EMERGING INFECTIOUS DISEASES

Tracking trends and analyzing new and reemerging infectious disease issues around the world

A peer-reviewed journal published by the National Center for Infectious Diseases

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Biological Warfare

Dengue Reemergence

Cryptospordium Disinfection

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

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Letters

National Symposium on Medical and Public Health Response to Bioterrorism

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Dispatches

Bioterrorism Symposium cont'd.

Commentary

Book Review

News and Notes

About the First National Symposium on Medical and Public Health Response to Bioterrorism

D.A. Henderson
Johns Hopkins Center for Civilian Biodefense Studies

On February 16-17, 1999, in Arlington, Virginia, 950 public health officials, physicians, and other medical personnel, along with government, military, and intelligence experts gathered for the first National Symposium on Medical and Public Health Response to Bioterrorism. Participants were geographically diverse. Represented were 46 states, plus Washington, D.C., and 10 countries: Australia, Austria, Canada, England, Finland, France, Germany, Israel, Italy, and the Netherlands.

The guiding force behind the symposium was the newly established Johns Hopkins Center for Civilian Biodefense Studies, which hopes the discussions will lead to a framework and partnership for strategic planning. The other main sponsors were the Department of Health and Human Services, Infectious Diseases Society of America, and American Society for Microbiology. Twelve other public health professional societies supported the conference.[1]

The list of speakers included D.A. Henderson, director of the Johns Hopkins Center for Civilian Biodefense Studies; Christopher J. Davis, former senior intelligence analyst for chemical and biological warfare matters on Britain's Defense Intelligence staff; Jessica Stern, Council on Foreign Relations and author of the book The Ultimate Terrorists; Joshua Lederberg, Nobel laureate and professor and president emeritus of Rockefeller University; Col. Gerald W. Parker, director of the U.S. Army Medical Research Institute of Infectious Diseases; Thomas V. Inglesby and Tara O'Toole, Johns Hopkins Center for Civilian Biodefense Studies; and Philip K. Russell, Johns Hopkins School of Public Health.

Federal, state, and local officials reflected on the challenge of coordinating a multidisciplinary and interagency response to a biological attack. This array of speakers included Secretary of Health and Human Services Donna Shalala; Richard Clarke, National Security Council; Michael Osterholm, Minnesota Department of Health; and Jerry Hauer, director of New York City's Office of Emergency Management.

From their different backgrounds and perspectives, the more than 20 speakers addressed the following questions: Why are current concerns about bioterrorism real? Why must the medical and public health communities address the issue of bioterrorism? Which biological threats warrant the most concern? What is the possible aftermath of an act of biological terrorism?

A warning against complacency came from the symposium's closing speaker, Margaret A. Hamburg, assistant secretary for planning and evaluation, U.S. Department of Health and Human Services.

In making symposium presentations available here, the organizers hope to raise awareness of the medical and public health threats posed by biological weapons and to foster mutual understanding and collaboration among the diverse groups addressing the threat of bioterrorism.

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[1]American College of Preventive Medicine, Association for Professionals in Infection Control and Epidemiology, Association of Public Health Laboratories, Association of Schools of Public Health, Association of State and Territorial Health Officials, Commissioned Officers Association of the U.S. Public Health Service, Council of State and Territorial Epidemiologists, National Association of County and City Health Officials, National Association of Local Boards of Health, Partnership for Prevention, Public Health Foundation, and Society of Hospital Epidemiologists of America.

Bioterrorism: How Prepared Are We?

Donna E. Shalala
U.S. Secretary of Health and Human Services

Richard Preston's The Cobra Event, which he dedicates to public health professionals, weaves a chilling, but compelling tale about a lone terrorist's attack on Manhattan with a genetically engineered virus. Preston's thought-provoking novel raises a logical question: How do we successfully contain and combat the threat of bioterrorism? To meet this emerging threat, we must address four important challenges.

The first challenge is to be aware that an act of bioterrorism could happen. Its likelihood is entirely unknown, and an attack may never occur. However, we have seen terrorism emerge as one of the thorniest problems of the post-cold war era, and we have seen that terrorists are always searching for new weapons. We have already seen sarin nerve gas released in the Tokyo subway. Somewhere, sometime in the future, terrorists may well threaten to use, or attempt to use, a biological weapon against the United States. When discussing the possibility of a terrorist attack in the next few years, the president unequivocally stated, "This is not a cause for panic. It is cause for serious, deliberate, disciplined, long-term concern." In other words, we must not be afraid, but we must be aware.

Once we are fully aware that bioterrorism could happen, our second challenge is to be prepared. That is why the Department of Health and Human Services (HHS) is spending $158 million this fiscal year to prepare for bioterorrism and why the president has proposed increasing that investment by an additional $72 million in his Fiscal Year 2000 budget.

This investment will fund our ongoing Anti-Bioterrorism Initiative. To increase our level of preparedness, the initiative is expanding its activities in a number of key areas: surveillance, medical and public health response, building a stockpile of drugs and supplies, and research and development. We are improving and strengthening the U.S. public health surveillance network by enhancing our capability to detect and report outbreaks, conduct epidemiologic investigations, perform laboratory tests to identify biological agents, and communicate necessary information and advisories rapidly through electronic technology.

We are enhancing our medical and public health response capacity by spearheading an administrationwide effort to develop infrastructure at the local level by establishing in major American cities medical response teams to deal with the consequences of bioterrorism. We are also expanding our capacity to provide prophylaxis, medical care, and infection control on a massive scale. We are creating, and will be maintaining, an unprecedented national stockpile of drugs and vaccines for civilian use in case of a bioterrorist attack.

Finally, we are accelerating our research and development of rapid diagnostics, drugs, and vaccines, so we can more effectively address the threats and consequences of a bioterrorist attack. In addition, we will continue our work on the genome sequencing of organisms most likely to be used as bioweapons, so that we can not only quickly identify the biological agent, but also develop effective therapies. Our efforts in surveillance, medical and public health response, stockpile provision, and research and development will increase significantly our preparedness for bioterrorism.

If we want to be truly prepared, our third challenge is for the public health and medical communities to take the lead in our fight against bioterrorism. In a conventional terrorist attack, local "first responders," such as the police, firefighters, and paramedics, constitute the first line of defense. With bioterrorism, the public health and medical communities stand directly on the front lines. How well we respond to a threat or attack will depend on the preparedness of our public health and medical communities. For example, if a bioterrorist threat is issued—perhaps someone claims to have released a

deadly pathogen in a public place—physicians must be able to recognize and report cases that come to attention in emergency rooms and doctors' offices; public health officials must be able to conduct investigations to establish the likely site/time of exposure, the size and location of the exposed population, and the prospects for secondary transmission; and appropriately traned laboratory personnel must be available to identify the biological agent. Whether the release of a bioweapon is announced or surreptitious, affected persons may not have symptoms for days or even weeks, and by then they would be geographically dispersed. Quarantine is not practical because only one biological agent—smallpox—is communicable. Even with smallpox, it would be impossible to know whom to quarantine because of the spread of disease by secondary transmission and the difficulty in accurately identifying those who have been exposed. A strong electronic communications network would be needed to piece together early reports, as well as epidemiologic and laboratory data, to determine what had happened so that public health and law enforcement officials can take prompt action. The Centers for Disease Control and Prevention would play an important role in this process because of its particular expertise in surveillance, infectious disease, and public health. Everyone—from the physicians who first see victims to the scientists who identify the infectious agents—must coordinate their efforts.

That brings me to the fourth, and final, challenge: We must all work together. In the fight against bioterrorism, the federal government, particularly HHS, has a leadership role. Among other things, we need to support state and local planning efforts, provide training at every level, develop an infrastructure for delivering mass medical care, and offer expertise to our communities.

This is a fight we certainly cannot win by ourselves. Across the board, we must forge new working partnerships among health, public safety, and intelligence agencies. We need unprecedented cooperation among the federal government, state and local health agencies, and the medical community. We must ensure that plans for managing the medical consequences of terrorist acts are well integrated and coordinated with other emergency response systems.

Close collaborative efforts are necessary also because microbes do not respect boundaries of culture, language, or territory. An act of bioterrorism cannot be contained by any national border or barrier. When it comes to microbes, we are not protected, in the words of the Indian poet Tagore, "by narrow domestic walls." Since these organisms recognize no boundaries, in our battle against them, neither can we. Because we share a common future, we must share a common resolve. As Dr. Gro Bruntland, the director-general of the World Health Organization, has said, when it comes to public health and safety, "Solutions, like the problems, have to be global..." As we work together to counter bioterrorism, we must pool our will and our resources to meet the challenges.

The Emerging Threat of Bioterrorism

James M. Hughes
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

The threat of bioterrorism focuses attention on overall preparedness to address the challenges posed by new and reemerging infectious diseases. Bioterrorism scenarios illustrate the diversity of disciplines and perspectives required to confront these threats, whether naturally occurring or purposely caused. The need to strengthen existing and develop new partnerships is clear.

Since late 1992, a number of large, complex outbreaks have occurred in the United States. These include the epidemic of over 400,000 cases of waterborne cryptosporidiosis in Milwaukee, the outbreak of severe, unexplained acute respiratory disease now known as hantavirus pulmonary syndrome in the Spring of 1993, the nationwide foodborne salmonellosis outbreak caused by contaminated ice cream that accounted for an estimated 250,000 cases in the fall of 1994, and the increasing problems posed by antimicrobial-resistant organisms in community and health-care settings. Epidemics of plague in India, Ebola hemorrhagic fever in Central Africa, avian (H5N1) influenza in Hong Kong, Hendra virus infection in Australia, and Nipah virus infection recently in Malaysia and Singapore required an international response. During the hantavirus, plague, and Ebola investigations, concerns regarding the possibility of bioterrorism were raised early in the investigations, though these concerns were not supported by subsequent findings.

Investigating these outbreaks in collaboration with local, national, and international partners has provided a number of important lessons, which are reinforced by the threat of bioterrorism. We must avoid complacency and stress preparedness through careful planning and testing of emergency response plans. There is a critical need to strengthen surveillance systems and epidemiologic and laboratory capacity in clinical and public health settings. The outbreaks have illustrated disruptions of travel and commerce and potential threats to national security. The complications of naturally occurring, complex epidemics underline the global implications of local problems. These lessons are directly relevant to the threat of bioterrorism. The challenges of recognizing disease resulting from the clandestine release of an infectious agent are considerable, given the potential for geographic dispersion of the agent (through travel) during the incubation period. The public health approach to bioterrorism must begin with the development of local and state plans formulated collaboratively by the public health, emergency response, and law enforcement communities, which must work together closely in this phase if an epidemic is to be detected in a timely manner, which is critical to its appropriate management. Local health departments and health-care workers will be on the front lines in detection and response. Infection control practitioners, emergency department personnel, microbiologists, first responders, emergency management personnel, and local, state, and federal law enforcement personnel will play vital roles and must engage with each other during the planning stage. Close collaboration between the clinical and public health communities will also be critical.

From a public health perspective, timely surveillance, clinician awareness of syndromes potentially resulting from bioterrorism, epidemiologic investigation capacity, laboratory diagnostic capacity in both clinical and public health laboratory settings, and the ability to rapidly communicate critical information at the local level to those who have a need to know and to manage public communication through the media will be vital. In addition, ensuring the timely availability of an adequate supply of antimicrobial drugs, antitoxins, and vaccines is a formidable challenge. Deployment and administration of stockpiled components to those affected or at greatest risk are also critical.

Address for correspondence: James M. Hughes, National Center for Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mail Stop C12, Atlanta, GA 30333, USA; fax: 404-639-3039; e-mail: jmh2@cdc.gov.

Recognition of the need for local, regional, and national preparedness for bioterrorism provides an opportunity to strengthen the public health system and its linkages with current and new partners. As President Bill Clinton said in his address at the National Academy of Sciences in January 1998, "These cutting edge efforts will address not only the threat of weapons of mass destruction, but also the equally serious danger of emerging infectious diseases. So we will benefit even if we are successful in avoiding these attacks"(1).

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View from the Hill: Congressional Efforts to Address Bioterrorism

S. Anthony McCann
U.S. House of Representatives, Washington, D.C., USA

In government—and particularly in the federal government—ideas normally come from the bottom up. When finally approved, proposals are reasonably well thought out in terms of what we are going to do and why we are going to do it. Sometimes knowledge of "what" we are going to do far exceeds the ability to explain why we are going to do it. However, for bioterrorism we are better able to talk about the "why" than the "what." When Congress received a request from the administration to address bioterrorism, we had only the vaguest idea what they wanted to do. As a result, the availability of funds was delayed until an operating plan was in place. We are still fleshing out exactly how to approach this problem, what the roles of the various agencies are, and what the legal issues are.

It is incumbent upon the community to spend more time studying the proposal and coming back to Congress with more detail.

As the scientific community examines the issues involved in bioterrorism, an education campaign should be undertaken to inform the public and the members of Congress at the local and national levels. Many people equate bioterrorism with chemical or explosive accidents that are obvious and identifiable. The insidious nature of bioterrorist attacks should be better explored and communicated.

Finally, over the last 20 or 25 years, efforts to bring about structural reform in state and local governments and in local public health departments have eroded. Efforts by Congress to fund the bioterrorism initiative may have a dual effect: they may not only improve our ability to respond to a bioterrorist incident but also may strengthen state and local health departments.

S. Anthony McCann is Staff Director for the House Appropriations Subcommittee handling the budgets for the Departments of Labor, Health and Human Services, and Education. In this capacity, Mr. McCann provides support and makes policy recommendations to the Chairman and majority members for over $70 billion in discretionary programs under the subcommittee's jurisdiction. Mr. McCann also served under the Bush Administration as Assistant Secretary for Finance and IRM and Chief Financial Officer of the Department of Veterans Affairs.

Address for correspondence: S. Anthony McCann, U.S. House of Representatives, Appropriations Committee, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, 2358 Rayburn House Office Building, Washington, D.C. 20515-6024, USA; fax: 202-225-3509.

Finding the Right Balance against Bioterrorism

Richard A. Clarke
The White House, Washington, D.C., USA

For the first time the Deparment of Health and Human Services is part of the national security apparatus of the United States. That reflects a change in our views on chemical and biological defense programs. Almost 5 years ago at the bidding of the president we began to look at what has come to be known as "asymmetrical threats," ways in which opponents (be they nations or terrorist groups) could attack us without directly engaging our military forces. At the same time we were faced with two events that drew our attention to chemical and biological threats. Iraq used chemical weapons on Iran and on its own citizens and appeared to be concealing a biological weapons program. Also, the hitherto unknown Japanese cult Aum Shinrikyo used sarin nerve agent in the Tokyo subway; the cult failed in an attempt to use biological weapons against Americans in Japan.

In 1998, the president launched the first national effort to create a biological weapons defense for the United States. While some believe that the response is not strong enough, many others think that the proposed program exaggerates the threat, that biological weapons are too unpredictable, and that the only big biological weapons program died with the Soviet Union. However, the former Soviet Union was not the only state engaged in biological weapons research and development. Almost every nation on the State Department's list of nations that sponsor terrorism has engaged in chemical and or biological weapons development. If these nations have armed, trained, funded, and advised terrorist groups, they could cross the line and provide terrorists with chemical or biological weapons. Finally, some critics say that until we really know about a specific threat to use these weapons against the United States, we should not be raising the specter of horror; instead we should be quietly working in Geneva to improve the ban on biological weapons. We are pushing in Geneva, but that is not enough. When we learn of a specific threat, it will be too late to do research and development, too late to procure medicines, too late to train local authorities.

The current bioterrorism initiative includes a new concept: the first-ever procurement of specialized medicines for a national civilian protection stockpile. As new vaccines and medicines are developed, that program can be expanded. The initiative includes invigoration of research and development in the science of biodefense; it invests in pathogen genome sequencing, new vaccine research, new therapeutics research, and development of improved detection and diagnostic systems. The 2-year program provides for Department of Health and Human Services research, almost tripling the previous 2-year effort, in addition to ongoing work in the Defense Department, and it includes a reinitiation of the federal program to help state and local public health infrastructure and surveillance systems.

The biological weapons protection program is part of the overall chemical and biological protection effort, which includes aid to state and local governments for first-responder training, planning, exercises, and equipment.

Richard A. Clarke serves as the country's first National Coordinator for Security, Infrastructure Protection and Counter-Terrorism. He was Deputy Assistant Secretary of State for Intelligence in the Reagan Administration and served in the Bush Administration as Assistant Secretary of State for Politico-Military Affairs.

Address for correspondence: Richard A. Clarke, National Security Council, 17th and Pennsylvania Avenue, N.W., Washington, D.C. 20504; fax: 202-456-9360.

Historical Trends Related to Bioterrorism: An Empirical Analysis

Jonathan B. Tucker
Monterey Institute of International Studies, Monterey, California, USA

Since the Japanese doomsday cult Aum Shinrikyo released sarin nerve gas on the Tokyo subway in March 1995, killing 12 people, terrorist incidents and hoaxes involving toxic or infectious agents have been on the rise. Before the late 1990s, the Federal Bureau of Investigation (FBI) typically investigated a dozen cases per year involving the acquisition or use of chemical, biological, radiologic, or nuclear materials; however, FBI opened 74 such investigations in 1997 and 181 in 1998 (1). Although 80% of these incidents have been hoaxes, some were unsuccessful attacks (2).

The vulnerability of civilian populations to chemical, biological, radiologic, or nuclear terrorism has been widely discussed, but information on historical cases is anecdotal and often inaccurate (3). Without a realistic threat assessment based on solid empirical data, government policymakers lack the knowledge they need to design prudent and cost-effective programs for preventing or mitigating future incidents.

Responding to this knowledge gap, the Chemical and Biological Weapons Nonproliferation Project at the Monterey Institute's Center for Nonproliferation Studies has compiled an open-source database of all publicly known cases from 1900 to the present in which domestic or international criminals or terrorists sought to acquire or use chemical, biological, radiologic, or nuclear materials. As of January 31, 1999, the database contained 415 incidents, both domestic and international. Each entry draws on multiple sources and includes a detailed description of the event and a list of citations.

The project has conducted a preliminary analysis of the data to discern patterns over time in the frequency of such incidents, the underlying motives, and the choice of agent and target. The ultimate goal is to identify which types of individuals or groups are most likely to acquire and use toxic or infectious materials and for what purposes.

Since the Monterey Database has been compiled from journalistic accounts and other unclassified sources, it may not be comprehensive or fully accurate. Incidents have been recorded only if they came to the attention of law enforcement or the news media, so the database does not include events that were not detected or whose existence remains secret. Despite these limitations, the information in the database indicates trends and patterns of behavior that may assist intelligence and law-enforcement personnel in focusing their monitoring efforts.

Database Findings

Most of the incidents in the Monterey Database involve chemical or biological agents rather than radiologic or nuclear materials (Figure 1). The cases have been divided into three categories: terrorist events, criminal events, and state-sponsored assassinations. To be classified as a terrorist event, an incident must involve an organization or person that conspires to use violence instrumentally to

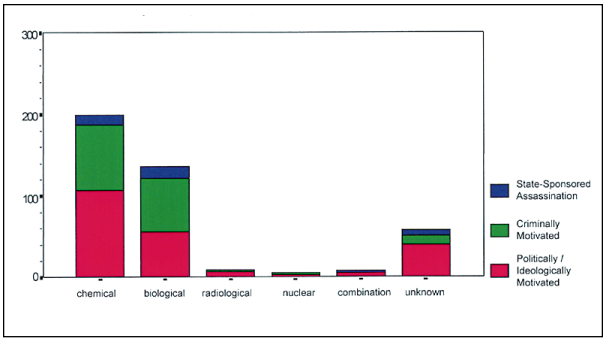

Figure 1. Overall database: Distribution of incident by type, 1960–Jan. 31, 1999 (415 cases).

Address for correspondence: Jonathan B. Tucker, Chemical and Biological Weapons Nonproliferation Project, Center for Nonproliferation Studies, Monterey Institute of International Studies, 425 Van Buren Street, Monterey, CA 93940, USA; fax: 831-647-6534; e-mail: jtucker@miis.edu.

advance a political, ideologic, or religious goal. Criminal incidents, in contrast, involve extortion, murder, or some other nonpolitical objective. Of the 415 incidents involving chemical, biological, radiologic, or nuclear materials, 151 cases are terrorist events for which information is sufficient to permit cross-case comparison. These incidents have been classified according to type of agent, event, target, motive, and group (Figure 2).

"Type of event" includes the following categories: 1) conspiracy to acquire and use an agent, 2) attempted acquisition, 3) possession, 4) threatened use, 5) actual use, and 6) hoax or prank. Most of the 151 incidents involve threatened or actual use, although rarely with the intent of inflicting mass casualties. Of the 151 terrorist incidents, a subset of 33 involves biological agents (22 alleged biological cases were dropped from the analysis because they lacked key pieces of information). Many of the biological-agent cases are hoaxes.

Since 1985, the number of terrorist incidents involving the threatened or actual use of chemical, biological, radiologic, or nuclear materials has risen sharply; a more modest increase has occurred in efforts to acquire such agents. When criminal and terrorist incidents involving chemical or biological agents are examined, two large peaks become apparent (Figure 3a). The 1995 peak was associated primarily with Aum Shinrikyo and related

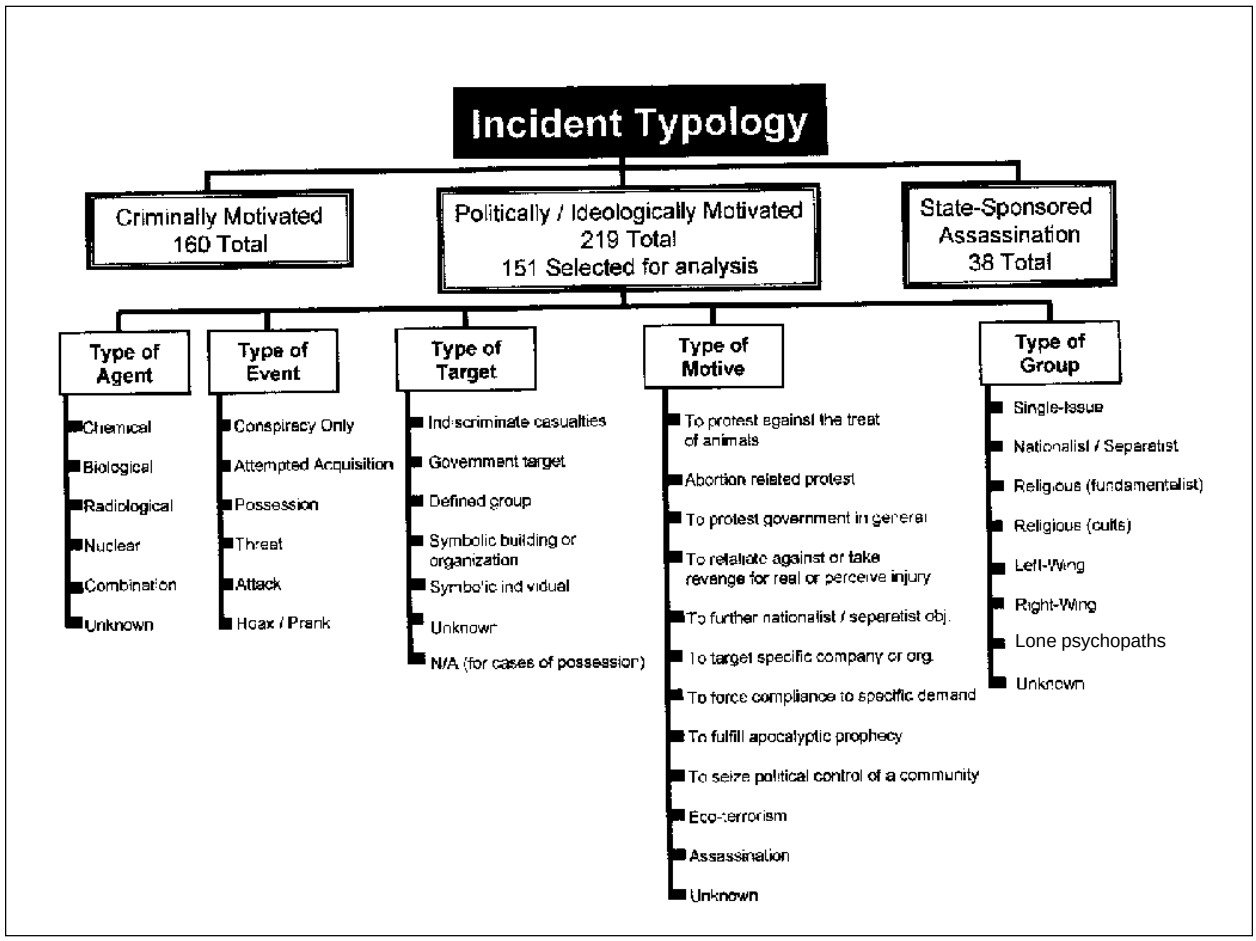

Figure 2. Standardized typology used in analysis of politically or ideologically motivated incidents.

copycat attacks in Japan; in 1998, incidents of actual use again increased abruptly (Figure 3a).

Hoaxes involving chemical or biological agents have shown two peaks in frequency over the past 30 years (Figure 3b). The 1986 peak in chemical hoaxes was inspired by the second series of Tylenol poisonings, while the dramatic rise in biological hoaxes in 1998 is attributable to the flurry of anthrax threats in the United States. The first wave of anthrax hoaxes followed the well-publicized arrest on February 18, 1998, of Larry Wayne Harris, a microbiologist linked to white-supremacist groups, after he allegedly threatened to release "military-grade anthrax" in Las Vegas (4). Although Harris's anthrax turned out to be a harmless veterinary vaccine strain, sensational media coverage appears to have had the unintended effect of popularizing this agent among potential perpetrators.

The categories of terrorist organizations involved in the acquisition and use of chemical, biological, radiologic, or nuclear materials have changed over time. Omitting incidents involving lone terrorists, recent years have seen a rise in cases involving three types of terrorist organizations: single-issue groups such as those dealing with abortion and animal rights; nationalist and separatist groups such as Chechen rebel organizations, the Kurdistan Workers Party, and the Tamil Tigers of Sri Lanka; and

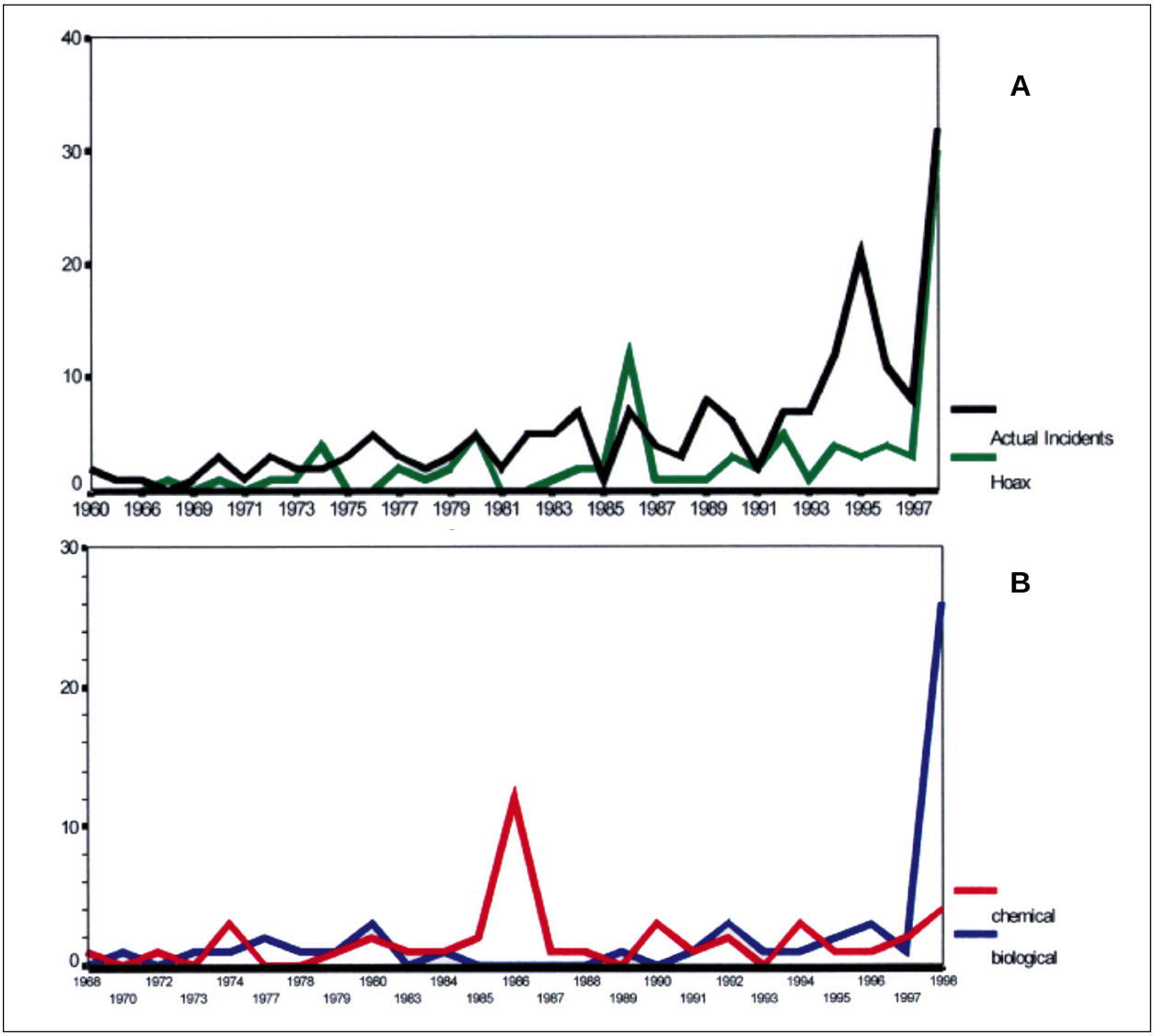

Figure 3. (A) Actual chemical and biological incidents vs. hoaxes, 1960–1998 (278 cases). (B) Chemical and biological hoaxes over time, 1960–1998 (93 cases: 43 chemical, 50 biological).

apocalyptic religious cults such as Aum Shinrikyo (although Aum accounts for nearly all the latter cases). No clear pattern is apparent in the types of groups involved in biological incidents, although religious fundamentalism as a motivation has emerged within the past 5 years.

