Epidemiology of Bioterrorism

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Since the discovery of Iraq's biological weapons program, concern regarding the threat of biological warfare has increased (1). Anthrax immunizations; increased nuclear, biological, and chemical defense training; improved detection systems and protective gear; and increased vigilance have been instituted to protect the military.

However, the military is not the only population at risk for biological attack. To effectively counter the potentially devastating effects of an attack, we need to understand the basic epidemiologic principles of biological agents used as weapons.

A biological agent is commonly portrayed as a genetically engineered organism resistant to all known vaccines and drugs, highly contagious, and able to harm thousands of people. However, alleged attacks by the Aum Shinrikyo did not result in a single illness from a biological agent (2), and the successful 1984 contamination of salad bars in The Dalles, Oregon, by a religious cult involved a common salmonella strain that was not lethal or contagious and was susceptible to antibiotics (3).

Therefore, our level of suspicion and diligence in identifying and reacting to a biological attack must remain high, since the attack may not follow an expected pattern. Furthermore, a small outbreak of illness could be an early warning of a more serious attack, and recognition and prompt institution of preventive measures (such as effective vaccines and antibiotics) could save thousands of lives.

To facilitate the rapid identification of a bioterrorist attack, all health-care providers and public health personnel should have basic epidemiologic skills and knowledge of what to expect in such a setting.

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Differential Diagnosis

Any small or large outbreak of disease should be evaluated as a potential bioterrorist attack. This initial investigation does not have to be time consuming or involve law enforcement. A look at the facts surrounding the outbreak to determine if anything seems unusual or indicative of bioterrorism should suffice. Since a disease outbreak can be the result of intentional contamination, the differential diagnosis of an outbreak should first be considered. The possibilities include a spontaneous outbreak of a known endemic disease, a spontaneous outbreak of a new or reemerging disease, a laboratory accident, or an intentional attack with a biological agent. Epidemiologic tools can assist in differentiating between these possibilities.

The cause of a disease or even the occurrence of something unusual may be very difficult to determine, especially if the initial cases are few. Surveillance needs to be more than routine. Not only unusually high rates of illness but also unusual diseases should signal a warning. For example, even one case of inhalation anthrax should cause immediate concern and action.

Unlike chemical terrorism, biological terrorism is not immediately obvious but may appear insidiously, with primary-care providers witnessing the first cases. However, it may not even be emergency room personnel who first detect a problem. The first to notice could be a hospital laboratory seeing unusual strains of organisms, or the county epidemiologist keeping track of hospital admissions, or even pharmacists distributing more antibiotics than usual, 911 operators noticing an increase in respiratory distress calls, or funeral directors with increased business. All epidemiologic data should be tracked and aggressively followed to ensure the most rapid recognition and response.

Epidemiologic Approach

The basic epidemiologic approach in the evaluation of a potential bioterrorist or biowarfare attack is not different from any

standard epidemiologic investigation. The first step is to use laboratory and clinical findings to confirm that a disease outbreak has occurred. A case definition should be constructed to determine the number of cases and the attack rate. The use of objective criteria in the development of a case definition is very important in determining an accurate case number, as both additional cases may be found and some may be excluded, especially as the potential exists for hysteria to be confused with actual disease. The estimated rate of illness should be compared with rates during previous years to determine if the rate constitutes a deviation from the norm.

Once the case definition and attack rate have been determined, the outbreak can be characterized in the conventional context of time, place, and person. These data will provide crucial information in determining the potential source of the outbreak.

Epidemic Curve

Using data gathered on cases over time, an epidemic curve can be calculated. The disease pattern is an important factor in differentiating between a natural outbreak and an intentional attack. In most naturally occurring outbreaks, numbers of cases gradually increase as a progressively larger number of people come in contact with other patients, fomites, and vectors that can spread disease. Eventually, most of the population has been exposed and is immune to further disease, and the number of cases, or epidemic curve, gradually decreases. Conversely, a bioterrorism attack is most likely to be caused by a point source, with everyone coming in contact with the agent at approximately the same time. The epidemic curve in this case would be compressed, with a peak in a matter of days or even hours, even with physiologic and exposure differences. If the biological agent is contagious, it is possible to see a second curve peak after the first, as original cases expose originally unexposed persons to the agent. The steep epidemic curve expected in a bioterrorism attack is similar to what would be seen with other point source exposures, such as foodborne outbreaks. Therefore, the compressed epidemic curve is still not pathognomonic for an intentional bioterrorism attack.

If a specific group has been exposed, the epidemic curve may indicate the time of exposure. From this information, a possible incubation period can be calculated, which can assist in determining the potential cause of illness, as well as suggesting a possible intentional attack (if the incubation period is shorter than usual as a result of an unusually high inoculum or more effective exposure route). Calculating the incubation period may also help determine if the disease is spread from person to person, which is extremely important to effective disease control measures.

Epidemiologic Clues

As steep epidemic curves can be seen in natural point-source exposures, additional characteristics of the outbreak should be investigated in determining whether it is the result of a biological attack (4,5). None of the following clues alone constitute proof of intentional use of a biological agent, but together they can assist greatly in determining if further investigation is warranted. 1) The presence of a large epidemic, with greater case loads than expected, especially in a discrete population. 2) More severe disease than expected for a given pathogen, as well as unusual routes of exposure, such as a preponderance of inhalational disease as was seen in Sverdlovsk after the accidental release of aerosolized *Bacillus anthracis* spores (6). 3) A disease that is unusual for a given geographic area, is found outside the normal transmission season, or is impossible to transmit naturally in the absence of the normal vector for transmission. 4) Multiple simultaneous epidemics of different diseases. 5) A disease outbreak with zoonotic as well as human consequences, as many of the potential threat agents are pathogenic to animals. 6) Unusual strains or variants of organisms or antimicrobial resistance patterns disparate from those circulating. 7) Higher attack rates in those exposed in certain areas, such as inside a building if the agent was released indoors, or lower rates in those inside a sealed building if an aerosol was released outdoors. 8) Intelligence that an adversary has access to a particular agent or agents. 9) Claims by a terrorist of the release of a biologic agent. 10) Direct evidence of the release of an agent, with findings of equipment, munitions, or tampering.

Even with the presence of more than one of the above indicators, it may not be easy to determine that an attack occurred through

nefarious means. For example, it took months to determine that the outbreak of salmonellosis in Oregon was caused by intentional contamination of salad bars (3). Other outbreaks, such as the hantavirus outbreak in the Four Corners area of the United States, have been thought of as possible results of intentional contamination (7). Even if no conclusive answer can be derived quickly, the means employed in determining the cause of an attack will still provide medical personnel with information that may prevent illness and death.

Recommendations for Preparedness

Improved awareness and readiness should a bioterrorism attack occur include education of all medical personnel, especially primary-care providers and emergency personnel first to see patients affected by a biological attack. Training should include basic epidemiologic principles as well as clinical information on diagnosing and treating agents that pose the highest threat. Training should be refreshed periodically to ensure that skills remain current.

Improved surveillance efforts should be instituted with as close to real-time data gathering as possible. All facets of surveillance should be used, to include emergency visits, laboratory data, pharmacy use, school absenteeism, or any other data that correlate with an increase in infectious disease. Robust surveillance systems are essential to detecting any emerging or reemerging disease. Quick recognition of any change in disease patterns will facilitate determining the source and preventing further exposure, which should be the key driving force behind any epidemiologic investigation. Through strong epidemiologic training, a close attention to disease patterns, and a healthy respect for the threat of biological terrorism, potential problems can be discovered rapidly, and actions can be taken to decrease the impact of disease, regardless of its origin.

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Vaccines in Civilian Defense Against Bioterrorism

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In the United States, over the past half century, we have lived under the protective umbrella of vaccination programs that shield our population from a dozen serious and sometimes fatal naturally transmitted illnesses. Vaccination has been the single most cost-effective public health intervention. However, the value of vaccines in protecting the population against the deliberate release of infectious organisms is not so clear-cut.

The U.S. armed forces have recognized the military value of vaccines against biological threats and have a long-standing research and development program for a series of vaccines to protect service members from hostile use of a biological agent. Vaccination against anthrax is under way in all three armed services. The Department of Defense has a large program to develop and license additional vaccines for biological defense. For the military, vaccination is an effective means of countering a known threat because the population at risk is easily defined and a high level of vaccine coverage can be achieved.

In evaluating the role of vaccines for protecting the civilian population, quite different answers are reached. Despite the protective efficacy of vaccines against individual organisms, the very high costs and the great difficulties involved in vaccinating large populations, along with the broad spectrum of potential agents, make it impossible to use vaccines to protect the general population against bioterrorism. Thus, vaccines cannot be considered a first line of defense against bioterrorism for the general population, as they can be for the relatively small military population. However, if suitable vaccines can be made available, they have several potential uses: control of a smallpox epidemic and prevention of a global pandemic, postexposure prophylaxis against anthrax (with antibiotics), and preexposure prophylaxis in first-responders at high risk, laboratory workers, and health-care providers.

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Smallpox and anthrax, which pose the greatest risk for causing large numbers of casualties in the event of an effective release by a terrorist group, are at the top of the list of threat agents. Licensed vaccines against both anthrax and smallpox that protect against aerosol transmission are available. An existing licensed plague vaccine is protective against flea-transmitted disease but not against aerosol challenge in animal experiments or against pneumonic plague. This vaccine is in limited supply, and the manufacturer has recently ceased production.

The Department of Defense Joint Vaccine Acquisition Program has several experimental vaccines in development (Table). These vaccines will be further developed and tested with the intent of obtaining products licensed by the U.S. Food and Drug Administration.

Table. Vaccines against biological agents

Licensed vaccines	Vaccines in research and development
Anthrax	Vaccinia (cell culture)
Smallpox (vaccinia)	Botulinum toxoids
Plague	Tularemia
	Q fever
	VEE, EEE, WEE

VEE, Venezuelan equine encephalitis; EEE, Eastern equine encephalitis; WEE, Western equine encephalitis.

Smallpox

One vaccine in development that is of great importance to civilian biodefense is the vaccinia virus vaccine made in cell culture. A new national stockpile of vaccinia vaccine is urgently needed to respond to the possible threat of a

deliberate release of smallpox virus. Even though such release is unlikely, the consequences of being unprepared would be a global catastrophe. An unchecked epidemic in today's unvaccinated, densely packed urban populations linked by rapid air travel could kill millions. The only possible course of action would be to mount a global effort to control the spread and eradicate the disease using vaccinia virus vaccine. The number of deaths due to secondary and subsequent spread of this highly contagious virus would be determined by the rapidity of the public health response, the effectiveness of a vaccination campaign, and, most importantly, the availability of vaccine.

The national stockpile (fewer than 7 million doses of vaccinia virus vaccine) is insufficient to meet national and international needs in this scenario. The stockpile is also deteriorating and has a finite life span. The vaccine was made using the traditional method of scarifying and infecting the flanks and bellies of calves and harvesting the infected lymph. No manufacturer exists today with the capability to manufacture calf lymph vaccine by the traditional method. Replacing the stockpile will require the development and licensure of a new vaccine using modern cell-culture methods. This development program, which will include process development, validation of a new manufacturing process, and extensive clinical testing, will be expensive and may take several years (1).

Obstacles to the development of the vaccine include the lack of satisfactory stocks of vaccinia immune globulin necessary for managing complications of vaccination. Clinical testing cannot proceed without a supply of vaccinia immune globulin. As part of the development effort, the problems associated with manufacture of sufficient quantities of vaccinia immune globulin will have to be addressed and solved. The Department of Defense program is moving ahead with development of a cell-culture vaccine by using a cloned strain of vaccinia derived from another strain. Both civilian and military requirements could be met by a combined and expanded development effort using either the cloned strain or one of the licensed vaccinia strains. The development costs will undoubtedly be high, as for any new biologic product, but the cost of preparedness is insignificant when weighed against the costs of an unchecked smallpox epidemic.

Anthrax

Anthrax is the second threat that requires a major research and development effort to meet civilian needs. A covert attack, which exposes an urban population to an anthrax spore aerosol, is thought by some to be the most likely scenario for a bioterrorism attack. If the release is detected or the first cases are rapidly diagnosed, rapid action can save many lives. Providing the exposed population with antibiotics followed by vaccination could be lifesaving for exposed persons who would otherwise become ill with untreatable inhalation anthrax in the subsequent few weeks. Prophylactic antibiotics alone will prevent disease in persons exposed to antibiotic-susceptible organisms, but incorporating vaccination into the treatment regime can greatly reduce the length of treatment with antibiotics. Without vaccination, antibiotics must be continued for 60 days; if effective vaccination can be provided, this can be reduced to 30 days. Vaccination of persons affected by an attack will also face the issue of environmental contamination of urban areas after an attack. Stockpiling a vaccine capable of inducing protective immunity with two doses could be extremely valuable in reducing the impact of a terrorist release of anthrax.

The current anthrax vaccine manufactured by Bioport (formerly the Michigan Department of Public Health Laboratory) is an alum-adsorbed, partially purified culture filtrate of *Bacillus anthracis* with a high protective antigen content. The schedule for administration is 0, 2, and 4 weeks and 6, 12, and 18 months. This vaccine is safe and efficacious and is being used by the armed forces to protect personnel against the use of anthrax as a weapon. Immunization of rhesus monkeys followed by a high-dose aerosol challenge has convincingly demonstrated the capability of this vaccine to protect against aerosol challenge with *B. anthracis* spores. The multiple dose requirement, however, is a drawback for civilian use.

