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The Growing Threat of Biological Weapons

The terrorist threat is very real, and it's about to get worse. Scientists should concern themselves before it's too late

Steven M. Block

For half a century, America has participated with the world's nuclear powers in an uneasy standoff of mutually assured destruction. Despite the seemingly relentless proliferation of nuclear arms, there's reason to hope that some version of the current stalemate will continue to hold. Against this backdrop, terrorist factions and "nations of concern" (the current government euphemism for rogue states) have sought ways to leverage their chances. In the jargon of the day, they seek a means to wage "asymmetric warfare" against a more powerful, nuclear-capable adversary. Asymmetric warfare concentrates on the use of unconventional (and affordable) weapons and tactics, ranging from traditional guerrilla fighting to the deployment of new weapons of mass destruction. Ironically, the supremacy in conventional weaponry established by the U.S.—and demonstrated to lethal effect during the 1991 Gulf War—has made asymmetric warfare all the more attractive. Figuring prominently in the arsenal of asymmetric warfare are both biological and chemical weapons. Although it may be something of a misnomer to label most current forms of these agents as "weapons of mass destruction," their power is nevertheless considerable. Worse still, it is now increasing, and these weapons are emerging as a serious threat to peace in the 21st century. Here I explore the historical development and use of biological weapons, as well as some recent trends in their evolution and the prospects for containing their proliferation.

Steven M. Block is a professor of biological sciences and of applied physics at Stanford University, and a member of JASON. *Address: Department of Biological Sciences and Department of Applied Physics, Gilbert Hall, Stanford University, Stanford, CA 94305–5020. Internet: sblock@stanford.edu*

The Plague and Anthrax

Biological warfare is not a new phenomenon. The ancient Romans, and others before them, threw carrion into wells to poison their adversaries' drinking water. In the 14th century the Tatars catapulted the bodies of bubonic-plague victims over the city walls of Kaffa, a Black Sea port that served as a gateway to the Silk Road trade route. People inside the city soon came down with the disease, suggesting that the maneuver may have worked—but the tactic may have exceeded the Tatars' operational goals. Some of the city's inhabitants escaped in sailing ships, which happened to be infested with rats, carrying fleas infected with the causative agent of plague, the bacterium *Yersinia pestis*. The escaping ships entered various Italian ports that subsequently served as foci for the spread of the disease. Over the next three years, the bubonic plague—the Black Death—raged northward, wiping out nearly a third of Western Europe.

It was not until the 19th century that the microbial basis for infectious disease was understood. One of the first illnesses to be explained by the new germ theory was anthrax, an infectious disease common to sheep and cattle. Indeed, the primary architects of the germ theory—Robert Koch, Louis Pasteur and Joseph Lister—were instrumental in describing anthrax and its containment. Koch was the first to isolate and describe the anthrax bacterium *(Bacillus anthracis)*. Pasteur developed the first animal vaccine against anthrax, which, together with Lister's ideas about antiseptic precautions, helped turn the tide against outbreaks of the disease.

Anthrax is only weakly communicable in humans and rarely causes disease, unless the bacterium comes into contact with the bloodstream through a wound (causing cutaneous anthrax) or is ingested in contaminated meat (resulting in intestinal anthrax). However, *Bacillus anthracis* has the ability to form resistant spores, which can remain viable for over a hundred years if kept desiccated and out of direct sunlight. Breathing in significant numbers of spores (typically estimated at about 10,000) can lead to inhalation anthrax in humans, which was historically called "woolsorter's disease" because spores were prevalent in the contaminated wool of sheep in 19th-century England. Inhalation anthrax is a very deadly disease in humans. Unless treated with large doses of a penicillin-type antibiotic within the first day or so of exposure it has a mortality rate in excess of 80 percent. This is to be contrasted with smallpox, which has a mortality rate of "only" around 30 percent. Only some filoviruses, such as Ebola, which cause hemorrhagic fevers, have comparable rates of mortality.

All of this suggests why *Bacillus anthracis* became the agent of choice for most biological warfare programs. Consider the properties of anthrax. It is convenient: Variants of the anthrax bacterium can be isolated worldwide (although not all possess equal virulence), and great quantities of spores

Leif Skoogfors/Corbis

Figure 1. Biohazard suits are the first line of defense against contamination for response teams entering a "hot zone"—the site of a biological-weapon release. A number of civil and military organizations—including the Department of Defense, the Centers for Disease Control and Prevention, the Federal Emergency Management Agency as well as local emergency medical services, fire and hazardous material experts and law enforcement specialists—now hold workshops and training sessions throughout the United States as part of a "Domestic Preparedness" program in case of a terrorist attack with a bioweapon. The challenge is to integrate these forces to mount an effective response under various attack scenarios. Here Marines prepare for a military exercise in Jacksonville, North Carolina.

can be readily prepared from liquid cultures. It is robust: Once desiccated and stabilized, hardy spores have a long shelf life and are well suited to weaponization in a device that can deliver a widespread aerosol. It is self-terminating: Airborne spores remain infectious until they fall to the ground, where most become inactivated by sunlight. It is effective: After inhalation the spores produce disease with a high mortality and morbidity. It can be contained: Anthrax is not very communicable, thereby reducing the risk that it will spread beyond the intended target. Moreover, a well-established vaccine exists that can prevent the onset of the disease, allowing it to be used safely by the aggressor. This is a two-edged sword, of course, since the vaccine may be available to the target population as well. For this reason alone, anthrax doesn't quite qualify as the perfect bioweapon.

There are certain other drawbacks to anthrax as a weapon. The number of spores that must be delivered to the lungs to produce the disease is quite high compared with some other infectious agents—it has been estimated that certain viruses and rickettsiae may communicate disease with just a single particle. Finally, for conventional anthrax, antibiotic treatment can be effective if administered quickly. Even so, of all the natural biowarfare agents, anthrax traditionally ranks near the top of everyone's short list.