The preferred choice of target has also changed over time. If one examines 135 terrorist incidents for which the target is known, two types of targets have increased in frequency: the general civilian population (with the apparent intent of inflicting indiscriminate casualties) and a symbolic building or organization.

Motivations for the terrorist use of chemical, biological, radiologic, or nuclear materials appear to encompass a wide range of objectives. (For each case, two analysts separately determined the "best fit" to a menu of motivations.) In descending order, the main motivations are: 1) to promote nationalist or separatist objectives; 2) to retaliate or take revenge for a real or perceived injury; 3) to protest government policies; and 4) to defend animal rights (Figure 4). A similar breakdown of motivations is found in the incidents involving biological agents, except for the greater prominence of apocalyptic prophecy (Figure 5). Nearly all the latter cases are linked to Aum Shinrikyo, which may be either an outlier or a trend-setter.

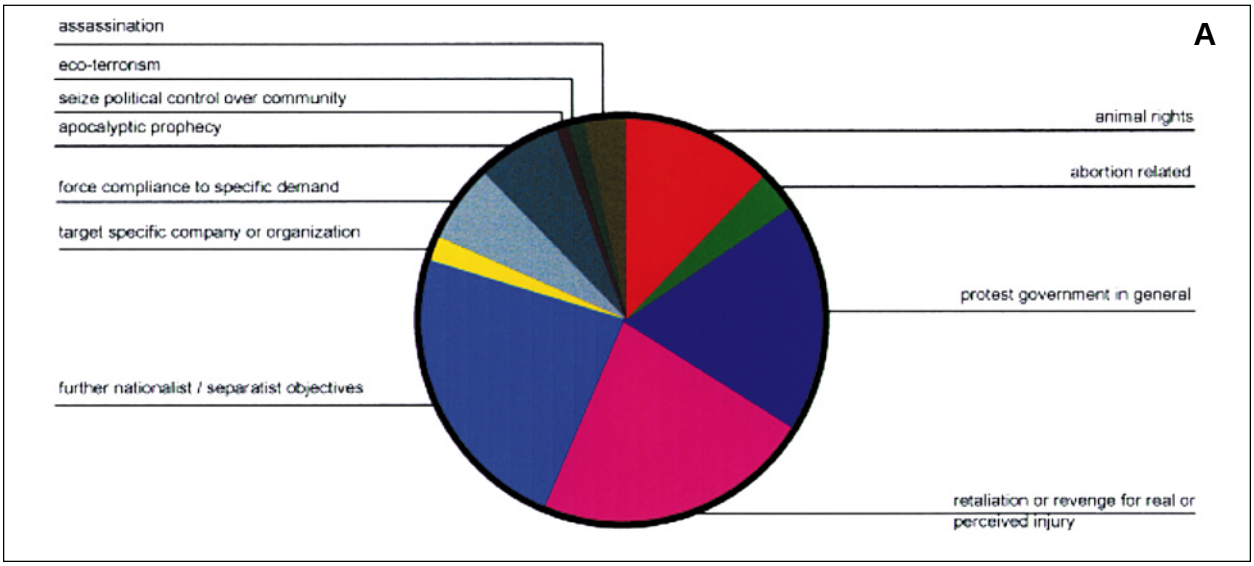

Figure 4. Distribution of motivations for chemical and biological terrorism incidents, 1960–Jan. 31, 1999 (147 cases).

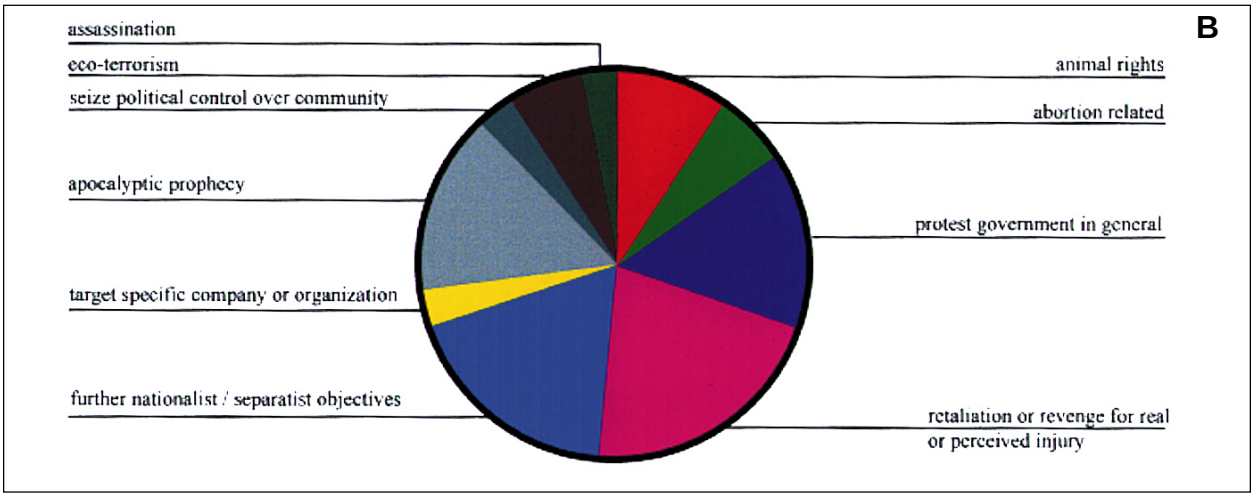

Figure 5. Distribution of motivations for biological terrorism incidents, 1960–Jan. 31, 1999 (33 cases).

The motivations underlying terrorist incidents with chemical, biological, radiologic, or nuclear materials appear to have shifted over time. The predominant motivation from 1975 to 1989 was to protest government policies. Since 1990, however, the leading motivations have been to further nationalist or separatist objectives and for retaliation or revenge. In 1993, because of Aum Shinrikyo, apocalyptic prophecy also emerged as an important motivation. The prominence of these three motivations becomes even greater when only incidents involving biological agents are examined.

In addition to compiling the incidents database, the project commissioned historical case studies of seven terrorist groups or individuals that acquired or employed biological agents (Table 1). Two of the cases appear to be apocryphal, but the five confirmed cases share a number of characteristics that may be diagnostic

Table 1. Comparison of Values Across Selected Bioterrorist Incidents

Case	Motivation/Objective	Ideology	Target(s)	Agent(s)	Delivery	Outcome
Weather Underground (1970)	Temporarily incapacitate U.S. cities to demonstrate impotence of the federal government	Revolutionary movement opposed to American imperialism and the Vietnam War	Urban populations in the United States	Reportedly sought to obtain agents at Ft. Detrick by blackmail of gay soldier	Reportedly planned to put incapacitating CW/BW agents in urban water	Report originated with U.S. Customs informant; case probably apocryphal
R.I.S.E. (1972)	Kill off most of humanity to prevent the destruction of nature, then start human race over with a select few	Perpetrators were college students influenced by ecoterrorist ideology and 1960s drug culture	Initially entire world population, later narrowed to residents of five states around Chicago	Eight microbial pathogens including agents of typhoid fever, diphtheria, dysentery, and meningitis	Planned BW aerosol attacks (dispersed by aircraft) and contamination of urban water supplies	Attack aborted when cultures were discovered; the two main perpetrators then fled to Cuba
Red Army Faction (1980)	Allegedly planned BW attacks against West German officials and business leaders	Marxist-revolutionary ideology	Specific targets unknown	Group member allegedly cultivated botulinum toxin in a Paris safe-house	Unknown	Probably an erroneous report, later repudiated by German government (BKA)
Rajneeshee Cult (1984)	Scheme to incapacitate voters to win local election, seize political control of county	Indian religious cult headed by a charismatic guru	Residents of the town of The Dalles and Wasco County, Oregon	*Salmonella* Typhimurium	Multiple methods, mainly contamination of restaurant salad bars	Plot revealed when the cult collapsed and members turned informant
Minnesota Patriots Council (1991)	Cause harm to the federal government, obtain personal revenge	Anti-government tax protesters; right-wing "patriot" movement	IRS officials, U.S. deputy marshal, local law enforcement officials	Ricin extracted from castor beans obtained by mail-order	Planned to deliver ricin through skin with DMSO and aloe vera, or as dry aerosol	Group was penetrated by FBI informants; four key members arrested
Aum Shinrikyo (1995)	Prove an apocalyptic prophecy, eliminate enemies and rivals, halt an adverse court ruling, seize control of Japanese government	New Age doomsday cult seeking to establish a theocratic state in Japan, with a charismatic, power-hungry leader	Mass civilian populations, individual opponents of cult, judges ruling against and police investigating cult	Biological agents (anthrax, botulinum toxin, Q fever Ebola virus) and chemical agents (sarin, VX, hydrogen cyanide)	Attempted on at least 10 occasions to disperse BW agents in aerosol form; all known attacks failed	Multiple CW attacks (in Matsumoto, Tokyo, and assassination campaign) killed at least 20 people and injured more than 1,000
Larry Wayne Harris (1998)	To alert Americans to the Iraqi BW threat; seeks separate homeland for whites in the United States	Links to Christian Identity and white supremacist groups (e.g., the Aryan Nation)	Made vague threats against U.S. federal officials on behalf of right-wing "patriot" groups	Obtained plague and anthrax (vaccine strain), reportedly isolated several other bacteria	Discussed the dissemination of BW agents with crop-duster aircraft and other methods	Arrested when he talked openly about BW terrorism and made threatening remarks to U.S. officials

BW, biological weapons; CW, chemical weapons; DMSO, dimethylsulfoxide; IRS, Internal Revenue Service; FBI, Federal Bureau of Investigation.

of groups and individuals most likely to engage in bioterrorism (Table 2). These characteristics include diffuse objectives, a sense of grandiosity, and a paranoid, conspiratorial, or apocalyptic world view that may lead to "defensive aggression." Such terrorists also lack a domestic political constituency that might restrain them from engaging in indiscriminate violence. Religiously motivated cults such as Aum Shinrikyo and the Rajneeshees are cut off from the outside world and are often guided by a charismatic, all-powerful leader, making them less subject to societal norms. Other factors not listed in the table include a tendency to escalate terrorist violence over time and to use innovative weapons and tactics.

Incidents of bioterrorism in the Monterey Database are extremely diverse in terms of type of group and motivation. The trend in recent years has been away from left-wing terrorism and toward nationalist-separatist groups and individuals or ad hoc groups bent on revenge. There has also been an apparent rise in incidents perpetrated by violent sects or cults that believe in apocalyptic prophecy.

Even if the motivation to inflict mass casualties exists, however, few terrorist groups possess the scientific-technical resources required for the successful large-scale release of a biological agent. Aum Shinrikyo, which had considerable wealth and scientific expertise, failed in 10 separate attempts to carry out open-air attacks against urban targets with aerosolized anthrax spores or botulinum toxin (6).

Table 2. Selected Motivational Factors Associated with Bioterrorism

Cases	Charismatic leadership	No outside constituency	Apocalyptic ideology	Loner or splinter group	Sense of paranoia and grandiosity	Defensive aggression
R.I.S.E.	X	X		X	X	X
Rajneeshee Cult	X	X		X	X	X
Minnesota Patriots Council	X	X	X	X	X	X
Aum Shinrikyo	X	X	X		X	X
Larry Wayne Harris		X	X	X	X	X
Apparently Apocryphal Cases						
Weather Underground	X				X	
Red Army Faction	X				X	

Conclusions

The Monterey Database indicates that incidents involving biological agents have been quite rare, with 66 criminal events and 55 terrorist events over the 40-year period from 1960 to 1999, although the frequency of such incidents (mainly hoaxes) has increased sharply in recent years. The historical record includes few cases in which criminals or terrorists sought to inflict mass casualties with biological agents, and none in which they succeeded. Only eight criminal attacks with biological agents led to casualties, inflicting a total of 29 deaths and 31 injuries. Of the terrorist attacks with biological agents, only one resulted in casualties: the use by the Rajneeshee cult in 1984 of *Salmonella* Typhimurium bacteria to contaminate restaurant salad bars in The Dalles, Oregon. This event caused 751 cases of food poisoning, none fatal (5).

In summary, the historical record suggests that future incidents of bioterrorism will probably involve hoaxes and relatively small-scale attacks, such as food contamination. Nevertheless, the diffusion of dual-use technologies relevant to the production of biological and toxin agents, and the potential availability of scientists and engineers formerly employed in sophisticated biological warfare programs such as those of the Soviet Union and South Africa, suggest that the technical barriers to mass-casualty terrorism are eroding.

Acknowledgments

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Dr. Tucker is director of the Chemical and Biological Weapons Nonproliferation Project, Center for Nonproliferation Studies, Monterey Institute of International Studies.

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The Threat of Biological Attack: Why Concern Now?

David W. Siegrist
Potomac Institute for Policy Studies, Arlington, Virginia, USA

For a biological attack to occur, three elements must be in place: a vulnerable target, a person or group with the capability to attack, and the intent (by the perpetrator) to carry out such an attack. Much of what can be done to limit the capability and the intent of potential attackers is already on its way to being accomplished. The most work, and the highest return on investment, involve reducing the vulnerability of the United States to both intentional and unintentional pathogen releases.

Vulnerability to Biological Attack

Among weapons of mass destruction, biological weapons are more destructive than chemical weapons, including nerve gas. In certain circumstances, biological weapons can be as devastating as nuclear ones—a few kilograms of anthrax can kill as many people as a Hiroshima-size nuclear weapon (Figure).

The United States is unprepared to deal with a biological attack. Over the past several years, preparedness strides have been made, especially in the largest cities. However, much of the needed equipment is not available. Pathogen sensors are not in place to detect that a biological attack has taken place. New medicines are needed. In combating terrorist attacks, treatment is a more practical approach than prevention; yet many biological agents are extremely difficult to treat with existing medicines once the symptoms appear. In addition, many of the most important prophylactic drugs have limited shelf lives and cannot be stockpiled. Moreover, their effectiveness could be compromised by a sophisticated attacker.

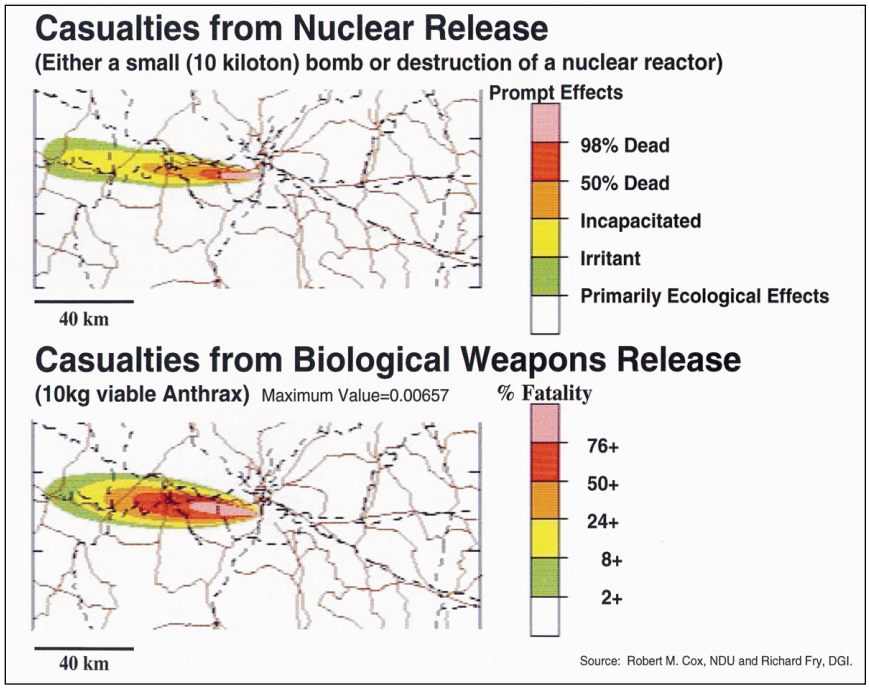

Figure. Effects of a nuclear and a biological weapons release.

Local emergency medical response capability is limited. A number of localities define a "mass casualty event" as one with more than a dozen casualties, far fewer than an intentional biological release could cause. Emergency room capacity in major cities can be overwhelmed all too quickly by more common emergencies. Much emergency medical capability is also located in downtown areas that may be targeted for attack.

The National Disaster Medical System has voluntary access to approximately 100,000

Address for correspondence: David W. Siegrist, Potomac Institute for Policy Studies, 1600 Wilson Boulevard, Suite 1200, Arlington, VA 22209, USA; fax: 703-525-0299; e-mail: siegrist@potomacinstitute.com.

hospital beds across the country to cope with a large-scale medical emergency. However, not all of those beds have the specialized means for patient respiration and supportive therapy that may be needed in a crisis. Such equipment is not available in large numbers (>5,000), even from deployable field hospital Department of Defense war stocks (1). Further, current federal plans favor not evacuating injured people from the affected area but may relocate patients who were already in hospitals to free up local bed space (2). This indicates that localities need to increase their own capabilities. The federal government will augment local efforts, not supersede them.

Steps are being taken to decrease U.S. vulnerability to biological attack. Technical research is being supported, needed medicines and vaccines will be acquired, and emergency response templates are being developed. One of the reforms was setting up the Office of State and Local Domestic Preparedness Support within the Department of Justice. The office has developed a set of objective criteria that measure domestic readiness to deal with an attack by a weapon of mass destruction. No locality has yet qualified for the top ranking—being prepared for such a crisis (3).

Perpetrator Capability

Biological weapons can range in lethality from salmonella used to temporarily incapacitate to super bubonic plague engineered for mass casualities. Biological weapons include ricin, which an extremist may use to assassinate a single local official, as well as pathogens with high transmissibility and broad potential impact. Biological agents may be used to kill or disable humans or to attack plants or animals to harm a nation's economy. Given that broad scope, biological attacks have already taken place and continue to be a distinct probability for the foreseeable future (4). However, of greatest concern is the capability to deliver a sizable lethal attack against a population center.

Technical Capability

Making reliable biological weapons requires art as well as science. Such weapons are not readily adaptable to "cookbook" type recipes that can be implemented by novices. Nevertheless, technical expertise and sophistication about biological processes have become much more widespread. Moreover, even though technical expertise is required to produce high-quality, military-grade biological weapons and reliable means of dissemination, terrorist applications are less demanding.

Making biological weapons requires sample cultures; the means to grow, purify, and stabilize them; and the means to reliably disseminate them. All these tasks pose substantial but not insurmountable challenges. More than 1,500 biological culture libraries worldwide, as well as numerous research institutions and natural sources, maintain sample cultures (5). Growth media and fermenters to multiply the sample cultures are widely available. Purifying, concentrating, and stabilizing agents is demanding and dangerous but not a great technical challenge. Freeze-drying the product and milling it into particles of a uniform respirable size requires even more technical capabilities. A state sponsor may be needed to do it, although companies and institutes regularly spray dry and mill commercial microbes. Moreover, a respirable aerosol of germs can be achieved through other high-pressure devices.

Biological production and weapon-producing facilities can be small, inexpensive, and inconspicuous. Equipment to develop biological arms may have legitimate commercial and research purposes, as well as nefarious ones. Unlike nuclear weapons, biological weapons do not require unique ingredients that are ready objects of arms control.

Institutional Capability

Depending on their sophistication, terrorist groups may or may not have the capability to build broad-impact biological weapons. However, most nations have the capability to make biological weapons. Some 18 nations are believed to have done so, including the former Soviet Union and several nations the State Department lists as supporting terrorism.

Intention to Use Biological Weapons

Why would anyone wish to use biological weapons? A leading entity with a motive to perpetrate a biological attack could be a rogue state as an act of clandestine warfare. The very strength of a superpower may provide an incentive to adversaries to challenge this strength unconventionally.

If a rogue regime were to mount such an unconventional asymmetric attack, they might

choose biological weapons because their extreme destructive potential is concentrated in a relatively small and unremarkable package with virtually no detectable sensor signature. Because of the agent's incubation period, the perpetrators might be gone before anyone knew that an attack had been made. Finally, biological agents, unlike ballistic missiles, lend themselves to clandestine dissemination.

Warfare itself may be becoming more total and losing much of its political character in some situations. Biological weapons, which kill people but leave infrastructure intact, could become the "poor man's neutron bomb."

In the past, the essence of terrorism was to make a political statement through violence. It was a political act designed to influence an audience. Levels of violence were carefully calculated so as to draw attention but not to be so high as to alienate supporters or trigger overwhelming response from authorities. That continues to be a main theme of conventional terrorism. However, in so-called postmodern or superterrorism, the aim is to maximize the number of casualties (6). This reflects a shift in the goal of the terrorists, from trying to make a political statement through violence to maximizing damage to the target as an end in itself. Such terrorists may be motivated by ethnic or religious considerations, among others (7).

Even conventional terrorism tends to escalate levels of violence to keep garnering attention. The threat of biological weapons imparts high levels of fear that may make them desirable to perpetrators who wish to terrorize, even more than to kill. Threats have to become increasingly credible after the initial shock of specious threats has diminished. Even a minor biological attack, made to demonstrate credibility, could have a disproportionate impact. Thus, a certain subset of terrorists may be motivated to commit mass casualty terrorism, including biological terrorism.

Nonintentional Pathogen Releases

Certain kinds of biological assaults can be predicted with even higher confidence than bioterrorist attacks. Stephen Morse, Defense Advanced Research Projects Agency, has said that Mother Nature is the greatest terrorist. Since infectious diseases were widely dismissed as a world health threat some 30 years ago, nature has loosed some 30 new or reemerging infectious diseases on the world (Table) (8). An influenza pandemic was averted 2 years ago by the alert and energetic actions of epidemiologists in Hong Kong and around the world. Slower reactions might have permitted the pathogen's genes to shuffle among human and avian infections to make the flu strain readily transmissible from person to person. Multidrug-resistant tuberculosis is increasing rapidly in Russia in part because of lack of adequate antibiotics (9). More health challenges are almost certainly in store. Causes contributing to emerging disease outbreaks (overcrowding, deforestation, airline travel) will likely continue (9).

Health security and national security needs overlap. If the United States prepares to confront and defeat intentional human releases of pathogens, we will be better prepared for the unpredictable but robust threats likely to occur from nature. For emergency medical response, patients need rapid and efficacious treatment, whether the source of an outbreak of disease is intentional or natural. Medical research needs drugs that treat disease after symptoms become apparent. Such drugs might target common features of disease (10), e.g., inflammation cascade and toxic shock. Aerosol challenge is also typical of both military threats and other airborne pathogens; vaccines that enhance mucosal immunity may mitigate them. Expression of specific genes that may be critical and unique to a number of pathogens might one day be inhibited by medicine.

Effective and safe multipurpose and specific drug treatments would help in the battle against both naturally occurring and intentional releases of infectious disease. Through advanced biotechnology, we could begin to reverse the offense-defense mismatch that now greatly favors disease over cure.

Conclusions

Vulnerability and capability, two prerequisites of bioterrorism, are in place. Enhancing emergency medical preparedness and supporting advanced pharmaceutical research for multivalent drugs, among other measures, will help us deter and defeat deliberate and naturally occurring pathogen releases, as well as increase the general health and well-being of the population. The intention of potential attackers is difficult to manage. Therefore,

Table. New and reemerging viruses (8)

Viruses	Date	Family	Comments
New			
Human herpesvirus 6 (HHV-6)	1986	Herpesvirus	
Human herpesvirus 7 (HHV-7)	1990	Herpesvirus	
GS viruses (hepatitis)	1994	Flavivirus	
Human herpesvirus 8 (HHV-8)	1995	Herpesvirus	
Reemerging			
Cocoa swollen shoot		Badnavirus	Destroyed 200 million cocoa trees in West Africa.
Dengue		Bunyavirus	
Ebola		Flavivirus	
Equine morbillivirus	1994	Morbillivirus	Emerged in Brisbane, Australia. Causes acute respiratory disease with high mortality in horses. Believed to cause a fatal encephalitis in humans.
Hantaan group		Bunyaviruses	
Phocine distemper	1987	Morbillivirus	Caused death rates in seals in the Baltic and North Sea. Similar viruses subsequently recognized as responsible for porpoise and dolphin deaths in the Irish Sea and the Mediterranean.
Rabbit calicivirus disease /Viral hemorrhagic disease	1985	Calicivirus	Emerged in China, spread naturally through UK and Europe. Introduced to Wardang Island off the coast of South Australia to test potential for rabbit population control, accidentally spread to mainland decimating rabbit populations.
Rift Valley fever		Bunyaviruses	
Tomato spotted wilt		Bunyavirus	
Whitefly-transmitted geminiviruses (group III geminiviruses)		Geminivirus	

limiting our vulnerability is the most promising way to prevent or mitigate biological attacks on the United States.

Mr. Siegrist is research fellow at the Potomac Institute for Policy Studies and is director of Studies for Countering Biological Terrorism. He is also an adjunct faculty member at Georgetown University, where he was National Strategy Public Policy Fellow and where he teaches classes on national security. He is the project leader of Countering Biological Terrorism in the U.S., from Oceana Press (May 1999).

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Nuclear Blindness: An Overview of the Biological Weapons Programs of the Former Soviet Union and Iraq

Christopher J. Davis
Johns Hopkins University Center for Civilian Biodefense Studies

The demise of the biological weapons capability of the United States in 1969 and the advent of the Biological and Toxin Weapons Convention in 1972 caused governments in the West to go to sleep to the possibility of biological weapons development throughout the rest of the world, as technically knowledgeable workers were transferred and retired, intelligence desks were closed down, and budgets were cut. By 1979, despite the Sverdlovsk anthrax release, a senior British government policy official described any biological weapons threat as nebulous. President Nixon's biological weapons disarmament declaration in 1969 had conveyed the impression that biological weapons were uncontrollable and that the U.S. program had not been successful in producing usable weapons (when in fact the opposite was true). Add to this the rise of truly intercontinental ballistic missile delivery of nuclear weapons, and the stage was set for what I have termed "nuclear blindness" and defined as "the tunnel vision suffered by successive governments, brought on by the mistaken belief that it is only the size of the bang that matters." Throughout this period, both the former Soviet Union and Iraq conceived, albeit in different ways, their new biological weapons programs. It took until 1989-1991 for government technical experts in the West to persuade the world and their own governments that these programs were real and of enormous potential importance to the security of the West, if not the whole world.

Too many times in the past we have failed to anticipate future developments; refused to think the unthinkable and expect the unexpected. Too many times we have been out maneuvered by those who take the time to think and plan and do not simply rely on reacting to events. We must learn to think like our potential adversaries if we are to avoid conflict or blunt an attack, because only superior thinking and planning (not just better technology) will enable us to survive biological warfare.

Address for correspondence: Christopher J. Davis, Og House, Ogbourne St. George, Marlborough, Wiltshire, SN8 1TF, United Kingdom; fax: 44-(0)-1672-841418; e-mail: christopher.davis1@virgin.net.

The Former Soviet Union

The origins of the biological weapons program of the former Soviet Union stretch back to statements by Lenin, and experimental work was under way by the late 1920s. The modern era was ushered in, however, only with the postwar military building program, which established infrastructure for research, development, testing, production, and delivery of a variety of agents and weapons.

On the other side of the globe, the allied biological weapons program had grown from the fledgling efforts of British research into anthrax and the development of the World War II–anthrax cattlecake retaliation weapon into a large U.S.-based research and development (R&D) and production capability. By 1969, the U.S. military had accepted seven type-classified agents, and, at plants such as the one at Pine Bluff in Arkansas, they could produce 650 tons of agent per month for filling into weapons. This thriving offensive program was unilaterally abandoned in 1969 as a result of a complicated mixture of politics, secret intelligence information, new technological developments, and the Vietnam War. These developments gave impetus to the creation of the Biological and Toxin Weapons Convention, originally drafted by the British but finalized by the Soviet Union. Although the Soviet Union signed the Convention at its inception in 1972, it did not believe that the United States would be so foolish as to abandon its biological weapons capability, regarding the disarmament agreement as a 'worthless piece of paper.'

In 1973 and 1974, the Soviet Politburo formed and funded the organization known most recently as Biopreparat (Chief Directorate for Biological Preparations), designed to carry out offensive biological weapons R&D and production concealed behind legal and civil biotechnology research. At no time did civilian biotechnology work ever comprise much more than 15% of the activity at any of the 52 sites under the aegis of Biopreparat. Ultimately it was controlled by the Ministry of Defense, the Military Industrial Commission, and other state organs, all the way up to the Central Committee and what became eventually the Office of the President. Its head, a general, retained special access to the Central Committee from its inception, and through its links with the Academies of Science and Medical Science, Ministry of Health, and the Anti-Plague Institutes, recruited a generation of scientists who elsewhere in the world underpinned the expanding pharmaceutical and biotechnology industries and academic life-sciences research. The whole system probably employed at its height at least 50,000 people, many of whom were scientists and technicians with very high security clearance that identified them as part of a biological weapons program more closely held and more secret than its nuclear weapons counterpart. The system was always able to draw on the best from any source but was, to a certain extent, self-sufficient. Not all of the 52 establishments were occupied with microbiology or weapons—some were workshops, garages, and cover operations; others supported the program directly with fermenter design and construction or building of weapons test chambers; while yet others carried out advanced research, which would then be given to other institutes for development. Often there was internal competition, with one project being given to a number of facilities to see who would come up with the best idea. In its first 15 years alone, Biopreparat probably cost at least 1.5 billion rubles to create and run—a large sum for life-sciences R&D but relatively modest compared with the cost of nuclear weapons R&D and, therefore, in terms of strategic weapons, extremely cost-effective.