Studies in progress may find ways to allow modification of the schedule. Vaccine supply is limited, as is production capacity. As a result, at least for the immediate future, the armed forces will require the entire available supply. This vaccine is made by a method developed before the advent of molecular biology and requires dedicated facilities because *B. anthracis* is a spore-forming organism. In addition to having a

multiple-dose requirement, the vaccine is not highly purified and contains multiple extraneous proteins. The characteristics of the vaccine and the constraints on the present method of manufacturing argue strongly against procuring large amounts for civilian use when the technology and the science base exist to rapidly develop a second-generation, improved anthrax vaccine.

Anthrax depends on two toxins (lethal factor and edema factor) for virulence. A protein called protective factor is an essential component of both toxins. The protective factor content is the basis for the effectiveness of the current vaccine. A vaccine based on purified protective factor made by recombinant technology has been protective in animals (2). Use of a modern adjuvant with purified recombinant protective factor should make it possible to have a very effective two-dose vaccine. A recent report of the Institute of Medicine Committee on Research and Development to Improve Civilian Medical Response to Chemical and Biological Terrorism makes a strong case for a major research and development effort leading to an improved second-generation vaccine (1).

Questions regarding the ability of existing anthrax vaccines to protect against anthrax strains engineered to contain additional virulence genes have been raised in Russia (3). Research is needed to address this and related questions about the pathogenesis of anthrax and protective immunity.

The value of vaccinating law-enforcement and emergency response personnel, who must respond to threats (real or otherwise), depends on the nature of their work and the immediacy of the threat. Laboratory personnel who must work with unknown materials and with high concentrations of known infectious materials must be vaccinated. These are additional justifications for moving ahead with a vigorous development program for anthrax and smallpox vaccines.

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Vaccines, Pharmaceutical Products, and Bioterrorism: Challenges for the U.S. Food and Drug Administration

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In regards to bioterrorism, the goal of the U.S. Food and Drug Administration (FDA) is to foster the development of vaccines, drugs and diagnostic products, safeguards of the food supply, and other measures needed to respond to bioterrorist threats. Many products (vaccines, therapeutic drug and biological products, food, devices, and diagnostics) regulated by FDA could be affected by bioterrorism. Pathogens or pathogen products adapted for biological warfare include smallpox (variola), anthrax (*Bacillus anthracis*), plague (*Yersinia pestis*), tularemia (*Francisella tularensis*), brucellosis (*Brucella abortus, B. melitensis, B. suis, B. canis*), Q fever (*Coxiella burnettii*), botulinum toxin (produced by *Clostridium botulinum*) and staphylococcal enterotoxin B. New products are needed to diagnose, prevent, and treat these public health threats.

FDA is participating in an interagency group preparing for response in a civilian emergency. This group includes representatives of the Department of Defense; the Veterans Administration; and components of the Department of Health and Human Services (DHHS), such as the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and Office of Emergency Preparedness. In addition, FDA will be proposing standards for the use of animal efficacy data in approving new products to counter chemical and biological agents. The agency is also participating in setting a broad-based federal research agenda to facilitate the government's preparedness against bioterrorism; is identifying facilities and activities suitable for the production of biological weapons; is involved in product development, review, and testing; and is ensuring that appropriate product surveillance and sponsor compliance are executed in accordance with regulations.

FDA's regulation of medical products is based on science, law, and public health considerations (Figure 1). Research conducted at FDA (in particular at the Center for Biologics Evaluation and Research) contributing to biological warfare defense and other counterbioterrorism efforts is in the following areas: design of new vaccines (e.g., pox viruses); pathogenesis and mechanism of replication of biological warfare agents; new methods and standards to expedite the review of new vaccines and immunoglobulins (e.g., mucosal protection against a pathogen); and stem cell protection and chemokine/cytokine and angiogenic agent defense mechanisms. The development framework of most biological and traditional drug products is shown in Figure 2. The principal evaluation and research and development phases before a drug is submitted to FDA for approval can take 1 to 3 years. The clinical research and development program (investigational phase), depending on the agent and clinical indication, can take 2 to 10 years. The marketing application review period generally is 2 months to 3 years (average 1 year). Once a product is approved, long-term postmarketing surveillance, inspections, and product testing are performed to ensure the quality, safety, and efficacy of the product, as

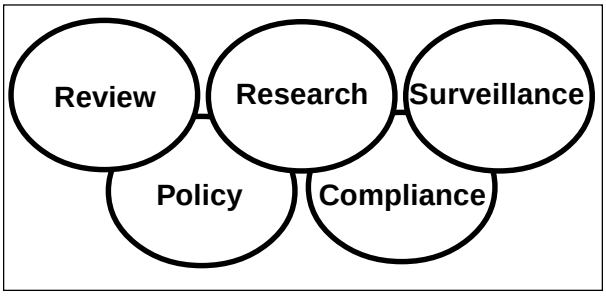

Figure 1. Regulation of medical products.

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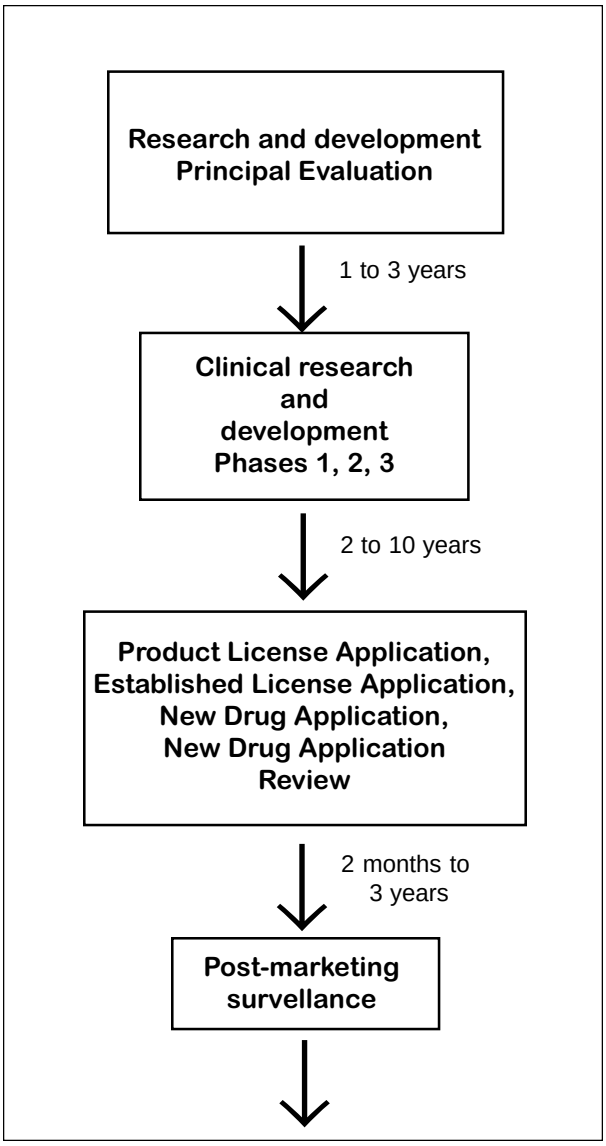

Figure 2. Development of biological and tradition drug products.

well as appropriate product labeling. Accelerating product development is important in many situations, including bioterrorism. Mechanisms for advancing medicines through the approval process have been developed for severe and life-threatening illnesses. For drugs and biologic products, these mechanisms include expedited review and fast-track development, as well as accelerated approval and priority review of marketing applications. For a priority product, complete review of marketing applications is 6 months.

Many of the biological warfare defense products pose difficult problems with regard to obtaining clinical efficacy data. For many of these infectious agents or toxins, human efficacy trials cannot be performed, as such studies would involve exposing healthy human volunteers to a lethal or permanently disabling agent without proven therapy and field trials. In most cases, such trials are not feasible because pockets of natural exposure do not exist. To address this dilemma, FDA will be proposing that the use of animal efficacy data be allowed when appropriate (1). This proposed rule would identify the types of data required. Safety, pharmacokinetic, and immunogenicity data will still be necessary in humans. Product safety will likely be evaluated in healthy human volunteers at doses and routes of administration anticipated in field use.

Some scientific considerations for animal studies include the toxic agent's pathophysiologic mechanism of toxicity and how the test drug or biologic product prevents it and the validity of the animal study endpoint in humans. In addition, data showing that drug effectiveness in animals predicts efficacy in humans would be needed. Finally, product recipients should be given follow-up after treatment to affirm product safety and efficacy.

For licensure or other approval, a biological warfare defense product must have an acceptable quality, safety, efficacy, and potency profile. Likewise, the product must have acceptable stability characteristics and be produced in compliance with current good manufacturing practices.

A case study of anthrax vaccine can serve as an example of our capability to respond to a bioterrorist threat. Only one licensed anthrax vaccine (Bioport Corp.) is available. This vaccine consists of a membrane-sterilized culture filtrate of *B. anthracis* V770-NP1-R, an avirulent, nonencapsulated strain. The culture filtrate is adsorbed to aluminum hydroxide and formulated with benzethonium chloride (preservative) and formaldehyde (stabilizer). The administration schedule consists of 0.5 ml injected subcutaneously at 0, 2, and 4 weeks, 6, 12, and 18 months, and then annually thereafter. The vaccine was licensed in 1970. The efficacy data in support of the license consisted of a single-blind, well-controlled field study (2). The vaccine efficacy was 92.5% (lower 95% confidence limit of 65%). Of the 26 cases of anthrax in this study, 21 were cutaneous and 5 (4 fatal) were inhalation (2 in the placebo group, 0 in the vaccinated group, 3 in the unvaccinated group).

In December 1985, the Federal Register (3) published the FDA's advisory panel review of the efficacy of anthrax adsorbed. The panel recommended that this product be placed in category I (safe, effective, and not misbranded) and that the appropriate license be continued because there was substantial evidence for this product.

Studies of new anthrax vaccine products are in progress. They include protective antigen–based vaccines, e.g., purified protein from *B. anthracis* culture or live-attenuated spore vaccine. Production and product testing will differ for each of these candidate vaccines. The immunogenicity of the product in humans and animal models should be assessed. The cell-mediated immunity elicited by the vaccine may also need to be evaluated. One of the immune correlates of protection of anthrax vaccines is likely to be the antibody response to protective antigen. However, the quantitative relation of antiprotective antigen antibody to protection has not been established in humans but is being investigated by the Department of Defense. Animal challenge and protection models, especially rabbit and nonhuman primate models, may be particularly useful. Passive transfer of protection, also an indication of the importance of antibodies for protection, has been observed in animal models. Therefore, human challenge protection studies and new field efficacy trials are not feasible in studying the efficacy of new anthrax vaccines. Animal challenge and protection studies against spores will be important for new vaccines based on protective antigen. Comparisons of immune responses in human cohorts receiving new or licensed vaccines should be performed.

Data should be obtained on various target populations, including adults and children, to evaluate the safety of new anthrax vaccines. Systemic and local adverse events are particularly important to monitor. For live-attenuated and vector vaccine approaches, the potential for transmission to others will be an important consideration in clinical development and use. After these vaccines are licensed and administered, the safety and adverse reactions of these vaccines should be assessed.

In conclusion, FDA will be providing a critical link in access of new medicines for biowarfare defense (Table). The expected outcomes of these activities include safe and effective products to treat or prevent toxicity of biological and chemical agents; methods to rapidly detect, identify, and decontaminate hazardous organisms; a greater ability to ensure the safety of the food supply; and a greater ability to provide appropriate medical care and a public health response.

Table. Proposed activities of the U.S. Food and Drug Administration to counter bioterrorism

1. Enhancing the expeditious development and licensure of new vaccines and biological therapeutics through research and review activities—anthrax vaccine and antisera to botulinum toxin, for example.
2. Enhancing the timeliness of application reviews of new drugs and biological products and new uses of existing products.
3. Participating in the planning and coordination of public health and medical response to a terrorist attack involving a biological or chemical agent(s).
4. Participating in the development of rapid detection and decontamination for agents of bioterrorism such as *Clostridium botulinum* toxins, *Yersinisa pestis, Bacillus anthracis*.
5. Ensuring the safety of regulated foods, drugs, medical devices, and biological products; arrange for seizure and disposal of affected products.
6. Developing techniques for detection of genetic modifications of microorganisms to make them more toxic or antibiotic- or vaccine-resistant.
7. Rapidly determining a microbe's sensitivity to drug therapy.
8. Determining the mechanism of replication and pathogenicity or virulence of identified organisms including elements that can be transferred to other organisms to circumvent detection, prevention, or treatment.
9. Enhancing adverse product reporting surveillance capabilities.

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Smallpox: Clinical and Epidemiologic Features

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Clinical and Epidemiologic Characteristics of Smallpox

Smallpox is a viral disease unique to humans. To sustain itself, the virus must pass from person to person in a continuing chain of infection and is spread by inhalation of air droplets or aerosols. Twelve to 14 days after infection, the patient typically becomes febrile and has severe aching pains and prostration. Some 2 to 3 days later, a papular rash develops over the face and spreads to the extremities (Figure 1). The rash soon becomes vesicular and later, pustular (Figure 2). The patient remains febrile throughout the evolution of the rash and customarily experiences considerable pain as the pustules grow and expand. Gradually, scabs form, which eventually separate, leaving pitted scars. Death usually occurs during the second week.

