BIO-TERRORISM THREATS:
POTENTIAL AGENTS AND THEORETICAL PREPAREDNESS

39th Interscience Conference on Antimicrobial Agents and Chemotherapy
Day 3 - September 28, 1999

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Bioterrorist Threats: Potential Agents and Theoretical Preparedness

Jason C. Sniffen, DO; Jeffrey P. Nadler, MD

The History and Extent of the Threat

Dr. Michael Osterholm offered opening remarks, as well as the first segment, to a widely attended morning symposium on the third day of the 39th ICAAC, addressing issues in bioterrorism. He pointed out that the use of biologic agents as a weapon is not a new concept. Germany and Japan both had experience in that capacity in the World Wars of this century. In fact, in 1943 the US began research into the offensive uses of biologic agents. This program was discontinued in 1969 by the Nixon administration. The US was one of many nations to sign the biological weapon convention document declaring the use of biological warfare unacceptable. It is worthy to note that Iraq and the former Soviet Union, two nations known to have had extensive biological weapon manufacturing since that time, were also among the participants.

Society in general does not appear ready to acknowledge the use of biologic agents as methods of mass destruction. This is partly because they are not aware of significant biologic exposures in the past. It is generally not appreciated that these capabilities exist. Perhaps the very idea of this method of harming innocent people is so repugnant that it is
often dismissed. This widespread belief has generally held true, but as
the Irish Republican Army has been quoted to say, "You have to be lucky
all of the time, we have to be lucky just once."

Osterholm described the coming of age of bioterrorism in an era where
the technology to cultivate these agents in mass quantities has
simultaneously matured with the methods to effectively disseminate them.
These events have occurred at a time when intelligence agencies are
inadequate to monitor the activities of a broad range of potential
perpetrators, including rebels, state-sponsored organizations, and cultist
groups with apocalyptic beliefs. Additionally, there appears to be no
shortage of sources for agents to be used in bioterrorism, with 453 known
repositories in 67 nations. Fifty-four of these sites holding anthrax and 18
with stores of plague will ship or sell these isolates with few or no
questions asked.

Dr. Osterholm yielded the presentation of specific organisms to the
speakers to follow, but introduced the likely methods of dissemination as
aerosolization or ingestion. Large gathering places such as malls, office
buildings, and airports, as well as big cities, would serve as logical
targets. The question does not appear to be if, but when and how bad it
will be.

Smallpox

Dr. John Bartlett filled in for Peter Jahrling of USAMRIID for a segment
devoted to one of the likely potential bioterrorist agents, smallpox.[2] The
use of this agent to intentionally cause human disease dates back to
1754 during the French and Indian War, when infected blankets were
given to Native Americans as a "token of good fortune." The last case of
smallpox occurred in 1977, but official viral stores remain at the CDC and
at Vector in Novosibirsk, Siberia. However, it is suspected that 17
countries harbor stores of this virus. These facts led the World Health
Organization to delay the disposal of their own smallpox isolates.

The natural history of human smallpox has been defined. Spread is from
infected individuals with a rash by direct contact or aerosolization.
Patients with smallpox who do not exhibit a rash are generally not
infectious. On day 4, asymptomatic viremia occurs, and the first signs of
fever appear on day 8. Days 12 to 14 are associated with a rise in degree
of fever as well as severe aching pains and prostration. Some 2 to 3 days
later, a papular rash develops over the face and spreads to the
extremities, soon becoming vesicular. The rash typically evolves into
pustular lesions and lasts about 2 weeks. Roughly 4 days later survivors
experience a resolution of fever.

Although smallpox can be confused with chickenpox, several distinctions
are known. Most physicians recognize the superficial crops of lesions with
a truncal predominance, appearing in varying stages of evolution in a
typical case of chickenpox. In contrast, smallpox infection produces
deeper skin lesions on the face and extremities (including the palms and
soles), which tend to evolve at the same pace. Additionally, under most
circumstances, chickenpox has a benign course, while smallpox has a 30% mortality rate.[3]

Epidemiologic review describes an illness that moves in 12-14 day waves with a "disease multiplier" of 10 to 20. For example, 10 initial cases would become 100-200 after 12-14 days. Additional cases would likely appear during the next wave at days 24-28, with total cases ranging from 1000-4000.

There is no proven treatment, but there is interest in cidofovir as potential therapy. With the lack of effective therapies, decontamination is important after exposure. Standard disinfectants are effective for surfaces, and hot water and bleach are necessary for exposed clothing and linens.

Vaccination before exposure or within 2 to 3 days after exposure affords good protection against disease and may prevent mortality when given as late as 4 to 5 days after exposure. However, vaccine is in short supply when one considers the size of the population at risk. The CDC possesses only 6-7 million doses, and WHO 500,000 doses. Vaccine is awkward to administer, can be associated with uncommon but significant side effects such as encephalitis, and is contraindicated in pregnancy, immunodeficiency, and in those with eczematous or exfoliative skin disorders.

Most experts believe that anthrax and plague are among the likely agents for bioterrorism. Dr. Thomas Inglesby Jr, of Johns Hopkins University School of Public Health, gave an up-to-date review of these pathogens.[4]

**Anthrax**

As little as 100 kg of powdered *Bacillus anthracis* could cause 300,000 to 3 million deaths if released under the proper environmental circumstances into a densely populated region. The Iraqi government has admitted to producing as much as 8,000 liters of anthrax at their biologic weapon sites discovered during the Persian Gulf conflict.

