

Invited submission to the Committee on Government Reform
for its November 14, 2001 Hearing: Comprehensive Medical
Care for Bioterrorism Exposure

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Preparing a Medical Response to
Bioterrorism

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- A broad view of the problem
- Seeking affordable protection
- Identifying research needs
- How much protection is obtainable?

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**Preparing a Medical Response to Bioterrorism
Written Testimony of Meryl Nass, MD
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Overview of biowarfare agents

When planning responses to bioterrorism, there are a wide range of existing pathogens and toxins to consider, and untold genetically engineered organisms that might be encountered. Anthrax and smallpox have long been considered the most likely microorganisms that will be used, based on their innate ability to be easily disseminated, their high mortality rates and relative ease of preparation. Many nations, and potentially some terrorist groups, have the scientific and technical ability to weaponize these two diseases. It is thought that a smaller number of nations or groups can produce more technically demanding, or genetically engineered organisms.

It makes sense, certainly in the short term, to be prepared for anthrax and smallpox; but in the longer term, we should anticipate a much greater range of possible pathogens. For example, NOVA (1) and three NY Times reporters (2) have shown that the Soviet Union developed horrifying, genetically engineered germs for which there is currently no adequate response. A modified Legionella bacterium that produces multiple sclerosis after an episode of pneumonia is one such microorganism. Scientists with the know-how to create such germs have left the Soviet Union, and could be anywhere on earth. Therefore, although important, simply preparing for anthrax and smallpox is insufficient for the challenges faced now.

There are 3 levels of complexity for biological weapons

a) Low technology organisms: smallpox, anthrax, plague, brucella, tularemia, cholera, typhoid, shigella. These were weaponized circa 1940 by various nations and require no advanced technology to produce in quantity. They may be disseminated using widely available means.

Countermeasures (antibiotics, antivirals and vaccines) are generally known and effective.

b) Higher tech weapons developed in the US, USSR, Iraq and other nations more recently. These organisms require sophistication to produce and disseminate, but the know-how to produce them (or the weapons themselves) may have been transferred to any nation or group. Examples are the Legionnaire's Disease-Multiple Sclerosis bacterium, or vaccine-resistant viruses or bacteria.

Countermeasures are not generally known, but may have been created by the weapons' developers.

c) Ever more complex and difficult-to-respond-to microorganisms, which could be developed now or in the foreseeable future. These might, for example, apply advances in knowledge of the human genome, and genetic variability among different populations, to create organisms specifically tailored to certain groups or military

needs. Examples might be a bacterium that secretes cytokines causing autoimmune diseases, but would only affect those of Scandinavian descent, or a gastrointestinal infection that produces sterility. In each case, autoimmune destruction of tissue would be irreversible.

There are unlikely to be effective countermeasures available for these pathogens.

What do the recent attacks signify?

- No attempt was made to use anthrax for mass casualties, such as dissemination in a subway tunnel or ventilation system
- The letters were taped shut, in an apparent attempt to prevent spores from escaping en route
- Although the letters contained weaponized anthrax, they informed recipients of their contents, so that effective antibiotics could be started. The perpetrator desired to frighten, not to kill
- The media targets were probably chosen to ensure the attacks were publicized
- Members of Congress might have been targeted because Congress controls programs for bioterrorism.
- Anthrax-tainted letters may have preceded the September 11 attacks. CDC has advised those who spent more than an hour in the American Media News building since August 1, 2001 to take prophylactic antibiotics (3).

Our responses to these anthrax attacks have been relatively successful. But congratulations are not in order: the anthrax attacks we experienced, terrible as they were, were actually a “best case” scenario. The attacks can almost be viewed as a drill, designed to assess our readiness for a truly malicious biowarfare attack. Possibly this is what the perpetrator was after: to test us, and send a wake-up call.

Had an enemy put undetectable but deadly quantities of anthrax into envelopes without a warning letter, many more casualties could have ensued. Antibiotics would only be started after people became ill. How would we know which facilities to test for spores? If an antibiotic-resistant anthrax had been used, most of those inhaling an infectious dose would die. If anthrax were released in a subway tunnel, instead of an envelope, thousands of deaths could be anticipated.

Although the attacks appear to have been done for effect, the ramifications have been significant. Mail remains in storage, undelivered for weeks. Millions of dollars are being spent for electron beam machines to sterilize the mail. Congressional offices remain closed, until removal of anthrax spores can be assured.

