

## **The Threat of Bioterrorism**

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I was pleased to be asked at this important conference to share with you my perspectives as to the practical realities of a bioterrorist event. It seems to me most appropriate at such conferences as these to be specifically reminded of the human tragedy implicit in a bioterrorist event.

But let me begin by commending our hosts, the International Centre for Genetic Engineering and Biotechnology, for its initiative in convening this conference. Over the past two years, I have attended in the United States more meetings dealing with bioterrorism than I would care to enumerate. But whether dealing with policy, strategy or tactics, they have shared one remarkably similar characteristic. While they have been replete with policy analysts, diplomats, politicians, members of the military, police and intelligence communities, as well as a liberal smattering of chemists and physicists, qualified biologists of any type have been a scarce commodity. Even more uncommon have been those with a background in public health or medicine. And, I have yet to attend any meeting where there was anyone in attendance who seemed to have had first-hand experience with an epidemic of any sort.

It is entirely possible that on the international scene, participation by those in public health and medicine may be more common. I would hope so because the use of biological weapons poses entirely different problems than do the chemical and nuclear ones. Besides being more greatly to be feared, it is recognized that preventing or deterring the production of biological weapons is vastly more difficult; that verification poses unique, almost insoluble problems; and that steps in the manufacture, transfer and dissemination of biological agents have unique dimensions of their own

I regret to say that the virtual absence of our American medical and public health communities from discussions of bioterrorism has been in part, self-determined, the subject being regarded variously as abhorrent, unimaginable or outside the scope of medical concern. Our National Institutes of Health have had no research or educational programs; the Centers for Disease Control have been little involved; and our academic medical centers have not been engaged in discussions or planning. Within the past year, several of us have made a deliberate effort to engage the public health and medical communities in contemplating the problems. I am happy to say that they have responded with keen interest and profound concern with resultant echoes which have carried to the highest levels of government.

The substance of what I have shared with them in national meetings, I will recapitulate with you today, albeit in abbreviated form.

It is generally agreed that the first evidence of intent to use a bioweapon will almost certainly be the appearance of cases in doctors' offices and hospital emergency rooms. The rapidity with which those manning the emergency rooms reach a proper diagnosis and the speed with which preventative or therapeutic measure are applied could well spell the difference between 1000s and perhaps tens of thousands of casualties. However, there are today few indeed who have ever seen so much as a single case of smallpox or plague or anthrax or, for that matter, would recall from the recesses of memory the characteristics of such cases.

Most persons reviewing the subject of bioweapon threats detail a long list of potential pathogens but, in fact, only a handful share the characteristics of being reasonably easy to prepare and to disperse and being able to inflict sufficiently severe disease so as to paralyze a city. In 1994, at a meeting of U.S. and Russian bioweapons experts at our National Academy of Sciences, Russian experts presented their conclusions as to the agents most likely to be used, conclusions which seemed to the group as a whole to be not unreasonable. Smallpox headed the list followed closely by anthrax and plague. None of these agents has so far effectively been deployed as a biological weapon and thus, no real world events exist which provide the basis for suggesting likely scenarios. However, for smallpox, we have had several well-documented importations into Europe over recent decades; two bear recounting.

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Before doing so, let me recall for you that the disease, smallpox is caused by a virus which is spread from person to person, each infected person, in turn, experiencing the characteristic fever and rash. There are no mild, subclinical infections among unvaccinated persons. About 30% of all unvaccinated patients died of the disease. There was, and is, no specific treatment.

