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Biological Terrorism: Who's Concerned?

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Little more than a decade ago, the microbial world, admittedly, was viewed by many in this and other industrialized nations as a rapidly fading concern. Microbiology was not yet a dead science and infectious disease specialists were not yet extinct but the trends were clear. That misplaced complacency was rudely jarred, first by AIDS, and then by a parade of other agents, which you know well.

Happily, there is now a growing acceptance of the fact that there are extant, serious microbial challenges with more to be expected and that there is, in fact, a real potential for the microbial world to cause extremely serious and wholly unanticipated problems. Strategic plans to counter these are beginning to take shape and some resources are even being made available to implement them.

However, over the past five years, another component of this new microbial agenda has begun to unfold. It is generated by the growing recognition that there are now nations and dissident groups who have both motivation and skill to selectively cultivate some of the more dangerous pathogens and to deploy them as agents in acts of terrorism or war. Iraq was discovered after the Gulf War to have had a startlingly large biological weapons program and, in 1995, it was confirmed that it had produced, filled and deployed bombs, rockets and aircraft spray tanks containing Bacillus anthracis and botulinum toxin.[1] Its work force and technological infrastructure are still intact.[2] The Japanese cult, Aum Shinrikyo, which in 1995 released the nerve gas Sarin in the Tokyo subway was later discovered to have, as well, plans for biological terrorism.[3] Included in its arsenal were large quantities of nutrient media, botulinum toxin and drone aircraft equipped with spray tanks. It was also discovered that members of this group had traveled to Zaire in 1992 to obtain samples of Ebola virus

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Happily, there is now a growing acceptance of the fact that there are extant, serious microbial challenges with more to be expected and that there is, in fact, a real potential for the microbial world to cause extremely serious and wholly unanticipated problems. Strategic plans to counter these are beginning to take shape and some resources are being made available to implement them.

However, over the past five years, another component of this new microbial agenda has begun to unfold. It is generated by the growing recognition that there are now nations and dissident groups who have both motivation and skill to selectively cultivate some of the more dangerous pathogens and to deploy them as agents in acts of terrorism or war. Iraq was discovered after the Gulf War to have had a startlingly large biological weapons program and, in 1995, it was confirmed that it had produced, filled and deployed bombs, rockets and aircraft spray tanks containing Bacillus anthracis and botulinum toxin.[1] Its work force and technological infrastructure are still intact.[2] The Japanese cult, Aum Shinrikyo, which in 1995 released the nerve gas Sarin in the Tokyo subway was later discovered to have, as well, plans for biological terrorism.[3] Included in the arsenal of weapons which was seized were large quantities

of nutrient media, botulinum toxin and drone aircraft equipped with spray tanks, ~~and~~ it was ~~found~~ also discovered that members of this group had traveled to Zaire in 1992 to obtain samples of Ebola virus for weapons development.

However morally repugnant the use of microbial organisms for terrorist purposes or even warfare, the fact is that this has become a real and growing threat. The number of countries engaged in biological weapons experimentation has grown from four in the 1960s to eleven in the 1990s.[4] ~~The~~ Meanwhile, bombing of the World Trade Center and the Oklahoma City Federal Building dramatized the serious problems which even small dissident groups can cause.

The entire August 6 issue this year of the Journal of the American Medical Association is given over to a comprehensive review and examination of the problems posed by biological terrorism and biological warfare and the initiatives to counter this threat which are ~~now~~ underway both nationally and internationally. Three important themes are woven ~~throughout~~ the 14 papers. First is the fact that significant action on the part of ~~our~~ government to deal meaningfully with the threat posed to the civilian population ~~by biological weapons~~ date back less than two years and, as yet, ~~is~~ New activities are minimally marginally funded and supported. Second is the recognition that prevention of such episodes or countering them will be extremely difficult. Recipes for making biological weapons are now available on the Internet[5] and even groups with modest finances and basic training in biology and engineering could develop, should they wish, an effective weapon. Third is the fact that detection or interdiction of those intending to use biological weapons is next to impossible. Thus, the first evidence of serious intent to use such weapons will almost certainly

be the appearance of cases in hospital emergency rooms. Many of you here thus constitute the front line of defense whether or not you desire it. It is you who will have the responsibility for first suspecting and diagnosing cases of smallpox or anthrax or plague or botulism. The rapidity with which you reach the proper diagnosis and the speed with which prevention or therapeutic measures are applied could well spell the difference between 100s and perhaps tens of thousands of casualties. I wonder how many here have ever seen even a single case of one of these pathogens or, for that matter, would recall from the recesses of memory the characteristics of such cases. I wonder how many diagnostic laboratories would be prepared to confirm promptly such a diagnosis. I expect virtually none.