The World Wars

The First World War saw one of the first attempts to use anthrax during warfare, directed—ineffectively—against animal populations. Instead, WWI became infamous for its introduction of poisonous mustard gas, which was used effectively against humans. (By odd coincidence, WWI also overlapped with a deadly outbreak of influenza, the Great Pandemic of 1918, which eventually killed more people than the Great War itself.) International revulsion at the horrors of WWI led to the signing of the Geneva Protocol of 1925, which went into force on February 8, 1928, with 29 participating nations, including the U.S. The treaty contained "A Protocol for the Prohibi-

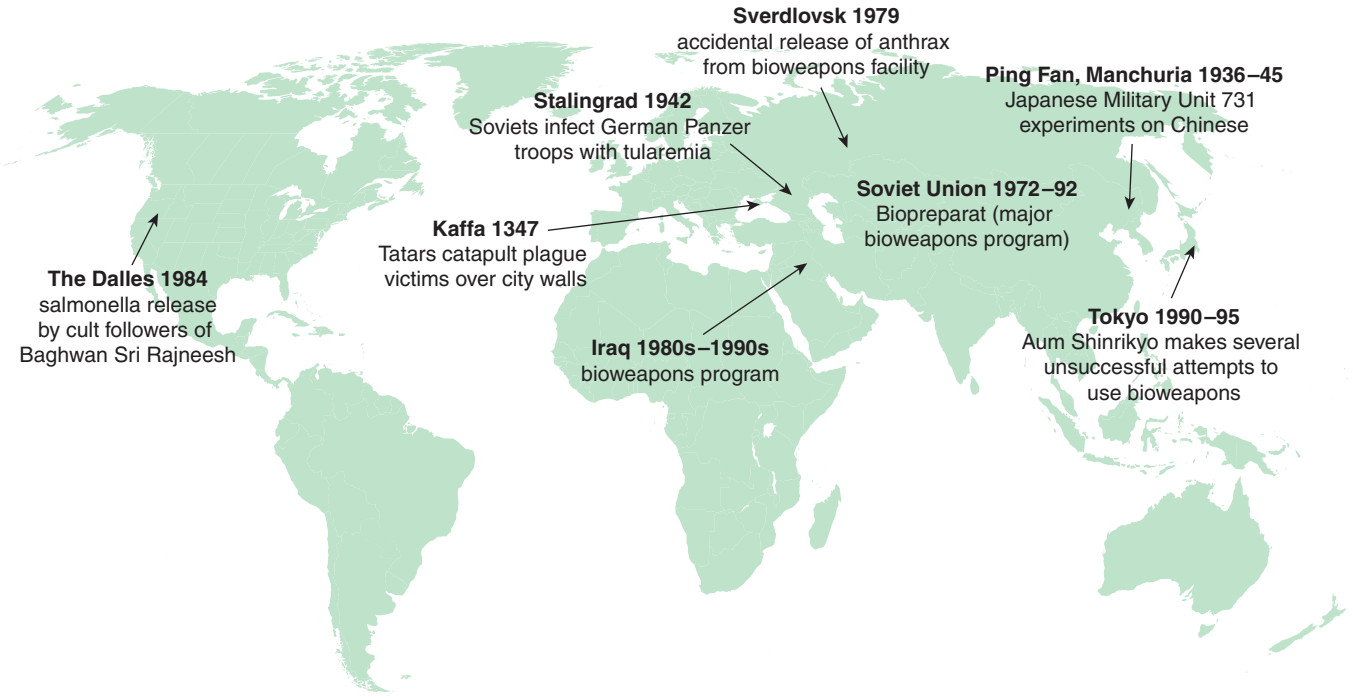


Figure 2. Historical incidents involving biological weapons span the globe and range from relatively modest events, such as salmonella poisoning of salad bars in The Dalles, Oregon in 1984, to the notorious experiments by the Japanese military during the 1930s and 1940s, in which many thousands of Chinese were killed with infectious agents. Not all historical events are listed here.

tion of the Use in War of Asphyxiating gas, and of Bacteriological Methods of Warfare."

Although the Geneva Protocol didn't expressly forbid the production and development of biological weaponry, it did ban all use during war. Disappointingly, neither the U.S. nor Japan ratified the treaty before the advent of World War II, when anthrax and other bioweapons were secretly being developed by both countries—as well as by Germany, the U.S.S.R. and Great Britain. The Japanese and British bioweapons programs were particularly extensive, but no documented use of agents ever occurred during combat. This may have been due to residual respect for the 1925 treaty or, what seems more likely, from the relative immaturity and associated imperfections of bioweapons technology.

There were some notorious instances of biological warfare during this period, however. The Japanese Military Unit 731 at Ping Fan, Manchuria, experimented extensively with bioweapons, killing thousands of prisoners of war with anthrax, cholera, plague, dysentery and other infectious agents. They also released plague on the Chinese civilian population of Chekiang Province on several occasions by dropping from airplanes laboratory-grown fleas fed on infected rats. The Soviets may have deliberately infected German Panzer troops with tularemia during the Battle of Stalingrad in 1942, by far the costliest battle of WWII, but the ensuing outbreak soon spread to both sides and resulted in more than 100,000 cases of the disease.

Unlike the years following WWI, the post-WWII period heard little public debate concerning the need to limit bioweapons—perhaps owing to the global preoccupation with nuclear arms that began in 1945. With the advent of the Cold War, the U.S. biowarfare program (begun in 1942 and aided by postwar intelligence from the Japanese) went into overdrive. Over the course of the next 25 years, the U.S. would quietly develop, test and weaponize at least 10 different biowarfare agents, including bacteria, viruses and microbe-derived toxins. The U.S. not only experimented with human disease, but also targeted economically vital agriculture with fungal weapons such as wheat rust and rice blast. The Soviets had a program that was every bit a match for the American one, but concentrated on a different subset of diseases. Both countries stockpiled plenty of anthrax.

A good deal of effort on both sides went into attacking the problem of weaponization. Biowarfare agents may be deadly, but they are also labile and difficult to deliver to the intended target. It took years of experimentation before the U.S. and Soviet programs eventually succeeded in developing effective means of stabilization and distribution—in the form of explosive bomblets or aerosol-spray weapons that could be delivered by aircraft or ballistic missiles. Today, the operating principles of such delivery devices are among the most closely held national secrets. This is entirely appropriate, given the relative ease with which most other aspects of the bioweapons problem are tackled.