The potential for smallpox as an aerosolized agent was vividly demonstrated in an outbreak in Germany in 1970 (11). That year, a German electrician returning from Pakistan became desperately ill with high fever and diarrhea. On January 11, he was admitted to a local hospital and isolated in a separate single room on the ground floor because it was feared he might have typhoid fever. He had contact with only two nurses over the next three days. On January 14, a rash developed and on 16 January, the diagnosis of smallpox was confirmed. He was immediately transported to one of Germany's special isolation hospitals and more than 100 000 persons were promptly vaccinated. After the diagnosis of smallpox was made, hospital patients and staff were quarantined and remained so for four weeks. Patients and staff were vaccinated, very ill patients receiving VIG first. However, the patient had had a cough, a symptom seldom seen with smallpox and, as you know, coughing can produce a large volume. small particle aerosol much as one would expect were smallpox to be used as a terrorist weapon. Subsequently, 19 cases occurred in the hospital, including four in other rooms on the patient's floor of the hospital; eight on the floor above; and nine on the third floor. One of those afflicted was a visitor who had spent less than 15 minutes in the hospital and had only briefly opened a corridor door, easily 30 feet from the patient's room, to ask directions. Three of the patients were nurses, one of whom died. And this was in a well-vaccinated population. One needs no better illustration than this to understand that smallpox virus in an aerosol has a considerable capacity to spread over a considerable distance and to infect at low dosages.

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The experience of Yugoslavia in February 1972 is also instructive in comprehending the havoc created even by a small outbreak. Yugoslavia's last previous case of smallpox had occurred 45 years before, in 1927. Nevertheless, Yugoslavia, like most countries throughout the world had continued population-wide vaccination to protect itself should an importation occur. In 1972, a pilgrim returning from Mecca became ill with an undiagnosed febrile disease. Friends and relatives visited from a number of different areas and two weeks later, 11 of them developed high fever and rash. None were aware that others were ill and physicians who saw the patients failed to make a correct diagnosis. Few had ever seen a case of smallpox.

The first cases were correctly diagnosed four weeks after the first patient became ill but, by then 150 persons were already infected. The cases were occurring in widely separated areas of the country. By the time of diagnosis, the 150 secondary cases had already begun to expose yet another generation and, inevitably, questions arose as to how many undetected cases there might be. Each of the neighboring countries closed its borders to all traffic. The country was in panic.

Government health authorities saw no alternative but to launch a nation-wide vaccination campaign. Mass vaccination clinics were held and check points along roads were established where vaccination certificates were examined. Twenty million persons were vaccinated. Hotels and residential apartments were taken over, cordoned off by the military and all known contacts of cases forcibly moved into these centers under military guard. Some 10 000 persons spent two weeks or more in such isolation. Nine weeks after the first patient became ill, the outbreak was stopped -- 175 patients had developed small pox and 35 had died -- and this was in a generally well-vaccinated population and it was, in fact, a small outbreak.

What might happen if smallpox were to be released today in a European or U.S. city? First, it is important to recall that routine vaccination was stopped in most countries between 20 and 25 years ago. Thus, there are large numbers who have never been vaccinated and, for all others, vaccine immunity has been waning steadily. Based on what we know, it is unlikely that more than 25% would have any residual

U.S. city? First, it is important to recall that routine vaccination was stopped in most countries between 20 and 25 years ago. Thus, there are large numbers who have never been vaccinated and, for all others, vaccine immunity has been waning steadily. Based on what we know, it is unlikely that more than 25% would have any residual protection. A release of smallpox would go unnoticed until cases with rash began to appear perhaps 9 or 10 days later. With patients being seen by different physicians in different clinics none of whom had ever before seen a smallpox case, it is probable that days would elapse before the diagnosis of smallpox was confirmed and an alarm sounded.

Assume that 250 persons had been infected and required hospitalization --in brief, a small outbreak. As soon as smallpox was suspected, this number would soon be submerged in a much larger group of patients, perhaps 300 or 400 persons, all with illnesses with fever and rash but whose diagnosis was uncertain. Some would be reported from other cities and other countries. Where would these patients be hospitalized? It is doubtful that there are more than perhaps 50 to 75 hospital beds in most cities which provide for negative pressure isolation.

What of contacts? Based on experience in other outbreaks, the number of contacts of confirmed or suspected cases would number in the thousands, if not tens of thousands. Would they be isolated as in Yugoslavia and if so, where?

Predictably, there would be an immediate clamor for mass vaccination. Only a few countries have retained stocks of still potent smallpox vaccine and of those that do, most have no more than a few hundred thousand doses. Present reserves of vaccine would rapidly disappear and there is, at present, no manufacturing capacity anywhere to produce additional vaccine. Under emergency circumstances, 30 to 36 months might elapse before significant new stocks became available. Containment of a spreading outbreak would have to rely entirely on the isolation of patients and contacts, much as was done before Jenner discovered the vaccine in 1796.