None of the most pathogenic agents, such as smallpox or anthrax, has so far effectively been deployed as a biological weapon and thus, no real world event exists which provides the basis for suggesting likely scenarios. However, for smallpox, we have had several well-documented importations into Europe over the past 25 years and these bear reflection.

But first, is smallpox a candidate organism? This is the face of smallpox. **(SLIDE 1)** No other widely transmissible agent comes close to the 20% case-fatality rate of variola major. Susceptibility is high. Routine vaccination in the United States ceased 25 years ago and throughout the world some 20 years ago.[6] Although stocks of variola virus are known to be present in only two laboratories--one in the U.S. and one in Russia--one cannot be certain that there are not other strains in other countries, perhaps long held, possibly even recently acquired. The virus is easily grown and in a

cool, dry environment survives very well as an aerosol. One group, in fact, rates smallpox as being highest in rank order of probability of use, followed by plague, anthrax and botulinum.[7]

Its potential as an aerosolized agent was vividly demonstrated in an outbreak in Germany in 1969.[8] That year, a German electrician returning from Pakistan became desperately ill with high fever and cough. **(SLIDE 2)** He was admitted to a small local hospital and isolated in a separate single room on the ground floor because ~~of concern that~~ it was found typhoid fever. he might have ~~a communicable infection.~~ Three days later a rash developed, the diagnosis of smallpox was quickly made, the patient was immediately transported to a special smallpox hospital many miles distant and more than 100 000 persons were promptly vaccinated. Hmmm, 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, ~~but fortunately, cough seldom accompanied a smallpox infection. This case proved to be the exception.~~ **(SLIDE 3)** Subsequently Seventeen ~~subsequent~~ cases occurred in the hospital including four **(SLIDE 4)** in other rooms on the patient's floor of the hospital; seven on the floor above; and eight 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. In all there were 20 cases of whom four died. And this was in a well-vaccinated population.

We can also look to the experience of Yugoslavia in February 1972.[6] Its last previous case of smallpox had occurred in 1927, 45 years before. Nevertheless, Yugoslavia, like most countries throughout the world at that time, 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. **(SLIDE 5)** Most were unaware that the others were sick and physicians who saw the patients failed to make a diagnosis. Few had ever seen a case of smallpox.

One of the 11 patients who acquired smallpox was a 30-year-old teacher who quickly became critically ill with the hemorrhagic form, **(SLIDE 6)** a form not readily diagnosed even by experts. He was first given penicillin at a local clinic but as he became increasingly ill he was transferred to a dermatology ward in a city hospital, then to a similar ward in the capital city and finally, to a critical care unit because he was bleeding severely and going into shock. He died without a definitive diagnosis. He was buried two days before the first case of smallpox was diagnosed.

The first cases were correctly diagnosed four weeks after the first patient became ill but, by then 150 persons were already infected. Among them were 38 who were infected by the young teacher, including two physicians, two nurses and four other hospital staff, and these many cases occurred in widely separated areas in different parts 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 other yet undetected cases there might be. The country was in panic.

Government health authorities saw no alternative but to launch a nation-wide vaccination campaign. Mass vaccination clinics were held; check points along roads were established **(SLIDE 7)** where vaccination certificates were examined. 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. Meanwhile, each of the neighboring countries closed its borders to all traffic. Nine weeks after the first patient became ill, the outbreak finally stopped--175 patients had developed smallpox, half of them infected through hospital spread, and 35 had died--and this was in a generally well-vaccinated population.

What would be the likely scenario and possible response were a smallpox aerosol such as was generated in the German hospital to be dispersed in Grand Central Station, New York or at the San Francisco airport? Two weeks later would find cases of smallpox scattered across this and other countries, at least some of the most serious and most highly infectious cases, the hemorrhagic form, undoubtedly escaping recognition until well after hospital admission. Panic such as occurred in Yugoslavia would be all but inescapable and with this would come a demand for population-wide vaccination in many areas.

Presently available reserves of vaccine in the United States might vaccinate as many as seven to ten million persons but there it would end. There are now no vaccine production facilities anywhere and international reserves of vaccine are limited. With an heroic effort, additional vaccine conceivably might be produced and made available in perhaps 12 to 18 months.