Modern-Day Transgressions

On November 25, 1969, under President Nixon, the U.S. announced that it would unilaterally and unconditionally renounce all biological weapons. Following executive order, the U.S. program was summarily terminated, and the Department of Defense was instructed to destroy all remaining stockpiles of weapons based on biological agents. This order was extended the following year to cover toxin weapons, including biologically produced toxins.

The existing American stockpiles of biological weapons were destroyed between May 1971 and May 1972.

These welcome developments paved the way for the landmark international treaty of April 10, 1972, the Biological and Toxin Weapons Convention (or BWC)—which has now been signed by 160 nations and ratified by 143. Among the countries that have signed and ratified the treaty are the U.S., Great Britain, China, the Russian Federation, Iraq, Iran, Libya and North Korea—some of which figure prominently in reports of actual or suspected bioweapons programs. Eighteen nations signed the treaty but subsequently failed to ratify it—including Egypt, Syria and Somalia—and 34 nations haven't even signed it, including Israel.

The BWC, which went into force in March 1975, took ambitious steps to ban both biological and chemical weapons, including their development, production, procurement or stockpiling for any hostile purpose or use in armed conflict. Unfortunately, the BWC incorporated no provisions to investigate or follow up on suspicious activities. It lacked "teeth."

Perhaps the greatest BWC transgression of all occurred between 1972 and 1992, when a truly massive bioweapons effort was under way in the Soviet Union. Despite endorsing the BWC Treaty, the Soviet Union carried out ultra-secret bioweapons work right up until it collapsed in 1990. Some experts contend that a low, but significant, level of research still exists today. Revelations of the staggering scope of the Soviet program have only recently come to light, after the much-publicized defection of Ken Alibek—formerly Colonel Kanatjan Alibekov—the Deputy Director of *Biopreparat*, the Soviet state "pharmaceutical" agency charged with carrying out bioweapons research.

Alibek has called Biopreparat "the darkest conspiracy of the cold war" and tells a chilling tale. During the heyday of the Soviet program, Alibek supervised as many as 32,000 people (out of 60,000 in the program) at nearly 40 facilities spread throughout the Soviet Union—effectively a "toxic archipelago." Here the Soviets worked not only on perfecting "conventional" biological weapons based on anthrax, glanders and plague, but also on weaponizing deadly (and highly contagious) viruses such as smallpox, Marburg and Ebola. In contrast to the American bioweapons effort, the Soviets considered the best bioweapons agents to be those for which there was no prevention and no cure.

It was during Biopreparat's heyday, in 1979, that the "Sverdlovsk incident" occurred. In April and May of that year, about 100 people and uncounted livestock suddenly died of anthrax in Sverdlovsk (now Yekaterinburg), a city of 1.2 million people. All the victims were located within a narrow band directly downwind of a secure microbiological facility run by the military. The Soviet authorities blamed the deaths on contaminated meat (intestinal anthrax), whereas U.S. agencies attributed the deaths to inhalation anthrax. The latter explanation would constitute *prima facie* evidence for violation of the BWC. International investigations followed, some involving noted Harvard biologist Matthew Meselson. His group's reports, although somewhat critical, initially seemed to lend credence to the Soviet explanation. However, subsequent findings and detailed witness accounts left little room for doubt.

Today, it appears that the deaths were precipitated by a shift worker at the microbiological installation who removed a critical filter that had clogged. The filter happened to be on the output of a drying machine used to remove liquid from industrial-scale cultures of anthrax spores, which were being produced for bioweapons. An aerosol of spores was released from the unit's exhaust pipes over a period of several hours before the mistake was discovered. Sverdlovsk suffered the single largest epidemic of inhalation anthrax in history. In 1992, former Russian President Boris Yeltsin formally acknowledged the true origin of the outbreak.

The current economic and political climate in the former Soviet Union raises the disturbing likelihood that their bioweapons experts will be forced to seek employment elsewhere, resulting in unwelcome proliferation. The analogous problem arises for former Soviet nuclear experts, of course, but bioweapons issues have received comparatively little attention and scant resources.

The BWC was also clearly violated by Iraq, which established extensive programs for the development of both chemical and biological weapons under Saddam Hussein in the early 1980s. Details of these programs only surfaced in the wake of the Gulf War, following investigations conducted by

bacterial disease	causative agent
anthrax	*Bacillus anthracis*
brucellosis	*Brucella suis, B. melitensis, B. abortus*
glanders	*Burkholderia mallei, B. pseudomallei*
plague	*Yersinia pestis*
Q fever	*Coxiella burnetii*
Rocky Mountain spotted fever	*Rickettsia rickettsii*
tularemia	*Francisella tularensis*
typhus	*Rickettsia prowazeki*
viral disease	**causative agent**
smallpox	variola major
viral encephalitis	Venezuelan equine, eastern equine, tick-borne encephalitis virus
African hemorrhagic fever	Ebola, Marburg, Congo-Crimean virus
South American hemorrhagic fever	Junin, Machupo, Sabia, Flexal, Guanarito virus
other	Rift Valley, Lassa, yellow fever virus
fungal disease (of crops)	**causative agent**
rice blast	*Magnaporthe grisea*
rye stem rust	*Puccinia graminis* forma specialis *avenae*
wheat stem rust	*Puccinia graminis* forma specialis *tritici*
biological toxin	**source**
botulinum toxin	*Clostridium botulinum*
enterotoxin B	*Staphylococcus aureus*
epsilon toxin	*Clostridium perfringens*
ricin	*Ricinus communis* (castor bean)
shiga toxin	*Shigella dysenteriae, S. flexneri*

Figure 3. Biological agents that could be used in a weapon include various bacteria, viruses, fungi and toxins. Adapted from the CDC Select List of Agents, U.S. Department of Health and Human Services 42CFR Part 72, RIN 0905–E70. Available at: http://www.cdc.gov/od/ohs/lrsat/42cfr72.htm#Summary_Changes.