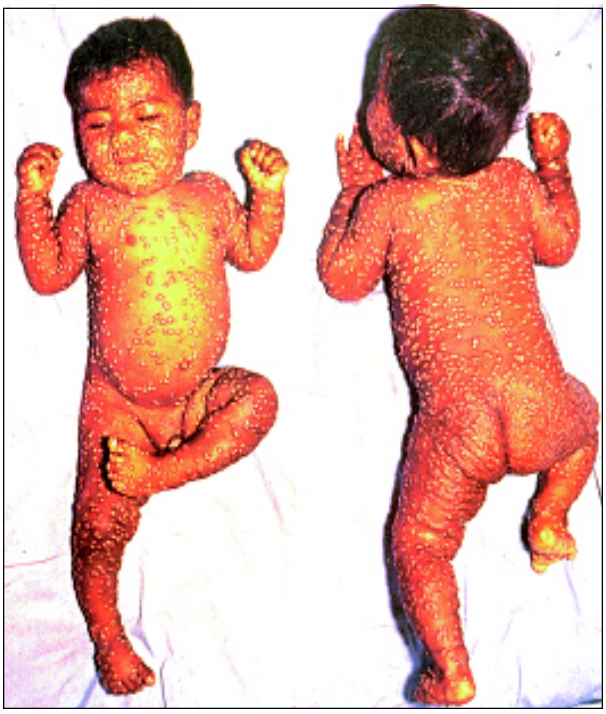

Figure 1. Most cases of smallpox are clinically typical and readily able to be diagnosed. Lesions on each area of the body are at the same stage of development, are deeply embedded in the skin, and are more densely concentrated on the face and extremities.

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The disease most commonly confused with smallpox is chickenpox, and during the first 2 to 3 days of rash, it may be all but impossible to distinguish between the two. However, all smallpox lesions develop at the same pace and, on any part of the body, appear identical. Chickenpox lesions are much more superficial and develop in crops. With chickenpox, scabs, vesicles, and pustules may be seen simultaneously on adjacent areas of skin. Moreover, the rash in chickenpox is more dense over the trunk (the reverse of smallpox), and chickenpox lesions are almost never found on the palms or soles.

In 5% to 10% of smallpox patients, more rapidly progressive, malignant disease develops, which is almost always fatal within 5 to 7 days. In such patients, the lesions are so densely confluent that the skin looks like crepe rubber;

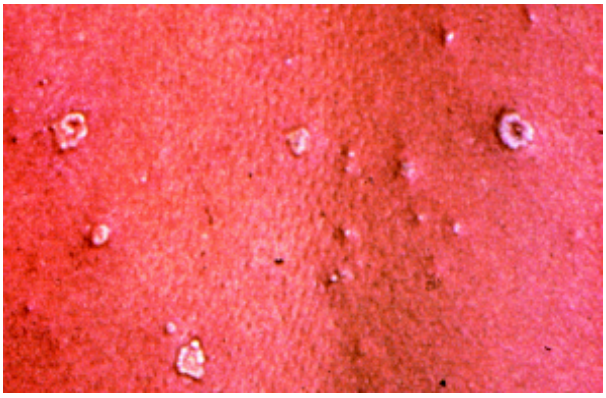

Figure 2. The lesions of chickenpox develop as a series of "crops" over several days and are very superficial. Papules, vesicles, pustules, and scabs can be seen adjacent to each other. The trunk is usually more affected than the face or extremities.

some patients exhibit bleeding into the skin and intestinal tract. Such cases are difficult to diagnose, but they are exceedingly infectious.

Smallpox spreads most readily during the cool, dry winter months but can be transmitted in any climate and in any part of the world. The only weapons against the disease are vaccination and patient isolation. Vaccination before exposure or within 2 to 3 days after exposure affords almost complete protection against disease. Vaccination as late as 4 to 5 days after exposure may protect against death. Because smallpox can only be transmitted from the time of the earliest appearance of rash, early detection of cases and prompt vaccination of all contacts is critical.

Smallpox Vaccination

Smallpox vaccination is associated with some risk for adverse reactions; the two most serious are postvaccinal encephalitis and progressive vaccinia. Postvaccinal encephalitis occurs at a rate of 3 per million primary vaccinees; 40% of the cases are fatal, and some patients are left with permanent neurologic damage. Progressive vaccinia occurs among those who are immunosuppressed because of a congenital defect, malignancy, radiation therapy, or AIDS. The vaccinia virus simply continues to grow, and unless these patients are treated with vaccinia immune globulin, they may not recover. Pustular material from the vaccination site may also be transferred to other parts of the body, sometimes with serious results.

Routine vaccination is only recommended for laboratory staff who may be exposed to one of the orthopoxviruses. There are two reasons for this. First is the risk for complications. Second, U.S. national vaccine stocks are sufficient to immunize only 6 to 7 million persons. This amount is only marginally sufficient for emergency needs. Plans are now being made to expand this reserve. However, at least 36 months are required before large quantities can be produced.

The potential of smallpox as a biological weapon is most dramatically illustrated by two European smallpox outbreaks in the 1970s. The first occurred in Meschede, Germany, in 1970 (1). This outbreak illustrates that smallpox virus in an aerosol suspension can spread widely and infect at very low doses.

Another outbreak occurred in Yugoslavia in February 1972 (1). Despite routine vaccination in Yugoslavia, the first case in the 1972 outbreak resulted in 11 others; those 11, on average, each infected 13 more. Other outbreaks in Europe from 1958 on showed that such explosive spread was not unusual during the seasonal period of high transmission, i.e., December through April. One can only speculate on the probable rapidity of spread of the smallpox virus in a population where no one younger than 25 years of age has ever been vaccinated and older persons have little remaining residual immunity.

Where might the virus come from? At one time, it was believed that the smallpox virus was restricted to only two high-security laboratories, one at the Centers for Disease Control and Prevention in Atlanta, Georgia, and one at the Russian State Centre for Research on Virology and Biotechnology, Koltsovo, Novosibirsk Region. By resolution of the 1996 World Health Assembly (WHA), those stocks were slated to be destroyed at the end of June 1999. The desirability of such an action was reaffirmed by a World Health Organization Expert Committee in January 1999. On May 22, 1999, WHA, however, passed a resolution postponing destruction until 2002, by which time any promise of the variola virus stocks for public health research could be determined. Destruction of the virus would be at least one step to limit the risk for the reemergence of smallpox. However, despite widespread acceptance of the 1972 Bioweapons Convention Treaty, which called for all countries to destroy their stocks of bioweapons and to cease all research on offensive weapons, other laboratories in Russia and perhaps in other countries maintain the virus. Iraq and the Soviet Union were signatories to the convention, as was the United States. However, as reported by the former deputy director of the Russian Bioweapons Program, officials of the former Soviet Union took notice of the world's decision in 1980 to cease smallpox vaccination, and in the atmosphere of the cold war, they embarked on an ambitious plan to produce smallpox virus in large quantities and use it as a weapon. At least two other laboratories in the former Soviet Union are now reported to maintain smallpox virus, and one may have the capacity to produce the virus in tons at least monthly. Moreover, Russian biologists, like physicists and chemists,

may have left Russia to sell their services to rogue governments.

Smallpox is rated among the most dangerous of all potential biological weapons, with far-reaching ramifications.

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Smallpox: An Attack Scenario

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Smallpox virus, which is among the most dangerous organisms that might be used by bioterrorists, is not widely available. The international black market trade in weapons of mass destruction is probably the only means of acquiring the virus. Thus, only a terrorist supported by the resources of a rogue state would be able to procure and deploy smallpox. An attack using the virus would involve relatively sophisticated strategies and would deliberately seek to sow public panic, disrupt and discredit official institutions, and shake public confidence in government.

The following scenario is intended to provoke thought and dialogue that might illuminate the uncertainties and challenges of bioterrorism and stimulate review of institutional capacities for rapid communication and coordinated action in the wake of an attack.

Capacity To Detect a Bioterrorist Attack and To Diagnose an Unusual Disease

April 1

The vice-president visits Northeast, a city of 2.5 million. His itinerary includes an awards ceremony, an appearance at a local magnet school, and a major speech at the local university. A crowd of 1,000 people, including students, is gathered in the university auditorium. Hundreds more wait outside, where the vice-president stops to shake hands and respond to queries from the media.

The Federal Bureau of Investigation (FBI) has information suggesting a possible threat against the vice-president from a terrorist group with suspected links to a rogue state. The group is known to have made inquiries about acquiring biological pathogens, including smallpox, and is suspected of having procured aerosolization equipment. FBI decides its information is too vague and too sensitive to pass on to the Department of Health and Human Services, local law enforcement authorities, or the state health department.

April 8

FBI informants report rumors that something happened while the vice-president was in Northeast.

April 12

A 20-year-old university student goes to the university hospital emergency room with fever and severe muscle aches. She is pale, has a temperature of 103°F, and is slightly leukopenic, but the physical exam and laboratory results are otherwise normal. She is presumed to have a viral infection and is sent home with instructions to drink fluids and take aspirin or ibuprofen for muscle aches. Later that day, a 40-year-old electrician arrives at the emergency room with severe lower backache, headache, shaking chills, and vomiting. He appears pale and has a temperature of 102°F and a pale erythematous rash on the face. The patient is a native of Puerto Rico, where he visited 10 days earlier. A diagnosis of dengue fever is considered, and the patient is discharged with ibuprofen and instructions to drink fluids.

April 13

Over the course of the day, four young adults in their twenties come to the university hospital emergency room with influenzalike symptoms and are sent home.

April 14

The female student returns to the emergency room after collapsing in class. She now has a red, vesicular rash on the face and arms and appears acutely ill. Her temperature is 102°F; her blood pressure is normal. She is admitted to an isolation room with presumptive diagnosis of

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adult chickenpox. She has had no contact with others known to have chickenpox.

April 15

The electrician first seen on April 12 returns to the emergency room by ambulance. He too has a vesicular rash and appears very ill. He is also admitted to an isolation room with presumptive diagnosis of chickenpox.

That evening at 6 p.m. the infectious disease consultant and the hospital epidemiologist meet on the elevator. The infectious disease specialist has just finished examining the student and the electrician, both of whom have vesicular rash on the face, arms, hands, and feet. The skin lesions are evolving in phase. The possibility of smallpox is raised. The infectious disease specialist takes a swab specimen from the electrician's skin lesions, sends it to the laboratory, and requests that it be examined by electron microscopy by an experienced technician. The doctor assures the technician that he will be vaccinated if the specimen shows smallpox. At 7:00 p.m., electron microscopy shows an orthopoxvirus consistent with variola—the smallpox virus.

At 7:15 p.m. the hospital epidemiologist declares a contagious disease emergency. The two patients are moved to negative-pressure rooms with HEPA filters. Visitors and hospital staff not already caring for and in contact with patients are forbidden to enter the floor. Infection-control nurses begin interviewing staff to determine who has been in face-to-face contact with the patients during initial emergency room visits and admission. The hospital epidemiologist calls the chair of the department of medicine and the hospital vice-president for medical affairs.

Within 45 minutes the chair of the department of medicine and the president of the hospital are meeting with the infectious disease physician, the hospital epidemiologist, the hospital vice-president for public relations, and the hospital's general counsel. The city and state health commissioners join the meeting by phone. The need to vaccinate and isolate all contacts of the patients is recognized and discussed. It is decided to secure the hospital. No one is allowed to leave until all persons are identified so that they can be vaccinated as soon as vaccine can be obtained from the Centers for Disease Control and Prevention (CDC). The possibility of identifying and vaccinating other patient contacts (e.g., family members not now in the hospital) is discussed, but no decisions are made because the hospital's legal authority for doing this is unclear.

Half an hour later, the state health commissioner calls FBI. He also contacts CDC to request that smallpox vaccine be released for hospital staff and patient contacts. Because vaccine supplies are limited, CDC requests that the diagnosis of smallpox first be confirmed at CDC. CDC calls FBI and arranges to fly a three-person Epidemic Intelligence Service team to Northeast for assistance.

By 9:30 p.m., an FBI special agent arrives at the hospital, secures biological samples taken from the patients, and drives them to Andrews Air Force Base, where a military aircraft flies the samples to CDC's Biosafety Level 4 laboratory in Atlanta, Georgia. FBI requests that city police be called to help maintain order and ensure that no patients, staff, or visitors leave the hospital until all occupants have been identified and their addresses have been recorded. More FBI agents and city police arrive on the hospital grounds.

Hospital visitors are confused and angered by police refusal to allow anyone to leave the hospital. No explanation is given for the containment to staff, visitors, or the police. Ambulances are rerouted to other hospitals. The rumor that smallpox has broken out rapidly spreads through the building, as do rumors that a terrorist wanted by FBI is in the building. A fight erupts between people trying to leave the facility and the police. Three people are injured and sent to the emergency room. More police and FBI agents arrive and surround the building.

The local television networks report the scene outside the hospital on the late night news. The hospital public relations representative explains that the lock-in is temporary and intended only to gather names and addresses so that people can be contacted and treated if a suspected, but unnamed, contagious disease is confirmed. CNN arrives and demands access to the hospital and affected patients. Rumors about what the contagious disease might be include Hong Kong flu, meningitis, Ebola virus, smallpox, and measles.

The mayor and state attorney general's office are contacted by the health commissioner. There is a phone discussion with the hospital's general counsel and epidemiologist about the right to impose quarantine. Visitors, nonessential personnel, and new patients are blocked from

entering the hospital, but visitors already in the building are allowed to leave after their names and addresses are recorded.

FBI, however, is reluctant to allow anyone to leave the building. This provokes a lengthy exchange among the FBI agent-in-charge, the city police chief, and hospital administrators and attorneys. The dispute is resolved after a series of phone calls between FBI headquarters and the state attorney general's office.

Early Response

11:30 p.m.