The main purpose of the enormous Biopreparat capability was to hide biological weapons research, development, and production formerly carried out solely in Ministry of Defense establishments behind a facade of nominally civilian biotechnology and pharmaceutical enterprises. The two systems, the former Ministry of Defense complex of biological weapons facilities and the new Biopreparat facilities, continued to operate side-by-side. The Ministry of Defense facilities themselves probably employed another 15,000 workers and had a separate budget, so that the potential within the system as a whole, which is how it should be considered, was large and dwarfed the by-then long-abandoned U.S. offensive program. Its capacity for production of agent was measured not in tons but in hundreds of tons for each of at least nine separate sites, primarily plague, tularemia, glanders, anthrax, smallpox, and Venezuelan equine encephalomyelitis.

Another mission of Biopreparat was to apply advances in biotechnology (genetic engineering, in particular) to improving the biological weapons capability of the former Soviet Union. This mission took several forms, supported primarily by the then vice-president of the Academy of Sciences, Yuri Ovchinnikov, the most influential Soviet biomedical scientist of the 1970s. He saw a way around arms control treaties and weapons conventions by using microbes to produce biologically active substances that would replace classic chemical weapons; their production could then be concealed in the biotechnology or pharmaceutical industry. He also envisaged that the government would use genetic engineering to produce a new generation of biological weapons agents with enhanced capability for expressing toxins and other biologically active substances and to improve overall weapons effectiveness. The outcome of the first of these two programs is not known, but the latter was very successful. Moreover, the new Biopreparat-based program was able to address all aspects of agent production and delivery, not just the most advanced microbiological ones. It built strength in depth, having as its main aims to improve industrial production scale-up techniques, microbial production rates, yields of viable microorganisms, virulence, and resistance of microorganisms to antibiotics; to maximize viability of agent during dissemination and increased survivability of biological aerosols; and to enhance the ability of microorganisms to degrade the target's natural defenses. The leaders of the program foresaw increasing encroachment of international arms control

processes into the territory of sovereign states. Thus, they perceived the need for its weapons to become invulnerable to first strike or counterattack. Key technical targets associated with such an approach were the development of dry solid particulate agent formulations, miniaturized production facilities, mobile production and filling facilities, strains resistant to multiple antibiotics, cruise missile dissemination system, and combination organisms.

By addressing every aspect of weapon production, from selection of new strains of organisms to the behavior of biological aerosols under every possible condition of climate and topography, through the genetic engineering of antibiotic resistance and the design of optimum dissemination and delivery systems, the former Soviet Union was able to envisage the achievement of a miniaturized mobile production and weapon-making capability invulnerable to clandestine monitoring, invasive arms inspection, or attack in the event of war (because it was beyond identification); agents precisely matched to particular scenarios and human targets and incapable of being treated; a variety of dissemination systems, including cruise missiles; agents resistant to degradation by heat, light, cold, UV radiation, ionizing radiation, and various antibiotics; and dry formulations of agents capable of remaining viable in long-term storage.

By the time of the breakup of the former Soviet Union, from which the Russian Confederation emerged in 1992, much had been achieved and war mobilization plans were in place for the surge production of huge quantities of the agents mentioned earlier, as well as a number of others, such as Marburg virus. Of overwhelming importance has been the capability to undertake a strategic attack using plague or smallpox. Intercontinental ballistic missiles with MIRVed warheads containing plague were available for launch even before 1985, and SS-11 and SS-18 missiles have been mentioned in this connection. Concepts of use had been developed for each of the biological agents formally accepted into use by the army. For instance, the principal agents designated as tactical or operational for use on the battlefield were tularemia and Venezuelan equine encephalomyelitis, whereas anthrax and Marburg virus were nominated for attacking rear areas. The third category of agents comprised the highly transmissible agents smallpox and plague, which were categorized as strategic weapons and destined for use against enemy population centers.

What happened after Vladimir Pasechnik (the former general director of Science Production Organisation Farmpribor and director of The All Union Scientific Research Institute of Ultra Pure Biopreparations in Leningrad [St. Petersburg]) defected in 1989 constitutes a long and complex story, but in January 1991 the first-ever visit to Biopreparat facilities was undertaken, by a joint U.K./U.S. technical team, under a cloak of secrecy. After the subsequent defection of Kanadjan Alibekov (a former senior deputy director of Biopreparat) in 1992, the United States and the United Kingdom were certain enough that the offensive biological weapons program was continuing that they challenged the new Russian regime openly about it as late as 1993. By then substantial changes had taken place within Biopreparat, and today a concerted effort is under way to help the Russians civilianize these former biological weapons R&D establishments. However, questions remain about the Russian program: What happened to the part of the program in Ministry of Defence facilities that western experts have been unable to visit? What happened to plans detailing every aspect of production and deployment? What happened to the Ovchinnikov bioregulator program? What happened to the thousands of personnel involved in the Biopreparat program? What happened to the R&D centered on anticrop, antiplant, and antilivestock biological weapons? What happened to the stocks of seed cultures of biological weapons agents designed to be used to fuel the mobilized production of weapons? Was there space-based biological weapons capability? Was there any human genetics-related biological weapons research?

Despite the passage of nearly 10 years, the fundamental change in political structure of Russia, the extreme economic upheaval and budget restrictions, the reorientation of Biopreparat's work, and the help and support given by the West to civilianize programs and stop the transfer of technology and scientists into illegal biological weapons programs, the capability of the old Russian Ministry of Defence sites remains largely unknown.

Iraq

Iraq has stated that its biological weapons program dates to at least 1974. It was carried out

in great secrecy, after the Biological and Toxin Weapons Convention had been signed. The program was first conducted in an ostensibly civilian organization called the State Organization for Trade and Industry until this was superseded by the Military Industrial Commission. As with all other major military programs, biological weapons R&D was able to call upon many of its leading scientists who undertook undergraduate or postgraduate training in the west. Much of what happened between the supposed inception of the program in 1974 and the establishment of a group of biologists within the Al-Muthanna chemical weapons complex in 1984 is unknown.

In 1987, the Al-Muthanna research group was transferred to the Al-Salman facility, and work was expanded to include the investigation of fungal and antiplant agents; 1988 saw the establishment of the Al-Hakam Factory, an industrial-scale production facility designed to produce anthrax and botulinum toxin for filling into weapons. This project was completed quickly by using equipment from nominally civilian facilities, such as those used to produce vaccines; the factory itself produced biological agent, which was filled into weapons and deployed in late 1990. The program was further expanded in 1990 when viruses were added to the range of agents under development and production capacity was enhanced by the acquisition and integration of civilian biotechnology facilities by the Military Industrial Commission.

According to the Iraqis, the program was terminated in 1991, after the adoption of UN SCR687, and agents, weapons, munitions, and documents were destroyed. However, the United Nations Special Commission (UNSCOM) believes that from 1991 to 1995 Iraq actively preserved biological weapons capability.

The Agents, Weapons, and Means of Delivery

The UNSCOM belief that three biological agents were filled into weapons is supported by Iraqi statements concerning the filling of munitions and their deployment ready for delivery. For one of these agents, *Botulinum* toxin, UNSCOM also possesses objective evidence; the other two were probably anthrax and *Clostridium perfringens* spores. Approximately 380,000 liters of *Botulinum* toxin were manufactured, along with 84,250 liters of anthrax spores and 3,400 liters of *C. perfringens* spores. In addition, 2,200 liters of aflatoxin were produced. All these figures represent preconcentration totals and may be underestimates. Ricin toxin and the antiplant agents wheat bunt and corn smut were also produced. Camel pox is known to have been under development as well. This disparate list of biological agents, which at first seems to contain substances not previously conceived as potential offensive biological weapons agents, on closer inspection reveals a rationale based on the possession of a multipotent arsenal having lethal, incapacitating, oncogenic, ethnic, economic, terror, and variable time-onset capabilities. In addition, these agents are capable of being used to attack people through the lungs and the skin, as well as with carriers such as triethylamine, CN or CS, or as a toxic coating in fragmentation weapons.

Agents were filled into various weapons for dissemination. By the end of 1990, according to Iraqi statements, 25 SCUD/Al-Hussein missiles were readied for use with biological weapons warheads (each carrying 145 liters of agent) and deployed for action. At least 160 R400 retarded aerial bombs, carrying the distinctive black-stripe identification around them, may also have been filled with 90-liter charges of *Botulinum* toxin and ready for use. UNSCOM has evidence to corroborate the Iraqi claim. The Iraqis also intended to fill R400 bombs with anthrax and aflatoxin. Originally designed and filled with chemical agents, 155-mm shells were also tested with a ricin toxin fill. At least three fuel drop tanks were completely modified and fitted with Venturi mechanisms to facilitate aerosol release, for dispersal of 2,200-liter loads of anthrax and possibly *Botulinum* toxin, using F1 aircraft as the delivery means.

Postscript

UNSCOM has no confidence that Iraq has abandoned its biological weapons program. The true scale and scope of the Iraqi biological weapons program are, despite all UNSCOM's efforts, still not known.

Dr. Davis is consultant in Pharmaceutical Medicine and Applied Physiology and director of the ORAQ Consultancy Ltd., United Kingdom.

Aum Shinrikyo: Once and Future Threat?

Kyle B. Olson
Research Planning, Inc., Arlington, Virginia, USA

On March 20, 1995, members of the Aum Shinrikyo cult entered the Tokyo subway system and released sarin, a deadly nerve agent. The subway attack was the most deadly assault in an ongoing campaign of terror waged by this mysterious cult. Four years later, with Aum Shinrikyo attempting to rebuild itself, many in Japan and around the world are asking whether the "Supreme Truth Sect" poses a current or future threat. Answering this question may further our understanding, not only of the Aum but also of other extremist and terrorist groups.

Aum Shinrikyo began its public campaign of terror on June 27, 1994. On that Monday in Matsumoto, a city of 300,000 population 322 kilometers northwest of Tokyo, a group of cult members drove a converted refrigerator truck into a nondescript residential neighborhood. Parking in a secluded parking lot behind a stand of trees, they activated a computer-controlled system to release a cloud of sarin. The nerve agent floated toward a cluster of private homes, a mid-rise apartment building, town homes, and a small dormitory.

This neighborhood was targeted for a specific reason. The dormitory was the residence of all three judges sitting on a panel hearing a lawsuit over a real-estate dispute in which Aum Shinrikyo was the defendant. Cult lawyers had advised the sect's leadership that the decision was likely to go against them. Unwilling to accept a costly reversal, Aum responded by sending a team to Matsumoto to guarantee that the judges did not hand down an adverse judgment. A light breeze (3 to 5 knots) gently pushed the deadly aerosol cloud of sarin into a courtyard formed by the buildings. The deadly agent affected the inhabitants of many of the buildings, entering through windows and doorways, left open to the warm night air. Within a short time, seven people were dead. Five hundred others were transported to local hospitals, where approximately 200 would require at least one night's hospitalization.

After successfully completing their mission, the cultists drove off to Kamakuishki, a rural community at the foot of Mount Fuji, home to golf courses, parks, dairy farms, small villages, and the headquarters of Aum Shinrikyo in Japan. The cult's facilities consisted of a number of motley buildings, factories, and dormitories.

Aum Shinrikyo's next major act of violence would serve as a wake-up call to the world regarding the prospects of weapons of mass destruction and terrorism. On the morning of March 20, 1995, packages were placed on five different trains in the Tokyo subway system. The packages consisted of plastic bags filled with a chemical mix and wrapped inside newspapers. Once placed on the floor of the subway car, each bag was punctured with a sharpened umbrella tip, and the material was allowed to spill onto the floor of the subway car. As the liquid spread out and evaporated, vaporous agent spread throughout the car.

Tokyo was experiencing a coordinated, simultaneous, multi-point assault. The attack was carried out at virtually the same moment at five different locations in the world's largest city: five trains, many kilometers apart, all converging on the center of Tokyo. The resulting deaths and injuries were spread throughout central Tokyo. First reports came from the inner suburbs and then, very quickly, cries for help began to flow in from one station after another, forming a rapidly tightening ring around the station at Kasumagaseki. This station serves the buildings that house most of the key agencies of the Japanese government. Most of the major ministries, as well as the national police agency, have their headquarters at Kasumagaseki.

By the end of that day, 15 subway stations in the world's busiest subway system had been affected. Of these, stations along the Hbiya line were the most heavily affected, some with as many as 300 to 400 persons involved. The

Address for correspondence: Kyle B. Olson, Research Planning, Inc., 6400 Arlington Blvd., Suite 1100, Arlington, VA 22042, USA; fax: 703-237-8085; e-mail: kolson@rpihq.com.

number injured in the attacks was just under 3,800. Of those, nearly 1,000 actually required hospitalization—some for no more than a few hours, some for many days. A very few are still hospitalized. And 12 people were dead.

Within 48 hours of the subway attack, police were carrying out raids against Aum Shinrikyo facilities throughout Japan. Police entered cult facilities carrying sophisticated detection systems and wearing military-issued chemical gear (which was issued to the Tokyo police the week before the subway attack).

The real target of the raids that began on March 17 was the building known as Satyan 7, a supposed shrine to the Hindu god Shiva, the most prominent figure in the Aum Shinrikyo religious pantheon. In reality, the building housed a moderately large-scale chemical weapons production facility, designed by cult engineers, with first-rate equipment purchased over-the-counter.

Although the facility's design was crude by industry standards, it was nonetheless very capable of producing the sarin used in the Matsumoto attack. At the time of the Tokyo attack, however, Satyan 7 was not in service, having been mothballed after an accident during the previous summer. In an effort to get the plant back into production, the cult had, during the fall of 1994, unsuccessfully attempted to recruit Russian chemical-weapons engineers. The cult was adept at recruiting educated professionals (scientists and engineers), but most were young and largely inexperienced. Satyan 7 was designed to produce sarin, not on a small terrorist scale, but in nearly battlefield quantities: thousands of kilograms a year.

Chemical weapons were not, however, the only option available to the Aum. The first cult laboratory for toxin production was actually in place by 1990 and was subsequently replaced with two new laboratories, one at Kamakuishki and the other in Tokyo. Aum dabbled in many different biological agents. They cultured and experimented with botulin toxin, anthrax, cholera, and Q fever. In 1993, Ashahara led a group of 16 cult doctors and nurses to Zaire, on a supposed medical mission. The actual purpose of the trip to Central Africa was to learn as much as possible about and, ideally, to bring back samples of Ebola virus. In early 1994, cult doctors were quoted on Russian radio as discussing the possibility of using Ebola as a biological weapon.

The cult attempted several apparently unsuccessful acts of biological terrorism in Japan between 1990 and 1995. As early as April 1990, the cult had tried to release botulin toxin from a vehicle driving around the Diet and other government buildings in central Tokyo. In early June of 1993, another attempt was made to release botulin toxin, this time in conjunction with the wedding of the crown prince. A vehicle equipped with a spray device was driven around the imperial palace as well as the main government buildings in central Tokyo.

Later that month, pursuing an alternative technology, the cult attempted to release anthrax spores from its mid-rise Tokyo office building laboratory. At that time, police and media reported foul smells, brown steam, some pet deaths, and stains on cars and sidewalks. Then, in March 1995, just before the sarin subway attack, an attempt to spray botulin toxin in the subway at Kasumagaseki Station was preempted by a cult member who opted not to load the improvised briefcase sprayers with actual agent.

No injuries were reported in any of these biological events despite the fact the cult was dealing with very toxic materials. The cult's failures can be attributed to a variety of factors. The cult may not have had the right agents or the right technologic facilities; they could have overcooked the bioagents or not known how to use them. While the cult was well financed, it was not very successful in its efforts to recruit biological scientists. Still, the possibility exists that casualties associated with some of these releases might have not been detected or were attributed to other causes.

The cult's operations were worldwide, promoting a theology drawn from different sources, including Buddhism, Christianity, Shamanism, Hinduism, and New Age beliefs. Cult membership around the world was likely 20,000 to 40,000. One cult leader estimated the cult's net worth in March of 1995 at about $1.5 billion. The money was collected through donations, tithing, sales of religious paraphernalia, videotape and book sales, and other sources. The cult conducted seminars and hosted training courses for members, offering indoctrination in Aum's teachings, charging believers from hundreds to tens of thousands of dollars for attending these sessions. Aum Shinrikyo also had a number of commercial enterprises, even a

company that manufactured computers. Imported components from Taiwan were assembled in a cult factory at Kamakuishki and sold in Aum's computer store in downtown Tokyo. The cult also ran a chain of restaurants in Tokyo and several other Japanese cities.

Another source of income was the practice of green mail. Aum would threaten to establish a cult compound in a city and, if the city fathers did not bribe them to go away, the cult would set up shop. Several cities paid rather than have Aum establish operations there. The cult manufactured illegal drugs and had a marketing agreement with the Japanese Mafia (the Yakuza). In 1996, the Yakuza would be found responsible for the assassination of the cult's lead scientist, Dr. Hideo Murai, in the days following the Tokyo subway attack. Concerned at his frequent televised appearances, the Yakuza silenced him for fear that he would betray the linkage between the two shadowy groups. Extortion, theft, and murder were also part of the cult's fund-raising activities. Among the cult leaders, "Doomsday guru" Shoko Ashahara is the undisputed head. Ashahara (born Chizuo Matsumoto) had numerous exalted titles, including venerated master, yogi, and holy pope. Highly charismatic, this partially blind, apparently very talented yoga instructor was very ambitious politically and financially. He and more than 20 of his followers ran for Parliament in 1989. They were defeated, which some Japanese analysts have suggested marks the moment when the cult's leader elected to pursue weapons of mass destruction and the violent overthrow of the established order.

Millennial visions and apocalyptic scenarios dominate the group's doctrine, evidenced by the prominent role of Nostradamus as a prophet in Aum Shinrikyo teaching. Ashahara has, on many occasions, claimed to be the reincarnated Jesus Christ, as well as the first "enlightened one" since the Buddha. He has frequently preached about a coming Armageddon, which he describes as a global conflict that would, among other things, destroy Japan with nuclear, biological, and chemical weapons. According to Ashahara, only the followers of Aum Shinrikyo will survive this conflagration.

Another cult leader, Fumihiro Joyu, now 35 years old, was a bright young engineer with the Japanese space program, specializing in artificial intelligence. He left that organization to go to work for Aum, where he very quickly rose through the ranks, ultimately to head the cult's operations in Russia. Joyu oversaw this important cult expansion, among other things "investing" as much as $12 million in the form of payoffs to well-placed officials. The cult's investment paid off with expedited access to office buildings, dormitories, and other facilities throughout Russia. At the time of the Tokyo subway attack, the cult's principle venture in Russia was the Moscow-Japan University, with headquarters in offices across the street from the Bolshoi Ballet. Their senior Russian partner in the university was a man by the name of Oleg Lobov, at that time also chairman of Russia's National Security Council and a close confidant of Boris Yeltsin.

Joyu was convicted of perjury after the subway investigation, but he received an extremely light sentence (3 years) for his involvement in the cult's activities. Joyu has apparently maintained close ties to the cult, and he is slated for release toward the end of this year. After leaving prison, he may make a play for leadership of the remaining cult elements. He is the most charismatic member of the cult, other than Ashahara. In the days right after the Tokyo subway attack, he was on Japanese television so frequently, and featured in magazines and newspapers so often, that he became a teen heartthrob.

In the days and weeks immediately following the gas attack, more than 200 key members of the cult were arrested. Approximately 120 are still in jail, on trial, or have been convicted. Ashahara himself has been on trial for 3 years. The trial may continue for 5 or 6 years, a judicial timetable that is aggressive by Japanese standards in cases where the defendant refuses to cooperate with the prosecution. Three cult members involved in the attack are still at large. Russian operations were ended by legal action and the assets seized by the government. The cult's legal status in Japan as a church has been revoked, but many of its assets are unaccounted for.

Today, Aum Shinrikyo is once again soliciting donations, collecting tithes, selling materials to members, holding seminars, conducting training, and selling computers. Active recruiting is under way. Aum Shinrikyo is holding 50 "educational" seminars a month for current and potential members. The cult has

offices throughout Japan, around Tokyo and other cities, and, according to Japanese sources, they maintain 100 hide-outs throughout that country as "safe houses." These sources estimate that at least 700 members are live-in, fully committed devotees. Mind control is still a part of the cult's package. Cult members can be seen in Aum-owned houses wearing bizarre electric headsets, supposedly designed to synchronize their brain waves with those of the cult's leader.

What is the message that these events to impart policy-makers? The objective of the Tokyo subway attack was not irrational. The objective that day was to kill as many policemen as possible; Aum Shinrikyo had become aware of police plans to conduct raids against cult facilities, beginning on March 20. The cult's timetable could not permit that interruption.

Aum's actions were perfectly logical within the context of their value system. They were a self-legitimized group that had rejected and, ultimately, felt obliged to confront society. Outnumbered as they were by Japanese police and military might, one can argue that developing and even using an asymmetric capability was a logical consequence of their situation. Unable to achieve their objective—political power—through legitimate means, they determined that a preemptive strike was necessary.

Is Aum Shinrikyo a potential threat? Is Shoko Ashahara just the first of many, or has he been relegated to the scrap heap? These are open questions we will be forced to grapple with for many years to come.

Mr. Olson is adviser, consultant, and writer on high-technology terrorism, the threat of chemical and biological weapons, and the practical challenges of arms control; member of the Central Intelligence's Nonproliferation Advisory Panel; guest lecturer on chemical and biological weapons terrorism at the Defense Nuclear Weapons School, Air War College, Naval War College, and U.S. Air Force Special Operations School, and an adjunct faculty member at George Washington University.

The Prospect of Domestic Bioterrorism

Jessica Stern
Council on Foreign Relations, Washington, D.C., USA

Would domestic terrorists use biological weapons?[1] The conventional wisdom among experts has been that terrorists "want a lot of people watching, not a lot of people dead" and are unlikely to turn to weapons of mass destruction.[2] A new school of thought proposes that improved technology has made biological attacks resulting in hundreds of thousands or millions of deaths all but inevitable. While terrorists are increasingly interested in weapons of mass destruction, proponents of the latter view exaggerate the threat. Using biological weapons to create mass casualties would require more than having biological agents in hand. The terrorists would need to disseminate the agent, which presents technical and organizational obstacles that few domestic groups could surmount. In addition, relatively few terrorists would want to kill millions of people, even if they could.

For most terrorists, the costs of escalation to biological weapons would seem to outweigh the benefits. Most modern terrorists have had substantively rational goals, such as attaining national autonomy or establishing a government purportedly more representative of the people's will. Escalating to such frightening weapons would result in a massive government crackdown and could alienate the group's supporters. Biological weapons are also dangerous to produce. A number of Aum Shinrikyo members reportedly damaged their own health while working on biological agents. Additionally, some terrorists may perceive moral constraints.[3]

Address for correspondence: Jessica Stern, Council on Foreign Relations, 1779 Massachusetts Ave. NW, Washington, D.C. 20007, USA; fax: 202-986- 2984; e-mail: jessicas@alum.mit.edu.

Candidates for successful use of biological weapons represent the intersection of three sets: groups that want to use these weapons despite formidable political risks; groups that can acquire the agent and a dissemination device (however crude); and groups whose organizational structure enables them to deliver or disseminate the agent covertly. The intersection of these sets is small but growing, especially for low-technology attacks such as contaminating food or disseminating biological agents in an enclosed space. Major attacks are also becoming more likely. In the sections that follow, we consider eroding motivational, technical, and organizational constraints.

Motivational Factors

Getting Attention

Some terrorists may turn to biological weapons because they believe it would attract more attention to their cause than conventional attacks. Studies of perceived risk show an inexact correlation between scientists' assessment of risk and the level of fear invoked by risky technologies and activities.[4] Biological weapons are mysterious, unfamiliar, indiscriminate, uncontrollable, inequitable, and invisible, all characteristics associated with heightened fear.

Economic Terrorism

Unlike conventional weapons, radiologic, chemical, and biological agents could be used to destroy crops, poison foods, or contaminate pharmaceutical products. They could also be used to kill livestock. (Conventional weapons could be used for the same purposes, albeit less efficiently.) Terrorists might use these agents to

[1] This essay summarizes Jessica Stern, "Terrorist Motivations and WMD," in Peter Lavoy, Scott Sagan, and Jim Wirtz, ed., Planning the Unthinkable, in press, 2000.
[2] Brian Jenkins has made this statement about terrorists on numerous occasions. For example, see Brian Michael Jenkins, "International Terrorism: A New Mode of Conflict," in David Carlton and Carolo Schaerf, eds., International Terrorism and World Security (London: Croom Helm, 1975), 15. On terrorists' purported aim to harass, see Kenneth Waltz, "Waltz Responds to Sagan," in Scott D. Sagan and Kenneth Waltz, The Spread of Nuclear Weapons: A Debate (New York: Norton, 1995), 94-96.
[3] For examples, see Jessica Stern in Lavoy.
[4] See for example Paul Slovic, Baruch Fischoff and Sarah Lichtenstein, "Facts and Fears: Understanding Perceived Risk," in Richard Schwing and Walter Albers, eds., Societal Risk Assessment: How Safe is Safe Enough? (New York: Plenum Press, 1980), 181-216.

attack corporations perceived to be icons of the target country, for example, by contaminating batches of Coca-Cola, Stolichnaya vodka, or Guinness stout. Terrorists could attempt to disseminate anthrax with the explicit goal of imposing expensive clean-up costs on a target government.

Millenarianism

The millenarian idea is that the present age is corrupt and that a new age will dawn after a cleansing apocalypse. Only a lucky few (usually selected on the basis of adherence to doctrine or ritual) will survive the end of time and experience paradise.[5] Some millenarians believe that the saved will have to endure the 7 years of violence and struggle of the apocalypse, and they want to be prepared.[6] Shoko Asahara, leader of the doomsday cult that released sarin gas in the Tokyo subway in 1995, killing 12, told his followers that in the coming conflict between good and evil they would have to fight with every available weapon.[7] A similar belief system explains the attraction to survivalism by Identity Christians, white supremacists who believe in an imminent Armageddon.

Premillennial Tension

Slight tension connected with the millennium presumably affects most people. Many are concerned about the Y2K problem, the prospect that computer systems will malfunction or fail at the end of 1999. Some fear the breakdown of air-traffic control systems and are planning to avoid traveling around January 1, 2000. Others fear an accidental launch of Russian nuclear missiles due to malfunctioning computers. Many are stockpiling food and medicine or will have extra cash on hand in case automated banking systems fail. Some feel vague religious fears. Members of antigovernment groups and religious cults are often vulnerable psychologically and appear to be especially affected by premillennial tension. Larry Wayne Harris, a white supremacist and born-again Christian, predicts that the Y2K bug will cause a civil war in the United States and that after January 1, 2000, the government will be unable to deliver welfare checks and food stamps for at least 3 years.[8] He predicts that biological attacks could be carried out by domestic groups fighting for their heritage, traditions, and communities, causing devastating plagues like those described in the Bible's Book of Revelation.[9] He urges all U.S. citizens to prepare. For some domestic groups, preparation involves stockpiling weapons and training to use them.

Exacting Revenge or Creating Chaos

Politically motivated terrorists who desire to change societies rather than destroy them might avoid killing very large numbers of people because the political costs would exceed the benefits.[10] Some terrorists, however, want to annihilate their enemies or demolish the societal order. William Pierce, leader of the neo-Nazi organization National Alliance, aims to initiate a worldwide race war and establish an Aryan state. "We are in a war for the survival of our race," he explains, "that ultimately we cannot win... except by killing our enemies... It's a case of either we destroy them or they will destroy us, with no chance for compromise or armistice."[11] Creating social chaos is thus a worthwhile objective in Pierce's view. Ramzi Yousef, organizer of the World Trade Center bombing, claimed he was exacting revenge against the United States.[12] Osama bin Laden seems to have similar motives.

Mimicking God

Terrorists hoping to create an aura of divine retribution might be attracted to biological agents. The fifth plague used by God to punish the Pharaoh in the Bible's Book of Exodus was murrain, a group of cattle diseases that includes

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[5]While millenarian doctrines are generally religiously based, some are not. See Jean E. Rosenfeld, "Pai Marire: Peace and Violence in a New Zealand Millenarian Tradition," Terrorism and Political Violence, 7, no. 3 (autumn 1995), 83.
[6]"End Times Jitters," interview with Michael Barkun, Klanwatch Intelligence Report (summer 1997), 17.
[7]FBIS-SOV-97-09, 6 May 1997. Source Moscow Trud, 6 May 1997, 1-2.
[8]Author Interview with Larry Wayne Harris, 9 February 1999.
[9]Testimony of Larry Wayne Harris, State of Ohio v. Stephen Michael Wharf.
[10]The nature of the constituency is a key variable here. If the terrorists' constituents see the targeted group as subhuman, or if terrorists have no clear constituency, political constraints against macro-terrorism are less likely to bind.
[11]Quotes from Klanwatch Intelligence Report (May 1996), 6-8.
[12]Gail Appleson, "Bomb Mastermind Gets Life in US Prison," Reuters, 9 January 1997.

anthrax. In the fifth chapter of Samuel I, God turned against the Philistines and "smote them with emerods." Medical historians consider these emerods a symptom of bubonic plague.[13] Some terrorists may believe they are emulating God by employing these agents.