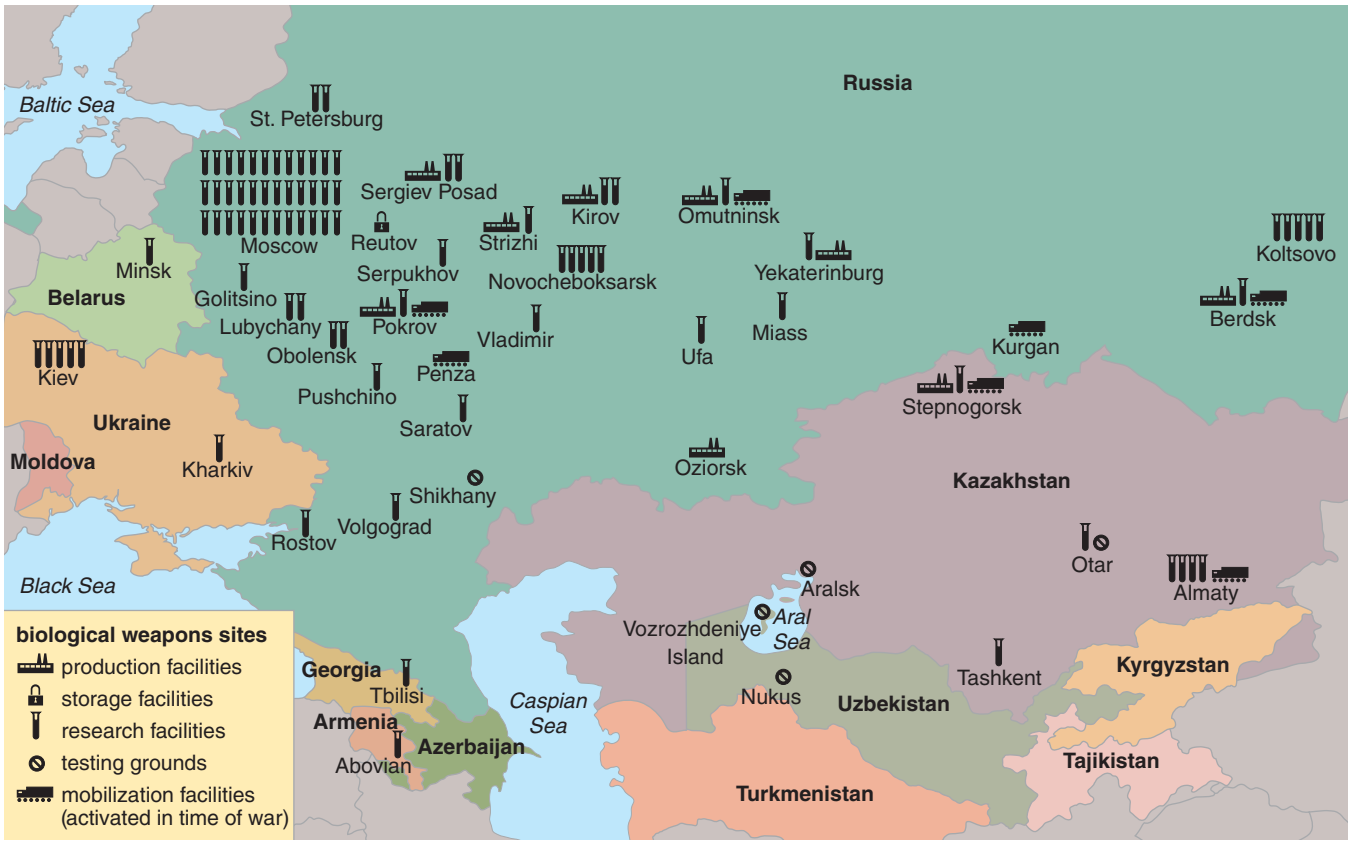


Figure 4. Institutes and facilities constituting the Soviet Union's enormous bioweapons program—*Biopreparat*—involved nearly 60,000 people at 40 sites during the 1970s and 1980s. The ultra-secret program violated the 1972 Biological and Toxin Weapons Convention, which the Soviet Union signed, and it was not dismantled until 1992. The egregious transgression is a testament to the weakness of biological-weapons treaties and conventions that cannot be enforced. The current economic and political situations in the former republics of the disbanded Soviet Union also raise the question of how out-of-work bioweapons scientists are finding gainful employment. (Adapted from Smithson 1999).

the United Nations Special Commission (UNSCOM) in charge of Iraqi disarmament. As a result of these investigations, more is known today about the once-secret bioweapons program in Iraq than that of almost any other nation. Iraq maintained several distinct facilities, including those at the Muthanna State Establishment (the principal chemical weapons plant), Salman Pak (the main biowarfare research center, just south of Baghdad), the "Single-Cell Protein Production Plant" at Al Hakam (the main bioweapons production facility, allegedly built to produce animal feed) and the Foot and Mouth Disease Center at Al Manal (a site for biowarfare research on viruses).

The Al Hakam facility began mass production of weapons-grade anthrax in 1989 and eventually generated at least 8,000 liters (based on declared amounts). This plant was not bombed during the Gulf War in 1991, and its true role in Iraq's bioweapons program was not established until 1995, at which point the U.N. ordered its destruction. Relevant portions of the facilities at Salman Pak and Al Manal were also destroyed, either by the Iraqis themselves or under direct UNSCOM supervision.

In the aftermath of the Gulf War, Iraq officially acknowledged that it had worked with several species of bacterial pathogen—including *Bacillus anthracis*, *Clostridium botulinum* and *Clostridium perfringens* (which causes gas gangrene)—and several viruses—including enterovirus 17 (human conjunctivitis), rotavirus and camel pox. They also purified biological toxins, including botulinum toxin, ricin and aflatoxin. In total, a half million liters of biological agents were grown.

A Meaningful Bioweapons Treaty

All told, it's suspected that more than a dozen sovereign nations possess some form of offensive bioweapons program, assuming one includes some republics of the former Soviet Union. How can this proliferation be controlled? One approach is to muster international resources to enhance and strengthen the provisions of the BWC—giving it some "teeth." This would include verification measures that monitor treaty compliance, including reciprocal inspection visits to suspected bioweapons facilities. This is an essential component of modern arms-control regimes, similar to those implemented for nuclear weapons treaties.