Could we respond effectively to a truly serious anthrax attack? Or an attack using more sophisticated pathogens? Anthrax may be the least frightening of the bioterrorism scenarios we could face in the future.

Yes, we can respond. How effectively we can respond is a challenge I will come back to later.

Proposed Defensive Measures

The following list is a general overview of what could identify and treat illnesses resulting from bioterrorism. Both generic (useful for a range of pathogens) and pathogen-specific measures should be developed, with an emphasis on developing responses that could be used for a variety of pathogens. Measures to boost immunity after an exposure should be studied; although this is a relatively new area of medical research, it could yield substantial dividends in addition to those for bioterrorism.

- 1) Strengthening our public health infrastructure is essential: sharing of knowledge regarding bioterrorism threats and appropriate responses, ability to provide appropriate laboratory assays and medical care at the local level, and improved communications between public health facilities are needed (4).
- 2) Stockpiling antibiotics is appropriate. There should be a range of antibiotics, including those for which adding resistance is more difficult. Researching storage methods to maximize effective shelf life would be useful. Possibly one or more novel antibiotics should not be licensed for mass use, but held in reserve for a bioterrorism response. It would be difficult for a perpetrator to engineer resistance to novel (unknown) antibiotics. Researching methods that encourage early anthrax spore germination in the exposed patient, and establishing an optimal duration of antibiotic use would be helpful, since we do not know whether 60 days of antibiotics will be sufficient for all those exposed to anthrax.
- 3) Vaccinations are useful, but the infinite variety of potential pathogens, the time needed to develop new vaccines, and the time lag for developing immunity following vaccination, conspire to make it unlikely they will be a robust form of defense. Vaccines are often ineffective against selected strains of microorganisms, and it is known that vaccine-resistant pathogens were sought out for biological weapons (5). Issues requiring urgent investigation include whether and how vaccines may lead to chronic illness. How would a genetically diverse population tolerate 50 or 500 vaccinations? Dr. Ken Alibek blames his severe allergies on multiple vaccinations (5), but there is no reliable research that addresses the issue.

4) Identifying the virulence factors present in all known pathogenic microorganisms, and their molecular targets, will allow us to develop generic responses to them. This will probably lead to use of fewer, more specific vaccine antigens. Decoding the genome of pathogens will yield the molecular composition of spores and toxins, permit analysis of their tertiary structures, and allow targeted countermeasures to be developed more easily. (The federal government is supporting this initiative.) Computer modeling of these structures might permit rapid drug design outside the laboratory, and creation of new drugs with novel mechanisms of action (6-7). We can anticipate that most genetically engineered pathogens make use of known virulence factors, so this approach can conceivably yield treatments for pathogens we have never seen before, in advance of an attack.

5) Many pathogenic microorganisms exert at least some of their effects through toxins. It is relatively simple (and inexpensive) to create libraries of antitoxins, or monoclonal antibodies that could inactivate toxins. This would almost certainly yield treatments that are more effective than antibiotics alone, and might work in the late stages of disease. These treatments would be harder to thwart than vaccines.

6) Such products can also be employed in early diagnostic tests; for example, monoclonal antibodies could help distinguish anthrax from influenza while the patient is still in the emergency room. Additional rapid diagnostic tests must be developed for smallpox, anthrax, and other expected pathogens (8). The federal government should provide specialized training, diagnostic kits and equipment, such as polymerase chain reaction (PCR) machines, to state and local laboratories, so that a) important results are made available to treating physicians in a timely manner, b) local communities are better able to respond to an attack, c) hoaxes can be quickly distinguished from real attacks, and d) the federal system will not be overwhelmed by the volume of samples to be tested. Cultures may yield useful information more rapidly than expected; anthrax colonies grow in 12-18 hours. Working with cultures on a compressed schedule, for instance, subculturing every 12 instead of 24 hours, may be useful and should be considered for unknown organisms. Identifying antibiotic resistance could be expedited by detecting known molecules that confer resistance, such as penicillinases, or their genes using PCR techniques.

7) Antivirals may be effective against some viral pathogens, including smallpox(9). Efficacy testing of libraries of licensed and unlicensed antiviral drugs needs to be performed for serious viral pathogens.