The specimen arrives at CDC. At midnight, the diagnosis of smallpox is confirmed. A phone conference with hospital staff, the city police chief, the state health commissioner, the state attorney general, the governor, CDC, FBI, an assistant secretary of the Health and Human Service (HHS), and staff from the National Security Council and the White House (32 people in all) focuses on whether and how to release the information to the media. The mayor and the governor will go on television in the morning with the health commissioner. The FBI director will also make a statement. The president will address the country at noon.

CDC makes arrangements to release smallpox vaccine early the next morning for use by patient contacts and the health-care teams caring for hospitalized victims.

April 16

Morning conference calls between CDC, FBI, HHS, the National Security Council, and state health authorities are set up. Federal officials now assume that a bioterrorist attack has occurred in Northeast. There is concern that other attacks might also have taken place but not yet come to light or that further attacks might be imminent.

A representative from the counterterrorism office of the National Security Council asks if it is necessary or desirable to attempt a complete quarantine of Northeast, including closure of the city airport and a ban on rail traffic leaving from or stopping in the city. The group agrees that such a step is neither feasible nor warranted. A heated debate follows about the advisability of vaccinating all hospital staff and visitors at all facilities where a single case of smallpox is clinically suspected. The state health commissioner presses for enough vaccine for the entire city of Northeast.

FBI and CDC are reluctant to begin mass vaccination until the dimensions of the outbreak are better understood. It is decided to vaccinate all hospital staff and any visitors to the floor where the patients were located. All direct contacts of the patients will also be vaccinated. By the end of the long phone conference, the decision is made to vaccinate all health-care personnel, first responders, police, and firefighters in any city with confirmed cases of smallpox.

CDC Epidemic Intelligence Service officers arrive in Northeast to assist the state epidemiologist, who is establishing a statewide surveillance and case investigation system. Efforts begin to develop a registry of all face-to-face contacts of smallpox patients and to monitor, daily, all contacts for fever. Anyone who has fever >101°F is to be isolated, at home if possible, and be followed for rash.

The state health department activates a prearranged phone tree to query all hospitals and walk-in clinics in the state about similar cases and counsels immediate isolation of all suspected patients.

An additional eight admissions for fever and vesicular rash are discovered. All patients are extremely ill; two are delirious. The university hospital emergency room records are searched, and staff attempt to contact all patients who had fever during the previous week. Three more probable smallpox cases are discovered. Telephone follow-up reveals that one has been admitted to another hospital out of state.

CDC and state health officials discuss possible strategies for managing the epidemic if there is insufficient vaccine for all patient contacts, as seems likely. Home isolation of nonvaccinated patient contacts is considered, but the legal authorities, practical logistics, and ethical implications of such a strategy remain unclear and unresolved.

After discussion among state health authorities and university hospital staff, it is decided that the university will serve as the city's smallpox hospital and will accept transfers of smallpox patients now hospitalized at other facilities in the state. Other hospitals will refer patients to the university hospital or to the state armory but will not admit patients with suspected smallpox. Physicians will be urged to avoid seeking admission for most smallpox

patients and to care for patients in their homes.

Arrangements are made by the state health commissioner to activate a state disaster plan, which establishes the armory as an emergency hospital for the quarantine of smallpox patients, in case the number of smallpox patients exceeds hospital isolation capabilities.

Quarantine and Vaccination

During the morning interagency phone conference, Department of Justice representatives raise questions about potential legal liabilities associated with adverse vaccine effects. The questions remain unresolved, but vaccination will proceed.

On the evening of April 16, the president goes on television to inform the nation of the bioterrorist attack by unknown terrorists, vows that the assailants will be identified and brought to justice, and urges calm and cooperation with health authorities.

The initial epidemiologic evidence and FBI information suggest that the smallpox release likely occurred during the vice-president's January speech at the university in Northeast. Efforts are begun to identify and vaccinate everyone who attended the speech. Additional health department personnel are detailed to help in the epidemiologic investigation. Media reports say that the government does not know how many people are sick or how widespread the outbreak might be.

By evening, 35 more cases are identified in eight emergency rooms and clinics around the city; 10 cases are reported in an adjoining state. CDC alerts all state health departments to be on alert for possible smallpox; CDC also urges prompt and strict isolation measures and instructs states to send specimens from suspected patients to its headquarters in Atlanta for definitive laboratory diagnosis.

April 17

In Northeast, 10,000 residents are vaccinated by the city and state health departments with assistance from volunteer physicians and nurses. Vaccination of the entire university student body, faculty, and staff is discussed and rejected by federal officials for fear that vaccine supplies will be needed for contacts of confirmed cases. State health officials continue to press for a statewide vaccination effort. Unions representing nurses and other health-care workers call for vaccination of all employees whose jobs involve direct patient contact.

April 18

An additional 20,000 residents of Northeast are vaccinated.

April 19

CDC and the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) determine that the infecting strain of smallpox was not bioengineered. The genomic sequence is entirely typical of known smallpox strains.

The student with the first diagnosed case dies. Ten more smallpox cases have been identified, bringing the number of confirmed cases to 50. The patients are located in four states, all in the mid-Atlantic area. Suspected cases are identified in five other states.

April 20

Governors of affected and unaffected states press, both behind the scenes and publicly, for emergency vaccine stocks to be distributed to states so that immediate action can be taken should an outbreak occur.

At the close of day 4 of the vaccination campaign, 80,000 have been vaccinated.

April 22-27

No new cases of smallpox with onset after April 19 have been confirmed, although many suspected cases with fever and rash due to other causes are being seen. In the states reporting confirmed smallpox cases, thousands of people are seeking medical care because of worrisome symptoms. CDC and state health authorities decide to issue a recommendation that patients with fever who cannot be definitively diagnosed be strictly quarantined and observed until the fever subsides. CDC and state health departments are flooded with calls from health-care providers seeking guidance on isolation procedures.

Some hospitals and health maintenance organizations (HMOs) complain to HHS that they cannot afford to isolate the many patients with fever and rash at their facilities and demand that the government pay quarantine costs. State health departments are similarly worried about the costs of quarantine.

Local media report an outbreak of sick children with rash in an area elementary school.

It is unclear whether the illness is chickenpox or smallpox. Television stations show film of parents arriving at school in midday to remove children from classrooms. A college basketball star is rushed to hospital by ambulance with an unknown illness. Local television reports that the athlete has high fever but no rash. Both stories are covered on the national evening news.

April 28

Smallpox is diagnosed in two young children in Megalopolis, a large city in another state. FBI and the National Security Council worry that these cases might signal another attack since the children have had no discernible contact with a smallpox patient or contacts. The possibility that there has been a new attack is weighed against the possibility that the children were infected by a contact of one of the first wave of patients who was missed in the epidemiologic investigation.

Members of the state congressional delegation demand that the federal government implement a massive citywide vaccination program. CDC notes that a Megalopolis-wide vaccination program would deplete the entire civilian vaccine supply.

The media report that the president, vice-president, cabinet representatives, and prominent members of Congress have been vaccinated, and the military has already begun to vaccinate the troops in affected states and Washington, D.C.

The Epidemic Expands

April 29

Over the course of the day, CDC receives reports of an additional 100 new cases of potential smallpox. Sixty of these are in the original state. The others are scattered over eight states. It is not immediately clear if these are truly smallpox or mistaken diagnoses. By evening, laboratory confirmation of smallpox is obtained at CDC. Two cases in Montreal and one in London are also reported. CDC and health agencies now recognize that they are seeing a second generation of smallpox cases. It is presumed that the latest victims were infected by contact with those who attended the vice-president's speech, but a second bioterrorism attack cannot be immediately ruled out. CDC enlists additional epidemiologists from around the country to join teams tracking patients and their contacts.

Another 200 probable cases are reported during the day. CDC receives thousands of requests for vaccine from individual physicians and announces that vaccine will be distributed only through state health departments. Governors of a dozen states are calling the White House, demanding vaccine. One state attorney general announces a suit against the federal government to force release of vaccine for a large-scale vaccination campaign.

The federal government announces that 90% of available vaccine stocks will be distributed to affected states, but cautions that the available quantity of vaccine can cover only 15% of those states' populations. Governors are to determine their own state-specific priorities and mechanisms of vaccine distribution. Federal officials also announce an accelerated crash vaccine-production program that will reduce vaccine-manufacturing time to 24 months.

April 30

A well-known college athlete dies of hemorrhagic smallpox. The rumor is reported that he was the victim of a new biological attack using a different organism since he did not develop the rash associated with classic smallpox. Television commentators misinterpret technical statements from a health-care expert; the commentators report that the athlete died of hemorrhagic fever, and they read clinical descriptions of Ebola virus infection on the air.

The White House and CDC receive dozens of calls from furious governors, mayors, and health commissioners, demanding to know why they were not informed of additional bioterrorist attacks using Ebola. Nurses, doctors, and hospital-support personnel in health centers walk off the job. Thousands of people who attended college basketball games where the deceased athlete played call the health department and ask for treatment.

HHS issues a press release explaining that the athlete did not have Ebola virus. FBI affirms that there is no reason to believe that an attack using any hemorrhagic fever virus has occurred, but FBI refuses to rule out the possibility that there has been more than a single bioterrorist attack using smallpox.

April 31

The widely publicized death of the college basketball star, plus dramatic footage of young

children covered with pox, drive thousands of people to emergency rooms and doctors' offices with requests for vaccination and evaluation of fever and other symptoms. This escalation in requests for evaluation and care hampers the ability of state health authorities and CDC to confirm the number of actual new cases.

May 1

The number of smallpox cases continues to grow. There are now >700 reported cases worldwide. In Northeast, the capacity of local hospitals to accommodate patients needing isolation has long been exceeded. Smallpox cases and suspected contacts are being isolated in the local armory and convention center, where volunteer physicians and nurses are providing care.

May 5

Epidemiologists are working around the clock to interview patients, trace the chain of infection, place contacts under surveillance, and isolate smallpox victims. The evidence continues to indicate that the vice-president's visit to Northeast was the occasion for the release, but some authorities remain concerned about multiple releases.

May 15-29

The third generation of the epidemic begins. Cases are reported in Northeast, parts of the country far beyond Northeast, and worldwide. The death rate remains 30%. Vaccine supplies are exhausted. Public concern is mounting rapidly. The president has declared states with the largest numbers of victims and people in quarantine to be disaster areas. Congress votes to release federal funds to pay for costs of quarantine. Over the next 2 weeks, 7,000 cases will have been reported.

May 30

The fourth generation of cases begins. By mid-June, 15,000 cases of smallpox will be reported in the United States. Twenty states report cases, as do four foreign countries. More than 2,000 will have died. The deceased include two members of the vice-president's staff and a secret service agent.

The city of Northeast, which is hardest hit by the epidemic, has experienced several outbreaks of civil unrest. The National Guard has been called in to help police keep order and to guard the facilities where smallpox cases and contacts are isolated. The mayor of Northeast is hospitalized with a heart attack.

Conclusions

The rate of development of new smallpox cases reported worldwide now appears to be stabilizing and perhaps subsiding. Vaccination of contacts has undoubtedly been of benefit. Perhaps more important is the seasonal decrease in the spread of virus as warmer weather returns.

Many business conventions scheduled to convene in Northeast during the early summer are canceled. Tourist trade, a major source of state income, is at a standstill. Many small businesses in the city have failed because suppliers and customers are reluctant to visit the area. Attendance at theaters and sports events is down markedly. In several states, public schools are dismissed 1 month early, in part because parents, fearful of contagion, are keeping their children home, and partly because teachers are refusing to come to work. Across the country, people refuse to serve on juries or attend public meetings for fear of contracting smallpox. In hospitals and HMOs where staff have not been vaccinated, health-care personnel have staged protests, and some have walked off the job.

The exponential increase in cases around the globe has caused some governments to institute strict, harshly enforced isolation and quarantine procedures. Human rights organizations report numerous cases of smallpox patients being abandoned to die or of recovering patients being denied housing and food.

Domestic and international travel is greatly reduced. Travelers avoid countries known to have smallpox. Some countries refuse to admit U.S. citizens without proof of recent smallpox vaccination. Others have imposed 14-day quarantines on all persons entering the country from abroad. A lucrative black market in falsified vaccination certificates has sprung up.

Congress has begun oversight investigations into the epidemic. A congressman accuses the U.S. Food and Drug Administration of deliberately obstructing the development of smallpox vaccine and vows to hold hearings into the matter. Congressional investigations of what FBI knew, when they knew it, and whom they talked with, are ongoing. Multiple lawsuits have

been filed on behalf of and against HMOs, hospitals, and state and federal governments. Several large HMOs refuse to pay states for costs associated with caring for patients in isolation wards and quarantine facilities. The states with largest numbers of cases have spent millions of dollars on the epidemic, including establishing quarantine operations, paying for added public health personnel, and overtime pay for police.

In the United States, periodic rumors of miracle treatments, many fueled by the media, provoke ardent demands on a beleaguered health-care system. Since vaccine supplies were depleted, many people seeking protection have turned to ancient techniques. Some physicians are practicing arm-to-arm transfer of vaccinia, with a few attempting immunization with inoculation of smallpox virus from pustules.

Smallpox continues to spread in many parts of the world, echoing its formerly endemic character. Without vaccine, the only control method is isolation, which hinders, but cannot halt, the spread of the disease. By year's end, endemic smallpox is reestablished in 14 countries. The World Health Assembly schedules a debate on reenacting a global smallpox eradication campaign.

Dr. O'Toole is a senior fellow at the Johns Hopkins University Center for Civilian Biodefense Studies. The Center, sponsored by the Hopkins Schools of Public Health and Medicine, is dedicated to informing policy decisions and promoting practices that would help prevent the use of biological weapons.