An international group of BWC participants has been convened since January 1995 to accomplish just that, under the chairmanship of Ambassador Tibor Tóth of Hungary. It carries the ponderous name of "The Ad Hoc Group of the States Parties to the Convention on the Prohibition of the Development, Prohibition, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction"—or simply the "Ad Hoc Group." By now the Ad Hoc Group has met for more than 50 weeks in Geneva. The draft treaty they have prepared is as ponderous as the group's name: It currently weighs in at several hundred pages, including an astonishing 1,500

"bracketed" paragraphs—which denote passages where there continues to be disagreement.

For the moment, progress of the Ad Hoc Group seems depressingly stalled. Embarrassingly, the United States itself bears a direct responsibility for many brackets, as it has steadfastly resisted certain attempts to establish provisions for inspections. The U.S. position is motivated by a desire to protect the interests of the powerful American biotechnology sector, which fears that inspection visits may be intrusive, or used as a pretext for industrial espionage. There has been limited progress on this front with the release last May of a joint statement by the Pharmaceutical Research and Manufacturers of America and the Federation of American Scientists who agreed on "managed-access" measures in support of verification.

Another sticking point rests on a constitutional issue: It is one thing for the U.S. government to authorize visits to its own labs and bases, but can it mandate visits to privately held facilities? Some have argued that such inspections may require warrants. However, under the Fourth Amendment, warrants are necessary only if actions rise to the level of a "search." Federal courts have generally held that the subject of a search must enjoy an expectation of privacy—but this standard is stricter for individuals than it is for corporate entities, particularly for industries that are highly regulated. Moreover, the Supreme Court has already recognized that valid exceptions exist to the warrant requirement—for example, for drunk driving, contraband and immigration documentation—and compliance with a vital international treaty certainly should qualify as a valid exception.

As the world's remaining superpower, the United States bears a unique responsibility to take the moral high ground in this process, assuming a leadership role in support of meaningful weapons treaties that establish international norms. A way must be found before a singular opportunity is lost.

Assessing the Terrorist Threat

Biological weapons have been called "the poor man's atom bomb." By any measure, the economic outlay required to develop offensive bioweapons capabilities is significantly less than that of a nuclear program. Less is needed in the way of equipment and infrastructure. The materials themselves are less rare. And less is required in the way of specialized knowledge for the biological aspects, since much of the information can be found in the public domain. Worldwide, trained microbiologists overwhelmingly outnumber nuclear physicists. All these aspects tempt not only nations of concern, but also non-state actors. In fact, it seems far more likely that biological agents will be used by terrorists than by warring nations. Although the terrorist use of bioweapons is likely to occur on a reduced scale, it could have worldwide ramifications under unfavorable circumstances.

Little of real consequence has occurred along these lines, but shots have been fired across the bow. In a bizarre episode that took place in September 1984, more than 750 people fell ill with food poisoning in The Dalles, Oregon. Thankfully, no one died. The cause of the epidemic was not uncovered by health authorities at the time. But in 1986, Ma Anand Sheela confessed at trial that she and other followers of the Baghwan Sri Rajneesh had spread salmonella bacteria, grown on the cult's Oregon ranch, in salad bars in four restaurants, all in an effort to keep voters from the polls so as to influence a local election. After serving two and a half years in federal prison, Sheela was released and deported to Europe.

Between 1990 and 1995, the well-financed Japanese apocalyptic cult Aum Shinrikyo launched a repeated series of attacks on civilians using both biological and chemical weapons. These culminated in the infamous sarin gas release inside the Tokyo subway system in March 1995, which left 13 people dead and sent more than 5,000 to the hospital. Before resorting to toxic gas, the group had reportedly attempted, unsuccessfully, to mount attacks with biological weapons on at least nine occasions over a five-year period. Aum Shinrikyo boasted a dozen or so members with biological training and had even gone so far as to buy a 500,000-acre sheep station in Banjawarn, Australia to serve as a site for operations and to carry out tests.

The cult worked to develop biological weapons based mainly on botulinum toxin and anthrax, although some members made an unsuccessful trip to Zaire to obtain Ebola virus. They also attempted, but failed, to acquire the rickettsia *Coxiella burnetii*, which causes Q fever. In their earliest attempts to carry out biological attacks, members of the cult sprayed homebrewed botulinum toxin on Tokyo streets, near two American airbases in Japan and at the Narita International Airport. All of these attacks failed—most likely because they worked with the wrong strain of *C. botulinum* (not all natural variants yield equal toxicity)

AP Photo/Henry Arvidsson/United Nations

Figure 5. Scud missiles were destroyed by the United Nations weapons inspectors in Iraq during the investigation of the country's bioweapons program after the 1991 Gulf War. Israel was purported to be a target for the long-range Iraqi Al Hussein Scud missiles armed with "non-conventional" warheads, including biological weapons.

and because their misting device may not have been up to the task. They later switched to anthrax, releasing spores in Tokyo near the Imperial Palace, the legislature and a foreign embassy. These tactics again failed, almost certainly because they used a vaccine strain of *B. anthracis*. And again, their spraying device may not have worked as intended.

Does this mean that we should all relax, because using bioweapons turns out to be harder than the perpetrators thought? Is the terrorist threat therefore exaggerated, as some have maintained? Those who claim that biowarfare agents can be brewed in a garage by practically anyone with a modicum of training may be guilty of overstating the case, but although there has been no shortage of exaggeration, that doesn't mean we're off the hook.

A lesson from the Aum Shinrikyo case is that any group bent on developing offensive bioweapons capabilities must overcome two significant problems, one biological and the other physical. First, it must acquire and produce stable quantities of a suitably potent agent. For a variety of reasons this is not the trivial task that it is sometimes made out to be. Second, it must have an effective means of delivering the agent to the intended target. For most, but not all, bioweapon agents, this translates into solving problems of dispersal. Programs in both the U.S. and the U.S.S.R. devoted years of effort to perfecting these aspects.