The Aura of Science

Terrorists may want to impress their target audience with high technology or with weapons that appear more sophisticated than conventional ones. Terrorists may find technology appealing for various reasons. William Pierce, who studied physics at California Institute of Technology, is interested in high-technology weapons. In his novel The Turner Diaries, right-wing extremists use nuclear, chemical, biological, and radiologic weapons to take over the world. Pierce believes he can attract more intelligent recruits to his organization over the Internet than through radio or leaflets.[14]

The Copycat Phenomenon

Domestic extremists have shown greater interest in chemical and biological weapons in the last 5 years. For example, in 1998, members of the Republic of Texas were convicted of threatening to assassinate with biological agents President Clinton, Attorney General Janet Reno, and other officials.[15] In May 1995, 6 weeks after the Aum Shinrikyo incident on the Tokyo subway, Larry Wayne Harris bought three vials of *Yersinia pestis*, the bacterium that causes bubonic plague. No law prohibited Harris or any other U.S. citizen from acquiring the agent. The law has been tightened up since, although many fear it is still not restrictive enough. The Federal Bureau of Investigation (FBI) Director Louis Freeh reports that "a growing number—while still small—of 'lone offender' and extremist splinter elements of right wing groups have been identified as possessing or attempting to develop or use" weapons of mass destruction.[16]

In February 1998, Harris boasted to an informant that he had enough military-grade anthrax to wipe out all of Las Vegas. Eight bags marked "biological" had been found in the back of a car he and his accomplice were driving.[17] Several days later, federal authorities learned that the anthrax Harris had brought to Las Vegas was a vaccine strain not harmful to human health. Nevertheless, the incident frightened many people and sparked a proliferation of anthrax hoaxes and threats in the second half of 1998 continuing into 1999 by groups including Identity Christians and other antigovernment groups, extortionists, anti-abortion activists, and presumed prochoice groups. In many cases, the perpetrator's motives were unknown, but some incidents appear to have been student pranks, demonstrating the extent to which the threat of anthrax has entered U.S. consciousness (Table).

Technical Factors

With the end of the cold war and the breakup of the Soviet Union, weapons of mass destruction and their components have become easier to acquire. Underpaid former Soviet weapons experts may be providing biological weapons and expertise to Iran.[18] South African biological weapons scientists have offered their expertise to Libya.[19] State-sponsored groups are most capable of overcoming technical barriers to mass-casualty attacks, but the sponsor would presumably weigh the risk for retaliation before supporting this type of terrorist attack.

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[13]Hans Zinsser, Rats, Lice and History (Boston: Little Brown and Company, 1963), 110.
[14]Author interview with William Pierce, 22 April 1997.
[15] Madeline Baro, "FBI: Men Knew of Cactus Weapons, Threats," Associated Press/Corpus Christi Online, 27 October 1998; found at: http://www.callertimes.com/autoconv/newstexmex98/newstexmex57.html.
[16] Statement for the Record of Louis J. Freeh, Director, Federal Bureau of Investigation, before the United States Senate Committee on Appropriations; Subcommittee for the Departments of Commerce, Justice, and State, the Judiciary, and Related Agencies; February 4, 1999.
[17]One informant said that Harris said he had "military-grade anthrax." Another said Harris referred to a vaccine or a placebo. Proceedings before the Regular Federal Grand Jury, Testimony of Robert James, February 25, 1998, United States District Court, District of Nevada, p. 17. United States of America v. Larry Wayne Harris, Complete Transcript of Proceedings, CR-2-95-093, March 6, 1998, United States District Court, Southern District of Ohio.
[18]Judith Miller and William J. Broad, "Bio-Weapons in Mind, Iranians Lure Needy Ex-Soviet Scientists," New York Times, 8 November 1998, A1 and Miller and Broad, "Germ Weapons: In Soviet Past or in the New Russia's Future?" New York Times, 28 December 1998, A1.
[19]James Adams, "Gadaffi Lures South Africa's Top Germ Warfare Scientists," Sunday Times, 26 February 1995; Paul Taylor, "Toxic S. African Arms Raise Concern; US Wants Assurance '80s Program is Dead," Washington Post, 28 February 1995.

Table. Anthrax incidents in the United States, 1992–1999[a]

	Year		
	1992	1997	1998
No. incidents	1	1	37
No. persons affected[b]	20	100	5,529
Persons decontaminated, treated, or quarantined[b]	20	30	1,202
Targets	Residence	Religious organization	Government buildings and officials, individuals, clinics, religious institutions, antiabortion activists, financial institutions, schools, retail establishments, office buildings, media, nightclub
Purported motivators	Malicious	Anti-Semitism	Antigovernment, alleged research, antiabortion, prochoice retaliation, student pranks, delay court appearance
Dissemination technique(s)	Splattering	Mail	Dispersal on premises, modified cigarette lighter, moist towelettes, mail (envelope), explosive device, ventilation systems
Responses	Perimeter sealed, medical treatment	Perimeter sealed, decontamination, medical treatment	On-site inspection, evaluation perimeter sealed, pamphlets provided, quarantine, decontamination, medical treatment

[a]These data are presumed incomplete and may contain errors. Numbers are based on press reports and are not available for all years. Data not independently confirmed.
[b]Figures do not include incidents in which numbers are not available; actual totals, therefore, may be understated.
Chart prepared by Darcy Bender.

College-trained chemists and biologists could presumably produce biological agents, although they might have trouble disseminating them as aerosols. Microorganisms can be disseminated by air in two forms: as liquid slurries or as dry powders. While producing liquid slurries is relatively easy, disseminating them as respirable infectious aerosols over large open areas is not. Although dry powders can be disseminated far more easily, high-quality powders require substantial development, involving skilled personnel and sophisticated equipment. Milling biological agents would require a level of sophistication unlikely to be found among many domestic terrorist groups. Far more likely are low-technology incidents such as contaminating foods, poisoning livestock, or disseminating industrial poisons in an enclosed space. Such attacks could still be lethal. Major attacks cannot be ruled out; however, governments need to prepare.

Organizational Factors

In the mid-1980s, a little-known survivalist group called The Covenant, the Sword, and the Arm of the Lord (CSA) acquired a large drum of cyanide with the intention of poisoning water supplies in major U.S. cities. At the time, CSA was unusual among terrorist groups in that its sole objective was large-scale murder rather than influencing government policies. CSA overcame two of three large obstacles to successful employment of a chemical agent. It had the motivation to use a chemical agent to kill large numbers and no political or moral constraints. The group had acquired a chemical agent, although not in sufficient quantity to contaminate city water supplies. The group's leaders had not recruited technically trained personnel and chose an unworkable dissemination technique. Moreover, the group lacked discipline and was easily penetrated by FBI. It is unlikely that CSA would make such mistakes if it were operating today, when antigovernment groups are so much more aware of the potential of poison weapons for inflicting mass casualties.[20]

CSA was run as a relatively open compound. Some members wrote articles in local papers espousing antigovernment beliefs, and some worked in neighboring towns. Several former CSA members became informants, often because they hoped to get their sentences reduced for other, unrelated, crimes. In recent years, however, antigovernment groups have become more aware of the danger of penetration by law-enforcement authorities and have devised a new way of organizing themselves called "leaderless resistance."[21] Members are encouraged to act on their own, minimizing their communication with the leadership of the movement. Timothy McVeigh operated according to this model. His bombing of the Oklahoma City Federal Building was originally conceived of by CSA, although it is not clear that McVeigh knew of CSA's earlier plot. If future terrorists with chemical or biological agents act on their own or in small, secretive groups, FBI may have difficulty apprehending them.

One of CSA's objectives was to establish a computerized, nationwide system linking right-wing groups. This goal has been achieved, although CSA is not exclusively—or even principally—responsible for this achievement. The nationwide linking of right-wing groups has implications that have not been adequately appreciated by the law enforcement community. The Internet makes terrorist acts easier to carry out. It facilitates leaderless resistance by allowing leaders of the movement to communicate with sympathizers worldwide without having to meet face-to-face with their followers.

The Likeliest Perpetrators

A small but growing number of domestic terrorists could attempt to use biological weapons in the belief that doing so would advance their goals. The most likely are religious and extreme right-wing groups and groups seeking revenge who view secular rulers and the law they uphold as illegitimate. They are unconstrained by fear of government or public backlash, since their actions are carried out to please God and themselves, not to impress a secular constituency. Frequently, they do not claim credit for their attacks since their ultimate objective is to create so much fear and chaos that the government's legitimacy is destroyed. Their victims are often viewed as subhuman since they are outside the group's religion or race.

Religiously motivated groups are increasing. Of 11 international terrorist groups identified by the Rand Corporation in 1968, none were classified as religiously motivated. By 1994, a third of the 49 international groups recorded in the Rand-St. Andrews Chronology were classified as religious.[22] Religious groups are not only becoming more common; they are also more violent than secular groups. In 1995, religious groups committed only 25% of the international incidents but caused 58% of the deaths.[23]

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[20]For example, Kerry Noble claimed that if CSA leader James Ellison met someone who knew something about biological agents, he might consider using them. Author interview with Kerry Noble, March 2, 1998.

[21]See Louis Beam, "Leaderless Resistance," The Seditionist, Issue 12, February 1992. Found at: http://www.louisbeam.com/leaderless.htm.

[22]Bruce Hoffman, "Viewpoint: Terrorism and WMD: Some Preliminary Hypotheses," Nonproliferation Review (spring-summer 1997): 45-52. Hoffman provides slightly different numbers in "Holy Terror": The Implications of Terrorism Motivated by a Religious Imperative (Santa Monica: Rand Corporation, P-7834, 1993).

[23]Hoffman, "Viewpoint," 48.

Identity Christians believe that the Book of Revelation is to be taken literally as a description of future events. Many evangelical Protestants believe in a doctrine of rapture: that the saved will be lifted off the earth to escape the apocalypse that will precede the Second Coming of Christ. Followers of Christian Identity (and some other millenarian sects), however, expect to be present during the apocalypse.[24] Because of this belief, some followers of Christian Identity believe they need to be prepared with every available weapon to ensure their survival.

Organizational pressures could induce some groups to commit extreme acts of violence. Followers tend to be more interested in violence for its own sake than in the group's purported goals, making them less inhibited by moral or political constraints than the leaders. Leaders may have difficulty designing command and control procedures that work. Offshoots of established groups may be particularly dangerous. Groups may also become most violent when the state is closing in on them, potentially posing difficulties for those fighting terrorism. Another factor is the nature of the leader. Charismatic leaders who isolate their followers from the rest of society often instill extreme paranoia among their followers. Such groups can be susceptible to extreme acts of violence.

Asked who he thought the most likely domestic perpetrators of biological terrorism were, John Trochman, a leader of the Montana Militia, said that extremist offshoots of Identity Christian groups are possible candidates, as are disaffected military officers.[25] Some antigovernment groups are attempting to recruit inside the U.S. military.[26] William Pierce also foresees the use of biological weapons by antigovernment groups. "People disaffected by the government include not only the kind of people capable of making pipe bombs. Bioweapons are more accessible than are nuclear weapons."[27]

Conclusions

Terrorism with biological weapons is likely to remain rare. This is especially the case for attacks intended to create mass casualties, which require a level of technologic sophistication likely to be possessed by few domestic groups. While state-sponsored groups are most likely to be capable of massive biological weapons attacks, the state sponsor would presumably have to weigh the risk for retaliation. As in the case of other low-probability high-cost risks, however, governments cannot ignore this danger; the potential damage is unacceptably high. Because the magnitude of the threat is so difficult to calculate, however, it makes sense to focus on dual-use remedies: pursuing medical countermeasures that will improve public health in general, regardless of whether major biological attacks ever occur. This would include strengthening the international system of monitoring disease outbreaks in humans, animals, and plants and developing better pharmaceutical drugs.

The risk for overreaction must be considered. If authorities are not prepared in advance, they will be more susceptible to taking actions they will later regret, such as revoking civil liberties. Attacks employing biological agents are also more likely and will be far more destructive if governments are caught unprepared.

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Dr. Stern is a Fellow at the Council on Foreign Relations. She is the author of The Ultimate Terrorists (Harvard University Press, 1999). She is currently writing a book on religious extremism worldwide.

[24]Author interview with Pastor Millar, 21 April 1998.
[25]Author interview with Trochman, 9 February 1999.
[26]Author interview with William Pierce, 22 April 1997.
[27]Author interview with William Pierce.

Potential Biological Weapons Threats

Mark G. Kortepeter and Gerald W. Parker
U.S. Army Medical Research Institute of Infectious Diseases,
Fort Detrick, Maryland, USA

The list of agents that could pose the greatest public health risk in the event of a bioterrorist attack is short. However, although short, the list includes agents that, if acquired and properly disseminated, could cause a difficult public health challenge in terms of our ability to limit the numbers of casualties and control the damage to our cities and nation.

The use of biological weapons has occurred sporadically for centuries, culminating in sophisticated research and testing programs run by several countries. Biological weapons proliferation is a serious problem that is increasing the probability of a serious bioterrorism incident. The accidental release of anthrax from a military testing facility in the former Soviet Union in 1979 and Iraq's admission in 1995 to having quantities of anthrax, botulinum toxin, and aflatoxin ready to use as weapons have clearly shown that research in the offensive use of biological agents continued, despite the 1972 Biological Weapons Convention (1,2). Of the seven countries listed by the U.S. Department of State as sponsoring international terrorism (3), at least five are suspected to have biological warfare programs. There is no evidence at this time, however, that any state has provided biological weapons expertise to a terrorist organization (4).

A wide range of groups or individuals might use biological agents as instruments of terror. At the most dangerous end of the spectrum are large organizations that are well-funded and possibly state-supported. They would be expected to cause the greatest harm, because of their access to scientific expertise, biological agents, and most importantly, dissemination technology, including the capability to produce refined dry agent, deliverable in milled particles of the proper size for aerosol dissemination. The Aum Shinrikyo in Japan is an example of a well-financed organization that was attempting to develop biological weapons capability. However, they were not successful in their multiple attempts to release anthrax and botulinum toxin (4). On this end of the spectrum, the list of biological agents available to cause mass casualties is small and would probably include one of the classic biological agents. The probability of occurrence is low; however, the consequences of a possible successful attack are serious.

Smaller, less sophisticated organizations may or may not have the intent to kill but may use biological pathogens to further their specific goals. The Rajhneeshees, who attempted to influence local elections in The Dalles, Oregon, by contaminating salad bars with *Salmonella* Typhimurium, are an example (5). Rather than having a sophisticated research program, these organizations could use biological pathogens that are readily available.

The third type are smaller groups or individuals who may have very limited targets (e.g., individuals or buildings) and are using biological pathogens in murder plots or to threaten havoc. The recent anthrax hoaxes are examples of this. Many biological agents could be used in such instances and the likelihood of their occurrence is high, but the public health consequences are low.

There are many potential human biological pathogens. A North Atlantic Treaty Organization handbook dealing with biological warfare defense lists 39 agents, including bacteria, viruses, rickettsiae, and toxins, that could be used as biological weapons (6). Examining the relationship between aerosol infectivity and toxicity versus quantity of agent illustrates the requirements for producing equivalent effects and narrows the spectrum of possible agents that could be used to cause large numbers of casualities. For example, the amount of agent needed to cover a 100-km^2 area and cause 50%

Address for correspondence: Mark G. Kortepeter, Operational Medicine Division, U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702-5011, USA; fax: 301-619-2312; e-mail: Mark_Kortepeter@DET.AMEDD.ARMY.MIL.

lethality is 8 metric tons for even a "highly toxic" toxin such as ricin versus only kilogram quantities of anthrax needed to achieve the same coverage. Thus, deploying an agent such as ricin over a wide area, although possible, becomes impractical from a logistics standpoint, even for a well-funded organization (7). The potential impact on a city can be estimated by looking at the effectiveness of an aerosol in producing downwind casualties. The World Health Organization in 1970 modeled the results of a hypothetical dissemination of 50 kg of agent along a 2-km line upwind of a large population center. Anthrax and tularemia are predicted to cause the highest number of dead and incapacitated, as well as the greatest downwind spread (8).

For further indication of which pathogens make effective biological weapons, one could look at the agents studied by the United States when it had an offensive biological weapons research program. Under that program, which was discontinued in 1969, the United States produced the following to fill munitions: *Bacillus anthracis,* botulinum toxin, *Francisella tularensis, Brucella suis*, Venezuelan equine encephalitis virus, staphylococcal enterotoxin B, and *Coxiella burnetti* (9). As a further indication of which pathogens have the requisite physical characteristics to make good biological weapons, one need only look next at the agents that former Soviet Union biological weapons experts considered likely candidates. The agents included smallpox, plague, anthrax, botulinum toxin, equine encephalitis viruses, tularemia, Q fever, Marburg, melioidosis, and typhus (10,11). Criteria such as infectivity and toxicity, environmental stability, ease of large-scale production, and disease severity were used in determining which agents had a high probability of use. Both the United States before 1969 and the former Soviet Union spent years determining which pathogens had strategic and tactical capability.

The National Defense University recently compiled a study of more than 100 confirmed incidents of illicit use of biological agents during this century (W.S. Carus, pers. comm. [4]). Of the 100 incidents, 29 involved agent acquisition, and of the 29, 19 involved the actual nongovernmental use of an agent, and most were used for biocrimes, rather than for bioterrorism. In the context of this study, the distinguishing feature of bioterrorism is that it involves the use of "violence on behalf of a political, religious, ecologic, or other ideologic cause without reference to the moral or political justice of the cause." The balance of incidents involved an expressed interest, threat of use, or an attempt to acquire an agent. In the 1990s, incidents increased markedly, but most have been hoaxes. The pathogens involved present a wide spectrum, from those with little ability to cause disease or disability, such as *Ascaris suum*, to some of the familiar agents deemed most deadly, such as *B. anthracis*, ricin, plague, and botulinum toxins (Table). During this period, the number of known deaths is only 10, while the total number of casualties is 990. However, the numbers should not give a false sense of security that mass lethality is not achievable by a determined terrorist group. The sharp increase in biological threats, hoaxes, information, and Internet sources on this subject seen in recent years indicates a growing interest in the possible use of biological pathogens for nefarious means (4).

In general, the existing public health systems should be able to handle most attempts to release biological pathogens. A working group organized by the Johns Hopkins Center for Civilian Biodefense Studies recently looked at potential biological agents to decide which present the greatest risk for a maximum credible event from a public health perspective. A maximum credible event would be one that could cause large loss of life, in addition to disruption, panic, and overwhelming of the civilian health-care resources (12).

To be used for a maximum credible event, an agent must have some of the following properties: the agent should be highly lethal and easily produced in large quantities. Given that the aerosol route is the most likely for a large-scale attack, stability in aerosol and capability to be dispersed (1 μm to 5 μm particle size) are necessary. Additional attributes that make an agent even more dangerous include being communicable from person to person and having no treatment or vaccine.

When the potential agents are reviewed for these characteristics, anthrax and smallpox are the two with greatest potential for mass casualties and civil disruption. 1) Both are highly lethal: the death rate for anthrax if untreated before onset of serious symptoms exceeds 80%; 30% of unvaccinated patients infected with

Table 1. Biological agents involved in bioterrorism or biocrimes[a]

	Traditional biological warfare agents	Agents associated with biocrimes and bioterrorism
Pathogens	*Bacillus anthracis*[b]	*Ascaris suum*
	Brucella suis	*Bacillus anthracis*[b]
	Coxiella burnetii[b]	*Coxiella burnetii*[b]
	Francisella tularensis	*Giardia lamblia*
	Smallpox	HIV
	Viral encephalitides	*Rickettsia prowazekii*
	Viral hemorrhagic fevers[b]	(typhus)
	Yersinia pestis[b]	*Salmonella* Typhimurium
		Salmonella typhi
		Shigella species
		Schistosoma species
		Vibrio cholerae
		Viral hemorrhagic fevers (Ebola)[b]
		Yellow fever virus
		Yersinia enterocolitica
		Yersinia pestis[b]
Toxins	Botulinum[b]	Botulinum[b]
	Ricin[b]	Cholera endotoxin
	Staphylococcal enterotoxin B	Diphtheria toxin
		Nicotine
		Ricin[b]
		Snake toxin
		Tetrodotoxin
Anti-crop agents	Rice blast	
	Rye stem rust	
	Wheat stem rust	

[a]Includes agents which were used, acquired, attempted to acquire, involved in a threat of use or an expressed interest in using. Reprinted with permission from Carus WS. Table 6: Biological agents involved. In: Carus WS. Bioterrorism and biocrimes: the illicit use of biological agents in the 20th Century. Working Paper, Center for Counterproliferation Research, National Defense University. August 1998, revised March 1999.
[b]These agents appear on both lists.

variola major could die. 2) Both are stable for transmission in aerosol and capable of large-scale production. Anthrax spores have been known to survive for decades under the right conditions (13). WHO was concerned that smallpox might be freeze-dried to retain virulence for prolonged periods (8). 3) Both have been developed as agents in state programs. Iraq has produced anthrax for use in Scud missiles and conducted research on camelpox virus, which is closely related to smallpox (2). A Soviet defector has reported that the former Soviet Union produced smallpox virus by the ton (11). 4) Use of either agent would have a devastating psychological effect on the target population, potentially causing widespread panic. This is in part due to the agents' well-demonstrated historical potential to cause large disease outbreaks (14). 5) Initial recognition of both diseases is likely to be delayed. For anthrax, this is secondary to the rare occurrence of inhalation anthrax. Only 11 cases of inhalation anthrax have been reported in the United States from 1945 to 1994 (15), and recognition may be delayed until after antibiotic use would be beneficial. For smallpox, given that few U.S. physicians have any clinical experience with the disease, many could confuse it for more common diseases (e.g., varicella and bullous erythema multiforme) early on, allowing for second-generation spread (12,16). 6) Availability of vaccines for either disease is limited. Anthrax vaccine, licensed in 1970, has been used for persons at high risk for contact with this disease. The U.S. military has recently begun vaccinating the entire force; however, there is limited availability of the vaccine for use in the civilian population. Routine smallpox vaccination was

discontinued in the United States in 1971. Recent estimates of the current number of doses in storage at CDC range from 5 to 7 million (12), but the viability of stored vaccine is no longer guaranteed.

Obtaining smallpox virus as opposed to other agents (e.g., anthrax, plague, and botulinum toxin) would be difficult, but if obtained and intentionally released, smallpox could cause a public health catastrophe because of its communicability. Even a single case could lead to 10 to 20 others. It is estimated that no more than 20% of the population has any immunity from prior vaccination (12). There is no acceptable treatment, and the communicability by aerosol requires negative-pressure isolation. Therefore, these limited isolation resources in medical facilities would be easily overwhelmed.

Anthrax can have a delayed onset, further leading to delays in recognition and treatment. In the outbreak of inhalation anthrax in Sverdlovsk in 1979, some patients became ill up to 6 weeks after the suspected release of anthrax spores (1). The current recommendation for prophylaxis of persons exposed to aerosolized anthrax is treatment with antibiotics for 8 weeks in the absence of vaccine or 4 weeks and until three doses of vaccine have been given (17). The amount of antibiotics required for postexposure prophylaxis of large populations could be enormous and could easily tax logistics capabilities for consequence management.

Other bacterial agents capable of causing a maximum credible event include plague and tularemia. Plague, like smallpox and anthrax, can decimate a population (as in Europe in the Middle Ages). An outbreak of plague could easily cause great fear and hysteria in the target population (as in the 1994 outbreak in India), when hundreds of thousands were reported to have fled the city of Surat, various countries embargoed flights to and from India, and importation of Indian goods was restricted (18). Both plague and tularemia are potentially lethal without proper treatment; however, the availability of effective treatment and prophylaxis may reduce possible damage to a population. Both are infectious at low doses. Pneumonic plague's person-to-person communicability and untreated case-fatality rate of at least twice that of tularemia make it more effective than tularemia as an agent to cause mass illness.

Other agents of concern include the botulinum toxins and viral hemorrhagic fevers. Once again, both are highly lethal. Botulinum toxin is a commonly cited threat, and Iraq has admitted to producing it. Since intensive care would be required in treating both illnesses and ventilator management is life-saving for botulinum, both would easily tax existing medical care facilities. However, botulinum toxin may be a less effective agent because of relatively lower stability in the environment and smaller geographic coverage than other agents demonstrated in modeling studies. Producing and dispensing large amounts are also difficult (W.C. Patrick, pers. comm.,19).

A number of different viruses can cause hemorrhagic fever. These include (but are not limited to) Lassa fever, from the Arenaviridae family; Rift Valley fever and Crimean Congo hemorrhagic fever, from the Bunyaviridae family; and Ebola hemorrhagic fever and Marburg disease, from the Filoviridae family. These organisms are potential biological agents because of their lethality, high infectivity by the aerosol route shown in animal models, and possibility for replication in tissue culture (16).

In summary, we know that biological pathogens have been used for biological warfare and terrorism, and their potential for future use is a major concern. Therefore we must be prepared to respond appropriately if they are used again. The technology and intellectual capacity exist for a well-funded, highly motivated terrorist group to mount such an attack. Although the list of potential agents is long, only a handful of pathogens are thought to have the ability to cause a maximum credible event to paralyze a large city or region of the country, causing high numbers of deaths, widescale panic, and massive disruption of commerce. Diseases of antiquity (including anthrax, smallpox, and plague), notorious for causing large outbreaks, still head that list. In addition, other agents, such as botulinum toxin, hemorrhagic fever viruses, and tularemia, have potential to do the same. By focusing on a smaller list of these low-likelihood, but high-impact diseases, we can better prepare for potential intentional releases, and hope to mitigate their ultimate impact on our citizens.

Many other pathogens can cause illness and death, and the threat list will always be dynamic.

We must, therefore, have the appropriate surveillance system and laboratory capability to identify other pathogens, and we must improve our public health and medical capabilities to respond to the short list of the most dangerous naturally occurring biological pathogens that could be used as bioterrorism weapons.

Dr. Kortepeter is a preventive medicine officer in the Operational Medicine Division at the U.S. Army Medical Research Institute of Infectious Diseases, where he teaches the medical management of biological weapons casualties.

Dr. Parker is Commander, U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, MD. USAMRIID conducts research to develop vaccines, medications, and diagnostics to protect U.S. service members from biological warfare threats and endemic infectious diseases.

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Epidemiology of Bioterrorism

Julie A. Pavlin
Walter Reed Army Institute of Research, Washington, D.C., USA

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.

Address for correspondence: Julie A. Pavlin, Department of Field Studies, Division of Preventive Medicine, Walter Reed Army Institute of Research, Washington, D.C. 20307-5100, USA; fax: 202-782-0613; e-mail: pavlinj@wrsmtp-ccmail.army.mil.

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.

Major Pavlin is chief of the Field Studies Department, Division of Preventive Medicine, Walter Reed Army Institute of Research. She has worked in the area of medical biodefense education. Currently she is developing national and international surveillance systems for emerging diseases with the Department of Defense's Global Emerging Infections Surveillance and Response System.

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Vaccines in Civilian Defense Against Bioterrorism

Philip K. Russell
Johns Hopkins School of Public Health, Baltimore, Maryland, USA

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.

Address for correspondence: Philip K. Russell, Johns Hopkins Center for Civilian Biodefense Studies, Candler Building, Suite 850, 111 Market Place, Baltimore, MD 21202, USA; fax: 410-223-1665; e-mail: biodefen@jhsph.edu.

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.

Dr. Russell is professor, Center for Immunization Research, Johns Hopkins School of Public Health; former Commander, United States Army Medical Research and Development Command.

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

Kathryn C. Zoon
U.S. Food and Drug Administration, Rockville, Maryland, USA

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

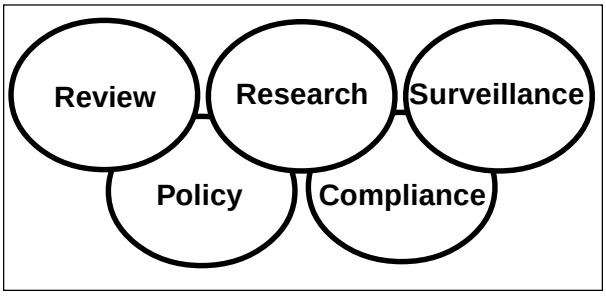

Figure 1. Regulation of medical products.

Address for correspondence: Kathryn C. Zoon, Center for Biologics Evaluation and Research, Food and Drug Administration, Mailstop HFM-1, 1401 Rockville Pike, Rockville, MD 20852, USA; fax: 301-827-0440; e-mail: zoon@cber.fda.gov

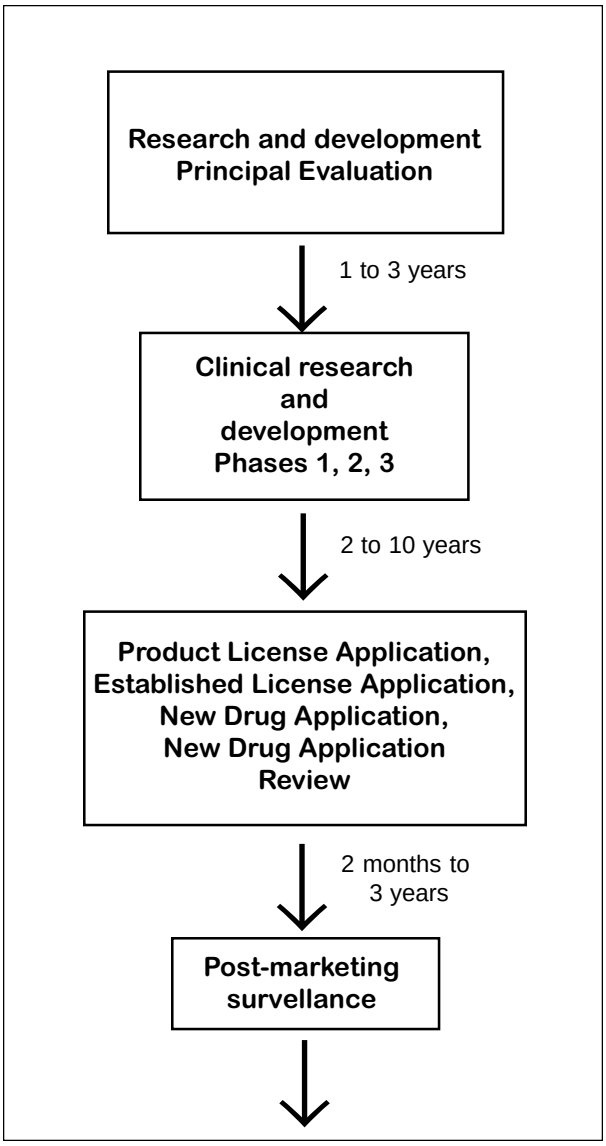

Figure 2. Development of biological and tradition drug products.