Aftermath of a Hypothetical Smallpox Disaster

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The second day of the symposium featured a discussion of a scenario in which a medium-sized American city is attacked with smallpox. Four panels represented various time milestones after the attack, from a few weeks to several months. Panelists discussed what they and their colleagues might be doing at each of these milestones. The goal of the responses was to communicate the complexity of the issues and to explore the diverse problems that might arise beyond the care and treatment of patients.

The scenario itself was a step-by-step account of a smallpox epidemic in the fictional city of Northeast. Tara O'Toole, the scenario's lead author, read the narrative account before each panel.

The panelists responded to the events as if the epidemic were real and they were actually trying to identify, contain, communicate, and otherwise deal with it. Panel members included experts on hospital, city, state, federal, and media responses. Representing the hospitals were John Bartlett and Trish Perl, Johns Hopkins Hospital; Julie Gerberding, Hospital Infections Program, Centers for Disease Control and Prevention; and Gregory Moran, Emergency Medicine, University of California at Los Angeles. Jerome Hauer represented New York City's response. Representing the state were Michael Ascher, California Department of Health Services Laboratory; Arne Carlson, former governor of Minnesota; Terry O'Brien, a Minnesota State Assistant Attorney General; and Michael Osterholm, Minnesota Department of Public Health. The federal representatives on the panels were Robert Blitzer, former counterterrorism chief with the Federal Bureau of Investigation; Robert DeMartino, Substance Abuse and Mental Health Services Administration; Robert Knouss, Office of Emergency Preparedness, Department of Health and Human Services; and Scott Lillibridge, Centers for Disease Control and Prevention. Joanne Rodgers, Johns Hopkins Medical Institutions Public Affairs, spoke to the response of the media. George Strait, the medical news director for ABC News, acted as moderator for each of the panels scheduled on day two. D.A. Henderson also helped to moderate.

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Identifying the Agent

At the start of the epidemic, 2 weeks after the bioterrorist attack, confusion reigns. There is uncertainty as to what the infection is and reluctance to diagnose smallpox even when it is suspected. It is unclear who is in charge of investigating and containing the epidemic. Outside, reporters are knocking on the hospital doors. The question of what took so long to identify the agent opens the panel. Smallpox, a nonspecific flulike illness, is hard to diagnose, replies an emergency medicine physician. The disease is not suspected because it was eradicated in the late 1970s. Any laboratory work on the first cases would initially be testing for a battery of other causes, such as other viral infections (e.g., monkeypox) or reactions to recent vaccinations. A window of 2 weeks before positive identification of smallpox may even be optimistic. The diagnosis would probably take much longer because of physicians' lack of familiarity with the disease.

When all the tests for other infections turn up negative and smallpox is strongly suspected, suggests a state laboratory chief, a conclusive result from the laboratories at the Centers for Disease Control and Prevention (CDC) or the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) would still be needed. These are the only two places in the United States equipped to identify smallpox virus in tissue samples. This part of the diagnosis is fairly straightforward but it would take at

least 1 day before the definitive results could be obtained.

Responding at the Hospital Level

Hospitals would probably isolate the early cases presumptively, even if smallpox was not suspected, since the symptoms would appear infectious. This is the opinion of a hospital infections expert. In the city, argues a state health department professional, several hospitals would each see one or two of the first few cases. The city health department would quickly become aware of the similarity of the cases in the various hospitals, recognize a potential outbreak (probably measles) and mobilize early to contain it.

Once smallpox is identified, the following organizations within city government would be notified: the police department, the local emergency management office, the city health commissioner's office, and, ultimately, the mayor's office. This process may be difficult since it requires integrating the health department into emergency management plans, an event with little precedent, notes a city emergency official.

Coordinating Response Efforts

Who is in charge, agree panelists, is one of the most important questions yearly in the epidemic, because any large-scale relief effort would require good management. Complicating the answer, however, are various levels of government, each with its own responsibilities and perspective on response, as reflected in panelists' remarks.

Acts of domestic terrorism are under the jurisdiction of the federal government, so several federal agencies become involved, starting with FBI. FBI is involved from the very beginning since any cases of smallpox would indicate a deliberate terrorist attack. A criminal investigation begins immediately. CDC is involved as soon as samples are sent for laboratory diagnosis.

The state government becomes involved at the outset, since major threats to public health are dealt with on the state level. The state health department starts its own investigation, and to reassure the public, the governor may act as a spokesperson for the management of the epidemic.

The city is involved from the outset, explains the city emergency management official, understanding that "bioterrorism is a local issue," which escalates very rapidly to state and federal levels. The local police and emergency management teams, as well as the city health commissioner, the city health department, and the mayor, are involved.

The problems of the city become state problems immediately, counters the former governor, because the news media treat any potential infectious disease outbreak as a regional problem. This forces the governor's hand. The governor has to move in because there is a need for one person to be in charge.

The most difficult situation is how to deal with the hospital patients. One danger in the early days is losing control of the crisis through panic. Once rumors about smallpox start to spread, many workers within the hospital walk off the job. Understaffing also leads to increased stress and confusion for patients and providers alike.

Even before federal and state command structures are in place, suggests a hospital infections control expert, hospital epidemiologists would already be addressing infection control issues. She notes that hospital infection control specialists would be on the phone to colleagues in other city hospitals alerting one another. Hospital epidemiologists, adds a state health official, would have a contact list of state, local, and federal public-health authorities who also would be notified.

Another problem in coordination becomes clear to panelists: the difficulty in sharing classified risk information among agencies and various levels of government. Any early warning, which could have contributed to a more effective response, was missing in the scenario. Even though the FBI had some early intelligence of the attack, the alerting of health care workers was nonexistent. The problem lies in the fact, assesses a state health department official, that health departments have never been seen as intelligence communities, nor has there ever been a precedent for passing such information to them.

On the federal level, CDC addresses the public health issues of the epidemic, and FBI addresses the law enforcement issues. These aims are not necessarily exclusive of one another, and the possibility of linking efforts is raised. Everyone interviewed as a part of the epidemiologic investigation may have to be interviewed as part of the criminal investigation as well. Perhaps the most effective way to accomplish this is to conduct both interviews simultaneously.

Some aspects of the two federal agencies may overlap, perhaps even conflict, in agendas. Specimens that are sent to CDC for positive identification of the smallpox virus may be needed by FBI as evidence for any eventual prosecution. In many ways, it may appear as if FBI is running the investigation. However, dealing with the sick, obtaining vaccine, and mobilizing the epidemiologic investigation at the local, state, and federal levels are outside the scope of FBI. CDC takes the lead on these public health issues, and together with FBI, coordinates the management of federal resources.

However, who is coordinating activities at the hospitals is still unclear, and the question of authority on that level is unresolved. Can outsiders come into a hospital and wield power, and if so, who are they? Federal responders may have ambiguous authority within a hospital and may add to the chaos. An FBI offical notes that his agency's role in the hospitals will simply be to inform the doctors and administrators of what the hospital needs to do to assist in the criminal investigation—keeping evidence and coordinating interviews with patients. However, this may still leave gaps of authority within the hospital.

In the scenario under consideration, the state identifies one hospital as the smallpox hospital, and this also presents a problem of coordination. The hospital itself has to work out the details of local quarantine and the distribution of medicine to the patients, and there is a need to protect the health-care workers and other hospital staff. Vaccine should be immediately available to these workers, and its distribution will have to be coordinated with CDC.

Outside the hospitals, an epidemiologic investigation will be taking place that will need to be coordinated with CDC. A CDC official points out the need for surveillance in the early days of the epidemic. To assist in collecting data necessary to identify the release source and people at risk, he recommends that CDC provide additional staff for much of the epidemiologic work, including mid- and senior-level investigators. Bringing in these outside experts should not represent a problem for local officials, he suggests, since CDC already has strong ties with state epidemiologists.

Informing the Public

How to control the message going to the public weighs heavily upon the minds of all panelists. Reporters on the hospital scene will quickly become aware of any rumors and will demand answers of any worker or official who is handy. Official channels will not be the only source of information during the epidemic, argues the public affairs specialist.

First responders, such as the police or fire officials, might show up with full biohazard protection; such an image immediately raises questions. The media will digest information from day one, whether or not there is an official statement from the city, state, or federal level.

Controlling the message that goes out over the airwaves could be extremely difficult, especially since there may not even be any consensus on what the message should be in the first place. Several panelists point out the need to ensure that information presented to the media is consistent and credible. The city emergency manager suggests that the mayor will work with federal and state officials to get consistent and credible information out to the public. One viable alternative to speculation and misinformation, proposes an FBI official, is to have a centralized joint information center, such as the one his agency set up in Oklahoma City after the bombing, with several experts answering all the questions that arise.

Regardless of how information is disseminated, the message must be carefully considered. If the flulike symptoms of smallpox are identified on the evening news, a flood of noninfected persons with stuffy noses or headaches could swell emergency rooms across the state. Other reports, such as upcoming quarantine efforts, may also spread panic and should be handled carefully. The types of stories the media choose to write present a challenge. The press will not only cover the crisis but the managers of the crisis. Plans for responding to questions about crisis management must be in place. Whether or not the message that goes out to the public includes mention of terrorism should be weighed.

The hospital infections expert pursues a different angle to the issue of information exchange. The difficulties in interviewing the public have not been solved, she points out. Who will do the interviews? How they will be coordinated with criminal investigations? Who will receive vaccine? And how will health-care workers be protected? Will the system be overwhelmed by false cases—people who think they have smallpox? Moreover, a basic problem

in the early days of the epidemic is the need for an infrastructure to handle the large volume of calls flooding the hospitals.

Handling Logistics

What will be the plan of action? Hundreds of people will have to be mobilized to interview the public, and hundreds more will be needed to administer vaccine. The distribution of antibiotics and vaccines represents a logistical problem that must be overcome.

As the epidemic grows and spreads to several states, friction between the levels of government grows. Governors are demanding vaccine supplies, fueling a larger debate of how vaccination should be handled. Tens of thousands of people are vaccinated, but many more still need vaccine. Media reports begin to be critical of the government's handling of the crisis.

What still needs to be done? With a growing number of deaths, the rise in the number of patients in quarantine, the loss of critical health-care workers and city emergency workers, within the city things are beginning to get out of focus, notes a city official. Asking how leadership will function inside the hospital, the hospital epidemiologist identifies a need for official responses that are well thought out, strong, and based on hard science.

The vaccine campaign poses significant issues. The limited supply of vaccine must be divided up and distributed according to greatest risk—persons who may have been infected or who care for those infected, argues an official in federal emergency management. Political leaders and essential city workers are other priority groups. A consensus must be reached as to how to proceed with the vaccinations. CDC is best suited to coordinate vaccine efforts, but the public health community must work towards an emergency. The governor, warns the city emergency manager, may step in and call the shots. There is a need for a public health emergency plan. Did the outbreak start from a single source or from multiple sources? This determination would help with vaccine management and allocation, but there is no answer. Moreover, testing facilities at CDC and USAMRIID are overwhelmed at this point in the epidemic.

Hospitals must deal with quarantine. Restrictions are imposed in the first days or weeks of an epidemic. Workers' fear of being sequestered causes them to leave hospitals understaffed. Many people are likely to stay at their posts if they feel they have reliable information and support, argues a mental health provider. Some, however, may leave the front lines to go home to their own families.

Legal Ramifications

According to a 1905 Massachusetts case, cites a state's assistant attorney general, compulsory vaccinations are not a violation of due process and are therefore legal. So the local, state, and federal levels of government have no obstacle to vaccinating those designated at risk.

A more difficult legal question is that of quarantining smallpox patients. Many of the public health codes used to allocate powers to government officials are old and may not be valid or useful. Also, court precedents from HIV cases may have heavily weighted matters in favor of due process. Minnesota, for example, requires a separate court hearing for each case of quarantine. Thus, quarantine may be possible in a hospital but not in the community.

Another basic legal question is whether the lines of legal support are clear to all officials, such as hospital guards and police officers. How far can police go to detain quarantined patients? The limits of emergency powers should be clearly delineated in any predisaster planning.

The epidemic is threatening to expand beyond the city into the rest of the country and even beyond. The World Health Organization (WHO) will probably become involved, and travel notifications have to be introduced.

Vaccine Supply

Even without adequate supplies of vaccine, much can be done with the existing stocks. Prevaccinating some health-care workers is a proactive approach. Having a sizable pool of prevaccinated professionals who can mobilize and act as emergency responders takes much of the pressure off local hospitals. One way to reduce secondary transmission (outside of vaccinating the contacts of the infected person), instructs the hospital epidemiologist, is good infection control—wearing filter masks and washing hands well. Another way of controlling the epidemic is through quarantine. While these measures are not a substitute for adequate vaccine supply, they can slow the epidemic.

One problem with the vaccine supply is that many more people want to be vaccinated than limited stores permit. There are not even enough stores of vaccine to prevent the spread of the epidemic. The existing 6 to 7 million doses of smallpox vaccine will not last forever, and the 36 months it takes for additional large-scale preparations is prohibitive, argues a vaccine campaign expert. Health officials will likely not have the time or resources to target precisely those people who have an actual need for vaccine. The need for vaccine will overwhelm the supply.

The cost of vaccine development may inhibit stockpiling, proposes a CDC official. Since an attack with smallpox is of low probability, large-scale production may be difficult to justify. A partnership between private industry and the government would help, however. Also, the cost of getting caught without an adequate supply could be disastrous.

Possible emergency measures to stretch the vaccine supply, proposes a smallpox expert, include arm-to-arm vaccination as pustules form on the arms of vaccinated people; vaccinia could be grown in massive amounts in tissue culture; and 30 million doses of vaccine could be contracted from South Africa.