But who is to say that a terrorist group might not find its own way to imperfect solutions? After all, a terrorist works under entirely different constraints. For one thing, there's no requirement for the dispersal to be very efficient, because bioweapons terror attacks are highly leveraged. If anthrax were released haphazardly in a major U.S. city and produced only a handful of cases, the public fear and disruption that would ensue might alone bring about the intended effect. Our public health system simply isn't geared up to handle an outbreak of this kind, which would, for a time, flood emergency rooms. A terrorist group might also be tempted to finesse the dispersal problem and release some contagious disease, with the aim of starting an epidemic or even a worldwide pandemic. Or it might choose to act covertly, perhaps attacking an economic target, such as crops or livestock, rather than a human population. There are many different options.

In my opinion, the terrorist threat is very real, and it's about to get worse. And opinions do count here, because quantitative risk assessment is a practical impossibility. As with nuclear war, successful bioweapons attacks are characteristically "low probability, high consequence" events. The expectation value of the risk is the product of a very small and a very large number, and such numbers carry great uncertainty.

AP Photo/Joe Marquette

Figure 6. Simple spraying device might be employed by a terrorist to deliver deadly biological agents in a crowd of people. Despite the apparent ease of such delivery methods, attempts by the Japanese cult Aum Shinrikyo evidently failed, in part, because of their spraying device. Here William C. Patrick, one-time chief of product development for the (now-defunct) U.S. bioweapons program, provides a demonstration to the House Select Committee on Intelligence in Washington on March 3, 1999.

The Smallpox Wildcard

All of which brings us to smallpox, the *bête noire* of bioweapons. Smallpox is a frequently lethal, highly contagious disease caused by the variola major virus. By the end of the second millennium, it had killed, crippled, blinded or disfigured one-tenth of all humankind who ever lived. In one of the greatest achievements of the 20th century, smallpox was finally eliminated after a decade-long, worldwide health campaign, which was launched in 1967 under the auspices of the World Health Organization (WHO), under the direction of Donald A. Henderson (now the director of the Center for Civilian Biodefense Studies at Johns Hopkins University). The last recorded case of smallpox occurred in Somalia in 1977, and the disease was officially declared eradicated in 1980.

Although there is no cure for smallpox, it can be prevented with a vaccine

derived from the vaccinia virus. The U.S. Public Health Service recommends re-vaccination every 10 years, but since routine vaccination of the U.S. population ended nearly 25 years ago, few Americans retain immunity today. The current stocks of the vaccine are negligible. Fortunately, there has been some recent action to correct this state of affairs. As of last September, the U.S. Centers for Disease Control and Prevention (CDC) have contracted for a 40-million-dose stockpile of the vaccine. The first batches of the vaccine are slated to be ready by 2004. However, some public-health scientists have questioned whether such a "small" stockpile is adequate. In the event of a simultaneous terrorist attack on several major cities, hundreds of millions of doses might be required to prevent the disease from spreading.

Whether terrorists could get access to the smallpox virus is still an open question. At the end of the heroic WHO campaign frozen stocks of the variola virus were maintained in trust by two organizations: the CDC and *Vector*, the Russian State Research Center of Virology and Biotechnology in Koltsovo, Novosibirsk, Russia. These stocks were originally scheduled to be destroyed on December 31, 1993, but this date has been repeatedly postponed as politicians and health officials debate the wisdom of retaining or destroying the remaining virus, given the growing bioweapons threat. For now, the decision has been deferred by the WHO until 2002. A concern shared by many is whether the Russian stocks are securely held. Ken Alibek has reported that Biopreparat secretly prepared smallpox-based bioweapons up until at least 1992, leading one to wonder how much viable smallpox virus might exist outside the official Koltsovo depository. If any weaponized material or viral stocks found their way to terrorist organizations, the consequences could be disastrous. Simply put, smallpox represents a direct threat to the entire world.

