a nonthreatening strain of anthrax. USAMRIID has been pursuing an alternative vaccine based on a genetically engineered version of one key antigen. The leader of this research, Col. Arthur Friedlander, says, "We're working with NIH on a fast track to get this into clinical trials." He acknowledges that researchers still don't know just how the vaccine works or whether the recombinant version will be as effective as the old broth. But he says that studies with "the best animal models," including nonhuman primates, indicate that results are "essentially the same" as for the old vaccine: 95% are protected, even against inhaled anthrax. DOD's Johnson-Winegar calls it "a very promising candidate," adding that it should begin clinical trials "early next year." CDC, meanwhile, is conducting a 1300-person trial of the licensed vaccine to learn whether the burdensome schedule can be cut from six shots to five.

Botulinum

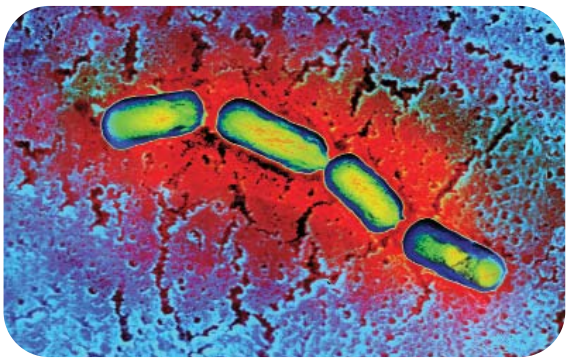
Smallpox and anthrax may be getting the most attention, but biodefense researchers have long been concerned about botulinum toxin, the deadliest of all potential toxic threats gram for gram. Produced by an anaerobic bacterium that can grow in ill-preserved food (*Clostridium botulinum*), it attacks the cholinergic nerve system, causing death by paralysis. Ingesting less than a millionth of a gram can be fatal. To fully protect against botulinum, a vaccine would have to trigger antibodies against all seven known strains, or serotypes, of the bacterium.

Botulinum toxin has been viewed as a potential bioweapon for decades; indeed, when an international arms control team swept Iraq in the mid-1990s, it found that Saddam Hussein's labs had churned out 19,000 liters of serotype A botulinum toxin and loaded some of it into warheads.

Defending against all possible botulinum weapons will be difficult, researchers say. But according to USAMRIID's Smith, public health and military researchers developed a vaccine in the 1970s that offered relatively broad protection. It uses modified versions of five toxins (called toxoids) to stimulate antibody protection against five serotypes. Omitted are two serotypes considered to be less toxic or difficult to manufacture. However, FDA has not licensed this "pentavalent" vaccine, and it remains difficult and dangerous to mass produce, requiring a dedicated manufacturing facility. Its crude mix includes formaldehyde and other components that make it highly reactogenic.

A new botulinum vaccine has been in the works now for more than a decade. Researchers at U.S. Army labs have used recombinant technology to genetically engineer yeast factories that produce four partly dismantled botulinum toxins of serotypes A, B, C, and F. Serotype E will be added soon. The resulting combination, says Smith, is a candidate to replace the old vaccine: one that could be manufactured more safely and inexpensively.

Botulinum vaccine experts are eager to begin clinical trials, but progress has been slow. The developmental project must now be carried forward by JVAP and its contractor, DynPort. "It's absolutely astounding" how cumbersome and expensive the process has become, says one observer. The recombinant serotype B vaccine was ready for testing 4 years ago, according to an expert, and "it could have gone into phase I trials then." Although military researchers have been in consultation with FDA for 2 years planning safety and efficacy tests for all four serotypes, clinical trials are still "nowhere in sight," a researcher says.



Toxic shock. Tiny amounts of toxin from botulinum pack a huge wallop causing lethal paralysis.

Fast track

Even if JVAP can produce new biodefense vaccines, all of them face a huge obstacle: Because the diseases they are designed to block do not circulate in the population, there is no way to stage classical efficacy trials in humans. Samuel Katz, a pediatrician and professor emeritus at Duke University—who sits on the Institute of Medicine's panel on military vaccines—says this is not a trivial problem. He points to the new smallpox vaccines as an example. Although researchers have long used measurements of antibodies and skin reactions to determine whether a smallpox vaccine is immunogenic, no one knows precisely which immune responses lead to protection. "Is this new vaccine more immunogenic, less immunogenic, more efficacious, less efficacious?" asks Katz. "I don't know how you're going to answer those questions."

FDA recognizes this dilemma and in 1999 issued a proposed rule that would allow the agency to license vaccines and drugs against bioweapons without human efficacy studies. FDA would base approval instead on "substantial evidence" from studies in two animal species but would pull such a product from the market if evidence surfaced that it did not work in humans. FDA says it does not know when it will make a final decision on the proposed rule.

Given all the uncertainty about bringing new biodefense vaccines to market and the myriad of federal agencies involved, a radical overhaul of the system seems likely. Since the terrorist attacks, says Russell, "people have begun to think about the total national interest rather than their bureaucratic territory." DOD's Johnson-Winegar is chairing a high-level government panel that, she says, is reviewing how to invest in a "national resource" for military and civilian vaccines; a dedicated government facility is "one of the options" being considered. That brings the discussion back to where it stood a decade ago, at the end of the Gulf War.

–JON COHEN AND ELIOT MARSHALL



Mass protection. Vaccination quickly curbs smallpox epidemics, as New York City learned during a scare in 1947.

CREDITS: (TOP TO BOTTOM) BSIP/PHOTO RESEARCHERS; BETTMAN/CORBIS