The Final Stage

The smallpox epidemic has become a major public health emergency affecting several cities in many states and at least four other countries. The event is identified as a terrorist attack, because no other source of smallpox outside a deliberate release exists. For those who have already contracted smallpox, antiviral drugs, such as cydolfivir, may be useful but these medicines may be just as scarce as the vaccines.

Secondary transmission got out of hand, vaccine use did not contain the epidemic, and standard planning did not work. Thus a state health official sums up the deficiencies of response. Hospital resources have been overwhelmed, with people flooding emergency rooms in the belief they have smallpox. These cases are added to hospitalized cases before and during the epidemic; yet there are not even enough beds for all the sick. The hospital staff have become physically and emotionally exhausted from the long hours and from seeing about a third of infected patients die.

Failure of containment has turned the outbreak from local to national and international. However, the epidemic would have been much worse, had it gone unchecked, notes a state health official. Containment was significant. The 15,000 smallpox cases could have easily been more than 100,000.

No perpetrators have yet been identified, despite combining the criminal and the epidemiologic investigations. Such methodical work, however, is important because, unless the intelligence community comes up with information or a tip, there is no other way to identify the source of the epidemic, explains an FBI offical.

Many of the problems in the epidemic could have been avoided or controlled if extensive plans had existed, panelists agree. The panelist speaking from a governor's perspective identifies leadership as the most pressing void. Should the city have been placed under immediate quarantine? Should martial law have been implemented? Is the designation of a single smallpox hospital a reasonable thing for any city to do? These are difficult questions to face in the wake of a disaster. Such issues must be addressed long before trouble strikes.

Who Will Pay for the Smallpox Epidemic?

The significant cost of curtailing the epidemic is debated. How will a smallpox hospital be financed, inquires a physician. The money might come from the federal government as emergency management funding, suggests a city emergency manager. The infrastructure and linkages within the public health community could be improved, the capacity for laboratory testing of samples could be increased, surveillance methods could be enhanced, and a health information strategy could be developed.

While the smallpox scenario is certainly frightening, experience with earlier epidemics (smallpox among them), knowledge of the issues, and expertise to deal with them show that in a crisis people from all disciplines pull together.

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Clinical and Epidemiologic Principles of Anthrax

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Background and Epidemiology

Anthrax is one of the great infectious diseases of antiquity. The fifth and sixth plagues in the Bible's book of Exodus (1) may have been outbreaks of anthrax in cattle and humans, respectively. The "Black Bane," a disease that swept through Europe in the 1600s causing large numbers of human and animal deaths, was likely anthrax. In 1876, anthrax became the first disease to fulfill Koch's postulates (i.e., the first disease for which a microbial etiology was firmly established), and 5 years later, in 1881, the first bacterial disease for which immunization was available (2). Large anthrax outbreaks in humans have occurred throughout the modern era—more than 6,000 (mostly cutaneous) cases occurred in Zimbabwe between October 1979 and March 1980 (3), and 25 cutaneous cases occurred in Paraguay in 1987 after the slaughter of a single infected cow (4).

Anthrax, in the minds of most military and counterterrorism planners, represents the single greatest biological warfare threat. A World Health Organization report estimated that 3 days after the release of 50 kg of anthrax spores along a 2-km line upwind of a city of 500,000 population, 125,000 infections would occur, producing 95,000 deaths (5). This number represents far more deaths than predicted in any other scenario of agent release. Moreover, it has been estimated (6) that an aerial spray of anthrax along a 100-km line under ideal meteorologic conditions could produce 50% lethality rates as far as 160 km downwind. Finally, the United States chose to include anthrax in the now-defunct offensive biological weapons program of the 1950s, and the Soviet Union and Iraq also admitted to possessing anthrax weapons. An accident at a Soviet military compound in Sverdlovsk in 1979 resulted in at least 66 deaths due to inhalational anthrax, an inadvertent demonstration of the viability of this weapon. The epidemiology of this inadvertent release was unusual and unexpected. None of the persons affected were children (7). Whether this is due to differences in susceptibility between children and adults or purely to epidemiologic factors (children may not have been outdoors at the time of release) is unclear.

Anthrax is caused by infection with *Bacillus anthracis*, a gram-positive spore-forming rod. The spore form of this organism can survive in the environment for many decades. Certain environmental conditions appear to produce "anthrax zones," areas wherein the soil is heavily contaminated with anthrax spores. Such conditions include soil rich in organic matter (pH <6.0) and dramatic changes in climate, such as abundant rainfall following a prolonged drought. Partly because of its persistence in soil, anthrax is a rather important veterinary disease, especially of domestic herbivores. In addition to encountering anthrax while grazing in areas of high soil contamination, these herbivores may also acquire the disease from the bite of certain flies (8). Vultures may mechanically spread the organism in the environment (9). Anthrax zones in the United States closely parallel the cattle drive trails of the 1800s (10).

Anthrax spores lend themselves well to aerosolization and resist environmental degradation. Moreover, these spores, at 2-6 microns in diameter, are the ideal size for impinging on human lower respiratory mucosa, optimizing the chance for infection. It is the manufacture and delivery of anthrax spores in this particular size

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range (avoiding clumping in larger particles) that presents a substantial challenge to the terrorist attempting to use the agent as a weapon. The milling process imparts a static charge to small anthrax particles, making them more difficult to work with and, perhaps, enabling them to bind to soil particles (11). This, in part, may account for the relatively low secondary aerosolization potential of anthrax, as released spores bind to soil, now clumping in particles substantially in excess of 6 microns. This clumping tendency, together with a high estimated ID_{50} of 8,000-10,000 spores may help explain the rarity of human anthrax in most of the Western world, even in areas of high soil contamination. Other potential bioweapons, such as Q fever and tularemia, have ID_{50} values as low as 1 and 10 organisms, respectively.

The Disease

Most endemic anthrax cases are cutaneous and are contracted by close contact of abraded skin with products derived from infected herbivores, principally cattle, sheep, and goats. Such products might include hides, hair, wool, bone, and meal. Cutaneous anthrax is readily recognizable, presents a limited differential diagnosis, is amenable to therapy with any number of antibiotics, and is rarely fatal. While common in parts of Asia and sub-Saharan Africa, cutaneous anthrax is very rare in the United States; the last case was reported in 1992 (12). Inhalational anthrax, also known as woolsorters' disease, has been an occupational hazard of slaughterhouse and textile workers; immunization of such workers has all but eliminated this hazard in Western nations. As a weapon, however, anthrax would likely be delivered by aerosol and, consequently, be acquired by inhalation. A third type of anthrax, acquired through the gastrointestinal route (e.g., consuming contaminated meat) is exceedingly rare but was initially offered by Soviet scientists as an explanation for the Sverdlovsk outbreak.

Inhalational anthrax begins after exposure to the necessary inoculum, with the uptake of spores by pulmonary macrophages. These macrophages carry the spores to tracheobronchial or mediastinal lymph nodes. Here, *B. anthracis* finds a favorable milieu for growth and is induced to vegetate. The organism begins to produce an antiphagocytic capsule and at least three proteins, which appear to play a major role in virulence. These proteins are known as edema factor (EF), lethal factor (LF), and protective antigen (PA). Following the A-B model of toxicity (13), PA serves as a necessary carrier molecule for EF and LF and permits penetration into cells. Edema toxin results from the combination of EF + PA, lethal toxin results from the combination of LF + PA. These toxins result in necrosis of the lymphatic tissue, which in turn causes the release of large numbers of *B. anthracis.* The organisms gain access to the circulation, and an overwhelming fatal septicemia rapidly ensues. At autopsy, widespread hemorrhage and necrosis involving multiple organs is seen.

Inhalational anthrax generally occurs after an incubation period of 1 to 6 days (14). During the Sverdlovsk outbreak, however, spontaneous cases appeared to arise as late as 43 days after the assumed release date (7). Such late cases are unexplained but have potentially serious implications for postexposure management of victims of aerosol exposure. After the incubation period, a nonspecific flulike illness ensues, characterized by fever, myalgia, headache, a nonproductive cough, and mild chest discomfort. A brief intervening period of improvement sometimes follows 1 to 3 days of these prodromal symptoms, but rapid deterioration follows; this second phase is marked by high fever, dyspnea, stridor, cyanosis, and shock. In many cases, chest wall edema and hemorrhagic meningitis (present in up to 50% of cases [15]) may be seen late in the course of disease. Chest radiographs may show pleural effusions and a widened mediastinum, although true pneumonitis is not typically present. Blood smears in the later stages of illness may contain the characteristic gram-positive spore-forming bacilli. Death is universal in untreated cases and may occur in as many as 95% of treated cases if therapy is begun more than 48 hours after the onset of symptoms.

While early recognition of anthrax is likely to require a heightened degree of suspicion, the diagnosis is supported by gram-positive bacilli in skin biopsy material (in the case of cutaneous disease) or in blood smears. A preponderance of gram-positive bacilli in swabs of the nares or in appropriate environmental samples might support a diagnosis of anthrax where intentional release is suspected. Chest radiographs exhibiting a widened mediastinum in the proper setting of fever and constitutional signs and in the absence of another obvious explanation (such as

blunt trauma, deceleration injury, or postsurgical infection) should also lead to a diagnosis of anthrax. This finding is only likely to occur late in the course of disease. Confirmation is obtained by culturing *B. anthracis* from blood.

Disease Management

While endemic strains of *B. anthracis* are typically sensitive to various antibiotics, including penicillin G, antibiotic-resistant strains do (on rare occasion) occur naturally (16) and can be readily isolated in laboratories. For this reason, as well as the convenience of twice-daily dosing, many experts consider ciprofloxacin (400 mg intravenously (i.v.) q 12 h) the drug of choice for treating victims of terrorism or warfare. Doxycycline (100 mg i.v. q 12 h) is an acceptable alternative, although rare doxycycline-resistant strains of *B. anthracis* are known. Conversely, however, the much lower cost of tetracyclines compared to quinolones may factor into therapeutic decisions, especially where large numbers of patients are involved. These recommendations are based solely on in vitro data and data from animal models (17); no human clinical experience with these regimens exists. In cases of endemic anthrax, or where organisms are known to be susceptible, penicillin G (2 million units i.v. q 2 h or 4 million units i.v. q 4 h) is recommended.

Postexposure prophylaxis against anthrax may be achieved with oral ciprofloxacin (500 mg orally q 12 h) or doxycycline (100 mg orally q 12 h), and all persons exposed to a bioterrorist incident involving anthrax should be administered one of these regimens at the earliest possible opportunity. In cases of threatened or suspected release of anthrax, chemoprophylaxis can be delayed 24 to 48 hours, until the threat is verified. Chemoprophylaxis can be discontinued if the threat is found to be false. Levofloxacin and ofloxacin would be acceptable alternatives to ciprofloxacin. In addition to receiving chemoprophylaxis, exposed persons should be immunized. On the basis of animal data (wherein an appreciable number of unvaccinated primates died when antibiotics were withdrawn after 30 days of therapy) (18), chemoprophylaxis is best continued until the exposed persons has received at least three doses of vaccine (thus, for a minimum of 4 weeks). If vaccine is unavailable, some recommend that chemoprophylaxis be continued for 8 weeks (19). The available vaccine was licensed (for preexposure prophylaxis) by the U.S. Food and Drug Administration in 1970 and is prepared from a formalin-treated culture supernatent of an avirulent *B. anthracis* strain. It is given in a preexposure regimen at 0, 2, and 4 weeks, and at 6, 12, and 18 months. Persons at continuing risk for exposure should receive yearly boosters. Exposed persons should receive at least three doses (at 0, 2, and 4 weeks), assuming no further exposure is likely, before discontinuing chemoprohylaxis.

Recently, a number of hoaxes involving a threatened release of anthrax have been promulgated (19,20), and guidelines have now been published to assist in the management of such threats (19). When evaluating a threatened release of anthrax, the lack of volatility of the disease, as well as its inability to penetrate intact skin, should be taken into account. These factors make it unlikely, in most cases, that persons coming in contact with letters, packages, and other devices purported to contain anthrax will be at risk for aerosol exposure. Moreover, because energy is required to aerosolize anthrax spores, opening a letter, even if it contained anthrax, would be unlikely to place a person at substantial risk. For these reasons, postexposure prophylaxis may not be necessary in many cases of threatened anthrax dissemination.

Anthrax has little potential for person-to-person transmission; standard precautions are thus adequate for health-care workers treating anthrax patients. Anthrax, as well as other bacteriologic and viral weapons, has an incubation period of >24 hours. This characteristic is not shared by conventional, chemical, and nuclear weapons and makes decontamination of infected persons admitted to hospitals days after exposure unnecessary in most cases. However, in certain cases, such as exposure to a threat letter involving an unidentified substance, where anthrax cannot readily be ruled out by Gram stain or other rapid diagnostic procedures, decontamination may be warranted. In such cases, decontamination may be accomplished by removing clothing, sealing it in a plastic bag, and showering with copious amounts of soap and water. Environmental surfaces and personal effects may be treated with 0.5% hypochlorite after the area in which the agent was released is investigated (19).

In summary, even though anthrax may be among the most viable of biological weapons, it is

also a weapon for which a licensed vaccine and good antimicrobial therapy and postexposure prophylaxis exist. Given the relatively short incubation period, and rapid progression of disease, however, identification of the exposed population within 24 to 48 hours and employment of therapeutic and prophylactic strategies are likely to present a challenge. Good intelligence regarding the capabilities of terrorist groups, as well as heightened awareness of the threat on the part of clinicians, first responders, and public health personnel remains a cornerstone of bioterrorism defense.