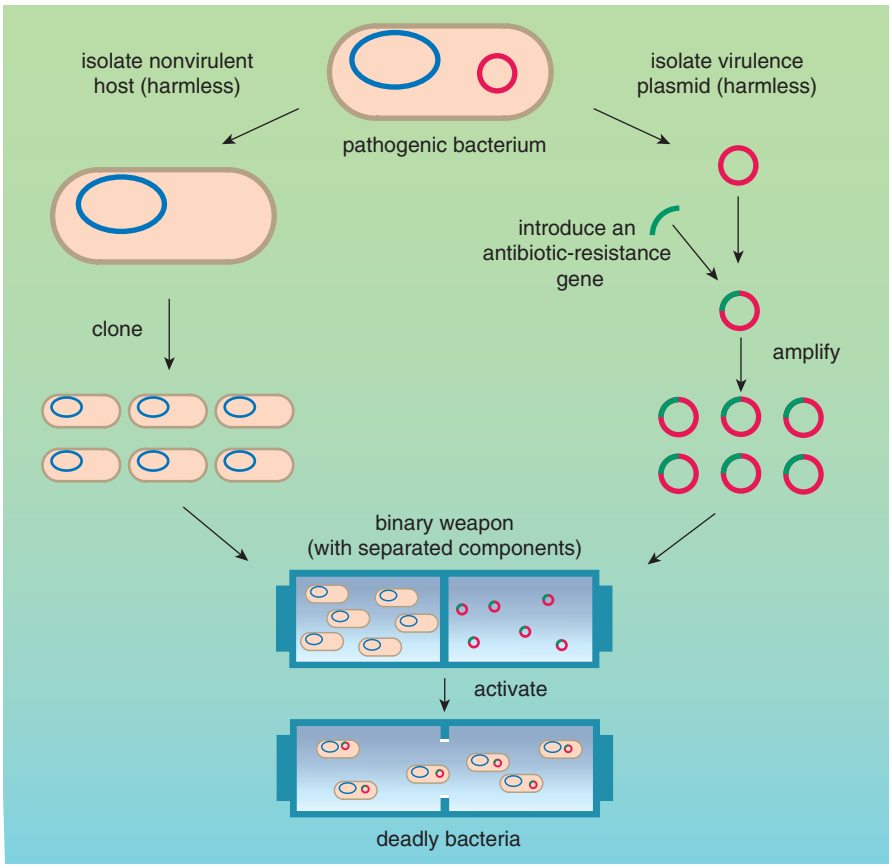


Figure 7. "Black biology" is the colorful name given to the dark art of employing modern techniques in molecular biology to create "new and improved" varieties of bioweapons. One such possibility includes the creation of a binary bioweapon, in which, for example, a virulence plasmid is separated from its bacterial host, thus allowing weapons manufacturers to work safely with the components (which are harmless on their own). The cloned bacteria and amplified plasmids can be placed into separate chambers within a device. When the contents of the chambers are mingled together with certain drugs or chemicals, a small fraction of the bacteria are induced to take up the plasmid, which confers antibiotic resistance. Subsequent regrowth of the bacteria in the presence of the antibiotic ensures that only recombinant, infectious cells carrying the virulence plasmid are produced. Unfortunately, there are many ways to use advances in biotechnology to create particularly effective bioweapons.

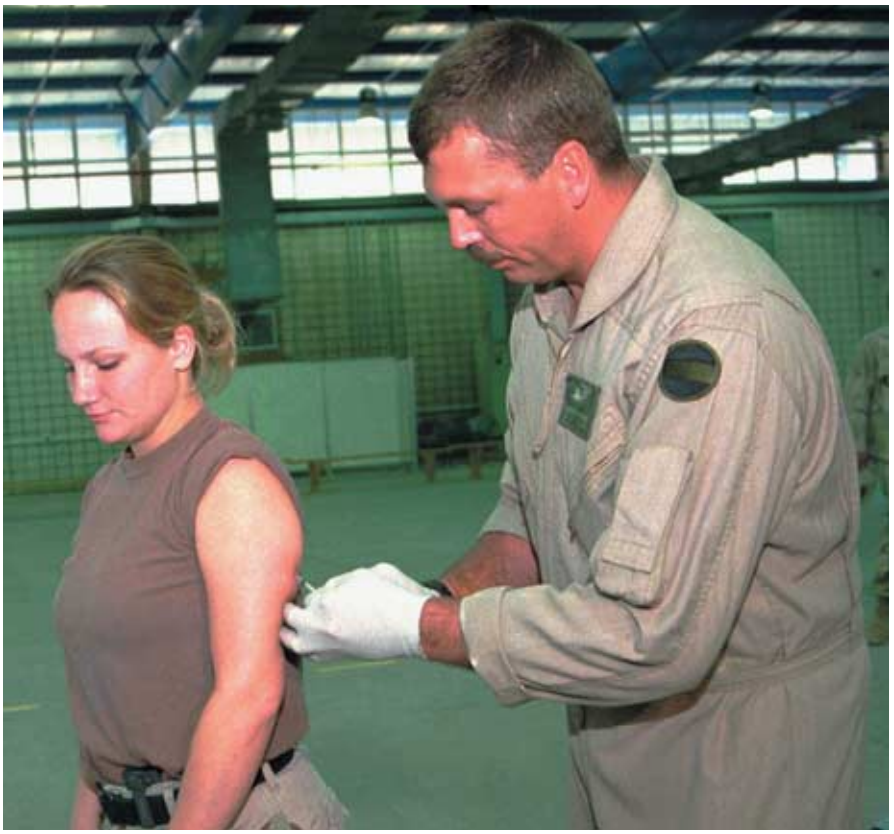
"Black Biology"

Beyond the smallpox scenario, what has people worried is the impact of modern biotechnology. For better or worse, the world is in the midst of a stunning revolution in the life sciences. Scientists have already determined the complete genomic sequences for more than 30 microbes and even more viruses. The DNA code for the cholera pathogen *(Vibrio cholerae)* was recently published, and the genomes of more than 100 other microorganisms are now being sequenced—including the bacteria that cause anthrax, plague, dysentery and typhoid. Of course, the new information is critical for answering fundamental and practical questions in biology and medicine, and will be put to direct, practical use in a myriad of health-related applications. But what about "black biology"? Could biotechnology be used to produce a new generation of biowarfare agents with unprecedented power to destroy? Or is this just alarmist hype? No one can say for sure, but many molecular biologists familiar with the relevant technologies seem inclined to a pessimistic view.

A key reason for pessimism is the ease with which genetic manipulations are now accomplished. Back in the summer of 1997, JASON (a group of primarily academic scientists, which consults on technical matters for the U.S. government and its agencies) addressed the problem of next-generation bioweapons threats. The JASON study explored a wide range of future possibilities open to genetically engineered pathogens, including some that could be achieved with the current state of the art and others that are—happily—still some way off. The prospects are sobering. Both bacteria and viruses may now be engineered to be qualitatively different from conventional bioweapon agents. In terms of bioweaponry, this includes imbuing them with such "desirable" attributes as safer handling, increased virulence, improved ability to target the host, greater difficulty of detection and easier distribution.

Several broad classes of unconventional pathogens were identified by JASON. These include "binary" bioweapons, which, by analogy with chemical weapons, are two-component systems in which each part is relatively safe to handle, but which become deadly in combination, and "designer" variations on genes, viruses and complete life forms, including chimeras that mingle existing components. Once gene therapy becomes a medical reality, the technology that allows the repair or replacement of defective genes might be subverted to introduce pathogenic sequences. "Stealth" viruses could be fashioned to infect the host but remain silent, until activated by a trigger. New zoonotic agents (those transmissible from animals to people) might be developed specifically for bioweapon purposes by modifying existing pathogens to seek human hosts. Finally, detailed knowledge of biochemical signaling pathways could conceivably be used to create "designer diseases."

Of course, some of these exotic possibilities seem downright superfluous given the dangers posed by the current generation of bioweapon agents. Then again, fusion-based hydrogen bombs seem superfluous, given the destructive power of fission-based weapons. For now, even the most rudimentary genetic manipulations could be used to enhance a bioweapons threat, for example by introducing antibiotic resistance into a weaponized bacterial strain.