8) Certain areas are particularly vulnerable to attack. These include municipal water supplies, ventilation systems of buildings, and tunnels. Ships and planes could be used, wittingly or unwittingly, as delivery systems for microorganisms or toxins. Biosensors or other detection methods should be available to monitor such areas. Although none yet have perfect sensitivity and accuracy, a variety of systems do exist to perform such tasks (8, 10-13). Simple HEPA filters installed in ventilation systems could trap anthrax spores, though they would not keep out all viruses and toxins. The material trapped by

filters could be routinely tested for microbes. For those places most at risk (for example, the New York City subways), sensors should be made available now, and replaced when better devices become available. Development of these devices has been under military control for more than a decade; in order to rapidly encourage the best approaches, and speed production, a streamlined system for evaluation and procurement should be considered.

9) Vaccine, drug and device development needs to be expedited, but safety testing cannot become a casualty of a streamlined review. Safety testing in animals can be made more rigorous; for example, more extensive toxicity testing and drug interaction studies can be performed for all new drugs and vaccines in animal models, and extensive testing in the pregnant animal model can be done. Human safety testing can be done in parallel with animal efficacy testing, for those drugs and vaccines that appear most promising. Additional effort could go into finding or developing animal models for human diseases that lack such models. It should be emphasized, however, that animal safety testing of new products is never sufficient to identify and rule out all problems that may occur in humans; human safety testing, using adequate numbers of subjects who are followed for adequate periods of time, is the *only* way to identify all but the rarest adverse reactions, prior to mass use.

10) The FDA should release its final rule on licensing of new biowarfare drugs and vaccines, so that its expectations for industry are clear (14).

11) Testing of new drugs and vaccines may require Biosafety Level 3 or 4 facilities, and access has been a bottleneck for development and licensure of new products for use against bioterrorism, although a large number of these facilities exist. These labs must be made available for testing the most promising drugs and vaccines, possibly through new procedures involving the Office of Homeland Defense, or the Secretary of HHS.

12) The Joint Vaccine Acquisition Program (JVAP) has been called “a terrible operation” by Dr. DA Henderson, the head of the new Office of Public Health Preparedness, and “a disaster” by Major General (Dr.) Phillip Russell, a former head of both Walter Reed Army Institute of Research and USAMRIID, who has recently been asked to supervise development of an improved anthrax vaccine (15). As bioterrorism expert Stephen Block pointed out, “We don’t have a general way of making a general vaccine that gets an arbitrary pathogen that lasts for any length of time... The fact of the matter is that making a vaccine is still very much a black art (16).” Vaccine development is difficult and time-consuming, and success cannot be predicted. The JVAP should be replaced. Top civilian vaccinologists who understand both the art and science of vaccine creation should be recruited to develop safe and effective vaccines, designed to work for a range of pathogens.

13) Research on spore decontamination is urgently needed. In general, either the DNA or the spore coat must be disrupted. Oxidizing agents and radiation are effective, but safer methods are needed. Improving mechanical removal of spores should be

explored. If one could get all the air moving in buildings, using vacuum cleaners or fans, and filter the air as it moved, most spores could be collected.

Anthrax and Smallpox: Treatments and Vaccines

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For anthrax, the number one priority is early detection of

- a) spores in the environment, and
- b) disease in the individual.

Early detection allows pre-emptive antibiotic treatment after an exposure, and as soon as patients present to a medical facility, for maximal survival rates provided the bacteria are sensitive to antibiotics.

Antitoxins, either in the form of antisera or human monoclonal antibodies, would probably be an effective treatment for cases diagnosed late, or unresponsive to antibiotics. Novel treatments, such as the mutant PA developed by John Collier at Harvard, are very promising but require additional animal and human trials before use (7).

A safe and effective, rapidly immunizing vaccine that would cover all anthrax strains and instill long-lasting immunity is highly desirable. It is not clear which high risk groups should receive the vaccine. According to the current vaccine's package insert, "If a person has not previously been immunized against anthrax, injection of this product following exposure to anthrax bacilli will not protect against infection (17)." Although the suggestion was made that persons exposed to anthrax who are allergic to antibiotics should instead be vaccinated, this is not an approved use of the vaccine. Because vaccine-induced immunity requires more than one vaccine dose, and anthrax kills quickly, post-exposure vaccination without antibiotics is ineffective at preventing or treating disease.

This is not the case for smallpox. There is a long incubation period for smallpox, and vaccination after exposure is known to prevent the disease or lessen its severity (18). Although smallpox is contagious from person to person, unlike anthrax, the disease only spreads after a rash develops. Thus, it is obvious that one is infectious, so measures such as quarantining cases, and vaccinating those who are exposed can be taken.