This is not a happy scenario to contemplate.

What of anthrax which has been so enthusiastically embraced by both Iraq and

the Aum Shinrikyo? Their interest, in part, stems from the fact that the organism is so easy to produce in large quantity.[9] In its dried form it is extremely stable. What the effect of aerosolized anthrax might be on humans had once 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 ~~was~~ is highly lethal. Just how lethal became evident in 1979 when in Sverdlovsk, located in central Russia, a military unit working with anthrax experienced some type of accident which resulted in the release of anthrax spores into the environment.[10]

(SLIDE 8) In all 77 cases were identified with certainty of whom 66 died. The cases lived or worked somewhere within a narrow zone extending some four kilometers south and east of the military facility.

The airborne release of anthrax spores occurred during a single day and may will have lasted no more than a few minutes. Meteorological data from the nearby airport showed that only on 2 April was there a north wind which blew in a direction coincident with the distribution of cases. The first cases became ill on 5 April, a Thursday, and five cases were in military reservists who were resident at the military compound only during the week commencing 2 April.

Further investigations revealed during this time anthrax deaths among sheep and cows ~~due to anthrax~~ in six different villages. The villages ranged up to 50 kilometers southeast of the military compound along the same axis as the human cases.

(SLIDE 9) Of the 58 cases with known dates of onset, only nine experienced symptoms within a week after exposure and some experienced the onset of disease as

late as six weeks after exposure. Whether the onset of illness occurred sooner or later, death almost always followed within one to four days after onset. A somewhat higher proportion of survivors after the fourth week ~~may have~~ resulted from the widespread application of penicillin prophylaxis ~~or from vaccination~~, both of which were distributed in mid-April throughout a population of 59 000 persons.

Meselson and his colleagues who have so well 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 produced 8000 liters of solution with an anthrax spore and cell count of 10^9/ml.[2]

One scenario for use of anthrax suggests a fishing vessel sailing around Manhattan Island at three knots per hour releasing anthrax spores at a rate of two kilograms per hour in a fairly stable overcast atmosphere.[11] A total of 400 000 casualties is estimated. This is ominous enough but, based on the Sverdlovsk experience and on experimental primate data,[12] new cases could be expected for a period of at least six weeks. Virtually any febrile condition would have to be tracked as presumptive anthrax, given the non-specific nature of early symptoms. Meanwhile, some sort of area-wide prophylactic program of vaccination (if there were supplies) and antibiotics (presuming enormous quantities were immediately available) would have to be administered for a period of two months or more to a population numbering several million persons.

The specter of biological weapons use is an ugly one, every bit as grim and foreboding as the picture which has been painted of a nuclear winter. As was done in

response to the nuclear threat, I believe that we, as a medical community, bear a primary responsibility to educate the public and policy makers. There is a need to build on the 1972 Biological and Toxin Weapons Convention to strengthen measures prohibiting the development and production of biological weapons and to assure appropriate compliance with agreements which are made. In a broader sense--there is the need to build a strong moral consensus utterly condemning biological weapons and to give preventive measures needed sustainability and priority.[13]

But this is not enough. We need to be as prepared to detect and diagnose, to characterize epidemiologically and to respond appropriately to the range of potential biological weapons as we are to respond to the threat of new and emerging infections. In fact, the needs are convergent. We need at international, state and local levels, a greater capacity for surveillance; we need a far better network of laboratories and better diagnostic instruments; we need a more adequate cadre of clinician-researchers broadly versed in diseases of both temperate and tropical areas.

Surely, if we can and are willing to spend tens of billions to deal with the threat of nuclear weapons, as is now the case we should be more than prepared to devote hundreds of millions to cope with the arguably greater threat of new and emergent infections, whether naturally occurring or induced by man.

To the question, "Who's concerned?", one has to reply today--"not many". It is critical that we all should be.

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EPIDEMIOLOGICAL PREPAREDNESS

+ Strengthen national reference, diagnostic and research capability -- esp. USAMRIID & NCID

+ Augment State surveillance capability utilizing federal personnel when required

+ Strengthen state Health department laboratories to perform reference diagnosis and training

+ Train Infectious Disease Specialists and Emergency Medicine Physicians to recognize key diseases

+ Support research in practical, simple, diagnostic methods for use in major hospitals

+ Support basic research in vaccines and disease pathogenesis to facilitate development of better methods for detection and diagnosis of agents