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.

Dr. Zoon is director of the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. As former director of the Division of Cytokine Biology in CBER, Dr. Zoon was actively involved with regulatory issues related to cytokines, growth factors, studies on interferon purification and characterization, and interferon receptors.

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Smallpox: Clinical and Epidemiologic Features

D. A. Henderson
Johns Hopkins Center for Civilian Biodefense Studies,
Baltimore, Maryland, USA

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.

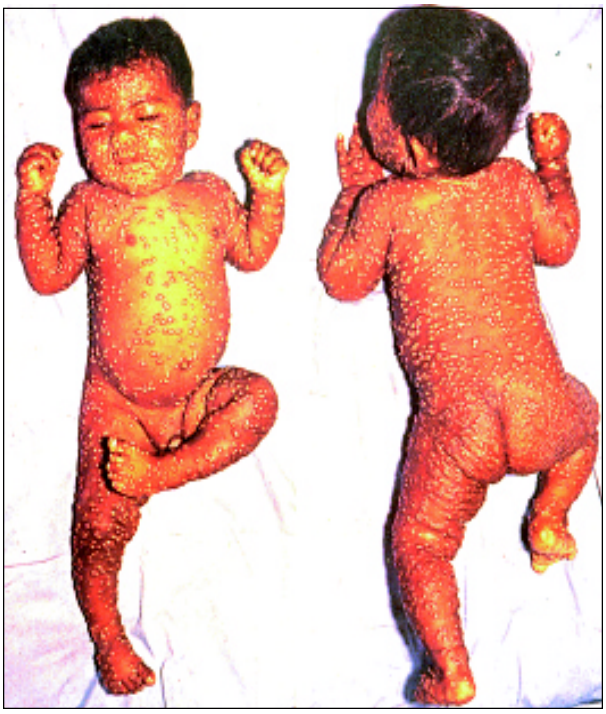

Figure 1. Most cases of smallpox are clinically typical and readily able to be diagnosed. Lesions on each area of the body are at the same stage of development, are deeply embedded in the skin, and are more densely concentrated on the face and extremities.

Address for correspondence: D. A. Henderson, Johns Hopkins Center for Civilian Biodefense Studies, 111 Market Place, Ste. 850, Baltimore, MD 21202, USA; fax: 410-223-1665; e-mail: dahzero@aol.com.

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;

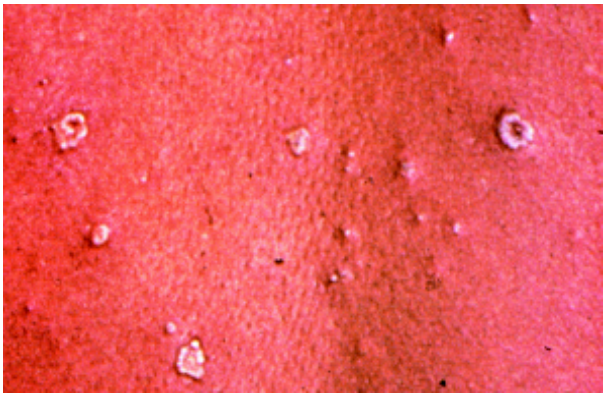

Figure 2. The lesions of chickenpox develop as a series of "crops" over several days and are very superficial. Papules, vesicles, pustules, and scabs can be seen adjacent to each other. The trunk is usually more affected than the face or extremities.

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.

Dr. Henderson is a distinguished service professor at the Johns Hopkins University, holding an appointment in the Department of Epidemiology. Dr. Henderson directed the World Health Organization's global smallpox eradication campaign (1966-1977) and helped initiate WHO's global program of immunization in 1974. He also served as deputy assistant secretary and senior science advisor in the Department of Health and Human Services.

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Smallpox: An Attack Scenario

Tara O'Toole
Johns Hopkins School of Public Health, Baltimore, Maryland, USA

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

Address for correspondence: Tara O'Toole, Johns Hopkins Center for Civilian Biodefense Studies, Candler Building, Suite 850, 111 Market Place, Baltimore, MD 21202, USA; fax: 410-223-1665; e-mail: biodefen@jhsph.edu.

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

Jason Bardi
Johns Hopkins University, Baltimore, Maryland, USA

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.

Address for correspondence: Jason Bardi, Johns Hopkins University, Center for Civilian Biodefense Studies, 111 Market Place, Ste. 850, Baltimore, MD 21202, USA; fax 410-223-1665; jsb14@jhunix.hcf.jhu.edu.

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.

Mr. Bardi is a freelance writer in Baltimore who holds degrees in biophysics and science writing from Johns Hopkins University.

Clinical and Epidemiologic Principles of Anthrax

Theodore J. Cieslak and Edward M. Eitzen, Jr.
U.S. Army Medical Research Institute of Infectious Diseases,
Ft. Detrick, Maryland, USA

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

Address for correspondence: Theodore J. Cieslak, Operational Medicine Division, USAMRIID, 1425 Porter Street, Ft. Detrick, MD 21702, USA; fax: 301-619-2312, e-mail: Ted_Cieslak@Detrick.Army.Mil.

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.

Dr. Cieslak is chief of Field Operations Department in the Division of Operational Medicine at the U.S. Army Medical Research Institute of Infectious Diseases at Ft Detrick, MD. Dr. Cieslak is working in the area of medical defense against biological warfare and terrorism.

Dr. Eitzen is chief of the Division of Operational Medicine at the U.S. Army Medical Research Institute of Infectious Diseases and adjunct associate professor of pediatrics and of military and emergency medicine at the Uniformed Services University of the Health Sciences in Bethesda, Maryland. He has worked in the area of medical defense against biological warfare and terrorism for the past 8 years.

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Anthrax: A Possible Case History

Thomas V. Inglesby
Johns Hopkins School of Medicine, Baltimore, Maryland, USA

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.

Address for correspondence: Thomas V. Inglesby, Johns Hopkins Center for Civilian Biodefense Studies, Candler Building, Suite 850, 111 Market Pl., Baltimore, MD 21202, USA; fax: 410-223-1665; e-mail: tvi@welchlink.welch.jhu.edu.

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?

Dr. Inglesby is assistant professor in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine. He works primarily with the Johns Hopkins Center for Civilian Biodefense Studies. He is also a physician, treating patients with human immunodeficiency virus at the Moore Clinic of the Johns Hopkins Hospital.

Applying Lessons Learned from Anthrax Case History To Other Scenarios

John G. Bartlett
Johns Hopkins School of Medicine, Baltimore, Maryland, USA

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.

Address for correspondence: John G. Bartlett, Johns Hopkins Center for Civilian Biodefense Studies, Candler Building, Suite 850, 111 Market Place, Baltimore, MD 21202, USA; fax: 410-223-1665; e-mail: biodefen@jhsph.edu.

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.

Dr. Bartlett is professor and chief of the Division of Infectious Diseases, Johns Hopkins University School of Medicine and president of the Infectious Diseases Society of America.

Addressing Bioterrorist Threats: Where Do We Go from Here?

Margaret A. Hamburg
Department of Health and Human Services, Washington, D.C., USA

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

Address for correspondence: Margaret A. Hamburg, Office of Planning and Evaluation, Department of Health and Human Services, HHH Building, Room 415F, 200 Independence Avenue, S.W., Washington, D.C. 20201, USA; fax: 202-690-7383.

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.

Dr. Hamburg is assistant secretary for Planning and Evaluation, U.S. Department of Health and Human Services, and former commissioner of health for the City of New York.

The Surveillance of Vero Cytotoxin-Producing *Escherichia coli* O157 in Wales, 1990 to 1998

Rachel M. Chalmers,* Sharon M. Parry,† Roland L. Salmon,* Robert M.M. Smith,* Geraldine A. Willshaw,‡ and Tom Cheasty‡
*Public Health Laboratory Service Communicable Disease Surveillance Centre, Cardiff, United Kingdom; †Welsh Combined Centres for Public Health, Cardiff, United Kingdom; ‡Central Public Health Laboratory, Colindale, London, United Kingdom

Population-based surveillance for Vero cytotoxin-producing *Escherichia coli* (VTEC) O157 has been carried out in Wales since 1990. The annual incidence has remained stable during the 9-year period (mean: 1.6 cases per 100,000 population); the rate is highest in children younger than 5 years of age. Blood in the stool is reported in fewer than half the cases, indicating the importance of screening all fecal specimens for VTEC O157.

Vero cytotoxin-producing *Escherichia coli* serogroup O157 (VTEC O157) was first recognized as a human pathogen in 1982 (1). Infection results in symptoms ranging from mild diarrhea to hemorrhagic colitis (abdominal pain, diarrhea, and blood in the stool). Hemolytic uremic syndrome (HUS), characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal failure, develops in 2% to 7% of cases (2). The number of laboratory isolations of VTEC O157 from human infections in England and Wales has risen from 76 in 1986 (3) to 1,087 in 1997 (4). However, the number of laboratories examining feces for VTEC O157 has increased in England, as have protocols emphasizing the importance of laboratory examination. Many surveillance networks worldwide have selection criteria for testing for VTEC O157, such as the presence of blood in the stools and clinical or age parameters (5). In contrast, population-based surveillance has been undertaken in Wales since February 1990, with all first-time acute-phase fecal specimens tested for VTEC O157 (6). The objectives of this surveillance are to measure the incidence of VTEC O157, identify outbreaks of infection, and describe the persons involved and the microbiologic characteristics of the isolates. We report on 9 years of surveillance through the end of 1998. Since the system is population-based, the figures differ from those in some published reports of specimens submitted to the reference laboratory (4,7,8).

Fecal samples were cultured on Sorbitol MacConkey agar (Oxoid, Basingstoke, UK) and incubated at 37°C for 18 hours (3). Sorbitol nonfermenting colonies were tested for latex agglutination with O157 antiserum (Oxoid) and were biochemically confirmed as *Escherichia coli* by API 20E (BioMerieux sa69280 Marcy L'Etoile, France). Laboratories were asked to send all presumptive VTEC O157 isolates to the Laboratory of Enteric Pathogens, Central Public Health Laboratory, London, for confirmation, phage-typing, and Vero cytotoxin typing (8).

Cases, defined as "isolation of VTEC, confirmed by standard methods, from a fecal specimen submitted by a resident of Wales," were reported to the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC) (Wales). Nine cases were excluded because the *E. coli* O157 isolate did not express Vero cytotoxin genes. Epidemiologic and clinical information was recorded on a standard structured questionnaire. Household contacts were screened where practicable and were included if they met the case definition. HUS,

Address for correspondence: Rachel Chalmers, PHLS CDSC (Wales), Abton House, Wedal Road, Cardiff CF4 3QX, United Kingdom; fax: 44-1-222-521-987; e-mail: rachel.chalmers @cdsc.wales.nhs.uk.

which in the United Kingdom is defined as renal impairment including oligouria and plasma creatinine elevated for age, microangiopathic hemolytic anemia, and thrombocytopenia, was diagnosed clinically.

The annual incidence was calculated by using as the denominator the mid-year population estimates for Wales (Office of National Statistics [ONS]), and the age and sex distribution of patients was calculated by using the mid-1996 population estimate (ONS). The Poisson distribution was used to calculate 95% confidence intervals (CI) for age-specific rates. To assess seasonality, the frequency of cases by month of onset was examined. (For asymptomatic cases, the date of the sample was used.) Incidence by health authority areas was calculated by using post-1996 boundaries. The proportions of cases with various symptoms were determined, and 95% CI were calculated by using standard error of proportions. The duration of illness (up to the date of interview), admission to hospital and length of stay, and proportion with HUS (95% CI) were calculated.

From 1990 through 1998, 415 cases were reported (mean = 1.6 per 100,000 population per year), with little change in incidence (1.0 per 100,000 population in 1994 to 2.8 per 100,000 population in 1995, when an outbreak of 49 cases occurred) (Table 1) (9). Seventy-four cases (17.8%) were part of six outbreaks involving Welsh residents (Table 1). Three of the outbreaks have been reported elsewhere (9-11). The remaining 341 (82.2%) were sporadic cases, of which 283 (83.0%) were index cases (the first reported from each household) (from 72.3% in 1998 to 96.2% in 1993). Fifty-eight (17.0%) sporadic cases were in household contacts; 26 of these patients had diarrhea, including five with blood in the stools.

Of 415 patients, 207 (49.9%) were males, ages 3 months to 89 years (mean = 25 years, median = 18 years, mode = 1). The incidence of VTEC O157 was highest in children younger than 5 years (8.8 per 100,000 population) (Table 2). The number of cases peaked in August, and more than half (227) of the cases occurred during July, August, and September. Only four cases occurred during December. Cases were reported from all five health authority areas in Wales. The highest incidence was in the northern and western areas (North Wales and Dyfed/Powys) (mean annual incidences 2.5 and 2.4 per 100,000 population, respectively). The lowest incidences were reported in the more densely populated areas of Gwent (1.1 per 100,000), Bro Taf (1.1 per 100,000), and Iechyd Morgannwg (1.0 per 100,000).

Of the 415 patients, 339 (81.7%, CI = 78.3%-85.7%) had diarrhea, 259 (62.4%, CI = 57.3%-66.7%) reported abdominal pain, and 192 (46.3%, CI = 41.3%-50.7%) had blood in the stool; 172 (41.4%, CI = 36.3%-45.7%) had hemorrhagic colitis. One third of the patients reported vomiting (32.3%, CI = 27.5%-36.5%) or feeling feverish (34.0%, CI = 29.5%-38.5%); 62 (14.9%, CI = 11.5%-18.5%) were asymptomatic. The highest proportion of asymptomatic cases was in the 25- to 34-year-old age group (18 [40.1%] of 44) who are often the caretakers of symptomatic patients;

Table 1. Occurrence and annual incidence of VTEC O157 in Wales, 1990–1998

Year	Total no. of cases (rate per 100,000 population)	No. of sporadic cases (no. of index cases)	No. of outbreak cases	Outbreak summary (setting, mode of spread, phage and verotoxin types)
1990	32 (1.1)	28 (24)	4	Psychogeriatric ward, person to person, PT14, VT1&2.
1991	39 (1.3)	30 (28)	9	Day nursery, person to person, PT49, VT2.
1992	41 (1.4)	41 (33)	0	-
1993	34 (1.2)	26 (25)	8	Community, Meat from 1 shop, PT49, VT2.
1994	29 (1.0)	29 (24)	0	-
1995	82 (2.8)	33 (30)	49	Day nursery, person to person, PT2 VT2.
1996	38 (1.3)	38 (31)	0	-
1997	55 (1.9)	51 (41)	3	Home for the elderly mentally infirm, person to person, PT2, VT2.
			1	Part of a European outbreak
1998	65 (2.2)	65 (47)	0	

Table 2. Age and sex distribution of cases of VTEC O157, Wales, 1990–1998

Age range	Total	Male	Female
<1	24 (7.9, CI = 4.9-11.9)	13 (8.3)	11 (7.5)
1-4	117 (9.0, CI = 7.4-10.7)	71 (10.7)	46 (7.2)
5-14	56 (1.6, CI = 1.2-2.1)	32 (1.8)	24 (1.4)
15-24	44 (1.4, CI = 1.0-1.8)	19 (1.1)	25 (1.6)
25-34	44 (1.2, CI = 0.8-1.6)	19 (1.0)	25 (1.3)
35-44	30 (0.9, CI = 0.6-1.2)	14 (0.8)	16 (0.9)
45-54	33 (1.0, CI = 0.7-1.3)	11 (0.6)	22 (1.3)
55-64	25 (0.9, CI = 0.6-1.5)	10 (0.7)	15 (1.1)
≥65	35 (0.9, CI = 0.5-1.1)	15 (0.9)	20 (0.8)
Total (mean)	415 (1.6, CI = 1.4-1.7)	207 (1.6)	208 (1.5)

Figures in parentheses are mean annual rates per 100,000 population, followed by 95% confidence intervals (CI) for age-specific rates.

in 17 cases HUS developed (4.1%, CI = 2.4%-6.5%), age range: 1 to 50 years (mean = 9 years, median = 3 years); 10 HUS patients were less than 1 to 4 years of age, for a complication rate in this age group of 8.5%.

Diarrheal illness lasted as long as 330 days (median and mode = 6 days); 118 (28.4%) patients were admitted to hospital. The length of stay, first recorded in 1994, was from 1 to 71 days (mode 1 day, median 4.0 days). The highest rate of hospitalization was among those >65 years old (25 [62.5%] of 40). The mean annual proportion of index cases hospitalized was 36.1% (24.0% in 1993 to 48.5% in 1992). From 1994 through 1998, only one person, an 88-year-old woman with diarrhea, died as a result of the infection.

Three hundred seventy-eight (91.1%) isolates were sent to the Laboratory of Enteric Pathogens for confirmation and typing. Of these, 62 (16.4%, CI = 6.4%-26.4%) had both verotoxin type (VT) 1 and VT2 genes, and 316 (83.6%, CI = 79.9%-87.3%) had VT2 only. Isolates belonged to at least 19 phage types (PT). The two most common PT were PT2 (160 isolates [42.3%]) and PT49 (48 isolates [12.7%]). Other PT accounting for 5% (19) or more isolates were PT1, PT4, PT8, and PT14. PT2 was the most common type in each year, with the exception of 1993, when PT49 predominated. PT and verotoxin type were linked: VT2-only strains included 98% (158 of 160) of the PT2 and all the PT49 isolates.

No relationship was found between the major PTs and clinical symptoms. More cases with strains producing VT1+2 had hemorrhagic colitis (39 [63.9%] of 61) than cases with VT2 only (120 [42.9%] of 280) (relative risk = 1.69, 95% CI = 1.18-1.88). In contrast, 16 of the 17 isolates from cases of HUS had the VT2 gene only. These isolates were predominantly PT2 (n = 10), but also included PT49 (n = 4), PT21 (n = 1) and RDNC (n = 1).

Foreign travel in the week before onset of symptoms was reported by 37 (8.9%) patients (0 in 1990 to 12 in 1998 [18.5%] of cases). The PTs among those who had traveled abroad differed from the overall pattern, the most common being PT8 (10 cases), RDNC (5 cases), and PT21 (4 cases).

Population-based surveillance of VTEC O157 in Wales has been undertaken since 1990 and is the most complete in the world. There is no evidence that pathology referrals have changed during the study period. General practitioners (primary-care physicians) were given no specific incentives for submitting specimens. Palmer et al. (12) showed that in 1996, 26% patients with suspected food poisoning attending general-practitioner clinics submitted fecal specimens. This is similar to the 27% reported during a study of patients with infectious gastroenteritis reporting to general practitioners in England (13). Although VTEC O157 is regarded as an emerging pathogen, in Wales its incidence has remained stable through 1998, and VTEC O157 is a rare (1.6 cases per 100,000 population) but serious disease.

Public health policy concerning VTEC O157 has been driven by the circumstances surrounding outbreaks (14). However, in Wales most cases (82.2%) occur sporadically, and because all first-time specimens and PTs are examined and epidemiologic investigations are conducted, it is unlikely that outbreaks were missed. The surveillance data, as well as providing a background against which to measure changes in incidence, have provided useful information about VTEC O157 infections. The presence of blood in the stool is often used in many countries as a criterion for examining for VTEC O157, yet fewer than half the Welsh patients reported the presence of blood, demonstrating the value of screening all acute-phase fecal specimens. Although 14.9% of cases were asymptomatic, the risk for transmission is still present because of the low infectious dose (11).

Strains of VTEC O157 can be differentiated rapidly by PT and Vero cytotoxin typing, although even from apparently sporadic cases a large number of isolates belonged to a few types, predominantly PT2/VT2 and PT49/VT2. Determining the VT produced appears to be a

microbiologic marker of severity, since hemorrhagic colitis was more often associated with VT1+2 strains, and all the cases complicated by HUS had VT2-only strains. These strains are consistently more prevalent than other VT types in cases of HUS in the United Kingdom (7) and elsewhere. Demonstration of VT by phenotypic tests or the presence of VT genes is definitive for VTEC O157. The presence of the H7 antigen is closely associated with VT positivity but is of secondary importance, as a significant minority of VTEC O157 isolated in England and Wales (14%-20% in 1992-1994) are nonmotile (8). There was some annual variation in PTs, although as in England the predominant phage type was PT2.

As with other surveillance reports, the highest incidence was in children younger than 5 years of age (8). Although fecal specimens are more likely to be available for this age group, the isolation rate is also high (6), and person-to-person spread is most likely (15). In Wales, person-to-person spread was the most important factor in four out of five outbreaks, including those in the children's day nurseries, which were the setting for the two largest outbreaks.

Continued surveillance for VTEC O157 will provide timely reporting of cases and detection and containment of outbreaks. Ongoing surveillance over the last 9 years in Wales has provided valuable information about VTEC O157 infections and demonstrated the wide range of associated clinical illness.

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Dr. Chalmers is a senior scientist with the U.K. Public Health Laboratory Service Communicable Disease Surveillance Centre in Cardiff. She has a research background in veterinary microbiology and protozoology and current interests in the epidemiology of occupational and food- and waterborne zoonoses.

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A Focus of Deer Tick Virus Transmission in the Northcentral United States

Gregory D. Ebel, Ivo Foppa, Andrew Spielman, and Sam R. Telford, III
Harvard School of Public Health, Boston, Massachusetts, USA

We screened salivary glands from adult deer ticks collected near Spooner and Hayward, Wisconsin, to determine whether deer tick virus, a recently described flavivirus, occurs with other tickborne agents in the upper Midwest. Intraacinar inclusions suggestive of replicating virus were detected in 4 (4.6%) of 87 ticks. The virus was isolated by suckling-mouse inoculation.

Pathogens transmitted by deer ticks (*Ixodes dammini*) affect the health of residents in areas of the northcentral United States. The diversity of infecting agents, the intensity of their transmission, and the concomitant risk for human infection are well documented and approach levels found in the Northeast (1-4). In northwestern Wisconsin, the risk to health from these ticks may increase as human recreational and industrial activities more frequently intersect with areas of enzootic transmission. In addition to the agents of Lyme disease (*Borrelia burgdorferi*), human granulocytic ehrlichiosis (*Ehrlichia microti*), and human babesiosis (*Babesia microti*), deer ticks in these foci might be infected with deer-tick virus (DTV), a recently described Powassan (POW)-like agent of the genus Flavivirus (5), and might pose an additional threat to human health in this region.

To determine whether this newly recognized agent infects deer ticks in a focus outside New England, we sampled ticks from two heavily infested sites in northern Wisconsin and assayed them for all four agents. Host-seeking adult ticks were collected by dragging a piece of flannel cloth over the vegetation during October of 1997 and 1998. We collected 481 adult deer ticks near Spooner and Hayward, Wisconsin, during 8 hours of sampling. A sample of the female ticks (87 of 271) was selected for analysis. Nonengorged female ticks were fed on uninfected laboratory rabbits to stimulate replication of infectious organisms and were removed after 4 to 5 days. Ticks were dissected individually on acid-washed microscope slides by using flame-sterilized forceps and razor blades. One of each pair of salivary glands was stained by the Feulgen reaction and examined by bright-field microscopy. The other was pooled with the salivary glands of four other ticks in Hanks' Balanced Salt Solution supplemented with fetal bovine serum (HBSS/FBS) for mouse inoculation and polymerase chain reaction (PCR) analysis. The slides used for dissection were examined for *B. burgdorferi* by direct fluorescent antibody (6). Male ticks were assayed for spirochetal infection only; they were homogenized in 50 µl PBS, and 10 µl of the resulting suspension was applied to 12-well microscope slides, air dried, and stained.

Deer ticks sampled near Spooner and Hayward, Wisconsin, maintain pathogens similar to those found in New England ticks and in comparable proportions (Table). In addition to the three agents enzootic near Spooner (4,7,8), we observed a staining pattern suggestive of viral replication (5) in the salivary glands of four ticks. To determine whether this agent was viral, we inoculated suckling mice intracerebrally with 0.03 ml of a clarified and sterile-filtered homogenate of the combined pools containing Feulgen-positive salivary glands. A sample of this homogenate was reserved for reverse transcriptase (RT)-PCR analysis. Siblings of suckling mice received 0.03 ml of sterile HBSS/FBS. On the morning of day 6 after inoculation, the mice that received salivary gland homogenate showed signs of profound neurologic dysfunction: their gait was disrupted, and they

Address for correspondence: Sam R. Telford, III, Department of Immunology and Infectious Diseases, 665 Huntington Avenue, Boston, MA 02115, USA; fax: 617-738-4914; e-mail: stelford@hsph.harvard.edu.

Table. Pathogens maintained by deer ticks, Spooner and Hayward, Wisconsin, 1997-98

Agent	Assay	No. examined	No. positive	% positive (95% CI)
Borrellia burgdorferi	Direct fluorescent antibody	220	83	37.7 (31.3, 44.5)
Babesia sp.	Microscopy	87	6	6.9 (2.6, 14.4)
Ehrlichia microti	Microscopy	87	4	4.6 (1.3, 11.4)
Deer tick virus	Microscopy	87	4	4.6 (1.3, 11.4)

failed to right themselves when placed on their backs. By mid-afternoon they were moribund and died shortly thereafter. The time between inoculation and death was similar to that seen in DTV and POW infections, which kill suckling mice in 5 to 7 days (5,9).

To determine whether the putative viral agent was DTV, POW, or a related flavivirus, salivary glands that appeared infected were analyzed by RT-PCR. The clarified homogenate used for mouse inoculation was added to 350 µl of a lysis buffer, and RNA was extracted by RNEasy spin columns (Qiagen) as directed by the manufacturer. The resulting RNA-containing solution was reverse transcribed by using random hexamers at 42°C for 20 minutes. We added 5 µl of cDNA to an amplification mixture containing primers (TBE-1[5'-3' ACATGGCAGTACTGGGG) and TBE-2 (5'-3' CCCATCATGTTGTACAC]) designed to amplify an approximately 450-bp fragment of the *ns5* gene of Central European tickborne encephalitis (TBE). Reaction conditions were as follows: initial denaturation at 94°C for 1 minute, followed by 35 cycles of 94°C for 45 seconds, 40°C for 45 seconds, and 72°C for 1 minute. A final extension step of 72°C for 6 minutes was also performed. Bands of the correct size were excised and sequenced by the dideoxy-chain termination method and an automated DNA sequencer (Applied Biosystems, Foster City, CA). Sequences were compared with those accessioned in GenBank. Sequence alignments were generated with the PILEUP program of the Wisconsin Genetics Computer Group and then analyzed by the distance method using MEGA (10). Third codon positions were omitted to minimize sequence convergence due to homoplasy and to better reflect nucleotide changes resulting in amino acid differences. Analyses including third codon positions resulted in identical topologies with higher bootstrap values and longer branch lengths. Evolutionary distances were computed by the Kimura 2-parameter method, including both transitions and transversions. Distance trees were constructed by the neighbor-joining method, and their robustness was estimated by performing 500 bootstrap replicates. Phylogenetic analysis of this fragment (GenBank accession af135459) indicated that the virus was most closely related, but not identical, to DTV from northwestern Connecticut (af135460) (Figure 1). Because the *ns5* gene from our Spooner isolate was more closely related to DTV than to POW, this isolate is provisionally designated as deer-tick virus-Spooner (DTV-SPO).

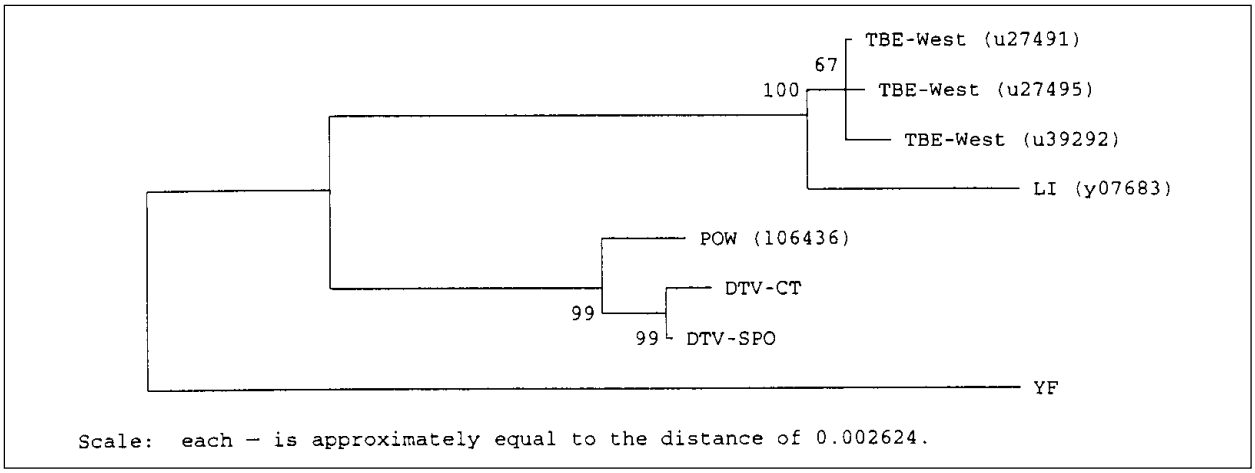

Figure 1. Phylogenetic relationships among tickborne flaviviruses based on a 376-bp fragment of the *ns5* gene. Distance analysis omitting third position nucleotides. Branch numbers are bootstrap confidence estimates on the basis of 500 replicates. GenBank accession numbers in parentheses. LI = Louping Ill; TBE-West = Western subtype tickborne encephalitis (Central European encephalitis); POW = Powassan virus; DTV = deer tick virus.

