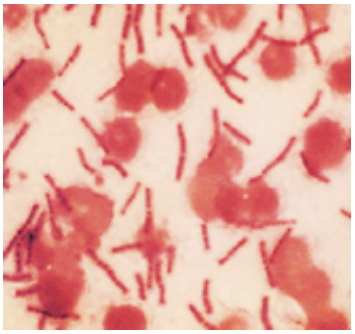
<< Return to article

The ABCs of Battling Bioterrorism

Why scientists are busily developing new vaccines—and why they are years away from stockpiling what we may need.



In the Gulf War, U.S. soldiers were vaccinated against anthrax bacteria, seen here in a blood smear from a rhesus monkey. (Image courtesy of U.S. Army)

By Cheryl Pellerin
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Anthrax, plague, smallpox, Lassa, Ebola. Some of the planet's most ancient scourges are back in the lab, together with a few recently discovered threats, as investigators work to develop vaccines against potential biological weapons.

While there have been no significant incidents of terrorism using biological or chemical agents since the 1995 sarin gas attack in a Tokyo subway, U.S. government agencies have been urgently preparing to counter a possible attack. The budget for work on biological defenses at the Defense Advanced Research Projects Agency, for example, went from nothing in 1996 to nearly $167 million in 2001.

A similar amount was allocated this year by the Centers for Disease Control and Prevention (CDC) in Atlanta, GA, which keep tabs on organisms that are deadly, easily disseminated and highly contagious. Last month, scientists gave an update on progress with vaccines to counteract likely biological agents at the 4th Annual Conference on Vaccine Research in Arlington, VA.

A Is for Anthrax

Anthrax, caused by *Bacillus anthracis*, is associated with the historical origin of immunology. In 1881, Louis Pasteur's development of a vaccine to protect domesticated animals from anthrax infection was a breakthrough in the use of attenuated (weakened) virulent organisms as a vaccine strategy.

Live attenuated anthrax vaccines have been widely used in veterinary medicine ever since. Similar vaccines have been licensed for human use in the former Soviet Union since 1953.

In recent decades, there has been growing concern about the potential use of anthrax as a bioterrorist weapon. In 1983, Congress heard that a single anthrax-carrying plane flying over Washington, D.C., on a calm night could produce 1 to 3 million fatalities.

"On that basis, the Defense Department decided for the first time in human history to vaccinate people not against an existing disease, but against the threat of using an organism to cause disease," said Arthur Friedlander, science advisor to the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, MD.

As a rule, U.S. troops are vaccinated before entering a combat zone where they could encounter biological agents. In the Gulf War, more than 250,000 doses of anthrax vaccine were administered, based on reports that Iraq could use anthrax as a biological weapon. That vaccine produced a 95 percent survival rate in rhesus monkeys, but how well it actually protects people against anthrax is still not known. In addition, some long-term health issues related to human use are still under study.

A new vaccine candidate, suspended in a gel, has proved successful against aerosol delivery of anthrax in animal studies so far. The Army is currently working with the National Institutes of Health to develop it, Friedlander said. "It's in the final stages in terms of formulation, and we hope to be into human trials [of its safety] in the next year."

B Is for Bubonic

Plague, caused by *Yersinia pestis*, continues to occur in many places around the world, including the U.S. Southwest where a dozen or so cases are reported annually. Bubonic plague affects the lymph nodes; pneumonic plague, the lungs.

The original plague vaccine provides some protection against bubonic plague in animal studies, but not against intake of *Y pestis* through the lungs. However, if it's used as a biological weapon, researchers expect that aerosol delivery is the most likely route. Untreated pneumonic plague is nearly always fatal.

Efforts to develop a new vaccine center on a genetically engineered candidate called F1-V, now moving into clinical trials. "To date, in vitro and in vivo evaluation of this vaccine candidate satisfies criteria for efficacy, safety and stability," said Gerard Andrews, chief of the bacteriology division of the Army's Research Institute of Infectious Diseases.

Andrews's research group is also considering a genetically engineered protein called Yersinia outer proteins, or Yops. A version called YopD seems to protect against a lethal dose in mice and needs further study.

C Is for Comeback Killer

The naturally occurring virus that causes smallpox was declared eradicated more than 20 years ago. As a result, manufacture of smallpox vaccine ground to a halt. Yet the possibility that smallpox, which has no cure, could be delivered to U.S. cities in an aerosol cloud is the most feared bioterrorist scenario.

At the same time the smallpox virus was eradicated in nature, the Soviet Union began an extensive program to develop it as a biological weapon that could be carried via intercontinental missiles. Russia still maintains a smallpox research program, as well as the technological capability to produce the virus.

Today the only smallpox virus known to exist is quarantined in two government research institutions —the CDC in Atlanta, GA, and the State Research Centre of Virology and Biotechnology in Novosibirsk, Russia. In compliance with a United Nations agreement, these last remaining supplies of the virus should be destroyed in 2002.

Biosafety Level 4 viruses, the most deadly of all, must be handled in special facilities designed to contain them. (Photo courtesy of Centers for Disease Control and Prevention)

From the pre-eradication era, 15.4 million doses of smallpox vaccine remain in the U.S. national stockpile. This amount "is probably insufficient to fully address the possible resurgence of smallpox transmission in the event of the intentional release of the virus as a bioterrorist weapon," said James LeDuc of the CDC's National Center for Infectious Diseases.

Last September, Acambis was awarded a government contract to produce a new smallpox vaccine using modern cell-culture techniques. (The technology used to produce the existing vaccine is now

outdated.) The initial target is 40 million doses—what LeDuc calls "a reasonable starting point for a national stockpile"—and the first production lots are expected in 2004.

This new vaccine will be held in reserve and released only in the event of confirmed cases of smallpox. "Since we can't use volunteers for otherwise fatal diseases," said Friedlander, "the best we'll be able to do is develop evidence of efficacy in the best animal models and then produce as much compelling evidence as possible" that the vaccine will work the same way in people.

D Is for Deadly in the Wild

Other, more recently identified viruses, like Lassa and Ebola, are already at large—mainly in Africa—without viable vaccine programs to counteract them, said Joseph McCormick of the University of Texas-Houston's School of Public Health.

Lassa fever infects 100,000 to 300,000 people a year with approximately 5,000 deaths. Ebola infects fewer people but has a much higher mortality rate.

"The hospitalization rate [for Lassa fever] is 98 to 147 per 100,000 per year," McCormick said. "If we had a disease like that in the United States, do you think we'd have a serious vaccine program?"

One reason we don't is that the Lassa and Ebola viruses require person-to-person contact to spread, unlike airborne smallpox or plague. As a result, they haven't been regarded as prime candidates for development as biological weapons.

In addition, since they are mostly found among the poorest populations in Africa, vaccine manufacturers lack a sufficient market to support vaccine production, even though "there are good candidate vaccines already developed for both viruses," McCormick said.

"It's somewhat of an irony to see that we are spending tens of millions of dollars on a vaccine for a disease that's eradicated," he added, "and there's virtually no money or very little money for these two vaccines."

E Is for Emergency Response

The CDC's strategic plan for addressing the deliberate release of biological or chemical agents depends on putting in place by 2004 a public health communication infrastructure, a network of diagnostic labs and an integrated disease surveillance and reporting system.

The national electronic infrastructure will speed the exchange of emergency health information among local, state and federal health agencies. In addition, a Web site will be created to help disseminate information on bioterrorism preparedness and training, both for health-care workers and the public.

Even if the United States manages to avoid the lethal threat of bioterrorism, the report says, tools developed in response to such potential hazards will help in natural disease outbreaks or industrial accidents.

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