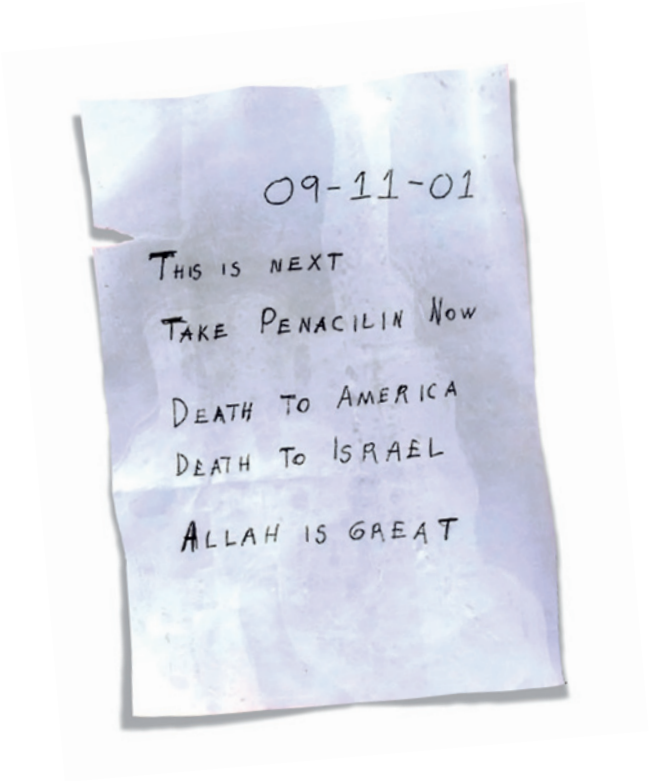


Since the anthrax attacks in 2001, some $60 billion has been spent on biodefence in the United States. But the money has not bought quite what was hoped.

THE PRICE OF PROTECTION

BY ERIKA CHECK HAYDEN

It took one routine smallpox vaccination to expose the holes in the United States' defences against bioterrorism. In January 2009, the jab was given to 20-year-old Lance Corporal Cory Belken of the US Marine Corps, as it is to many members of the military who are about to be deployed abroad, to protect him against a potential attack with the lethal virus. But in this case, the timing was unfortunate. Two weeks after the vaccination Belken was diagnosed with leukaemia; he then underwent chemotherapy that wiped out his immune system. Suddenly, the live vaccinia virus, the milder relative of smallpox used in the vaccination, was able to multiply into a dangerous infection.

Doctors turned to their only means of counter-attack: three smallpox drugs, two of them experimental and developed as part of US efforts to build up an arsenal against potential bioterror agents. The marine received 30 times the standard dose of the first drug, an approved antibody, to no avail. The second, called STS-246, had been used in only one person infected with vaccinia before. By the time doctors administered the third drug, CMX001, Belken had developed a bacterial infection that spread to his feet, brought him near death and required surgeons to amputate both his legs below the knees. Only after he received all three medicines did he start to recover — and it is still not known which of the drugs, if any, eventually helped.

The marine's case is just one of many events that have raised questions about the biodefence research and development enterprise that sprang from bioterror attacks in the United States ten years ago. Shortly after the terrorist attacks of 11 September 2001, anthrax spores sent to media outlets and politicians killed five people and compounded already widespread fear and horror. The incidents spurred the US government to launch a major scientific effort to develop 'countermeasures': diagnostics, vaccines and drugs against potential biological threats such as smallpox and anthrax. In a three-part strategy, the federal government poured money into basic research at the National Institutes of Health (NIH); created the Biomedical Advanced Research and Development Authority (BARDA) to carry new concepts forward into further development and testing; and established BioShield, a US$5.6-billion programme to purchase the finished drugs and vaccines. But none of the links in this chain has worked exactly as it was supposed to.

Between 2001 and the end of this year, the federal government will have spent $60 billion on such biodefence efforts (see 'A decade of biodefence'), according to analyses from the Center for Biosecurity of the University of Pittsburgh Medical Center in Baltimore, Maryland. The money has helped to modernize the nation's crumbling public-health system, and BioShield has invested in a stockpile of 20 million doses of smallpox vaccine, 28.75 million doses of anthrax vaccine and 1.98 million doses of four medicines to treat complications of smallpox, anthrax and botulism. But few researchers or policy-makers seem happy with an arsenal of six drugs that

R. SACHS/CNP/SYGMA/CORBIS

address only three of the potential threats — even if they are among the most serious. "The pipeline we rely on to provide those critical countermeasures — diagnostics, vaccines, antivirals, antibiotics — is full of leaks, choke points and dead ends," said Kathleen Sebelius, US Secretary of Health and Human Services, in a statement last year.