To more completely characterize the Wisconsin viral isolate, we amplified a 650-bp fragment of the viral envelope gene from the suckling mouse brain tissue. Extraction and reverse-transcription of RNA was conducted as previously described; PCR were also conducted as described, except that the primers ENV-A and POW-6 were used (5). PCR products were subjected to electrophoresis on a 2% agarose gel, yielding a product of the expected size, which was subsequently excised and sequenced. The nucleotide sequence of this fragment differs by 16% and 4% from published POW and DTV sequences, respectively. Phylogenetic analysis of this fragment (af135461) confirmed that the Spooner isolate clusters with DTV and POW (Figure 2).

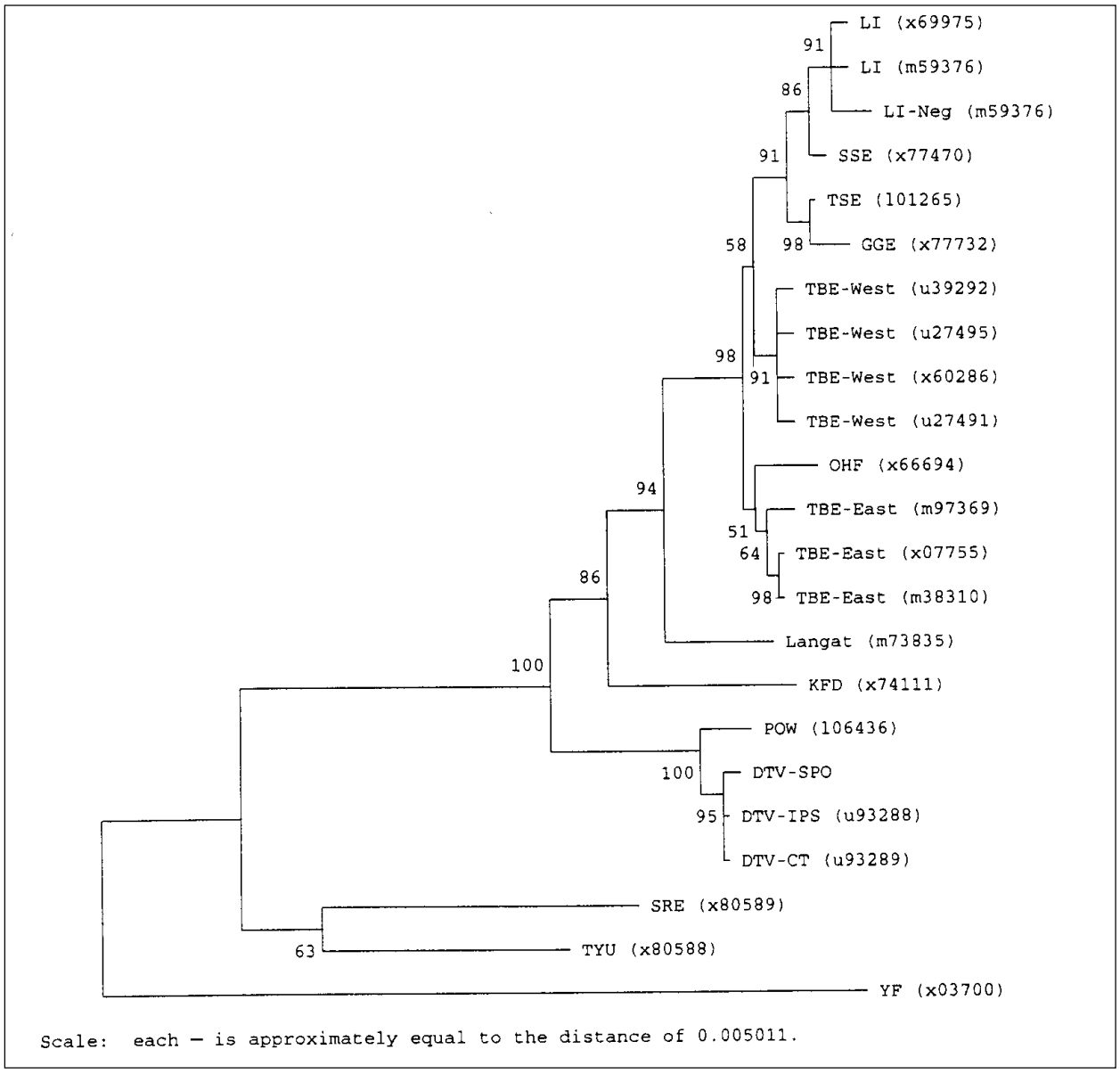

Figure 2. Phylogenetic relationships among tickborne flaviviruses on the basis of a 575-bp fragment of the envelope gene. Distance analysis omitting third position nucleotides. Branch numbers are bootstrap confidence estimates on the basis of 500 replicates. GenBank accession numbers in parentheses. LI = Louping Ill; SSE = Spanish sheep encephalitis; TSE = Turkish sheep encephalitis; GGE = Greek goat encephalitis; TBE-West = Western subtype tickborne encephalitis (Central European encephalitis); OHF = Omsk hemorrhagic fever; TBE-East = Eastern subtype tickborne encephalitis (Russian spring-summer encephalitis); KFD = Kyasanur Forest disease; POW = Powassan encephalitis; DTV = deer tick virus; SRE = Saumarez Reef virus; TYU = Tyuleniy virus; YF = yellow fever.

The resulting topology was virtually identical to that of other published trees analyzed by means of different optimality criteria (11,12).

This is the first report of an isolation of a TBE-group flavivirus from Wisconsin, and only the second report of a flavivirus in deer ticks. The antigenic relatedness of DTV and POW has not yet been determined. Arboviral classification has been on the basis of serologic methods (International Catalogue). A fourfold or greater difference in titer measured by one or more serologic tests (neutralization, complement fixation) between homologous and heterologous antisera raised to the viruses being compared is considered to support novelty (15). However, molecular phylogenetic analyses are increasingly becoming routine and can rapidly provide information on relatedness. Initial findings may subsequently be complemented by the time-tested serologic techniques. This paradigm for viral identification, where an agent of unknown pathogenic potential may be initially examined by PCR sequencing, has been recently used with much success with hantaviruses. New York virus, for example, was suggested to be a distinct subtype of Sin Nombre virus because its nucleocapsid protein gene sequence differed by 10% to 12% (16). Other northeastern U.S. hantavirus isolates from *Peromyscus leucopus* clustered with each other in phylogenetic analysis (forming a "clade") rather than with Sin Nombre virus from the southwestern United States. Similarly, despite the geographic distance of their transmission foci, DTV-SPO forms a clade with the two original DTV isolates from New England rather than with the sole molecularly characterized POW isolate, which derives from nearby Ontario. Accordingly, although conclusions regarding the novelty of DTV should be regarded as tentative pending serologic studies, molecular evidence strongly suggests that DTV is a new subtype of POW.

The clinical implications of human infection with DTV are not known. Powassan encephalitis, however, often follows a severe clinical course, with a 10.5% case-fatality rate and severe sequelae (hemiplegia, wasting, severe headaches) in 47.1% of survivors (9). The genetic distance (Figure 2) between DTV and POW isolates is roughly similar to the difference between eastern TBE isolates (Russian spring-summer encephalitis) and Omsk hemorrhagic fever, viruses with radically different clinical presentations. We suspect that in contrast to infection with POW, human disease caused by DTV may be mild or asymptomatic. Although residents of northeastern and midwestern states are heavily exposed to deer ticks, an associated severe neurologic disease has not yet been described. Prevalence of DTV in host-seeking adult deer ticks was similar to that of the human granulocytic ehrlichiosis agent (4.3%), which indicates that residents of this region may be exposed frequently to the bites of DTV-infected ticks, and perhaps even more frequently than residents of our New England study sites (5). Alternatively, we may fortuitously have sampled in Wisconsin in an intense focus of transmission. European TBE group viruses persist in such enzootic microfoci, located within larger regions of lesser overall prevalence (14). Because these foci are so small, few residents of the region are exposed. The distribution of DTV, like that of babesiosis and Lyme disease, may spread from its initial foci to exposing the residents of much broader regions.

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Mr. Ebel is a doctoral candidate in the Laboratory of Public Health Entomology, Department of Immunology and Infectious Diseases. His research interests focus on the population biology of deer tick- and small-mammal-associated viruses.

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Dengue Reemergence in Argentina

G. Avilés,* G. Rangeón,† V. Vorndam,‡ A. Briones,§ P. Baroni,* D. Enria,* and M.S. Sabattini*

*Instituto Nacional de Enfermedades Virales Humanas (INEVH) "Dr. J.I. Maiztegui", Administración Nacional de Laboratorios e Institutos de Salud "Dr. C. Malbrán", Pergamino, Argentina; †Ministerio de Salud, Salta, Argentina; ‡Centers for Disease Control and Prevention, San Juan, Puerto Rico; and §Delegación Sanitaria Federal, Salta, Argentina

Aedes aegypti, eradicated from Argentina in 1963, has now reinfested the country as far south as Buenos Aires. In 1997, four persons with travel histories to Brazil, Ecuador, or Venezuela had confirmed dengue, and surveillance for indigenous transmission allowed the detection of 19 dengue cases in Salta Province. These cases of dengue are the first in Argentina since 1916 and represent a new southern extension of dengue virus.

Dengue History in Argentina

Several cases of dengue fever were reported in Argentina at the beginning of this century. Indigenous cases were reported in 1905, 1911, and 1916 in northern Argentina (Chaco, Corrientes, Formosa, and Misiones Provinces) (1). In February and March 1916, an epidemic with 15,000 reported cases occurred in Entre Rios Province along the Uruguay and Paraná Rivers in eastern Argentina. None of these patients had hemorrhagic symptoms. Since this epidemic, no indigenous cases had been reported until 1997 (1).

Aedes aegypti

In 1955, when the *Aedes aegypti* eradication campaign began in Argentina, an estimated 1,500,000-km^2 area was infested (Figure 1) (1). Santiago del Estero Province had the highest infestation rate, with *Ae. aegypti* found in 9.4% of localities and 5.3% of houses. This province is characterized by a warm summer and low socioeconomic conditions, with many houses lacking running water (1). The southern extension of *Ae. aegypti* distribution was 35 degrees south, the latitude of Buenos Aires (1). Buenos Aires was only minimally affected, with only 6 of 199,172 houses infested. By 1963, *Ae. aegypti* was considered eradicated from the country (1), but in 1986 the National Ministry of Health reported reinfestation in the north (2). The reinfested area is the area that was infested in 1955, including Salta Province. Buenos Aires Province was reinfested in 1991 and the Federal District in 1995 (2,3). In autumn 1997, high infestation levels (35% in 1996 and 18% in 1997) were found in houses in Buenos Aires Province and the Federal District (3). In Villa María, Córdoba Province (32 degrees south), *Ae. aegypti* was found in summer (February) of 1995, disappeared in winter, and reappeared in early

Figure 1. Geographic distribution of *Aedes aegypti,* 1955: Dengue risk area in Argentina.

Address for correspondence: G. Avilés, Instituto Nacional de Enfermedades Virales Humanas "Dr. Julio I. Maiztegui", Monteagudo 2510 (2700) Pergamino, Argentina; fax: 54-24-774-33045; e-mail: Gaby@inevh.sld.ar.

summer (December 1995) (4). The mosquito was also found in Buenos Aires Province (Zárate and Campana, 34.2 degrees and 34.4 degrees south, respectively) in February 1996 and October 1996 (early spring) (Avilés G, unpublished data). These findings indicate that *Ae. aegypti* may spend winter in refuges in temperate areas and may not necessarily be reintroduced during summer.

The presence of *Ae. aegypti* in most of the country and the reappearance of dengue fever in neighboring countries (Brazil, Paraguay, and Bolivia) increases the risk for dengue infection in Argentina. The Instituto Nacional de Enfermedades Virales Humanas "Dr. J.I. Maiztegui" is the National Reference Center of Dengue Diagnosis. This article summarizes the first dengue cases diagnosed in Argentina in recent years and documents the southernmost expansion of dengue in South America.

The Study

DEN 1 HAW, DEN 2 NGC, DEN 3 H87, and DEN 4 H241 strains were obtained from the Centers for Disease Control Laboratory, San Juan, Puerto Rico. Plaque reduction neutralization tests (PRNTs) were performed as described by Russel et al. (5), with an 80% plaque reduction endpoint. The enzyme-linked immunosorbent assay (ELISA) capture IgM test was done as described by Innis et al. (6) and Kuno et al. (7). Polymerase chain reaction (PCR) was done according to the protocol of Lanciotti et al. (8). The isolation attempts and immunofluorescence tests were done by injecting sera into C6/36 cells and using monoclonal antibodies against each of the serotypes (9).

Study Area

Salta Province is located in northwestern Argentina (Figure 2) in the subtropical area between 22° and 26°, 30 minutes south. A serosurvey was done in Orán, Salvador Mazza, and Guemes (Figure 2). Active surveillance was also conducted in Tartagal. Median temperatures in northern localities (Tartagal and Orán) are 26°C in summer and 19°C in winter. In Salta city the median temperatures are 22°C in summer and 15°C in winter.

Figure 2. Surveillance for dengue virus infections in Salta Province: Localities with cases.

Study Participants

Blood samples were collected at regional hospitals from patients seeking treatment for any illness.

Surveillance of Imported Cases

During the epidemiologic surveillance of the cases compatible with dengue, from January to November 1997 our laboratory received 16 samples from returning travelers who had suspected dengue (Table 1). Sera of four patients, returning from Brazil, Ecuador, and Venezuela, were positive by IgM-capture-ELISA. Cases from Ecuador and Venezuela were positive by PRNT, but the serotype could not be determined because of cross-reactions, possibly indicating secondary flavivirus infections.

Table 1. Imported dengue cases-Argentina, 1997

Patient no.	Travel history	Onset of symptoms	MAC-ELISA	Plaque reduction neutralization tests D1	D2	D3	D4
1	Brazil	02/14/97	Pos	---	---	---	---
2	Ecuador	unknown/97	Pos	1,280	1,280	80	<20
3	Venezuela	11/16/97	Pos	---	---	---	---
4	Venezuela	unknown/97	Pos	>1,280	>1,280	>1,280	>1,280

---Not done

Surveillance of Cases in Salta Province

A total of 404 sera were studied from Orán, Salvador Mazza, Santa Victoria, Tartagal, General Mosconi, Salta city, Junta del San Antonio, Aguaray, and Guemes during April through November 1997. Nineteen serologically positive samples were detected from four of these locations (Orán, Salvador Mazza, Tartagal, and Guemes) (Table 2). Twelve samples were positive by MAC-ELISA, indicating current or recent infections, and three of these had PRNT titers indicating primary DEN 2 infections. Three other samples had cross-reactive antibody patterns indicative of secondary flavivirus infections. Seven other samples were immunoglobulin (Ig)M negative, but positive by PRNT. Three of these showed PRNT titers indicating DEN 2 infections. Six additional samples were positive by PRNT, but the serotype could not be determined. Virus isolation attempts on 36 acute-phase samples had negative results, but one sample was diagnosed as dengue 2 by reverse transcriptase-PCR.

Epidemiologic and Clinical Data

We obtained epidemiologic and clinical information from nine patients. One, a man from Salvador Mazza, had fever, retroocular pain, malaise, muscle pain, and arthralgias and had traveled to Santa Cruz de la Sierra, Bolivia, before onset of symptoms. Seven other patients reported symptoms including headache, muscle pain, abdominal pain, arthralgias, rash, pharyngitis, and epistaxis. No hemorrhagic manifestations were reported. Six of these patients reported no travel history and must have become infected in Orán or Tartagal. Travel histories were not available from the other two patients.

Conclusions

Laboratory results show that imported cases of dengue arrived in Argentina during 1997, enabling local transmission in cities like Rosario and Buenos Aires. In northern Argentina, there is continuous traffic with Bolivia, Paraguay, and Brazil, where dengue is known to occur. We report early evidence of DEN 2 virus circulating in northern Argentina, where indigenous cases

Table 2. Surveillance for dengue virus infections, Salta Province, Argentina

Locality*	positive/ tested	Onset	ELISA IgM	PRNT D1	D2	D3	D4
Orán	6/161	--	Pos	20	320	80	<20
		--	Neg	80	80	160	20
		04/22/97**	--	<20	80	<20	<20
		04/28/97	--	20	>160	20	40
		05/16/97	Pos	640	1,280	640	80
		11/16/97	Pos	--	--	--	--
Salvador	7/113	--	Pos	<20	20	<20	<20
Mazza		--	Pos	<20	80	20	<20
		--	Pos	160	>640	>640	20
		--	Neg	<20	80	40	<20
		--	Neg	--	80	80	20
		--	Neg	20	40	--	<20
		--	Pos	<20	<20	<20	<20
Tartagal	3/7	08/30/97	Pos	80	>160	>160	<20
		10/26/97	Pos	<20	160	<20	<20
		11/23/97	Pos	640	>1,280	640	40
Guemes	1/100	--	Neg	<20	40	<20	<20
Unknown	2/6	--	Pos	<20	<20	<20	<20
			Pos	40	>160	80	<20

*Samples from the following localities were negative by IgM capture -enzyme-linked immunosorbent assay: Santa Victoria (2), General Mosconi (2), Salta city (11), Junta del San Antonio (1) and Aguaray (1).
**An acute-phase sample from this case was positive for DEN 2 by RT-PCR.

have occurred in Orán, Tartagal, Guemes, and Salvador Mazza. These cities are generally located along a highway going north into Bolivia, where DEN is endemic. Clinically, all cases were classic dengue fever. High PRNT antibody titers in the acute-phase samples indicated that dengue or other flavivirus infections had probably been present but had gone undetected. Only sporadic cases were found in the area under active surveillance, as in Texas in 1995 when isolated cases of indigenous transmission were detected (10).

The reestablishment of dengue in Argentina is of concern because of the following risk factors (11): 1) the presence of *Ae. aegypti* vector in high densities in several places (3); 2) the low levels of immunity in the human population in all areas that have been studied (1); 3) endemic virus in neighboring countries (12); and 4) the widespread presence of substandard living conditions, including the lack of running water, in areas where the virus is most likely to be introduced. Air conditioning is uncommon throughout the country, and the climate is subtropical in the north and temperate in the central region, where conditions are suitable for dengue transmission in summer. Surveillance should be continued and expanded in the most susceptible areas to monitor introduction and spread of this reemerging disease.

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Dr. Avilés is a biologist in charge of the Arbovirus Laboratory, National Reference Center of Dengue Diagnosis, Collaborative Center PAHO/WHO, Instituto Nacional de Enfermedades Virales Humanas "Dr. J.I. Maiztegui"-Administracion Nacional de Laboratorios e Institutos de Salud, Pergamino, Argentina. Her areas of expertise are arbovirology and medical entomology (mosquitoes). Her research interests include arboviruses (in humans and vertebrates), DEN, YF, WEE, EEE, VEE, and the competence of mosquitoes as vectors for arboviruses.

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Chlorine Disinfection of Recreational Water for *Cryptosporidium parvum*

Colleen Carpenter,* Ronald Fayer,*
James Trout,* and Michael J. Beach†
*U.S. Department of Agriculture, Beltsville, Maryland, USA; and
†Centers for Disease Control and Prevention, Atlanta, Georgia, USA

We examined the effects of chlorine on oocyst viability, under the conditions of controlled pH and elevated calcium concentrations required for most community swimming pools. We found that fecal material may alter the Ct values (chlorine concentration in mg/L, multiplied by time in minutes) needed to disinfect swimming pools or other recreational water for *Cryptosporidium parvum*.

The small size of the *Cryptosporidium parvum* oocyst (4-6 µm) and its resistance to many chemical disinfectants (e.g., chlorine) pose a challenge for standard filtration and disinfection procedures (1). Moreover, the low dose required for infection and the prolonged excretion of high numbers of oocysts make *C. parvum* ideal for waterborne transmission. Chlorinated recreational water facilities, such as public swimming pools and water parks frequently used by large numbers of diapered children, have been implicated in numerous outbreaks of cryptosporidiosis during the last decade (Table 1).

Previous studies of chlorine inactivation of oocysts have used oxidant demand-free water and glassware or chlorine demand-free reactors (1,24-31); none were performed in simulated recreational water (i.e., pH balanced, $CaCl_2$ added for hardness, organic material added). Therefore, Ct values (chlorine concentration in mg/L multiplied by time in minutes) calculated under oxidant demand-free laboratory conditions for disinfection of microorganisms such as *Cryptosporidium* may not be directly applicable to recreational water environments where additional organic material, such as urine, feces, hair, sweat, sloughed cells, and lotion, is present, pH is controlled, and calcium concentration is elevated. We report that under recreational water conditions fecal material alone has a large negative effect on chlorine inactivation of *C. parvum* oocysts, and therefore on pool water quality and the potential for disease transmission.

Address for correspondence: R. Fayer, USDA, ARS, LPSI, 10300 Baltimore Avenue, Bldg 1040, Beltsville, MD 20705, USA; fax: 301-504-5306; e-mail: rfayer@lpsi.barc.usda.gov.

Study Design

Oocysts of the AUCP-1 isolate were extracted from the feces of experimentally infected calves and cleaned of fecal debris with cesium chloride (32). The short exposure to cesium chloride followed by thorough rinsing with deionized water has no deleterious effects on the oocyst wall or oocyst survival. Oocysts cleaned by this method appear free from all organic fecal debris and other microorganisms and thus are potentially more susceptible to disinfectants than are oocysts surrounded by debris. Oocysts were stored at 4°C until use and were less than 1 month old when used.

Two experiments were conducted to determine how long oocysts would remain infectious when exposed to two concentrations of chlorine at two temperatures. Stock solutions of 2.0 ppm and 10.0 ppm HOCl in demineralized water (resistance measured 18 mega-ohm) were prepared with commercial laundry bleach (CLOROX). Chlorine concentrations were monitored with a digital chlorine colorimeter kit (LaMotte model no. DC 1100, Chestertown, MD). In experiment 1, one centrifuge tube (15 ml polypropylene, screw-top Falcon, Becton Dickinson, Franklin Lakes, NJ) was prepared containing 1 x 10^6 oocysts for each of the 28 temperature and time combinations. Tubes were centrifuged at 1,500 g for 15 minutes; supernatants were decanted, and oocyst pellets were resuspended in 12 ml of stock chlorine

Table 1. Outbreaks of cryptosporidiosis in recreational water facilities

Facility	Location	Disinfectant	No. of cases estimated/ confirmed)	Date (year)	Ref.
Pool	Doncaster, UK	Chlorine	[a]/79	1988	2
Pool	Los Angeles County	Chlorine	44/5	1988	3
Pool	British Columbia	Chlorine	66/23	1990	4
Pool	Gloucestershire, UK	Ozone/chlorine	[a]/13	1992	5
Water slide	Idaho	Chlorine	500/[a]	1992	6
Pool (wave)	Oregon	Chlorine	[a]/52	1992	7
Pool (motel)	Wisconsin	Chlorine	51/22	1993	8,9
Pool (motel)	Wisconsin	Chlorine	64/[b]	1993	9
Pool	Wisconsin	Chlorine	5/[b]	1993	9
Pool	Wisconsin	Chlorine	54/[b]	1993	9
Pool (motel)	Missouri	Chlorine	101/26	1994	10
Lake	New Jersey	None	2,070/46	1994	11
Pool	Sutherland, New South Wales	Chlorine	[a]/70	1994	12
Pool	Kansas	[a]	101/26	1995	13
Water park	Georgia	Chlorine	2,470/62	1995	13
Water park	Nebraska	[a]	[a]/14	1995	13
Pool	Florida	[a]	22/16	1996	14[c]
Water park	California	Chlorine	3,000/29	1996	13,15[c]
Pool	Andover, UK	Chlorine	8/[a]	1996	16
Lake	Indiana	None	3/[a]	1996	13
River	NW England & Wales	None	27/7	1997	17[c]
Pool	SW England & Wales	Ozone & chlorine	[a]/9	1997	17[c]
Fountain	Minnesota	Sand filter	369/73	1997	18
Three pools	Canberra, Australia	[a]	[a]/210	1998	19[c],20[c]
Pool	Oregon	[a]	51/8	1998	21[c]
Pools	Queensland	[a]	129/[a]	1997	21[c]
Pools	New South Wales	[a]	370/[a]	1998	22[c]
Pools	Hutt Valley, New Zealand	[a]	[a]/171	1998	23[c]

[a]No data available.
[b]Reference did not identify cases as estimated or confirmed.
[c]Reference is not peer reviewed and may not reflect a rigorous investigation of the outbreak.

solution. Tubes were then placed in controlled temperature water circulators (model 9101; Polyscience, Inc., Niles, IL) and incubated at 20°C or 30°C. For all mice to be the same age at the time of infection, tubes were prepared on 7 successive days and placed in the water circulators so that all incubations ended and all mice were inoculated on the same day (Table 2).

Because of the small volume in each tube, it was not possible to monitor the chlorine concentration daily. Therefore, readings were taken initially and after incubation, immediately before the mice were inoculated. Upon removal from the water circulators, all tubes were centrifuged at 1,500 g for 15 minutes, supernatant was aspirated, and pelleted oocysts were resuspended in 1 ml of demineralized water. Oocysts in each tube were then administered orally to four neonatal BALB/c mice by gastric intubation. Each mouse received 150,000 oocysts. Oocysts remaining in each tube were counted with a hemacytometer to verify dosage levels. Individual oocysts were counted in the clumps of 2 to 4 oocysts observed on days 5 through 7. Mice were euthanized by CO_2 overexposure 96 hours after intubation. To assess infectivity, hematoxylin- and eosin-stained histologic sections of ileum from each mouse were examined by brightfield microscopy for developmental stages of *C. parvum* (24).

Because the results from experiment 1 indicated a need to examine shorter times of oocyst exposure to chlorine, a second experiment was conducted in which oocysts were tested for viability after exposure to chlorinated water for 6, 12, 24, 48, and 72 hours (Table 2). To simulate actual pool conditions (33), chlorinated water was balanced between pH 7.2 and 7.8, and $CaCl_2$ was added to a concentration of 200 ppm to 400 ppm.

To simulate a swimming pool fecal incident and thereby test the effectiveness of chlorine on

Table 2. Contact times and infectivity for purified *Crytosporidium parvum* oocysts subjected to chlorination (Experiments 1 and 2)[a]

		2 ppm			10 ppm	
		Ct[b]	Infectivity		Ct[b]	Infectivity	
Expt.	Days (min.)	value	20ºC	30ºC	value	20ºC	30ºC
2	(360)	720	**4/4**	**4/4**	3,600	**4/4**	0/4
2	(720)	1,440	**4/4**	**3/4**	7,200	0/4	0/4
1	1 (1440)	2,880	**4/4**[c]	0/4	14,400	0/4	0/4
2	1 (1440)	2,880	**4/4**	0/4	14,400	0/4	0/4
1	2 (2880)	5,760	0/4	0/4	28,800	0/4	0/4
2	2 (2880)	5,760	0/4	0/4	28,800	0/4	0/4
1	3 (4320)	8,640	**4/4**	0/4	43,200	0/4	0/4
2	3 (4320)	8,640	0/4	0/4	43,200	0/4	**3/4**
1	4 (5760)	11,520	0/4	0/4	57,600	0/4	0/4
1	5 (7200)	14,400	0/4	0/4	72,000	0/4	0/4
1	6 (8640)	17,280	0/4	0/4	86,400	0/4	0/4
1	7 (10,080)	20,160	0/4	0/4	100,800	0/4	0/4

[a]Treatments in which mice were found infected are shown in bold.
[b]Hypothetical Ct value calculated by assuming constant chlorine concentration.
[c]Fraction represents number of mice showing developmental stages of *C. parvum* in the intestinal epithelium over the total number of mice inoculated, e.g., 4/4 indicates 4 mice were found infected out of 4 mice inoculated.

oocysts in the presence of organic material, three aquariums were each filled with 30 L of tap water balanced to meet standard pool regulations (33). The pH was maintained by adding NaOH or HCl, and the calcium level was maintained by adding $CaCl_2$. In one aquarium, sufficient chlorine was added to achieve and maintain 2.0 ppm, a normal pool concentration. In another aquarium used to represent a response to water contamination, chlorine was maintained at 10 ppm. In the third aquarium, calcium and pH were held at standard pool conditions, but no chlorine was added. The aquariums were maintained at room temperature and were covered with a glass plate to prevent evaporation. Chlorine, pH, and calcium values were monitored 4 times a day between 8:00 a.m. and 4:30 p.m. and adjusted to target levels when necessary.

Calculations for simulating a pool fecal accident in an aquarium were based on a 700,000-L swimming pool and an infected person excreting approximately 500 g of fecal material into the water (490,000 mg feces per 700,000 L pool = 0.7 mg/L; 0.7 mg/L x 30/L aquarium = 20 mg feces). The estimated ratio of fecal mass to water volume necessarily correlates with large contamination to maintain a ratio based on the small size of the aquarium and the need for a sufficient quantity of feces and oocysts for testing. The number of oocysts added was based on laboratory experience for recovery of oocysts from numerous 5-g fecal samples of bovine feces.

To simulate a loose fecal mass but not fully dispersed feces, dialysis tubing (SPECTRUM Medical Industries, Inc., Los Angeles, CA) with a molecular weight cutoff of 6,000 to 8,000 was used to contain the oocysts and fecal mixture. Fecal material came from a calf that tested negative for *C. parvum*. Feces were mixed with water to form a diarrhea-like consistency. To ensure the recovery of sufficient oocysts for later bioassay in mice, 2×10^6 oocysts in 20 mg of the fecal slurry were introduced into the dialysis tubing and then filled with water from the appropriate aquarium. Time points of 0, 6, 12, 24, and 48 hours of exposure were tested. Therefore, additional dialysis tubing containing oocysts and fecal material was added to each aquarium at specified intervals, and all were removed at the end of the incubation time. Oocysts were aspirated from the dialysis tubing, they were concentrated by centrifugation (1,500 g, 15 minutes), and 150,000 were intubated into each of 3 to 5 neonatal BALB/c mice as before. Necropsy of mice and assessment for infectivity were performed as in the previous experiment.