AP Photo/Gustavo Ferrari

Figure 8. Vaccination against anthrax for military personnel is a controversial issue in the United States, adding further complications to the process of building a defense against biological weapons. Mired in political scandal, the production of the vaccine has been delayed while existing inventories have dwindled. Here an Army sergeant administers a dose of the anthrax vaccine to a military specialist near Kuwait City in 1998.

Vaccination Woes

Anyone seeking to "improve" on wild-type anthrax might begin by introducing antibiotic resistance in the form of a gene for β-lactamase, which enzymatically destroys penicillin. Such a transformation is rather straightforward, and similar to the kind of thing done routinely today in molecular biology labs with non-pathogenic organisms. Disease caused by a multi-drug- resistant variant of anthrax would essentially be impossible to treat. Only those with prior immunity, conferred by vaccination, would stand much chance of survival.

Considerations such as this have helped to motivate the ongoing campaign to vaccinate all 2.4 million U.S. active and reserve troops against anthrax. The vaccination process, licensed by the Food and Drug Administration (FDA), requires a six-dose regimen over an 18-month period. The modern vaccine is prepared from a cell-free filtrate derived from an avirulent strain of *B. anthracis.* By most accounts the current anthrax vaccine is as safe as, perhaps safer than, typical vaccines, although every vaccine carries residual risk. This is why the oral (Sabin) polio vaccine will soon no longer be given to children in the U.S. Comprehensive vaccination programs have reduced polio to such an extent that the risk associated with receiving the oral dose, which leads to paralysis in a minuscule fraction of cases, now outweighs the chance of getting the disease itself.

Unfortunately, the U.S. military anthrax vaccination program has been mired in controversy and scandal. Prior to the program, the lone American company licensed by the FDA to produce anthrax vaccine in the U.S. was the state-owned Michigan Biologics Products Institute, and it was in danger of losing its license after inspections raised questions about potency and sterility of the vaccine. The troubled institute was bought out by Bioport, a company apparently created solely to take over its assets and land the lucrative government contract for the military. The most visible corporate director of Bioport is Admiral William Crowe, former chairman of the Joint Chiefs of Staff. Bioport thus became the exclusive purveyor of anthrax vaccine and applied for FDA approval of a Michigan plant to manufacture more. That approval is still at least six months out. Meanwhile, existing inventories have dwindled, and the military is running out of vaccine after administering fewer than half a million doses (out of 14 million). As a result, they've had to reduce monthly inoculations from 75,000 to 14,000 and suspend injections for all but front-line troops considered at greatest risk.

In Senate hearings held in July 2000, Republican Senator Tim Hutchison of Arkansas reacted to the situation as follows: "The terms of the contract relief (between the Department of Defense and Bioport) reduced the number of dosages to be produced by one half, charged U.S. taxpayers almost three times as much as originally negotiated, and provided Bioport an interest-free loan of almost $20 million. I

am wondering who negotiated such a contract."

Issues of procurement and safety aside, the most disturbing aspect of the anthrax-vaccination program is the unknown efficacy of the new vaccine. A limited study, completed back in 1962 among mill workers handling animal materials, demonstrated protection against the cutaneous form of anthrax for an earlier version of vaccine. However, no one is yet prepared to say whether the current formulation will provide adequate immunity against acute inhalation anthrax produced by a bioweapon. We may never really know, given the obvious ethical considerations of experimenting with the vaccine. It also seems possible that a strain of anthrax might be genetically engineered to circumvent the immunity conferred by the present vaccine. Does it therefore make sense to vaccinate all our military personnel? Well, perhaps not all, but the risks to frontline troops are very real, and the long interval required for the full immunization schedule demands foresight. In the end, one is left to make informed guesses.

The difficulties with the anthrax vaccine highlight an endemic problem: The U.S. has precious little in the way of vaccine production capabilities, and obtaining FDA approval for a new vaccine protocol requires at least two years, generally more. The vaccine industry faces serious issues analogous to the "orphan drug" situation in the pharmaceutical industry. If a lot of people are not dying of the disease, where is the market for the product? And how does a manufacturer protect itself from ruinous lawsuits? This is a topic that might be better addressed by the public rather than the private sector.

Prospects

The Clinton administration has allocated some $1.4 billion during fiscal 2000 to combat biological and chemical terrorism, a figure that has provoked sharp criticism in some quarters. But this number absolutely pales in comparison with the amount spent annually on maintaining U.S nuclear capability, which is at least 30-fold greater. It makes eminent sense to develop improved capability against bioweapons threats, and we should not have to wait for the biological equivalent of Hiroshima to rally our defenses.

There are also indirect benefits associated with such an investment—ones that nuclear spending certainly can't claim to match. Money spent on research to develop new types of sensitive detectors and related monitors for biowarfare agents will almost certainly carry over to the public-health sector in the form of rapid, improved diagnostics for disease. Money spent on coordinating and developing emergency response teams at federal, state and local levels will also establish better mechanisms for dealing with natural outbreaks of emerging diseases. Money spent on innovative surveillance approaches for detecting biowarfare attacks should also improve medical epidemiology. Money spent on vaccine research and delivery may help to buttress our limited capacity to protect the civilian, as well as the military, population. And money spent on stockpiling and positioning depots of smallpox vaccine may turn out to be the smartest hedge-bet of all.

Since 1945, a great many physicists have taken up the challenges posed by nuclear weaponry, and worked hard at both the national and international level to limit their destructive potential. But with the notable exception of a few of the old guard, such as Donald Henderson, Joshua Lederberg and Matthew Meselson, there has been comparatively little involvement by biologists in bioweapons issues. The case was put best by author Richard Preston, who wrote:

> The community of biologists in the United States has maintained a kind of hand-wringing silence on the ethics of creating bioweapons—a reluctance to talk about it with the public, even a disbelief that it's happening. Biological weapons are a disgrace to biology. The time has come for top biologists to assert their leadership and speak out, to take responsibility on behalf of their profession for the existence of these weapons and the means of protecting the population against them, just as leading physicists did a generation ago when nuclear weapons came along. Moral pressure costs nothing and can help; silence is unacceptable now.

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