Critics say that the effort has been hobbled by a lack of strategic thinking, focus and coordination between the federal agencies involved, and by unrealistic expectations of what the money could buy. "There was no evidence that they looked at what our top priorities are and asked, 'What's needed on the basic-science side?', 'What's needed on the development side?', and 'What's needed in the stockpile?'," says Andrew Pavia, an infectious-diseases doctor at the University of Utah in Salt Lake City. Until earlier this year, Pavia served on the National Biodefense Science Board, which advises the US Department of Health and Human Services (DHHS) and in March last year released a report, *Where Are The Countermeasures?*, that was critical of the federal biodefence effort.

What is more, developing therapies for diseases that are mercifully rare among humans is a unique challenge. Drug development is difficult at the best of times — and experts say that there is simply not enough money in biodefence to entice big companies into the field. "It is a bit discouraging considering we've spent more than $60 billion on this in the past decade," says Randall Larsen, a member of the Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism, which in a January 2010 'report card' gave the nation a failing grade for its ability to prevent a bioterror attack from causing huge casualties. "The question is whether it has been spent properly," he says.

PRIORITY PATHOGENS

That point is especially pressing now. The United States is in dire financial straits and may be forced to slash the research budgets of the NIH and other agencies if Congress does not agree on other spending cuts by 23 December. Still, some researchers think that ten years is simply too soon to expect payoffs from a research programme that essentially started from scratch. "There have been some really important lessons received from what has admittedly been a very large investment," says David Relman, a microbiologist at Stanford University in California who has been heavily involved in biodefence research and policy. "Perhaps with a more refined idea of the goal, [the money] might have been used in a more productive or effective way. But at the time, we didn't really know what we needed and we didn't know how hard it would be to make any of these things that we needed."

A pillar of the biodefence enterprise is the US National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, which got a $1.5-billion budget boost in 2003 and has so far received $14 billion for biodefence. It is there, say critics, that some early and crucial mistakes were made.

In a series of reports issued in 2002 and 2003, the NIAID outlined its plans to fund basic research aimed at the development of treatments and vaccines for more than 50 'priority pathogens' and toxins classified into three categories. Category A covers agents considered to be the most dangerous and likely to be used in an attack, such as smallpox and anthrax. Categories B and C include threats such as food- and waterborne illnesses. (The list was similar to a catalogue of 'select agents' kept by the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.) The agency also built 15 labs across the country — part of a building boom that has led, so far, to the planning, construction or renovation of nearly 20 labs for the study of dangerous pathogens at a cost of more than $2 billion.

But some experts say that attempting to tailor vaccines and treatments to individual pathogens is misguided: some of the pathogens are difficult to turn into bioweapons or just aren't very dangerous, and the costs of developing a large defensive arsenal are astronomical. It makes more sense, these experts say, to stockpile antibiotics and other medicines that could be used against many pathogens. "You can look at some of the vaccine investments, like for plague and [the bacterial disease] tularaemia, and wonder who decided that was the highest priority, as opposed to developing new antibiotics," says Pavia.

The NIAID reorganized its biodefence research efforts in 2007, increasing its focus on 'broad-spectrum' priorities that would work against multiple pathogens. And in June this year, a federal panel recommended trimming and reorganizing the CDC's select-agent list. But the NIAID is still funding research on plague and tularaemia vaccines, and defends the work, saying that research on tularaemia, for example, has yielded insights about immunity that are relevant to other pathogens. Michael Kurilla, director of the Office of Biodefense Research Affairs in the NIAID's Division of Microbiology and Infectious Diseases, points to recent work on a broad-spectrum antiviral drug that, he says, sprang from studies of the Nipah virus, a category C bioterror threat. He says that this demonstrates the value of continued work on such pathogens as well as model microbes such as the bacterium *Escherichia coli*. "If you say everyone should study *E. coli* because it's like everything else, you won't get those concepts that come out of some unusual bug and have other applications," he says.