Findings

In the first experiment, oocysts maintained at 20°C in 2 ppm chlorine for 1 and 3 days were infectious for mice. Oocysts maintained at higher temperatures or chlorine concentrations were not infectious for mice (Table 2).

In the second experiment, oocysts maintained at 20°C in 2 ppm chlorine remained infectious after exposure of 6 to 24 hours (Table

2). At 20°C and 10 ppm chlorine, oocysts exposed for 6 hours infected mice, whereas those exposed longer did not. At 30°C and 2 ppm chlorine, oocysts exposed for 6 hours infected all mice, those exposed for 12 hours infected 3 of 4 mice, and those exposed longer were not infectious. At 30°C and 10 ppm chlorine, oocysts held for 6, 12, 24, and 48 hours did not initiate infection; however, those held for 72 hours were infectious for 3 of 4 mice.

In the third experiment, tissues from all mice inoculated with the oocysts exposed to all incubation time points at 0, 2, or 10 ppm chlorine were found to contain developmental stages of the parasite in the intestinal epithelium. These findings indicated that oocysts in the presence of fecal material remained infectious even after exposure to 10 ppm chlorine for 48 hours.

Conclusions

Swimming is the second most popular recreational activity in the United States, with more than 350 million persons participating each year (34). The emergence of *C. parvum* as a major cause of recreational waterborne disease has prompted public health workers to reevaluate existing recommendations and regulations for water quality and use. Frequent fecal contamination of recreational water and the high level of *C. parvum* oocyst resistance to chlorine, the low oocyst dose required for infection, and high numbers of bathers make it imperative that we understand how oocyst inactivation is affected by recreational water conditions, including fecal contamination.

In our first experiment, to become noninfectious, purified *C. parvum* oocysts in chlorine demand-free deionized water required exposure to chlorine at a Ct value higher than 8,640. This value is relatively close to that obtained for disinfection under similar chlorine demand-free conditions (Ct = 7,200-9,600) (28). Purified *C. parvum* oocysts in chlorine demand-free water balanced to meet swimming pool standards (experiment 2) required even less time to be rendered noninfectious, i.e., exposure to 2 ppm chlorine for 2 days at 20°C or 1 day at 30°C. Incubation in 10 ppm chlorine rendered oocysts noninfectious in 6 hours or less at both temperatures, respectively.

The findings that oocysts in experiment 1 were infectious when exposed to 2 ppm at 20°C for 1 and 3 days but not for 2 days and that oocysts in experiment 2 infected 3 of 4 mice after exposure to 10 ppm chlorine at 30°C for 72 hours but not for shorter periods underscores the difficulty of performing these experiments. Such findings may be explained by the stickiness of the oocyst surface, which leads to clumping that can result in nonuniform sampling or possibly protection from inactivation. However, these outlying datapoints in experiments 1 and 2 are inconsistent with total oocyst inactivation observed in the shorter incubation times under the same conditions. It is unclear whether a few oocysts survived the exposure period or whether the infections were experimental artifacts. Environmental contamination of the mouse colony used for the bioassays is unlikely because no mice from the negative control litter used for this study or from >1,000 previous negative control mice used in this laboratory had developed a *C. parvum* infection. These data suggest that disinfection of *C. parvum*, in the absence of feces or other organic contaminants, may be less difficult than thought, particularly at the higher temperatures found in chlorinated recreational venues.

In contrast to experiment 2, in which fecal matter was absent, oocysts in experiment 3 were incubated under identical water and chlorine conditions but in the presence of feces (i.e., a simulated fecal accident) and remained infectious at all time points through 48 hours. Because this simulated accident was contained in a dialysis bag rather than being dispersed, it may not represent the best model for a dispersed diarrheal accident. Containment of oocysts with the organic material may actually have afforded some protection from inactivation. This highlights our incomplete understanding of *C. parvum* inactivation and the detrimental effect that organic or fecal contamination can play in recreational water.

Although the fecal accident simulated here could be considered major, the decrease in effective chlorine action is probably a conservative measure for recreational water since the simulation did not include additional biologic contaminants found in recreational water (i.e., sweat, hair, skin cells, lotion, urine, and algae). Because oocysts attach readily to biologic particles (35), such particles may provide a protective surrounding. The retarded inactivation of an already chlorine-resistant organism suggests that the current recommendation (36)

for responding to fecal accidents (20 mg chlorine/L for 9 hours to achieve a Ct value of 10,800) needs to be tested under appropriate conditions of water quality (33) in the presence of fecal and organic contaminants (both as tested here or dispersed in a pool) and revised as necessary.

Routine use of recreational venues by diapered children from day-care facilities, who have an elevated prevalence of *C. parvum* infection, increases the potential for waterborne disease transmission. Prevention plans that combine engineering changes (improved filtration and turnover rates, separate plumbing and filtration for high-risk "kiddie" pools), pool policy modifications (fecal accident response policies, test efficacy of barrier garments such as swim diapers), and patron and staff education should reduce the risk for waterborne disease transmission in public recreational water venues. Education efforts should stress current knowledge about waterborne disease transmission and suggest simple prevention measures such as refraining from pool use during a current or recent diarrheal episode, not swallowing recreational water, using proper diaper changing and handwashing practices, instituting frequent timed bathroom breaks for younger children, and promoting a shower before pool use to remove fecal residue.

Ms. Carpenter is a graduate student at Virginia Commonwealth University's Center for Environmental Studies. She is studying amoebae in Asian freshwater clams as biologic indicators of runoff from combined sewer outfalls into the James River. Ms. Carpenter's interests include the epidemiology of foodborne and waterborne parasitic protozoa.

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Cyclospora cayetanensis Among Expatriate and Indigenous Populations of West Java, Indonesia

David J. Fryauff,* Reinhard Krippner,† Purnomo Prodjodipuro,* Christa Ewald,† Shirley Kawengian,‡ Katrin Pegelow,§ Thomas Yun,¶ Claudia von Heydwolff-Wehnert,‡ Buhari Oyofo,* and Rainer Gross#

*U.S. Naval Medical Research Unit No. 2, Jakarta, Indonesia; †Embassy of the Federal Republic of Germany, Jakarta, Indonesia; ‡University of Indonesia, Jakarta, Indonesia; §SEAMEO-TROPMED Regional Center for Community Nutrition, Jakarta, Indonesia; ¶Embassy of the United States of America, Jakarta, Indonesia; #Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) GmbH, Eschborn, Germany

From January 1995 through July 1998, we investigated the occurrence of *Cyclospora cayetanensis* infection associated with gastrointestinal illness or diarrhea in foreign residents and natives of West Java, Indonesia. We found that *C. cayetanensis* was the main protozoal cause of gastrointestinal illness and diarrhea in adult foreign residents during the wet season. The parasite rarely caused illness in the indigenous population or in children.

Cyclospora cayetanensis is a newly recognized coccidian parasite associated with sudden onset of gastrointestinal illness and chronic diarrhea. In developing countries, cases occur sporadically, in a seasonal pattern, and primarily among western expatriates and travelers (1,2).

We recently reported multiple symptomatic cases of *C. cayetanensis* infection among European expatriates living in Jakarta, Indonesia; *C. cayetanensis* and *Giardia lamblia* were the intestinal parasites most frequently identified (6.4%) in cases of gastroenteritis or chronic diarrhea (3). We report here the results of a longitudinal evaluation of *Cyclospora* infection among expatriate populations of Jakarta and the results of two recent surveys of intestinal parasite infections in Indonesian children.

Three clinical diagnostic laboratories, each serving subpopulations of expatriate residents of Jakarta, Indonesia, participated in the longitudinal evaluation. The medical unit of the Embassy of the Federal Republic of Germany, a diagnostic center for an estimated 300 European expatriates, screened for ova and parasites in cases of gastrointestinal illness and diarrhea from January 1995 through July 1998. The Parasitology Department of the U.S. Naval Medical Research Unit No. 2 (NAMRU-2) provided diagnostic services for U.S. military staff and their families living in Jakarta during January 1996 to January 1998. The U.S. Embassy Medical Unit in Jakarta performed diagnostic parasitic tests for approximately 500 U.S. expatriate residents from January to December 1998.

All three laboratories performed wet-mount microscopy of fresh and formalin-ethyl acetate-concentrated feces stained with dilute iodine or merthiolate-iodine-formalin solution. All specimens were from persons with self-reported cases of gastrointestinal illness and diarrhea who sought medical attention. Confirmation of *Cyclospora* was based primarily on size and morphologic features relative to reference slides provided by J.H. Cross, Uniformed Service University of Health Sciences, Washington, D.C., and secondarily on acid-fast staining characteristics. The NAMRU-2 laboratory also routinely applied a modified, 22 mm x 40 mm

Address for correspondence: David J. Fryauff, U.S. NAMRU-2, Box 3, APO AP 96520-8132; fax: 62-21-424-4507; e-mail: fryauff@smtp.namru2.go.id.

Kato thick-smear technique to estimate parasite/ova density. Analyses were limited to autochthonous cases by evaluating patient histories and excluding those that were probably acquired outside Indonesia.

All 8- to 10-year-old Indonesian children attending 10 public schools in rural Sukaraja District, West Java, Indonesia, were examined for parasites and ova during December 1995. Direct wet-mount microscopy and modified Kato thick-smear examination of a fresh fecal specimen were performed. Two independent examinations were performed on each sample by clinical parasitologists. After informed parental consent, a subsample of 83 children was enrolled into a prospective study to monitor episodes of diarrhea following mebendazole de-worming. Stool samples were collected weekly or during gastrointestinal illness or diarrhea over 13 consecutive weeks of posttreatment observation (March to June 1996). Specimens were screened for parasites and ova as described above.

A hospital-based study to determine the causes of diarrhea among Indonesian residents of Jakarta was initiated in July 1997 as a collaborative study between the Departments of Microbiology and Parasitology, the Health Research Branch of the Indonesian Ministry of Health, and several participating Jakarta hospitals. A single stool sample was collected for testing from study participants who reported to the clinic with diarrhea lasting >72 hours. Preliminary analysis for parasitic causes associated with diarrhea was done in cases of children < 3 years old who were screened during the first 12 months (July 1997 to June 1998) of this 3-year study.

C. cayetanensis was the dominant pathogenic intestinal parasite, present in 29 (11.5%) of 253 cases of gastrointestinal illness and diarrhea among European expatriates who sought medical care during January 1995 to January 1998 (Table). *C. cayetanensis* was the most frequently identified pathogenic intestinal parasite each year, accounting for 8.6% to 15.1% of the annual diagnoses. All but one of these cases were in adults (30 years of age or older). Cases were clustered during the wet season (November–May), suggesting a seasonality of risk (Figure).

The second Jakarta-based laboratory that performed parasitologic screening on predominantly American families identified *C. cayetanensis* in 9 (9.1%) of 99 persons with gastrointestinal illness or diarrhea who sought care during a 24-month period. *Cyclospora* oocyst counts per gram of feces from these symptomatic *C. cayetanensis* cases were 100 to 327,600/gm; the highest counts were associated with early onset and acute symptoms. All nine *C. cayetanensis* cases were in adults.

The U.S. Embassy Health Unit in Jakarta identified 28 *C. cayetanensis* infections among 206 patients (13.6%) with gastrointestinal illness or diarrhea who were examined during an 11-month period in 1998. Pediatric infections, seen only in teenagers, accounted for 2 of the 28 cases. An apparent association was found between expatriates' risk for infection and the cooler wet season (October-May) (Figure).

A well population of 348 Indonesian schoolchildren was screened for intestinal parasite infections. The prevalence of intestinal helminth and protozoan infections among the children was 84% and 77%, respectively. Asymptomatic, low-density *C. cayetanensis* infections were found in 2 (0.6%) children.

A prospective study of 83 of these children was performed for 1,006 weeks of follow-up (average 12.2 weeks per child). Single or multiple samples of loose or watery stool (230 per 1,006 total samples) were collected from 71 of the 83 children. Although generally well and attending school, 26 (31.3%) of these 71 children had loose

Table. Parasites associated with self-reported gastrointestinal illness or diarrhea, German Embassy Health Unit, Jakarta, Indonesia

Year	No. examined	*Cyclospora cayetanensis* No. (%)	*Entamoeba histolytica*/ *E. dispar* No. (%)	*Giardia lamblia* No. (%)	*Trichuris trichiura* No. (%)	*Ascaris lumbricoides* No. (%)	*Blastocystis hominis* No. (%)
1995	104	9 (8.6)	8 (7.7)	4 (3.8)	5 (4.8)	1 (1.0)	23 (22.1)
1996	96	12 (12.5)	4 (4.2)	2 (2.1)	2 (2.1)	0	10 (10.4)
1997	53[a]	8 (15.1)	4 (7.5)	1 (1.9)	2 (3.8)	1 (1.9)	5 (9.4)
Total	253	29 (11.5)	16 (6.3)	7 (2.8)	9 (3.5)	2 (0.8)	38 (15)

[a]No laboratory diagnoses were performed during June and July 1997.

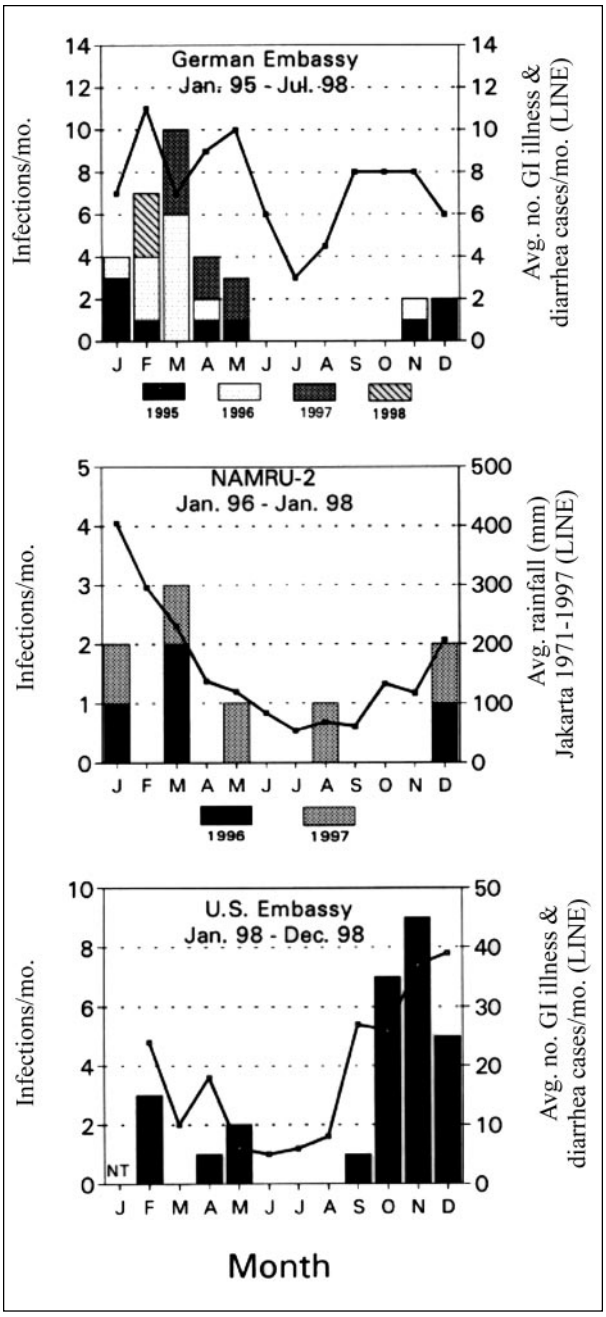

Figure. Monthly profiles of *Cyclospora* infection among gastrointestinal illness/diarrhea cases at private health laboratories serving expatriate populations of Jakarta, Indonesia.

or watery stools at least four times during follow-up. Low-density *C. cayetanensis* infections were identified in two (2.4%) children, for an incidence of two infections per 19.3 person-years.

In the first year of the 3-year Jakarta diarrhea study, 263 Indonesians were screened for parasites; 170 (64.6%) of these were children younger than 3 years of age (ave. = 10.9 months, SD = 7.5 months). No *Cyclospora* infections were found.

The relatively sudden appearance, since 1995, of *C. cayetanensis* infections among long-term expatriate residents of Jakarta may indicate either a new ability of local diagnostic laboratories to recognize an established parasite or new establishment of this pathogen in the urban environment of Indonesia. Recent parasitologic surveys conducted throughout Indonesia may not have been undertaken with sufficient sensitivity to detect *C. cayetanensis* and may have been conducted during periods of low transmission.

The high frequency with which *C. cayetanensis* infections were found in expatriate patients cannot be attributed to new staining or concentration methods. Three laboratories applied direct wet-mount microscopy to identify this agent, and each laboratory independently classified *C. cayetanensis* as the dominant pathogenic parasite associated with diarrhea. Despite moderately enhanced recovery of *C. cayetanensis* oocysts by formalin-ethyl acetate sedimentation, virtually all diagnoses were made from the initial findings of the direct wet-mount or the modified Kato thick smear and were not dependent on the concentration step.

Cyclospora infections were identified in the cross-sectional prevalence survey and the prospective study of rural schoolchildren but not in the diarrhea specimens from Jakarta infants during the year-long study. Unlike the *C. cayetanensis* infections among foreign residents of Jakarta, infections by this parasite in rural Indonesian children were rare and characterized by low parasite density, absence of symptoms, and sporadic appearance.

These disparate findings suggest various possibilities: 1) The absence of *Cyclospora* infection in young children with diarrhea, both expatriate and native Indonesian, may result from their lack of exposure to foods or other risk factors to which older children and adults are exposed. Additionally, Indonesian infants may be protected by maternally acquired passive immunity. 2) Fecal contamination of food and water in rural Indonesia may be sufficiently high that local children, by the age of 8 to 10 years, have effective clinical and parasitologic immunity to *Cyclospora* and other pathogens. Infection

of Indonesian children by other enteric pathogens may confer cross-protective immunity. 3) Urban transmission of *Cyclospora* may predominate among expatriate residents of Jakarta because of their atypical food preferences (imported, varied, fresh fruit and vegetables, restaurant-prepared) and preparations (prepared by servants, frequent use of raw garnish and salads).

The paucity of *Cyclospora* infections associated with loose stool or diarrhea in the rural and urban Indonesian children may not be atypical for these age groups. Among children of Bangkok (≤5) who were screened for diarrheal causes during 1985 to 1986, *Cryptosporidium* was the only protozoon associated with illness (4). If *Cyclospora* was also present in this population but classified as *Cryptosporidium* spp., these organisms collectively accounted for only 1.8% of cases and 0.3% of controls.

Among nearly 900 Jakarta expatriates of all ages, we saw relatively few pediatric cases of *Cyclospora* and suspect that infections in this age group may also go undetected. Our methods may not have been sufficiently sensitive to detect mild infections of *Cyclospora* in highly susceptible young persons or in asymptomatic older persons who have been sensitized, even without prior exposure to *C. cayetanensis*, by repeated new contact and long-term maintenance of other commensal and pathogenic parasite infections.

Despite the likelihood that pathogenic bacterial and viral agents are the principal causes of gastrointestinal illness and diarrhea among native and expatriate residents of Indonesia (5,6), our results clearly identify *C. cayetanensis* as commonly associated with these health problems.

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Dr. Fryauff heads the Parasitic Disease Program of the U.S. Navy Medical Research Unit No. 2 in Jakarta, Indonesia. His principal research interest is in malaria: drug trials for prevention and treatment, monitoring drug resistance, evaluating rapid diagnostics, and immunologic and epidemiologic studies.

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The First Major Outbreak of Dengue Hemorrhagic Fever in Delhi, India

L. Dar, S. Broor, S. Sengupta, I. Xess, and P. Seth
All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India

An outbreak of dengue hemorrhagic fever/dengue shock syndrome (DHS/DSS) occurred in 1996 in India in and near Delhi. The cause was confirmed as dengue virus type 2, by virus cultivation and indirect immunofluorescence with type-specific monoclonal antibodies. This is the largest such outbreak reported from India, indicating a serious resurgence of dengue virus infection.

An outbreak of dengue hemorrhagic fever/ dengue shock syndrome (DHF/DSS) occurred in Delhi, India, and its adjoining areas, from August through November 1996. We confirmed the etiologic agent of this outbreak as dengue virus type 2 by virus cultivation and indirect immunofluorescence with type-specific monoclonal antibodies. This is the largest culture-confirmed outbreak of DHF/DSS in India and indicates a serious resurgence of dengue virus infection in this country.

Dengue fever occurs worldwide, in nearly all tropical and subtropical countries (1). Dengue virus was first isolated in India in 1945 (2). All four virus types circulate and cause epidemics, but only occasional cases of DHF/DSS have been reported in India (3).

Delhi, situated in the northern part of India, had outbreaks of dengue virus infection due to different dengue virus types in 1967, 1970, 1982, and 1988, but no culture-confirmed cases of DHF/DSS were reported during these epidemics (4-7). Some cases of DHF were seen for the first time in 1988 (7). These were confirmed only serologically, by the hemagglutination inhibition test.

Delhi had its largest outbreak of DHF/DSS in 1996. The outbreak started the last week of August and continued until the end of November, peaking in mid-October (8,9). A total of 8,900 cases were reported, with a death rate of 4.2% (9). We report results of virologic testing of samples received at the All India Institute of Medical Sciences from patients with suspected dengue fever or denguelike illness from Delhi and its adjoining areas, along with a profile of the culture-confirmed cases.

Virus isolation was carried out on 149 samples received on ice from patients with acute illness. Serum was separated aseptically and stored at -70° C. The standard method of virus cultivation, which used the C6/36 clone of *Aedes albopictus* cell line, was followed with some modifications (10).

On days 5 and 10, cells were tested by indirect immunofluorescence assay (IFA) by using monoclonal antibodies to dengue virus types 1-4. If IFA was negative for dengue viruses on first passage, a second passage was made, and cells were again harvested on days 5 and 10 for IFA. All four dengue virus types (from the National Institute of Virology, Pune, India) were included as positive controls, and uninfected C6/36 cells were kept as negative controls.

Dengue viruses were isolated in C6/36 cells from 27 (18.1%) of 149 samples processed for virus isolation. Of the 27 isolates, 26 were identified as dengue virus type 2 and one as dengue virus type 1. Sixteen of the 27 isolates were from patients with DHF/DSS, while 11 were isolated from patients with uncomplicated dengue fever. Of the 27 culture-positive patients, 11 (40.7%) were in the 5- to 12-year age group (Table). However, the isolates were nearly equally distributed among children (<12 years) and adults. The ratio of male to female in these 27 cases was 12:15. The median duration of fever at the time of viral isolation was 4 days, on the basis of 24 culture-positive cases for which the duration of fever was available. After 5 days of

Address for correspondence: Shobha Broor, Department of Microbiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi-110 029, India; fax: 91-11-686-2663; e-mail: broor@hotmail.com.

Table. Age distribution of patients with culture-positive dengue

Age (years)	No. of cases
0-1	2
>1-5	1
>5-12	11
>12-20	7
>20-30	4
>30	2

fever, virus isolation was possible only from one patient. The median duration of viremia in dengue type 2 infection was also found to be 4 days in a detailed study on dengue viremia from Jakarta, Indonesia (11). Testing for immunoglobulin (Ig) M antibodies to dengue virus was performed on 270 serum samples by MAC-ELISA according to a standard protocol (12). Of 270 sera tested for antibodies to dengue virus by MAC-ELISA, 140 (51.9%) showed anti-dengue IgM antibodies. All samples from patients with a duration of fever ≥ 5 days were tested for anti-dengue IgM antibodies. In some samples, antibodies could be detected as early as the fifth day of fever. Three of the culture-positive acute-phase samples were also positive by MAC-ELISA.

Analysis of the outbreaks of dengue virus infection in Delhi indicates a seasonal trend. All outbreaks (including the one reported here) occurred during the monsoon (rainy) season (August to November) and subsided with the onset of winter. Dengue virus types 1, 2, and 3 have been isolated during dengue fever outbreaks (without DHF/DSS) in Delhi. Serologic studies have also shown that dengue infection has been endemic in this region (13). During the 1996 outbreak of DHF/DSS, we were able to identify dengue virus type 2 as the etiologic agent. This is the first culture-confirmed outbreak of DHF/DSS from Delhi and its adjoining areas and the largest reported outbreak of DHF/DSS from India.

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Dr. Dar is associate professor in the virology section of the Department of Microbiology at the All India Institute of Medical Sciences, New Delhi, India. His interests include diagnostic virology, viral immunology, and tuberculosis.

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Addressing the Potential Threat of Bioterrorism—Value Added to an Improved Public Health Infrastructure

The use of biological weapons was banned in 1972 by the Convention on the Prohibition of the Deployment, Production, and Stockpiling of Bacteriological and Toxin Weapons (1). Caches of biological weapons still exist, however, and their illegal use in military operations cannot be discounted entirely (2).

The threat of biological warfare seems remote to industrialized nations, which have enjoyed decades of peace and prosperity. In contrast, the threat of bioterrorism, in which biological agents are used by extremists as weapons against civilian populations, generates considerable anxiety. Although the likelihood of a bioterrorist attack is difficult to predict, the consequences of a successful attack could be devastating and cannot be ignored. Unlike attacks involving conventional or even chemical weapons, which could be readily detected and limited to a specific geographic area, an attack with a biological agent (and the resulting symptoms of exposed persons) could remain undetected for days, would be widely scattered, and depending on the etiologic agent, might not be identified immediately as a manmade event. Secondary cases would confound epidemiologic investigations as well.

Regardless of the source, surveillance of infectious diseases, detection and investigation of outbreaks, identification of etiologic agents and their modes of transmission, and the development of prevention and control strategies are responsibilities of public health agencies. Acquiring and sustaining the capability for an adequate response to bioterrorism requires thoughtful analysis and carefully integrated planning by these agencies, as well as law enforcement officials, emergency response physicians and other first responders, the military, and others. New partnerships will need to be forged and old ones strengthened.

Preliminary assessments of our nation's capabilities for responding to possible bioterrorist attacks have identified many deficiencies. From the public health perspective, these deficiencies include inadequate surveillance systems; lack of rapid diagnostic techniques; insufficient stockpiles and distribution systems of antimicrobial agents and vaccines; inefficient communication systems; and insufficient training of physicians, epidemiologists, and laboratorians. The deficiencies may be more pressing in certain disease areas than in others. Some diseases that are considered bioterrorist threats, such as anthrax and plague, are no longer important public health problems in most industrialized nations, so the capabilities and capacities for responding to outbreaks of these diseases may be at historic lows. These deficiencies in response capacity can be traced to the 1960s and 1970s, when complacency began to erode essential components of the public health infrastructure. Since the early 1970s, at least 25 previously unknown pathogenic agents and diseases have been identified, and in recent years mounting resistance to antimicrobial agents has confounded the treatment of many illnesses (3).

A strategic plan for reducing the consequences of new and reemerging infectious diseases (4) proposes corrective measures for addressing the infrastructure deficiencies: instituting better surveillance systems, improving diagnostic techniques, developing new vaccines and drugs, and conducting research and providing training in several areas. The measures needed to prevent and control emerging infections are strikingly similar to those needed to check the threat of bioterrorism. Improving capabilities and capacities for responding to one issue will almost certainly benefit the other. For example, developing rapid diagnostic techniques that would make it possible to quickly detect bioterrorist attacks involving anthrax, plague, or Q fever would have considerable usefulness in the routine clinical diagnosis of pneumonia. Distribution systems set up to deliver antimicrobial agents and vaccines after bioterrorist attacks would be indispensable in delivering antiviral compounds and influenza vaccine during a large pandemic. Surveillance and communication systems are fundamental components of an adequate public health infrastructure, so an electronic, integrated surveillance system based on standard architecture and vocabulary would serve all needs.

A value-added approach to infrastructure development is not a new concept in public health. In 1951, at the beginning of the cold war, the Epidemic Intelligence Service (EIS) was founded at the Center for Disease Control (CDC) (5,6). The EIS concept originated with Joseph W.

Mountin, founder of CDC, and was implemented by Alexander D. Langmuir. Noting the "dearth of trained epidemiologists," Langmuir proposed training a corps of young physicians that could "investigate outbreaks of disease in strategic areas." He also noted, "A broader but equally pressing need is to make available competent epidemiologists to assist in the planning and organization of the total civil defense program at all levels." Langmuir also observed that while "this dearth exists even in peacetime, defense needs exaggerate this deficiency."

In 1951, 22 young physicians and one sanitary engineer signed on as EIS Officers at CDC, where they received several weeks of instruction in epidemiology, biostatistics, and public health administration and then served for 2 years as field epidemiologists, either at CDC or in state health departments. EIS has been in operation since then, and as the purview of CDC expanded beyond infectious diseases, so have the size and composition of EIS and the training of EIS Officers. Surveillance, outbreak investigations, and research on the epidemiology of new diseases remain standard activities, however. EIS has rarely had occasion to investigate outbreaks caused by the intentional release of microorganisms (7,8). However, as Langmuir predicted in 1951, the program has increased public health preparedness and made important contributions to the control of communicable diseases. EIS now has more than 2,000 alumni, including nearly 200 scientists from abroad. Many alumni have moved on to distinguished careers in academia, industry, and clinical practice, but many others have filled key positions at federal and state public health agencies. Trained to consider diseases as problems of populations, EIS alumni remain a valuable resource when disease outbreaks occur.

As in 1951, civil defense, and particularly the use of biological agents against civilian populations, is of utmost concern. Efforts are under way to improve the capabilities of the public health system for detecting and responding to this threat. Also as in 1951, we have an opportunity to ensure that improvements made in response to the threat of bioterrorism have multiple uses and can be applied to other public health emergencies. Planning efforts to date have adopted this viewpoint. Developing a separate infrastructure for responding to acts of bioterrorism would be poor use of scarce resources, particularly if this infrastructure is never used. "Value added" should be the watchwords of the current initiative.