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What of anthrax which has been so enthusiastically embraced by both Iraq and the Aum Shinrikyo? As you know, their interest, in part, stems from the fact that the organism is so easy to produce in large quantity. In its dried form it is extremely stable. What the effect of aerosolized anthrax might be on humans once had to be inferred from animal experiments and the occasional human infection among workers in factories processing sheep and goat hides. What was clear is that inhalation anthrax is highly lethal. Just how lethal became evident in the 1979 Sverdlovsk epidemic.

In all, 77 cases were identified with certainty of whom 66 died. It is suspected that the actual total was, in fact, several hundred cases. The cases lived or worked somewhere within a narrow zone extending some four kilometers south and east of a military bioweapons facility. An accidental airborne release of anthrax spores occurred during a single day and may well have lasted only minutes. Further investigations revealed anthrax deaths among sheep and cows in six different villages ranging up to 50 kilometers southeast of the military compound.

Some cases experienced the onset of disease as late as six weeks after exposure but whether the onset of illness occurred sooner or later, death almost always followed within one to four days after illness began. From the available data, it is not clear that any treatment was effective once disease symptoms began.

Meselson and his colleagues who documented this outbreak calculate that the weight of spores released as an aerosol could have been as little as a few milligrams or as much as "nearly a gram". Note that Iraq acknowledged producing at least 8000 liters of solution with an anthrax spore and cell count of  $10^9$ /ml.

The ramifications of even a modest-sized release of anthrax spores in a city are profound. Bear in mind, of course, that the small particle aerosol penetrates interior spaces such that the risk is roughly equivalent whether an individual is inside or outside. Emergency rooms would begin seeing a few patients with high fever and some difficulty breathing perhaps 3 to 4 days following exposure. Once the diagnosis was made, one would be faced with the prospect of what to do. Should provision be

spaces such that the risk is roughly equivalent whether an individual is inside or outside. Emergency rooms would begin seeing a few patients with high fever and some difficulty breathing perhaps 3 to 4 days following exposure. Once the diagnosis was made, one would be faced with the prospect of what to do. Should provision be made to treat perhaps several hundred thousand possibly exposed persons with antibiotics for 6 or 8 weeks? Could this be done logistically? Should vaccine be administered to those who might have been exposed? Unfortunately, there is at present no vaccine available for civilian use. Should one be concerned about additional infections occurring as a result of anthrax spores being subsequently resuspended and inhaled by others? Finally, when does one permit any in the population to return to the affected area. This is a serious concern given the fact that anthrax spores may persist in the environment for 40 years or more and methods for decontamination are extremely costly and conceivably impossible for many settings. These are questions which, as we speak today, have yet to be addressed.

The specter of biological weapons use, especially involving smallpox or anthrax, is to me as grim and foreboding as the picture which has been painted of a nuclear winter. However urgent, I sense there are still all too few who sense the need for real urgency in addressing the problem. As was done 30 years ago with respect to nuclear weapons, I believe that we in the medical and public health community, bear a responsibility to educate both professionals and the public as to the nature of that threat. And indeed, this is a challenge to which we at a newly created Center for Civilian Biodefense Studies at Johns Hopkins University are responding, now joined by increasing numbers of our colleagues in public health and medicine. I would hope that others in the European public health and medical communities would join us.

There is no question but that we need to strengthen the BWC and to move aggressively to implement confidence building measures. In the meantime, I believe that there is an important concrete step which is impending and which should not be missed. Specifically, the World Health Assembly needs to reaffirm its decision taken in 1996 that all countries destroy their stocks of smallpox virus by June 1999. It would not guarantee that smallpox would not be used as a terrorist weapon but it would help.

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Today's biotechnology is vastly more sophisticated than that of even 10 years ago and change is occurring exponentially. Information of all types now moves across the Internet in real time for both good and doubtful intent and outcome. It is long past time for us to draw into the discussions on bioterrorism and its deterrence, the best minds in the field of biology, public health and medicine. This has scarcely been considered to date.