Despite the problems with basic biodefence research, critics see far more to complain about in the later stages of the process. The

A DECADE OF BIODEFENCE

OCTOBER–NOVEMBER 2001

Anthrax-laced letters are sent to media outlets and politicians, killing five people and prompting a major FBI investigation.

J. RAEDLE/GETTY IMAGES

JUNE 2002

US President George W. Bush signs a law creating a list of 'select' agents considered to be the biggest bioterror threats, including smallpox and anthrax (pictured).

EYE OF SCIENCE/SPL

JULY 2004

Project BioShield is created: a US$5.6-billion programme to purchase countermeasures against bioterror attacks.

NOVEMBER 2004

VaxGen of South San Francisco, California, is awarded some $877 million by BioShield for its anthrax vaccine. The contract is cancelled in 2006 after VaxGen fails to meet milestones.

DECEMBER 2006

Congress creates the Biomedical Advanced Research and Development Authority (BARDA), which assumes management of BioShield.

JULY 2008

Bruce Ivins (pictured), a scientist at the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, commits suicide as the FBI is preparing criminal charges against him for the anthrax attacks.

AP PHOTO/FREDERICK NEWS POST/S. YU

JULY 2009

BARDA orders 45,000 doses of anthrax drug from Human Genome Sciences of Rockville, Maryland. Later, the Food and Drug Administration declines to approve the drug.

FEBRUARY 2010

US Department of Justice concludes that Ivins alone was responsible for the anthrax attacks, and closes the investigation.

JUNE 2011

An advisory panel recommends trimming the select-agent list to only those posing the very greatest risk, such as the Ebola virus (pictured).

AMI IMAGES/SPL

JUNE 2011

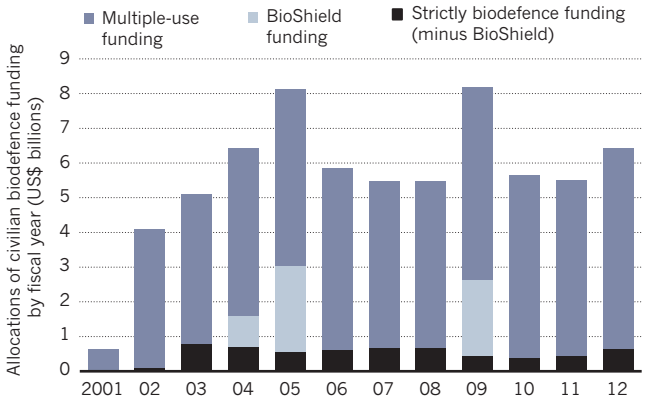
Legislators propose reauthorizing BARDA and funding BioShield at $2.8 billion for 2014–18.

therapies can't be rigorously tested in humans (it would be unethical to infect people with pathogens such as smallpox for testing). And government agencies had little idea how to go about developing such therapies.

The smallpox drugs CMX001 and STS-246 are cases in point. CMX001 is a version of an established antiviral drug called cidofovir that must be given as an injection. In 2000, Karl Hostetler, a chemist at the University of California, San Diego, formed Chimerix, a pharmaceutical company based in Research Triangle Park, North Carolina, to develop a cidofovir pill that could be taken by mouth.

BIODEFENCE IN BILLIONS

Much US biodefence funding has had additional uses, such as in public health. The government's BioShield programme buys finished drugs and vaccines.



C. FRANCO & T. K. SELL *BIOSECUR. BIOTERROR.* **9**, 117–137 (2011).

In September 2003, the NIAID awarded Chimerix a $36-million, five-year grant to develop CMX001 as a treatment for smallpox. The drug looked promising in tests on mice and rabbits, and Chimerix teamed up with the US Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland, to test it in monkeys infected with the related virus monkeypox. But the drug didn't cure the disease — owing, Chimerix said, to a quirk of metabolism not relevant to humans.

Meanwhile, SIGA, a pharmaceutical company based in New York, was racing ahead with STS-246, a small molecule that blocks viral maturation. In 2006, the company reported that its drug protected monkeys from monkeypox. While Chimerix struggled for funding, the federal government continued to award money to SIGA and, in October 2010, SIGA won a BARDA contract for STS-246 worth up to $2.8 billion. Chimerix protested — and SIGA's award was later whittled down to $433 million.