Detailed discussions regarding the adverse effect profile of the US' stored smallpox vaccine, and possible mandatory smallpox vaccinations, have taken place in a variety of public forums and in the media (19-22). Surprisingly, no discussion regarding the risks of anthrax vaccine has taken place, although the US population was attacked with anthrax, not smallpox. During the past four years, 520,000 military personnel were vaccinated for anthrax. This large cohort ought to provide comprehensive data on the vaccine's safety and efficacy.

The federal government is negotiating to purchase enough new smallpox vaccine to immunize every American, at an estimated cost of 2 billion dollars. The efficacy and adverse event profile for this novel smallpox vaccine have not been publicly discussed, and may not be known (15).

The cost to develop a commercial vaccine and bring it to market is estimated at \$400 to \$500 million. With streamlined trials and FDA review, the cost might decrease substantially. Parallel development of many vaccines using shared technologies might drop costs further. Using yeasts or other microorganisms for vaccine production, instead of eggs and calves' bellies, will result in lower costs.

The discussion of smallpox vaccine risks provides a framework with which to evaluate the risks and benefits of all vaccines. Smallpox vaccine is a particularly impure product, and historically has been made by harvesting the pustules of calves infected with cowpox. The vaccine is scratched on the skin, rather than injected, but still killed or severely injured between one and four people per million recipients. If it were given to all Americans, there would be an increased rate of serious reactions, because so many people are immunocompromised by disease or medical treatments. Careful risk/benefit analysis is therefore critical to making the best decision regarding who should be vaccinated, and when.

Science magazine reported last month that officials "are considering...mak[ing smallpox vaccine] available within a few months as an unlicensed 'investigational new drug (8).' How streamlined would the review process would be for such a product? Although the earliest vaccine recipients might receive vaccine under an experimental protocol, they should be enrolled in safety and efficacy trials, so that adequate data is collected and analyzed *prior* to vaccinating millions of Americans, who deserve a fully tested vaccine.

Pharmaceutical manufacturers have asked for indemnification from the federal government for potential liability related to production of bioterrorism vaccines. This could invite manufacturers to de-emphasize safety issues, and eventually increase the

government's cost for these vaccines considerably. Would receiving vaccine under an IND prevent recipients from seeking compensation if they had a severe reaction?

The US stockpiled 15 million doses of freeze-dried smallpox vaccine about thirty years ago, "but because the rubber seals are deteriorating, about a quarter are suspect (23)." Recent, small scale tests of vaccine in humans suggest that a 1:5 dilution will still induce immunity in 70% of recipients. How much residual immunity exists for those who were vaccinated decades ago is controversial (18). It is possible they may still be protected.

Smallpox is a virus, not a bacterium, and therefore will not respond to antibiotics. But it will probably respond to antivirals (9). And anthrax selected for bioterrorism might not respond to antibiotics. Their differences do not explain why the immediate procurement of 300 million doses of smallpox vaccine has assumed such importance, while obtaining anthrax vaccine for civilians has been entirely ignored. Nor do they explain why anthrax vaccine manufacture remains in the hands of a small start-up company, when the Secretary of HHS insisted smallpox vaccine be obtained only from large, reputable manufacturers (24). Since purchasing the anthrax vaccine facility over three years ago, the manufacturer has collected over \$100 million from the federal government, but not a single lot of new vaccine has been approved for use. The public should be informed how these apparently contradictory decisions with respect to anthrax and smallpox vaccines have been made.

Responding to Future Biological Weapons

At least forty known human pathogens could be used for biological warfare. (Many more could be used against crops or livestock.) Effective vaccines have been created for only a few. None have been stockpiled for use by the American people. What would it cost to develop vaccines for these pathogens and stockpile them for all Americans? Based on estimates for producing the new smallpox vaccine, whose development costs have already been paid, the total could easily exceed 100 billion dollars. And we might still be attacked with microorganisms or toxins for which we had no vaccine. Furthermore, the human cost (in adverse reactions) of administering that many vaccines is unknown.

Rather than choosing to develop individual vaccines, the use of attenuated strains or vectors carrying multiple virulence factors could produce immunity to many pathogens with one vaccination. Methods for developing animal models, and expediting safety testing, could be applied to development of many vaccines.