Although mainly a disease of grazing animals, up to 2,000 cases of cutaneous anthrax occur worldwide in humans each year. Gastrointestinal disease is seen infrequently. There have been no cases of inhalational anthrax in the US in 20 years.

Patients exposed to inhalational anthrax typically experience fever, dyspnea, headache, and chest pain. Untreated, these symptoms progress to a septic-like syndrome with meningeal involvement in about 50% of cases. Inhalational disease does not cause bronchopneumonia, but the chest x-ray often reveals a widened mediastinum, indicative of associated hemorrhagic mediastinitis and lymphadenitis. Secondary spread does not occur.

Standard blood cultures are usually identified as *Bacillus* species at 6-24 hours, but these cultures may be disregarded as a contaminant. If further identification is pursued, the *anthracis* species can be elucidated. This
gram-positive, nonmotile, nonflagellated, spore-forming bacillus takes on a bamboo-like appearance under light microscopy.

Decontamination procedures are instituted for those exposed. Initial treatment is IV ciprofloxacin until susceptibility testing is available because of concerns of engineered resistance to drugs like penicillin and doxycycline. A switch to oral therapy can be made at signs of improvement, with treatment carried out to 60 days.

Anthrax vaccine is mandated for all US military personnel but is not generally available to the public. For more information on anthrax, the interested reader can link to the CDC and FDA Web sites as well as the Anthrax Vaccine Immunization Program of the Department of Defense for the latest information.

Plague

There have been 390 cases of plague over the last 50 years in the US, most of which have followed an infected flea bite. The vast majority (84%) of these cases have been of the bubonic variety. Septicemic plague without the formation of buboes occurred in 13% of cases. Pneumonic plague has been the least common, accounting for only 2% of cases, but this variety would be the goal of a bioterrorist. Direct aerosolization of plague bacilli would be necessary to initiate this process, and person-to-person spread would continue to perpetuate the disease.

Symptoms begin 1-6 days after exposure, with fever, cough, and bloody or purulent sputum. Acrocyanosis of digits or the tip of the nose is a fairly distinctive feature, with other signs and symptoms similar to that of a septic syndrome. Chest x-ray reveals bilateral infiltrates or consolidation. Mortality is substantial without treatment.

Diagnosis can be made with PCR technology, although this is not widely available. Alternatively, Wright-Giemsa staining will demonstrate gram-negative bacilli with a safety-pin appearance.

First-line treatments consist of parenteral therapy with gentamicin or streptomycin, but oral doxycycline or fluoroquinolones may be used when mass casualties occur. Currently available vaccines for plague prevent only the bubonic form of the disease but do not prevent or even ameliorate pneumonic disease and therefore have no role in the management of bioterrorist outbreaks.

Hemorrhagic Fever Agents

Viral hemorrhagic fever viruses may also be used as bioterrorism agents.[5] Selected agents of the arenaviridae, bunyaviridae, and flaviviridae are potential candidates. These viruses induce fever, prostration, and diffuse vascular damage, often leading to thrombocytopenic hemorrhage. These hemorrhagic complications induce intense psychological discomfort in the observing population. Viral hemorrhagic fever patients require intensive medical care and substantial
resources. Without proper isolation practices nosocomial spread is not uncommon.

All of the hemorrhagic fever viruses, with the exception of hantavirus, present with viremia and can be detected via culture. The presence of IgM antibodies is the more commonly used method of detection.

The Role of the Infectious Disease Community in Responding to Bioterrorism

The final segment of the symposium on bioterrorism was appropriately left to Dr. John Bartlett. His focus was on the role of the infectious disease community and its interaction with public health infrastructure at the federal, state, and local levels when confronted with a potential bioterrorism event.

The federal government has recently allocated $258 million for planning and infrastructure to address issues related to bioterrorism. The CDC as well as state and local authorities will all play critical roles in preparation for and containment of a bioterrorist attack. However, Dr. Bartlett emphasized that the first responders will not be public safety workers (police, fire) as expected in chemical attacks, but rather medical personnel. These personnel will thus need to be trained to recognize early signs of infection with bioterrorism agents, initiate containment efforts, and alert local health officials.

In an effort to test the preparedness of one of the most progressive medical systems nationwide, Dr. Bartlett conducted a mock terrorist attack at Johns Hopkins. At 6 am one day earlier this year, Dr. Bartlett described a case of inhalational anthrax to the emergency department staff and inquired as to the fate of this fictitious patient. The diagnosis would probably be made as influenza, and the patient would be discharged. He then took a chest x-ray with a widened mediastinum to the radiology department and asked for a differential diagnosis. Although extensive, the list did not include inhalational anthrax. Next, he called the lab and asked what they would do if they discovered a blood culture that revealed Bacillus species. The reply was that it may be discarded as a contaminant, but physician request or a small cluster of positive cultures would prompt further identification and the correct diagnosis. When laboratory personnel were asked what next, they said they would call infection control. So Dr. Bartlett called infection control and asked their advice. They referred him to the state health department. He called the state health department and reached a recorded message to which he replied, "I am Dr. John Bartlett, Chief of Infectious Diseases at Johns Hopkins, and I have an urgent inquiry about bioterrorism." His call was returned 3 days later. It turned out that there was a system in place to initiate the proper cascade of events, but the phone number could not be found.

In summary, Dr. Bartlett successfully made the point that we as a medical community are not ready to handle a bioterrorist attack. Infectious disease physicians need to familiarize themselves with the presentation
and management of potential agents and learn how to activate an appropriate public health response. Critically important are efforts to come together as a medical community with a strong voice against bioterrorism and work to prevent research leading to the development and deployment of these agents.

References