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Anthrax: A Possible Case History

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Federal Bureau of Investigation (FBI) offices in five U.S. cities have received warnings of an imminent bioterrorist attack. Each threat indicated that a "shower of anthrax would rain on U.S. cities," unless certain demands were met immediately. One of these calls was in Northeast, a large city on the Eastern Seaboard with a metropolitan population of 2 million. The threats were credible, but no information was relayed to city officials in Northeast or elsewhere.

On the evening of November 1, a professional football game is being played in Northeast's outdoor stadium before an audience of 74,000. The evening sky is overcast, the temperature mild, a breeze blows from west to east. During the first quarter of the game, an unmarked truck drives along an elevated highway a mile upwind of the stadium. As it passes the stadium, the truck releases an aerosol of powdered anthrax over 30 seconds, creating an invisible, odorless anthrax cloud more than a third of a mile in breadth. The wind blows the cloud across the stadium parking lots, into and around the stadium, and onward for miles over the neighboring business and residential districts. After the anthrax release, the truck continues driving and is more than 100 miles away from the city by the time the game is finished. The anthrax release is detected by no one.

Approximately 16,000 of the 74,000 fans are infected by the anthrax cloud; another 4,000 in the business and residential districts downwind of the stadium also are infected. After the game, the fans disperse to their homes in the greater Northeast metropolitan area; some return to homes in neighboring states. A few are from other countries. The driver of the truck and his associates leave the country by plane that night. They will be many time zones away by the time the first symptoms of anthrax appear 2 days later.

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Two days after the game, hundreds of people in and around Northeast become ill with fever, cough, and (in some cases) shortness of breath and chest pain. Some of the sick self-administer over-the-counter cold remedies; some seek phone advice from physicians and nurses; others are seen in clinics, doctors' offices, and emergency departments throughout the city.

Influenza cases had been seen in Northeast 2 weeks before the game. Health-care providers seeing the new patients recommend bed rest and fluids for presumed flu. Specimens are sent to confirm influenza. A few of the sickest patients get chest radiographs to exclude pneumonia. Only in retrospect, after the source of illness is clear, will the widened mediastinum seen on a number of chest radiographs be recognized for the signal it carries. A few patients are hospitalized; some have blood cultures drawn. The 400 ill persons in the region are receiving care from so many different sources that the health emergency is not detected.

By November 4, nurses and physicians note the increased volume of serious upper respiratory illness, and some contact the city health department for treatment recommendations and a regional flu update. Blood cultures from the earliest patients grow gram-positive bacilli in seven laboratories around the city. The laboratories identify these as *Bacillus* species. No further identification is requested, and none is pursued.

By the evening of November 4, patients with the earliest symptoms are dying. The illness has been rapidly fatal, killing previously healthy young adults within 24 to 48 hours. Members of the medical community, now alarmed by these unexpected and unexplained deaths, urgently contact the state and city health departments. Health department officials contact the Centers for Disease Control and Prevention (CDC). By midnight November 4, 1,200 people around the city have fallen ill, 80 of whom have died.

Word that previously healthy persons are dying of a rapidly fatal illness spreads quickly among health-care providers in the state, and is

featured on local and national morning news shows. News media interview families of the deceased, physicians, and city health officials. Expert consultants appear on television to discuss potential diagnoses, including the new Spanish flu, Hong Kong bird flu, and many other infectious and noninfectious diseases. A rapid survey of city emergency departments and health clinics finds that persons of all ages and from all sectors of the city continue to come down with similar illness. The numbers have doubled since the previous day, inundating many health-care facilities.

The mayor convenes an emergency meeting of leading medical experts and health officials as reporters gather outside city hall. The assembled experts debate possible causes and responses to the illness. Many express great concern that a virulent strain of influenza or another highly contagious disease may be present. Isolation of all persons with fever, cough, or chest pain; expanded laboratory analyses; and rapid epidemiologic investigation are recommended. Blood and tissue specimens are sent to CDC for urgent analysis. CDC investigators are en route. During a news conference, the mayor describes the city's response to what appears to be a serious influenza outbreak, appeals for public calm, and is surprised by questions about the possibility of bioterrorism.

By noon November 5, intensive-care units and isolation beds across the city are full. Even patients receiving the most advanced medical care are dying. Patients are febrile, hypotensive, and seem to be in septic shock; some have meningitis. Still, there is no diagnosis. At some locations, the shock of rapid and unexplained deaths has created an atmosphere of desperation and confusion among hospital and clinic staff.

The recommended isolation protocols quickly fall apart as hospital and clinic staffs struggle to cope with the surge of patients. Fears of a contagious disease prompt hospital staff to don protective positive-pressure hoods; the news shows physicians working in this gear and explains that there are only two dozen or so such hoods available per hospital.

In the early evening of November 5, a university laboratory makes a preliminary diagnosis of anthrax from the blood culture of a young patient who died. The laboratory immediately notifies city and state health departments, which in turn notify CDC and FBI. The specimen is transferred to the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), where within hours experts report that rapid diagnostic tests support the preliminary diagnosis of anthrax.

The mayor of Northeast consults with officials from the city and state health departments, CDC, FBI, and USAMRIID. The working assumptions are that the disease in Northeast is anthrax and that it is the result of a bioterrorist attack. Widespread exposure to an anthrax aerosol is feared.

The mayor is outraged to learn that the FBI had not informed her of the credible anthrax threat to Northeast. She is also shocked that it has taken more than 80 deaths and hundreds of illnesses before anyone from the medical community came up with the diagnosis. She is informed that an anthrax vaccine exists, but it is unclear whether any will be made available for civilian use in Northeast. No one can yet estimate the probable scale of the epidemic or whether there has been a single or multiple attacks. CDC is seeking news of similar syndromes in other locations around the country. The mayor's medical advisors recommend that quinolone antibiotics be used for initial treatment of the sick. They also advise the same antibiotics for those exposed to anthrax but not yet sick, even though identifying the exposed will take time and requires more information. All that is known is that many (but not all) of the dying had been at the football game on November 1.

The mayor also is told that to prevent death, antibiotics must be given before symptoms occur, or at the latest, in the earliest hours after symptoms begin. Patients with serious symptoms are likely to die, no matter what anyone does. Available information suggests that the local supply of needed antibiotics will soon be exhausted; many local pharmacies were already emptied of antibiotics as the initial news of a lethal epidemic spread through the city. Given this shortage of antibiotics, one senior advisor asks the mayor to consider a triage plan that uses all available antibiotics to protect the exposed who are not yet sick. In this plan, antibiotics would be kept from those already sick and thus likely to die, regardless of treatment. The mayor requests immediate federal assistance in obtaining and distributing large supplies of antibiotics. Antibiotic shipments from other states are also urgently requested.

State officials notify hospitals around the city of the anthrax epidemic and warn them to prepare for a new surge of patients in the wake of the mayor's forthcoming TV address. Recommendations for the care of infected patients are sent to hospitals and clinics around the region.

The late night news is interrupted by the mayor announcing that anthrax had been released in the city. She outlines the recommended medical response and describes assistance Northeast is seeking from state and federal agencies. She urges that the needed antibiotics be taken by all those attending the football game. For those who attended the game and remain well, arrangements are being made to distribute antibiotics at 20 police stations and schools around the city starting immediately. Antibiotics will be distributed in packages sufficient for a 1-week supply. A second phase of distribution will commence with the arrival of new supplies of antibiotics. Eventually all those exposed will need to receive enough antibiotics to take for 60 days.

Persons feeling ill are instructed to report immediately to hospitals for treatment. The mayor reports that an official request for vaccine has been made to the federal government. She underscores that anthrax is not contagious. She again appeals for calm.

Tens of thousands rush to police stations and distribution centers before the antibiotics arrive. Communication between the distribution centers, the mayor's office, and the antibiotic suppliers is haphazard. No city plan exists or had even been considered for mass distribution of antibiotics. Some centers receive almost no antibiotics. At other centers, antibiotic supplies are rapidly exhausted.

At this point, there are effectively no antibiotics left in the city. Approximately 50,000 persons had obtained some quantity before supplies ran out, but there is no record of who has received them. Health-care facilities are unprepared to cope with the continually rising number of patients. By the early hours of November 6, 2,700 persons have become ill with anthrax, 300 of whom have died. Thousands more flood doctors' offices, clinics, and emergency departments, fearing that they are infected with anthrax.

On the morning of November 6, the mayor announces that schools and homeless shelters will be opened to the ill because hospitals can no longer accommodate new patients. The National Guard will keep order. The Office of Emergency Preparedness, Department of Health and Human Services, and the Federal Emergency Management Agency will provide some logistical support. The city has temporarily run out of antibiotics, but supplies from neighboring states are expected. Meanwhile, the media report that some of the dead were not at the football game and in fact were miles away from the stadium that day. Some reporters openly speculate that "antibiotics are being held back by city officials" and that "local authorities are losing control of the epidemic." They also report that false rumors of arriving antibiotic shipments have sparked mobs and violence at antibiotic distribution centers.

At midday November 6, epidemiologists report that some anthrax patients had not attended the game, suggesting that exposure had occurred over a wider area. In addition, computer models show that wind patterns may have blown anthrax spores downwind of the stadium for some miles. The antibiotic recommendations are now being expanded to include all persons living or working within an area defined by 8 miles east and 1 mile north or south of the stadium on November 1. The mayor is told by her advisors that, in fact, no antibiotic arrivals are imminent. Some states report they have no antibiotics to give, some are refusing to send shipments, and the federal government reports that it will be at least another 6 hours before its antibiotic resources arrive. Despite assurances that anthrax is not contagious, people with the ability to do so flee Northeast, causing traffic jams and increasing panic. Some train conductors, bus drivers, and pilots refuse to travel to Northeast, citing personal safety concerns and threatening to walk off the job if forced. As a result, train, bus, and plane traffic to and from Northeast is sharply disrupted. By midnight November 6, anthrax has sickened 3,200 people, 900 of whom have died.

Federal shipments of antibiotics have begun to arrive by November 7. The distribution centers, now increased to 40, continue to be variably stocked with medicine. A heavy National Guard presence is now evident at distribution centers to prevent violence. FBI officials report preliminary evidence that a truck was the source of the dispersal, though no suspects have been arrested and no group has

claimed responsibility. They confirm that threats of an anthrax attack were made in the week before the event. On televised interviews, families of the deceased promise legal action against the FBI for not revealing the threats, and against local and federal government for not supplying sufficient antibiotics and vaccine. Management of dead bodies becomes a growing crisis. Hospital and city mortuaries are full. Many funeral homes have closed. The state health department and CDC report that the deceased must be cremated. Some citizen and religious groups threaten that if cremation is enforced, there may not be full reporting of the dead, and private burial ceremonies would continue. By nightfall, 4,000 persons have fallen ill, 1,600 of whom have died.

By November 8, increasing numbers of the city's critical work force are absent, including police, firefighters, bus and subway operators, building managers, sewage treatment workers, electricity and water officials, and supermarket staff. Some are absent because of illness or death due to anthrax. Some skip work fearing contagious spread despite official statements to the contrary. Some simply fear violence in the city. Many of those with the means to leave the city do so.

National Guardsmen are able to fill some roles, but many tasks require specialized expertise. As a result, the public transit system is barely operational; some of the city's office buildings are shut down; response time for calls made to fire, police, and ambulance lengthens. Schools and universities are closed. State and city officials become increasingly concerned about an imperiled city infrastructure. Looting erupts.

The mayor holds a press conference to address false allegations that anthrax vaccine is being administered to select individuals in the city. She reports that federal authorities will make available some vaccine for those deemed at highest risk. But due to a national shortage of vaccine and military concerns that this attack may herald further attacks, there is only a highly limited amount of vaccine available. For the most part, the city will have to manage with antibiotics alone.

By evening, a total of 4,800 persons have become ill; 2,400 have died.

Aftermath

Of the 20,000 persons originally infected in Northeast, 4,000 died, most in the first 10 days after the attack. Some anthrax cases occurred in other cities, states, and countries where citizens attending that football game had returned home. Occasional cases occur beyond 10 days among persons refusing or discontinuing the long course of antibiotics. In all, approximately 250,000 persons receive antibiotics.

The media report that hundreds, if not thousands, needlessly died because of delays in antibiotic distribution, and further, that lifesaving antibiotics would have cost $100 per person—a price local and federal authorities had not been willing to pay. Military intervention in the form of martial law is avoided, despite calls by some federal authorities for a "modest military presence to keep peace and stability in a region clearly under attack." No group can be identified as the perpetrator, though FBI continues one of the largest investigations in its history. Many refuse to return to their homes downwind of the stadium and demand official compensation. Businesses downwind of the stadium are shut down. The stadium is largely abandoned. Newspapers brand the downwind area "the dead zone." Overall, city commerce suffers tremendous losses. The tourism industry collapses. City officials estimate it will be months or years before the city resumes a normal routine. Fear of anthrax may keep some away from Northeast indefinitely. On December 1, FBI receives a threat that anthrax will be released in five major U.S. cities over the next week.

This scenario is ominous. Such an epidemic would create extraordinary challenges for a modern American city. However, there is no need to give in to the ending of this story. Practical, modest preparedness efforts could make a difference and change the outcome. Many of the most useful efforts may be the result of ingenuity and depend on collaboration of experts from many disciplines.