Joseph E. McDade
Centers for Disease Control and Prevention,
Atlanta, Georgia, USA

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Current Status of Smallpox Vaccine

To the Editor: The possible use of smallpox virus as a weapon by terrorists has stimulated growing international concern and led to a recent review by the World Health Organization of the global availability of smallpox vaccine. This review found approximately 60 million doses worldwide, with little current vaccine manufacture, although limited vaccine seed remains available (1). Ongoing discussions in the United States suggest that the national stockpile should contain at least 40 million doses to be held in reserve for emergency use, including in case of a terrorist release of smallpox virus (O'Toole, this issue, pp. 540-6).

The current U.S. stockpile contains approximately 15.4 million doses of vaccinia vaccine (Dryvax) made from the New York City Board of Health strain of vaccinia and was produced by Wyeth Laboratories in 13 separate lots. The vaccine is lyophylized in glass vials with rubber stoppers and sealed with a metal band. When rehydrated, each vial contains 100 doses and has a potency of at least 10^8 plaque-forming units (pfu)/ml. Some vials of the vaccine stockpile have shown elevated moisture levels and thus failed routine quality control testing; however, the vaccine in these vials remains potent, and the failed lots have not been discarded.

The diluent used to rehydrate the vaccine contains brilliant green, which makes the vaccine easier to visualize when administered with bifurcated needles. Over time, the brilliant green has deteriorated, and most of the available diluent does not pass quality control. Discussions are under way with Wyeth to begin production of sufficient new diluent for the entire stockpile.

The vaccine is administered by superficial inoculation (scarification) with a bifurcated needle. Fewer than 1 million bifurcated needles are held as part of the stockpile. As with the diluent, Wyeth has been requested to produce additional bifurcated needles.

Vaccinia virus produces adverse reactions in a small percentage of vaccinated persons. Adverse reactions are treated with vaccinia immune globulin (VIG), currently only available from Baxter Healthcare Corporation (5,400 vials of VIG in stock). Each vial contains 5 ml of VIG; the recommended dose for postvaccine complications is 0.6 ml per kg of body weight. This volume is sufficient to treat adverse reactions in approximately 675 adults. Further, the entire stockpile of VIG has been placed on hold while the cause of a slight pink discoloration is investigated. Until the cause of the discoloration is determined or another approved supply of VIG is obtained, no vaccinia vaccine is being released. While unknown, the rate of adverse reactions in today's population is likely to be greater than seen during the global eradication campaign because of recent increases in the number of immunocompromised persons. The Department of Defense has recently contracted the processing of new lots of VIG (to be administered intravenously rather than by the intramuscular route like existing VIG stocks); however, maintaining adequate stocks of VIG will remain a challenge.

In the event of release of smallpox virus, persons at high risk and persons exposed but not yet showing clinical illness would be vaccinated immediately. Intensive case detection and vaccination of contacts and other persons at risk would follow. All vaccine, including lots retained after failed quality control tests, would be made available for emergency use. Previous studies have found that more than 90% of susceptible persons respond to vaccinia virus with a titer of 10^7 pocks/ml (2). In an emergency, consideration would be given to diluting the existing vaccine as much as 10-fold, so that each vial could conceivably contain 1,000 doses of vaccine, rather than the current 100 doses. The present vaccine container is sufficiently large to accommodate the added diluent. The absence of sufficient quantities of VIG to protect against adverse reactions during a mass immunization campaign would necessitate careful screening of those receiving the vaccine; some persons with adverse reactions would likely go untreated.

While the intentional release of smallpox virus would represent a global emergency, the existing national stockpile could be effectively used to limit the spread of disease and buy time while the pharmaceutical industry begins emergency vaccine production.

James W. LeDuc and John Becher
Centers for Disease Control and Prevention, Atlanta, Georgia, USA

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West Nile Fever in Czechland

To the Editor: After heavy rains in July 1997, extensive floods occurred along the Morava River, Czech Republic. Populations of *Aedes* mosquitoes increased rapidly in the flooded areas, prompting surveillance for mosquito-borne virus infections in the Breclav area, South Moravia. We collected 11,334 female mosquitoes (9,100 *Aedes vexans,* 917 *Ae. cinereus,* 11 *Ae. cantans,* 1,074 *Ae. sticticus*, and 232 *Culex p. pipiens*) from July through September 1997 and tested them for virus in 117 monospecific pools by intracranial inoculation of suckling mice. Seven virus isolates were obtained and identified by complement-fixation and neutralization tests. Six isolates (five from *Ae. vexans*, one from *Ae. cinereus*) were identified as the bunyavirus Tahyna, California serogroup, and one (strain 97-103 from 57 *C. p. pipiens* collected at Lanzhot, 48°40'N, 16°56'E, on September 17) was identified as the flavivirus West Nile (1). A crossed comparison of 97-103 and topotype Eg-101 (2) West Nile virus strains and their antisera (prepared in mice by three intraperitoneal doses at weekly intervals) by plaque reduction neutralization (PRN) on XTC-2 cells (3,4) showed their antigenic relationships: reciprocal titers of homologous/heterologous sera were 512/512 in Eg-101 and 512/64 in 97-103. Strain 97-103 has lower virulence than Eg-101 in that it does not kill adult ICR mice and may represent a subtype of West Nile virus.

Blood samples were obtained from 619 persons seeking treatment at hospital and outpatient clinics in the Breclav area from June 23 through September 29, 1997. Sera were inactivated at 56°C for 30 minutes, diluted 1:8, and assayed by PRN for antibodies against *c.* 30 plaque-forming units (PFU) per well of West Nile virus strains Eg-101 and 97-103. All sera causing 90% reduction of PFU at 1:8 dilution were titrated, and the highest serum dilution showing 50% PFU reduction was regarded as the titer. Antibodies neutralizing West Nile virus were detected in 13 (2.1%) persons: 2.8% of 179 male and 1.8% of 440 female. Persons with detectable West Nile virus antibody were questioned about their health history during the previous 5 years, and their medical records were reviewed; none recalled having had tickborne encephalitis (Central-European encephalitis [CEE] virus is the only other flavivirus present in Czechland) or having been vaccinated against CEE or yellow fever virus. Titers of PRN antibodies to CEEV were all below 16. Two of the seropositive persons had traveled abroad during the last 5 years: one to Croatia in 1996, and one to South Australia during 1951 to 1994.

Paired serum samples were obtained from 72 of the 619 persons examined. A significant increase (≥4 times) in antibody titer against West Nile virus between the first (acute-phase) and second (convalescent-phase) samples was detected four times: in 2 of 41 young persons (≤16 years of age) and in 2 of 31 adults (>16 years of age). Among the four seroconverting persons, only the two children had clinical symptoms compatible with West Nile fever. A 9-year-old boy had fever (39°C) for 4 days, sore throat, headache, muscle ache, pronounced fatigue, and nausea lasting approximately 6 days, with recovery after 13 days. Neutralizing antibodies to West Nile virus, Eg-101 and 97-103, were 64 and 32 on July 22 and 512 and 256 on August 4, respectively. A 9-year-old girl had fever (38°C-39°C) for 3 days, sore throat, headache, muscle ache, pronounced fatigue, nausea, vomiting, maculopapular rash (including flushed face), and slightly enlarged inguinal lymph nodes. The illness lasted approximately 7 days, with complete recovery after 17 days. Neutralizing antibodies to West Nile virus, Eg-101 and 97-103, were 64 and 32 on August 6 and 256 and 128 on August 20, respectively. Of the remaining nine seropositive persons lacking paired serum samples, one had severe headache, muscle ache, prolonged fatigue, nausea, pain on eye movement, maculopapular rash, and insomnia in summer of 1997. Two other persons had had "summer fever" (sore throat and lymphadenitis; headache with pain on eye movement) in 1997. The other persons who seroconverted did not report any substantial illness. In total, clinical symptoms in five persons are compatible with West Nile fever.

These are the first reported human cases of West Nile fever in Central Europe (5); an extensive outbreak occurred in Romania in 1996, with approximately 500 patients hospitalized and a 4% to 8% fatality rate (6,7). West Nile virus should be viewed as a potential agent of local sporadic cases, clusters, or outbreaks, even in temperate Europe. Environmental factors (including human activities) that enhance vector population densities (heavy rains followed by floods, irrigation, higher than usual temperatures due to global warming) might produce an increased incidence of West Nile fever and other new or reemerging mosquito-borne diseases. Surveillance for West Nile fever should monitor population density and infection rate of principal vectors, antibodies in vertebrates and exposed human groups, and routine diagnosis of human infections.

Zdenek Hubálek, Jirí Halouzka, and Zina Juricová
Institute of Vertebrate Biology, Academy of Sciences, Brno, Czech Republic

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Ofloxacin-Resistant *Vibrio cholerae* O139 in Hong Kong

To the Editor: Unexpected outbreaks of cholera occurred in many areas of the world in 1997-98, partly because of weather changes associated with the El Niño phenomenon (1). Outbreaks caused by antibiotic-resistant *Vibrio cholerae* O1 and O139 have been documented in the Indian subcontinent (2-4), Africa (5), and Ukraine (6).

In Hong Kong, nonduplicate bacterial strains of *V. cholerae* O1 and O139 isolated from patients and environmental sources and received in the Public Health Laboratory between January 1, 1993, and June 30, 1998, were identified by conventional biochemical tests (7,8) and API 20E (bioMerieux, France); serotyped by slide agglutination with polyvalent O1 and mono-specific Inaba and Ogawa antisera (Murex, Dartford, United Kingdom); and checked with O139 antiserum (Denka Seiken, Tokyo, Japan). Biotyped and antibiotic susceptibilities were determined by the Kirby-Bauer disk-diffusion assay (8-10). Antibiotics tested included chloramphenicol and tetracycline (from 1993 to 1996) and ofloxacin (added in routine testing from 1997). *V. cholerae* isolates available for further study were tested with the standard broth microdilution method (11) to measure minimum inhibitory concentrations (MICs) of susceptibilities to chloramphenicol, tetracycline, and ofloxacin.

No antibiotic resistance was seen in *V. cholerae* isolates in testing conducted from 1969 to 1995. The first *V. cholerae* isolate with reduced susceptibility to chloramphenicol but sensitive to tetracycline was encountered in Hong Kong in 1996. This O1 El Tor Ogawa strain was imported from Nepal. Since then, more O1 strains were isolated that exhibited reduced antibiotic susceptibilities to chloramphenicol and tetracycline but not to ofloxacin (12). In May 1998, seven *V. cholerae* O139 strains were isolated that displayed patterns of antibiotic susceptibilities strikingly different from those of O1 isolates; the former were all sensitive to tetracycline but showed reduced susceptibilities to chloramphenicol and ofloxacin. All *V. cholerae* O1 strains tested have been susceptible to ofloxacin; O1 isolates falling into intermediate categories for chloramphenicol and tetracycline susceptibilities (31% and 27.6%, respectively) were common.

The first isolate of *V. cholerae* O139 in Hong Kong came from the imported case of a patient who had traveled to other provinces of China (13,14). Isolation of O139 continued sporadically since then, with six cases between 1993 and the

1st quarter of 1998. In May 1998, a cluster of seven imported cases of *V. cholerae* O139 were reported with strains isolated from seven persons who became ill with severe diarrhea after visiting Zhuhai in Guangdong Province, China. Of 13 *V. cholerae* O139 isolates tested, 7 showed intermediate resistance to chloramphenicol and high-level resistance to ofloxacin (MIC 16 μg/ml) but no resistance to tetracycline (MIC 50s and MIC 90s were 0.25 μg/ml). This is the first evidence of a quinolone-resistant strain of *V. cholerae* O139 in Hong Kong. Of the O1 isolates, none were resistant to chloramphenicol and ofloxacin, but six were resistant to tetracycline (MIC 50s and MIC 90s were 0.25 μg/ml and 8 μg/ml, respectively).

Although all O1 isolates were sensitive to chloramphenicol, there was only a twofold difference in MIC90 to chloramphenicol between O1 and O139 isolates. MIC90s of ofloxacin for O139 were nearly 10 times higher than those for O1 strains.

The novel appearance of O139 resistant to ofloxacin with MICs of 16 μg/ml from Guangdong Province, China, was of special concern. Preliminary results using pulsed-field gel electrophoresis analysis of chromosomal DNA showed that these ofloxacin-resistant O139 strains had identical fingerprint patterns and probably belonged to the clone that had caused severe diarrheal disease in the region. Two previous surveys of *V. cholerae* antibiotic susceptibilities had not described any ofloxacin-resistant O139 strains (15,16). The potential for rapid spread of these strains threatens cholera prevention and control efforts that may still rely on chemotherapy.

Different antimicrobial resistance patterns of *V. cholerae* O1 and O139 were noted. Among the resistant O1 isolates, four were local, one was from other provinces of China, and one was from Thailand. All the resistant O139 isolates were imported from Guangdong Province, China. Antibiotic resistance was found in strains from local isolates and from neighboring countries. The unique patterns of antimicrobial resistance for the O1 and O139 isolates suggest different mechanisms of resistance. As quinolones are used heavily in this region to treat cholera and other enteric diseases, selective pressure could encourage emergence of ofloxacin resistance. Prudent use of antibiotics should be exercised during antimicrobial therapy and prophylaxis for cholera and other enteric diseases to decrease the selection of more resistant clones in our locality.

Kai Man Kam, Kit Yee Luey, Tze Leung Cheung, Kwan Yee Ho, Kwok Hang Mak, and Paul Thian Aun Saw
Department of Health, Hong Kong SAR Government

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Plant Pathology and Public Health

> The day will come when the sign of the plant pathologist will stand forth in the street alongside that of the physician and surgeon. . . . For what will it profit us if all the ills and diseases of the human race be banished and we then face starvation because of diseases and pests in our food (1).

To the Editor: Every year plant diseases affect human society, resulting in inadequate nutrition and economic loss. The potato famine in the mid-1800s is the best-known example of a fungal plant pathogen's effect on history (2-4); *Phytopthora infestans* has recently reemerged in the Americas (5). Among the silent problems that have enormous effects on human society each year are crop infections by geminiviruses and tomato spotted wilt virus (6). These plant viruses are transmitted by whiteflies, leafhoppers, or thrips to hundreds of species of plants. They cause diseases of crops and ornamental plants around the world.

More obvious problems include ergotism, caused by the alkaloids produced by the fungus *Claviceps purpurea*. Ergotism was associated with the growth of rye, particularly in cool climates that cannot support wheat, and was implicated in the aberrant human behavior responsible at least in part for the Salem witch trials and St. Anthony's fire (2,7). In the last 5 years, a new plant disease, sorghum ergot (*Claviceps africana*), has spread north from Brazil into the United States. This fungus also causes disease in Australia, a sudden change from its known occurrence in Africa (8). Sorghum is the fifth most important cereal crop in the world, with approximately 45 million hectares under cultivation for food, beverages, feed, and fodder (8). Ergot alkaloid toxicity has not yet been demonstrated, but potential nutritional and economic losses could have substantial impact on public health.

With our increased awareness of the fragility of the environment, including the quality of our drinking water, opportunities may exist for physicians to interact with plant pathologists. Concern is growing about the use of *Burkholderia cepacia*, a bacterial phytopathogen, for the biologic control of seedling diseases (9). Although *B. cepacia* is effective for the biologic control of fungal diseases in the agricultural environment (10), this bacterium could contaminate the public water supply and subsequently influence the health of the immunosuppressed or persons with cystic fibrosis (9-11). This risk exemplifies the need to integrate plant health measures with human and veterinary health guidelines.

Plant pathology and public health also intersect with post-harvest fungal infections of seed and grain, particularly *Aspergillus flavus* and *Fusarium moniliforme* (2), which produce aflatoxin and fumonisin, respectively. During the past 2 drought years in Texas, aflatoxin in contaminated corn and peanuts has become a public health problem. In 1998, more than 50 pet dogs died of aflatoxicosis, perhaps by eating aflatoxin B1-contaminated corn used in dog food (12).

Although the veterinary and medical communities are well aware of the risks associated with plant pathogens when they enter the animal or human food supply, more routine interactions with plant pathologists could benefit public health. For example, plant pathologists can often predict impending plant disease outbreaks. This information can be used by epidemiologists to sound a warning about impending food shortages or poor food quality, particularly in developing countries. Plant pathologists are also developing new types of resistance in host plants and alternative strategies for managing plant diseases. These measures should improve food quality and reduce the negative public health impact associated with plant diseases.

Karen-Beth G. Scholthof
Texas A&M University, College Station, Texas, USA

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Pet-Associated Zoonoses

To the Editor: We read with interest the article by Grant and Olsen on preventing zoonotic diseases in immunocompromised persons (1). We completely agree with the benefits of communication between physicians and veterinarians. However, we want to emphasize that pet-associated illnesses are not limited to the immunocompromised; pregnant women and young infants should be included in this high-risk category. Our recently published survey (2) reaffirms the need for education of the general public, parents, and—to a lesser extent—pediatricians regarding pet-associated hazards.

Leslie L. Barton,* Rodrigo G. Villar,† and Megan Connick‡
*University of Arizona Health Sciences Center, Tucson, Arizona, USA; †Indian Health Service, Gallup, New Mexico, USA; and ‡Washington University School of Medicine, St. Louis, Missouri, USA

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Clinical Infectious Diseases: A Practical Approach. K.R. Root, F. Waldvolgel, L. Corey, W.E. Stamm, editors. Oxford University Press, New York, 1999,1,013 pages.

This new text presents updated and valuable information to the clinician and brings to the forefront issues important for diagnosing and managing infectious diseases in an era of competing demands on resources and rapidly evolving health-care delivery systems. While other books on infectious diseases are available, the speed with which new diagnostic methods are developed and the unpredictable nature of microbial pathogens require that the clinical and health-care community be kept informed of new approaches to diagnosis. This is particularly true in today's medical environment, where international travel and world events compel the local medical community to broaden its scope beyond its former comfort zone. The editors and contributors to this book have successfully presented the diagnosis, management, and prevention of infectious diseases in a context that promotes the best of patient care and outcome.

The text has 1,013 pages of information, tables, charts, algorithms, and photographs provided by 150 contributors representing a broad array of internationally recognized expertise. The book's 103 chapters are logically divided into seven parts: Pathophysiology of Infectious Diseases, Diagnostic Methods in Infectious Diseases, Antimicrobial Drugs: Principles and Usage, Vaccines and Immunomodulary Agents, Infectious Disease Syndromes, Infections in Special Patient/Risk Groups, and Human Immunodeficiency Virus and AIDS. The first four provide sufficient background for focusing on the final three sections. The text includes 49 color plates with 54 photos that are bright, colorful, descriptive, and large enough for detail to be appreciated.

Specimen management is covered nicely in the chapters on bacteria, viruses, parasites, and fungi, although the apparent assumption is that the patient will usually be an adult. In some cases, specimens from pediatric patients may require different approaches to collection and to the amount of material to collect. In addition, the role of the swab as a collection device is not detailed enough, since there are so many types (e.g., Dacron-, rayon-, calcium alginate-, and cotton-tipped swabs), some of which are specifically recommended for use with certain agents or tests. More could have been presented regarding specimen transport, in light of the emergence of central core laboratory facilities for multihospital health systems and the use of distant facilities for microbiology analysis.

The 22 chapters on antimicrobial drugs and their appropriate use are complete and up to date. For example, a brief discussion of the recently emerged glycopeptide-intermediate *Staphylococcus aureus* is presented, as is information on inappropriate use of antimicrobial drugs, particularly vancomycin, and the emergence of extended-spectrum beta-lactamases. Pharmacokinetics, clinical indications and use, mode of action, clinical experience, adverse reactions, mechanisms of resistance, and other useful information are described, along with a generous array of very helpful summary tables and charts.

The primary diagnostic portion of the text is presented by syndrome, not by organism or individual disease. For example, tuberculosis is covered in the chapter on "Cavitary Pulmonary Disease," while varicella is discussed in "Infections with Rash." The annotated bibliography at the end of each chapter is very helpful: recent literature references are included where possible, along with italicized notes about the content and value of each reference selected. Pathogenesis is appropriately discussed in the section for each disease or agent rather than in an introductory section. The complexity of pathogenic mechanisms and host-parasite relationships within the microbial groups makes this approach a sound one. This section of the book is nicely introduced by valuable discussions on fever that set the stage for the subsequent syndrome presentations.

The section on infections in special patient populations and in special groups at risk is appropriate and informative and recognizes the unique needs and problems associated with these populations. Infections in immunocompromised patients, postsurgical wound infections, trauma, in-dwelling medical devices, transplantation, travelers, and alcohol and drug abuse are some of the special risks and groups presented. AIDS and HIV are considered separately in a seven-chapter section.

There are few negatives about this book. For ease of use, it might have been helpful for all information about specimen management to be

summarized in a single chapter. There were some controversial recommendations for blood collection at 1-hour intervals, and some may question the proposed use of direct antigen tests in spinal fluid for pediatric patients. Today vaginosis is recognized with more accuracy in the microbiology laboratory by Gram stain evaluation rather than by culture (as recommended in the book), which can often be inconclusive.

This book, while not inexpensive, will be an important addition to the resources available to clinicians and laboratorians alike.

J. Michael Miller
Centers for Disease Control and Prevention,
Atlanta, Georgia, USA

The Epidemiology and Control of Communicable Diseases

Surveillance and Investigating Outbreaks (November 22–23)
Control of Communicable Diseases (November 24–25)

Presented by the University of Western Australia (UWA), Department of Public Health's Summer School Program 1999, this interactive course will provide both an overview of communicable disease control and practical skills in surveillance, investigation, health outcomes, role of government, policy development and analysis, value, and limitations of legislation in the context of infectious disease control.

The presenter, Dr. Aileen Plant, is a medical epidemiologist with UWA and recently undertook a 6-month study leave with WHO, working with a new international surveillance and investigative network, TEPHINET.

Cost is $400 AUD per module with discounts for registration before August 31. Participants may enrol in one or both modules. Prior epidemiologic experience is not necessary. CME points for general practioners have been applied for.

To register, contact Serena Angelo at serena@dph.uwa.edu.au.

For information on UWA's Summer School go to http://www.publichealth.uwa.edu.au/events/summer/ or contact Melodie Kevan, Dept. of Public Health, The University of Western Australia Nedlands WA 6907; phone: 61-8-9380-1286; fax: 61-8-9380-1188; e-mail: melodie@dph.uwa.edu.au.

Antibiotic Resistance in Bacteria of Animal Origin

Institut Pasteur, Paris, France, November 29–30, 1999

This international symposium, organized as part of a European Concerted Action, will gather scientists from diverse disciplines (microbiology, epidemiology, ecology) to share data and actual knowledge on antibiotic resistance, especially in the veterinary field.

Objectives of this congress are the presentation of current recommendations of Concerted Action members, of current knowledge on antibiotic resistance, and of existing monitoring strategies, and the promotion of research funded by the European Union.

Information on this program and the topic of antibiotic resistance in bacteria of animal origin is available at http://www.fougeres.afssa.fr/arbao.

To receive conference materials, please forward your name, affiliation, postal address, phone and fax number, and e-mail address to P. Sanders, AFSSA-Fougères, La Haute Marche-Javené, BP 90203, 35302 Fougeres Cedex, France; phone: 33-29-994-7876; fax: 33-29-994-7877; e-mail: arbao@fougeres.afssa.fr.

Keystone Symposia on Molecular and Cellular Biology

Genetics, Pathogenesis and Ecology of Emerging Viral Diseases (J1)
Taos Civic Center, Taos, NM, January 24–30, 2000
Organizers: Michael J. Buchmeier and Clarence J. Peters
Abstract Deadline: September 24, 1999
Early Registration: November 23, 1999

Pathogen Discovery: From Molecular Biology to Diseases (J2)
Taos Civic Center, Taos, NM, January 24–30, 2000
Organizers: Georg Hess and Helen H. Lee
Sponsored by Roche Diagnostics
Abstract Deadline: September 24, 1999
Early Registration: November 23, 1999

Biological Threats and Emerging Diseases (F3)
Beaver Run Resort, Breckenridge, CO, April 8–13, 2000
Organizers: Gregory Milman, Joseph E. McDade and Gail H. Cassell
Abstract Deadline: December 8, 1999
Early Registration: February 8, 2000

For information or registration visit Keystones's Web site: http://www.symposia.com.

The 5th World Congress on Trauma, Shock, Inflammation and Sepsis-Pathophysiology, Immune Consequences and Therapy

Munich, Germany, February 29–March 4, 2000

Deadline for abstracts is October 30, 1999.
For further information contact: Eugen Faist, Dept. of Surgery, Ludwig-Maximilians-University Munich, Klinikum Grosshadern, Marchioninistrasse 15, 81377 Munich, Germany; phone: 49-89-7095-5461/2461; fax: 49-89-7095-2460; e-mail: faist@gch.med.uni-muenchen.de.

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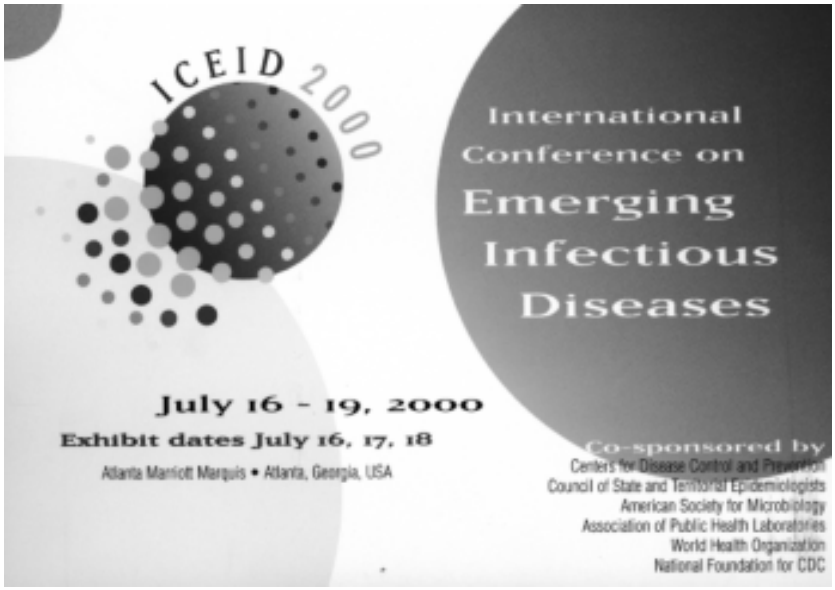

Hold the dates of July 16–19, 2000 for the International Conference on Emerging Infectious Diseases, a meeting of 2,500 specialists in infectious diseases. The program will include plenary sessions and symposia with invited speakers, presentations on emerging infections activities, and oral and poster presentations. Major topics will include current work on surveillance, epidemiology, research, communication and training, as well as prevention and control of emerging infectious diseases, both in the United States and abroad. Abstracts are invited and will be accepted beginning in September 1999.

The Call for Abstracts and Preliminary Program will be mailed in August 1999.

For more information, call ICEID management at 202-942-9248, e-mail meetinginfo@asmusa.org, or www.cdc.gov/ncidod/iced2k.htm.

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Emerging Infectious Diseases is a peer-reviewed journal established expressly to promote the recognition of new and reemerging infectious diseases around the world and improve the understanding of factors involved in disease emergence, prevention, and elimination.

The journal has an international scope and is intended for professionals in infectious diseases and related sciences. We welcome contributions from infectious disease specialists in academia, industry, clinical practice, and public health, as well as from specialists in economics, demography, sociology, and other disciplines. Inquiries about the suitability of proposed articles may be directed to the Editor at 404-639-4856 (tel), 404-639-3075 (fax), or eideditor@cdc.gov (e-mail).

Emerging Infectious Diseases is published in English and features the following types of articles: Perspectives, Synopses, Research Studies, Policy Reviews, and Dispatches. The purpose and requirements of each type of article are described in detail below. To expedite publication of information, we post journal articles on the Internet as soon as they are cleared and edited.

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Begin each of the following sections on a new page and in this order: title page, abstract, text, acknowledgments, references, tables, figure legends, and figures.

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Submit three copies of the original manuscript with three sets of original figures and an electronic copy (on diskette or by e-mail) to the Editor, Emerging Infectious Diseases, Centers for Disease Control and Prevention, 1600 Clifton Rd., MS C-12, Atlanta, GA 30333, USA; e-mail eideditor@cdc.gov.

Types of Articles

Perspectives, Synopses, Research Studies, and Policy Reviews: Articles should be approximately 3,500 words and should include references, not to exceed 40. Use of subheadings in the main body of the text is recommended. Photographs and illustrations are encouraged. Provide a short abstract (150 words) and a brief biographical sketch.

Perspectives: Articles in this section should provide insightful analysis and commentary about new and reemerging infectious diseases or related issues. Perspectives may also address factors known to influence the emergence of diseases, including microbial adaptation and change; human demographics and behavior; technology and industry; economic development and land use; international travel and commerce; and the breakdown of public health measures. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text.

Synopses: This section comprises concise reviews of infectious diseases or closely related topics. Preference is given to reviews of new and emerging diseases; however, timely updates of other diseases or topics are also welcome. Use of subheadings in the main body of the text is recommended. If detailed methods are included, a separate section on experimental procedures should immediately follow the body of the text. Photographs and illustrations are encouraged.

Research Studies: These articles report laboratory and epidemiologic results within a public health perspective. Although these reports may be written in the style of traditional research articles, they should explain the value of the research in public health terms and place the findings in a larger perspective (e.g., "Here is what we found, and here is what the findings mean").

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Book Reviews: Short reviews (250 to 500 words) of recently published books on emerging disease issues are welcome.

Letters: This section includes letters that give preliminary data or comment on published articles. Letters (500 to 1,000 words) should not be divided into sections, nor should they contain figures or tables. References (not more than 10) may be included.

News and Notes: We welcome brief announcements (50 to 150 words) of timely events of interest to our readers. (Announcements can be posted on the journal web page only, depending on the event date.) In this section, we also include summaries (500 to 1,500 words) of conferences focusing on emerging infectious diseases. Summaries may provide references to a full report of conference activities and should focus on the meeting's content.