Yet the case of the sick marine in 2009 showed that fighting biothreats can take a whole armamentarium of drugs. Belken's condition didn't improve until CMX001 was added to STS-246. "The reality is that we need two smallpox antiviral drugs," says Robert Kadlec, a former Senate staff member who helped to write the 2006 legislation that created BARDA.

The episode shows how challenging it is to develop therapies, especially when there are no good animal models or data showing whether the drug fights disease in humans. The smallpox virus infects only humans, for example, and monkeypox is an imperfect mimic. Yet authorities often need to rely on animal tests when they make expensive decisions about which drug to buy, and small biodefence companies can be dependent on the funding that results from these decisions.

"The regulatory process is still evolving, and the federal government doesn't have a clear sense of what it needs," says Jim Davis, executive vice-president of Human Genome Sciences in Rockville, Maryland. "It's frustrating for everyone involved." In October 2009, the US Food and Drug Administration (FDA) decided not to approve an antibody against anthrax developed by Human Genome Sciences — even though BARDA had already agreed to spend $326 million on the drug. The company had thought that it had met the FDA's criteria but, according to Davis, the agency decided that it wanted a drug that is more effective than the existing anthrax treatment, ciprofloxacin.

Robin Robinson, director of BARDA, says that the agency is funding the creation of better animal models. The DHHS reviewed medical countermeasures in 2010, and said that it will do more to try to help companies to bridge the gap between basic research and the clinic. The DHHS has also proposed reallocating $170 million in existing FDA funds to help update regulatory review in biodefence.

But revamping biodefence is going to take more money — and critics say that some of the $60 billion spent so far has simply been wasted. They point to a $533.8-million surveillance project called BioWatch, created by the Department of Homeland Security, which has deployed detectors for airborne bioterror agents in 30 cities. The system has been criticized in part because technicians must manually collect the air filters and take them to a lab for analysis, creating a delay of 10–34 hours before results are in and hampering the system's ability to provide an early warning. In a report entitled *BioWatch and Public Health Surveillance*, released last year, a committee convened by the US National Academies said that BioWatch faces "serious technical and operational challenges". The next-generation Biowatch is designed to improve the programme.

Much of the biodefence money didn't even go into research, as a breakdown of spending shows (see 'Biodefence in billions'). The CDC has received the most so far — $17.4 billion — and put the vast majority into bolstering an underfunded public-health infrastructure. The rationale is that the nation has little chance of fighting a bioterror attack without a strong system for detecting, reporting and treating any emerging infectious disease.

Most of the biodefence spending, in fact, has spin-offs into other fields; even BARDA is involved in developing medicines against threats such as pandemic flu. In all, only $11.99 billion of the $60 billion has been spent on programmes solely concerned with biodefence. That's just over $1 billion per year from 2001 to 2011.

Drug-makers often say that it takes at least $800 million and ten years to develop a single drug, so a much greater investment is required before the biodefence effort can yield many new countermeasures. Kadlec recommends that the United States spend $10 billion a year on biodefence in future.

FUNDING CRUNCH

Such sums seem unlikely to materialize. BioShield's funding is set to expire in 2013, and Congress has proposed refunding it at $2.8 billion for 2014–18 — about the same as before. Cutbacks are eroding some of the gains in public-health infrastructure: local health departments have lost 29,000 jobs, some 19% of the workforce, over the past three years.

Now, say observers, the federal government must take a hard look at its biodefence programme and devise a more coordinated strategy that strikes a balance between developing pathogen-specific countermeasures and working on a more generalized resilience to infectious disease. "If the expectations were that we were going to come up with a whole armamentarium of new products by 2011, that was probably unrealistic," says Relman. "It might make sense to pick a few [threats] that are at the top of all possible lists, but then to say, a lot of the rest of the work needs to be in creating a fertile ground for innovation and product development."

"We're at a point after ten years," says Michael Osterholm, director of the University of Minnesota's Center for Infectious Disease Research and Policy in Minneapolis, "where we have got to start producing the kinds of plans and cost estimates about what it will take for a country like ours to be prepared in a moderate way." Preparing for only the worst eventualities might now be the best the nation can do. ■ SEE COMMENT P. 153

Erika Check Hayden *is a senior reporter for* Nature *in San Francisco, California.*