One suggestion is to avoid stockpiling most vaccines en masse (25); long-term storage invites deterioration and a host of uncertainties. Instead, vaccines should be developed

and tested in animals and humans, but manufactured in small quantities at regular intervals. A federal surge capacity for vaccine manufacture should be created, and maintained. Then, depending on what vaccine was needed, it could be produced over a period of weeks in the desired quantity. Although testing would be needed to assure quality, test methods and release protocols are being designed to facilitate rapid manufacture and use. Traditionally, spore-forming organisms have required dedicated manufacturing facilities, because of persistent spore contamination. New research into decontamination methods will likely result in effective cleanup methods, possibly eliminating the need for individual vaccine production facilities for spore formers.

Many new vaccine technologies are in development: DNA plasmid vaccines and novel adjuvants are just two of these. It's time for FDA to look very closely at these technologies and decide whether or not they are safe. If not, discard them and stop wasting the industry's time. If they can be used, move them forward. This evaluation should be very deliberate and scientific. Critical regulatory decisions must be uninfluenced by political considerations, and Congressional oversight is needed to assure this.

Protection is Expensive, But Still Limited

A number of suggestions have been made for optimizing US preparation and responses for biological attack. I believe these approaches to be comprehensive and prudent. Methods were chosen with affordability in mind.

However, the cost of what was outlined may be more than our nation can afford. On this, Maj Gen John Parker, commanding general of Fort Detrick, and I agree (26). Furthermore, even if all the above measures were taken, there would continue to be weaknesses in our defenses that our enemies could exploit. Regrettably, our defenses can never catch up to the speed at which new pathogens and toxins can be created. It is doubtful that effective treatments will be available for many high-tech biological weapons developed with current, not to mention future, techniques. Our technologies have already outstripped our ability to control them.

It has been said that the arms race bankrupted the Soviet Union. One can conceive of biological terrorism preparations and responses bankrupting the United States.

Rethinking the nature of the threat

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The White House has suggested that recent anthrax attacks used an anthrax strain and an additive developed by the US biowarfare program. If true, this is a bitter pill: not

only must we fear the former Soviet Union and Iraq's bioweapons, but the fruits of our own government's biological warfare program.

Questions could profitably be asked about the origin of the anthrax recently used:

- Who had access to the American bioweapons stockpile? Who had the knowledge to prepare weaponized anthrax?
- What other microorganisms and toxins did the US program develop and produce, which could potentially also be used against us?
- The US biological weapons stockpile was supposedly destroyed before the Biological and Toxin Weapons Convention came into force. Who handled the destruction? Was destruction of all materials verified?
- A 1977 Senate hearing (the "Church Committee") found that not all the weapons had been destroyed, but that some, including a supply of 100 grams of anthrax, were stored for the CIA by a contractor, Becton-Dickinson (27). Were the materials destroyed following these revelations?
- Was the anthrax stored at Becton-Dickinson identical to that found in Senator Daschle's letter?
- Do foreign letters allegedly containing anthrax contain the same preparation as the US anthrax letters? Were they postmarked from the US?

Developing Solutions

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Our allies may understandably fear that they, too, could face a biological attack with weapons developed by the US program, as well as what the Soviets, Iraqis and others may have created. Here is one approach to the problem.

Two weeks ago, the US met with a number of our allies in Ottawa to develop networking approaches to bioterrorism. We should be networking to develop vaccines together, to order drugs together and to improve communications regarding epidemics, as well as creating mutual assistance plans, rapid response teams, and sharing of biotechnology.

But more than this, in the environment we now find ourselves, it could be in our best interest to "come clean" with our allies (and possibly, in the right circumstances, our

enemies) about what was created in our laboratories, and share all available countermeasures, as long as they share full knowledge with us of the bioweapons and countermeasures developed in their programs. This would make the diaspora of former biological warfare scientists much less threatening. Their knowledge would no longer be so valuable, once it had been shared with all biological defense establishments. This would reassure other nations that if US-made weapons were used on them, our best countermeasures would be available to respond. Similarly, we could be reassured that the best Soviet countermeasures were available to us. It would mean that scientists from many nations could be jointly engaged in finding solutions and countermeasures to some of the most horrific threats we face, and it would reduce the cost to any one nation of defensive measures.

Our species could be obliterated from the face of the earth using technologies widely available today. Our friends as well as our enemies know this; and they share this predicament with us. Thus it behooves us to create new forms and ideas if we are to effectively contain this threat.

When all is said and done, the words of Nobel laureate Joshua Lederberg sum up the situation. "There is no technical solution to the problem of biological weapons. It needs an ethical, human and moral solution if it's going to happen at all. There is no other solution."

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