Could the outcome have changed if state and local health officials had prior notification of the anthrax threats? Should laboratory practices be changed to increase the chance of early detection of anthrax? Should health-care workers become familiar with the early symptoms and signs of anthrax? What could hospitals do to prepare for epidemics of seriously ill patients? Could communities have plans for rapid mass antibiotic acquisition and distribution? Should anthrax vaccine be more widely available? How might health professionals and government officials

interact with the media to best inform the public and avoid misunderstanding and panic? What should the community, hospitals, and professional societies be doing? What should you be doing?

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Applying Lessons Learned from Anthrax Case History To Other Scenarios

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Northeast, the city described in the anthrax scenario (Inglesby, this issue, pp. 556-60) is actually Baltimore, a metropolitan area of 2 million population, with a football stadium that holds 74,000. Route 95 would be where the anthrax dispersion took place.

My test case started on February 13 at 6 a.m. when I went to the emergency room at Johns Hopkins University Hospital and asked to see the physician in charge. I described the typical case and asked what the procedure would be if a patient came down with these symptoms. The physician in charge had actually taken the specialized 8-hour training course on bioterrorism (one of five physicians in Maryland to have completed this course entitled "Train the Trainer"). Nevertheless, she confessed that the typical early case of inhalation anthrax would have a presumed diagnosis of flu, and the patient would probably be sent home. Despite the emphasis on emergency room physicians as the "early response team," the actual diagnosis would be made after hospitalization. Many seriously ill patients arriving at the same time might arouse suspicion, but the initial cases would likely be isolated events or would be dispersed in multiple emergency rooms.

There was a further problem. At the time of my visit, the emergency room was on "blue alert," meaning that all 28 beds were filled; the hospital was also filled. Furthermore, the whole city was on blue alert, probably because of the flu epidemic. Hospitals routinely run on marginal excess capacity. The pressures of managed care have resulted in a health-care system that has minimal elasticity, so on February 13, there were no beds for an anthrax epidemic.

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I then went to radiology; I showed the radiologist a classic case of inhalation anthrax and asked him how he would interpret the X-ray. He said that he would read it as widened mediastinum; the differential diagnosis did not include anthrax.

Then I went to the laboratory and asked the lead technician who has been in the laboratory for 25 years. He said that *Bacillus anthraxis* had never been isolated during his tenure. If it was recovered in blood cultures, it would be called "*Bacillus* species, a probable contaminant." However, more than three cases of *Bacillus* species would prompt a full identification, which would be available in 48 hours. That would trigger a call to the chief of Infectious Disease and to Infection Control. It would take 72 hours to get sensitivity test results—which is important since this information would drive the subsequent decisions regarding antibiotic prophylaxis to those patients or persons who had been exposed. My own response (if given the possibility of a case of inhalation anthrax) would be to call the state health department—the Maryland Department of Health and Mental Hygiene.

I got a recording and left a message that I had a query about bioterrorism, and it was important. The call was returned 3 days later. The state does have a response mechanism that is far along in planning and can be activated with a single phone call. The problem is that I did not know the number. No one else seemed to know the number; it is not in the hospital directory or on 911 listings.

How were we set in Baltimore to deal with antibiotics? What was the supply? At any moment, the city of Baltimore had 69,000 capsules of ciprofloxicin and 99,000 capsules of doxycycline. We could probably use a number of other flouroquinolones, and if the sensitivities proved that penicillin was active, we could use that as well. Access to antibiotics would not be a

major problem in this scenario of anthrax contamination.

Then I reviewed the statewide facilities and planning for a bioterrorist attack. One phone call to the state health department would set into motion a cascade of events that would include an immediate effort by state epidemiologists to review the data and confirm the diagnosis. They would then contact the Maryland Emergency Management Agency, the Federal Bureau of Investigation, Maryland Institute for Emergency Medical Services System, and other appropriate agencies. The Maryland Emergency Medical Agency coordinates relevant state agencies and also acts as spokesperson to the press.

Maryland Institute for Emergency Medical Services System has the capability for flash faxes to emergency rooms throughout the state but does not communicate with infection control programs and other parts of the hospital because somebody in the emergency room can always get that information. My perception is that Maryland does not have a good system to reach its practicing physicians, whose involvement is critical. To give antibiotics to tens or hundreds of thousands of persons in several days, it will be necessary to use more than the health department clinics and personnel. Notification and direction would have to be done through the press and through the medical society, but it is not clear how well this would work. There had been a few examples, however, of how this system would work in other settings. The Maryland Emergency Medical Agency, the system for public communication, is active about two to three times a year, primarily for ice storms and hurricanes. It has not been tested for a major epidemic, but at least it is a system that is established. The capacity for bodies in a morgue would be approximately 100, but there are contracts to get refrigerated trucks that would hold 40 bodies per truck. The system is set up so that Maryland Institute for Emergency Medical Services System can readily identify bed capacity for every hospital in Maryland including the number of available intensive care unit beds to facilitate referrals. No plan is available for stockpiling antibiotics or vaccines. Stockpiling of antibiotics is not necessary because the city could get an adequate supply from regional sites, and the Centers for Disease Control and Prevention has a $50 million budget allocated to this need. The great need is for deploying antibiotics in an expeditious way to thousands, presumably by using regional care sites and the thousands of physicians' offices; 3,000 emergency medical service providers could be available to assist, but the mainstay of care in any large epidemic would come from the private sector.

How does all this work? The good news is that we have a system set up where there is one person or one group that is coordinating the events and one point of contact that initiates the relevant cascade of events necessary for a response. Can this system respond the way it is expected to respond? The system has worked in natural disasters, but it may break down in a large outbreak of inhalation anthrax. For example, during a pfisteria crisis, many groups took the outbreak on as their issue. Representatives of Congress and influential citizens bypassed the governor, the mayor, the Maryland Emergency Management Agency and every other system to contact the White House, CDC, other agencies and various medical experts to deal with it. Many did not like the answers they got, so they bypassed standard channels, and many are unaware of the rules. A system with a single voice for communication with the press and providers is needed. The state has 13,000 beds, but a flu epidemic recently overwhelmed hospital capacity, and this was not even a big year for influenza. A recent large fire in Baltimore demonstrated that the city could not handle 100 casualties.

Finally, there is the issue of medical-care personnel resources to respond. Maryland has 16,000 physicians, 262 members of the Infectious Disease Society, and 400 emergency room physicians; in addition, every hospital has infection control personnel. In the event of a bioterrorist attack, these will be the first responders. They are the front line for patient contact with the health system. They will suspect or establish the diagnosis, develop systems to regulate hospital flow, make therapeutic policy, give treatment, and will provide prophylactic antibiotics and vaccines. Federal, state, and local health agencies play a central role in planning but do not have the facilities or field forces necessary to deal with sick patients and the thousands who need vaccines or antibiotics.

The gap in planning at the federal level has been the failure to include these diverse groups

at the table. We anticipate two responses. Different groups will make territorial claims on the issue; infectious disease physicians will say bioterrorism is what they are trained for, infection control practitioners will claim that epidemics are their special skill, emergency room physicians will claim that they will be the first to see those patients, and microbiologists will claim that they make the diagnosis. All have a role, and all should be included. The second response seems diametrically opposed. We suspect that it will be difficult to engender participation by relevant groups, despite their claims regarding discipline relevance. A bioterrorist attack is a low-probability event for nearly all cities when considered individually. Cleveland, Tulsa, or Sacramento are unlikely targets, just as Oklahoma City was an unlikely target. Medical providers are busy, and most of us have volunteered to the breaking point. It is not surprising that the "Train the Trainers" sessions on bioterrorism in Baltimore were attended by only five emergency room physicians and no representative of hospitals. Thus, enthusiastic participation by the critical players from the private sector is unlikely.

The major mechanism for recruitment is a carrot or a stick. Possibilities include making bioterrorism plans by hospitals a Joint Commission on Accreditation of Organization requirement, requiring this in RRC selected training programs, asking it on American Board of Internal Medicine boards, and incorporating it in medical school curricula. These possibilities would increase visibility of the issue but would not provide the proper regional training needed. The resources that now total $20 million should include an allocation to the private sector to permit training and planning programs that represent a true partnership between public and private sources.

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Addressing Bioterrorist Threats: Where Do We Go from Here?

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In discussing the threat of bioterrorism, planning, coordination, and preparedness are recurrent themes. State and local planning are of particular concern to me, having served as a local health officer and as health commissioner in New York City during the World Trade Center bombing. I have no doubts that the threat of terrorism within our borders is real. And several years later, when the sarin attack occurred in the Tokyo subway system, it was hard not to imagine what such an event would have meant in the New York subway system. A fundamental step toward addressing the threat of bioterrorism is comprehensive planning that focuses first and foremost on local preparedness and response capacity—integrating the role of state, regional, and federal governments, as well as state, regional, and national assets. To plan effectively, we have to think through the different types of scenarios that may confront us, including the announced release of a biological agent, the silent release of a biological agent, or some kind of hybrid event, such as having a bomb go off, that is followed by the release of a biological or chemical agent. In addition, we have to think about the scenarios where person-to-person transmission can occur or those with noncommunicable infectious diseases. Bioterrorism covers a very broad spectrum of concerns, from catastrophic terrorism with mass casualties, to microevents using low technology but producing civil unrest, disruption, disease, disabilities, and death. All these scenarios must be considered. We need to identify the assets and capabilities at all different levels and identify the gaps, critical players, policymakers, and stakeholders, and we must forge working relationships within the public health and health-care community as well as with outside partners. We need to develop shared understandings and mechanisms of communication. All of these efforts are best undertaken before an emergency or crisis.

We need to strengthen our nation's public-health infrastructure. This means enhancing our surveillance and epidemiologic capacity; our laboratory capacity to support surveillance efforts; and our communications systems to collect, analyze, and share data. A strong and robust public health system requires effective working partnerships with the medical care community. For a host of reasons over many years, the worlds of public health and medicine have existed too far apart, even though they share a common set of goals and the mission of promoting health and preventing disease. We need to build linkages and understanding.

We also need to make sure that the public health community works with medical providers to give them the kind of information they need to respond to infectious disease threats in the community, understand emerging disease trends, and implement appropriate prevention and control strategies. Improvements to health can be achieved through more effective daily working relationships and even through a crisis. In addition, we have to link with other partners beyond the public health and medical community, particularly law enforcement and intelligence. Through working together, we learn to share common understanding and language. Federal Bureau of Investigation surveillance is different from public health surveillance; yet, if we are going to be able to rapidly detect, diagnose, and control a bioterrorist event, we need to use both types of surveillance to inform our activities and ensure adequate preparedness.

Communication is vital. We must learn how to educate and communicate with policymakers. We should define policies to support our

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preparedness efforts, the true needs for new resources, and the places in which to invest.

Legal and regulatory issues dealing with quarantine laws and jurisdictional concerns, as well as with the availability or use of certain drugs or vaccines not licensed by the U.S. Food and Drug Administration for use in certain populations in an epidemic context, need to be addressed.

And lastly, we must address the challenge of informing the public and educating them about the reality of bioterrorism. We must develop the framework of understanding and support required to both put in place the systems to respond effectively in a crisis and to achieve a level of understanding that can form the foundation for sharing information and developing knowledge when a crisis occurs.

Hoaxes, a growing problem, offer an opportunity to examine our coordination and response. Thinking through the different types of hoaxes helps us develop protocols and strategies that lead to recognition of a true event.

Medical consequence management is an area to be explored. The conventional bomb—where something blows up, you come in, respond, take care of the injured, clean up, and then return, more or less, to life as it was before—is not going to be the case in a bioterrorist attack, particularly in a scenario with human-to-human transmission. Instead, cases will initially appear in a scattered, sporadic manner, but rapidly increasing and overwhelming the capacity of the health-care system and continuing in concentric circles of infection and disease. We cannot address consequence management in the way emergency plans traditionally have for earthquakes, fires, or bomb blasts. We need to build a system that brings together local, state, and national capacities in an ongoing way. We also must recognize the need to supplement our health-care delivery capacity with nonmedical support that may come in the form of police, National Guard, or possibly military support, both to assist in the provision of services and for crowd control and the maintenance of order. New systems of delivering care and treating patients will be needed. For example, how are we going to deliver off-site care? How are we going to ensure proper infection-control measures in that context and provide ancillary support services for medical care?

Another crucial aspect of effective medical consequence management requires access to necessary therapeutic products. We are in the process of creating a national stockpile of drugs and pharmaceutical products for civilian use. Given that a bioterrorist event is low probability and high consequence for any given locality, the federal government can step in and provide the leadership for creating and administering a national stockpile.

A related concern is the need to develop new tools for the medical management of bioterrorist threats. The research and development agenda needs to be addressed both through governmental efforts, including the National Institutes of Health, the Centers for Disease Control and Prevention, and the U.S. Army Medical Research Institute of Infectious Diseases, but also through private industry and other research institutions. Improved and more rapid diagnostic methods, new and better drugs for treatment or prophylaxis, and new vaccines, especially against anthrax and smallpox, are needed. In addition to biomedical research, further research into such diverse concerns as defining appropriate personal protective gear or decontamination procedures is fundamental to our overall preparedness for a bioterrorist attack.

The public health and medical community must look to the issue of prevention in terms of how to reduce access to dangerous pathogens. Are there strategies to prevent these often-frightening microbes from getting into the hands of those who might want to misuse them, and how can we reduce the likelihood that they will be misused? This means being concerned on an international level about such issues as the need to support the strengthening and enforcement of the Biological Weapons Convention. Finally, as a scientific community we should play a proactive role in scientific research. We need to shape policies against the nefarious use of biological agents, while safeguarding legitimate research. We need to ensure that research institutions and individual researchers keep track of the whereabouts of dangerous pathogens, handle them safely, and store them securely.

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