Bioterrorism Preparedness

Medicine – Public Health – Policy

Edited by
Nancy Khardori

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Preface

The range of diseases caused by biological agents and/or their toxins with the potential to be used intentionally against civilian populations is extensive and diverse. Some of these, for example anthrax, have been known to man since antiquity whereas others, for example Nipah virus, were recognized only recently. Even before the "microbial world" was seen or propagated, filth, fomites, carcasses, and cadavers were used to "transmit" disease and devastation to armies during wars.

It is interesting that the first specific biological agent, *Bacillus anthracis*, attributed to human disease by fulfilling Kochs postulates is also the one that has received most notoriety as a bioterrorism agent. The development of the science of bacteriology in the late 19th century expanded the scope of biological agents as weapons of mass destruction. The threat of nuclear and chemical weapons dominated during the 20th century, however. The cheap and easy to propagate biological agents remained in the background and were reported to be used against civilians in isolated incidents mostly by small organized groups or individuals. The United States anthrax attacks of 2001 followed the most devastating and vivid crime against humanity in recent history. The low technology method of successfully disseminating anthrax spores through the US postal service brought into focus the threat of biological agents as potential weapons of mass destruction.

As I looked at the list of diseases caused by "critical biological agents" I immediately realized I had had the opportunity to see a few patients with all of them over the past 32 years. Perhaps this is one of the best things about having had the privilege of working in two different continents and having worked both in the basic science discipline of microbiology and the clinical discipline of infectious diseases. The Infectious Diseases Group (including all the authors of this book) had already planned a regional continuing medical education program in collaboration with the Association of Practitioners in Infection Control (APIC) for November 15, 2001, mostly to address West Nile virus and antibiotic resistance. As the convener, I suggested we expand the scope of the program to include "bioterrorism agents". All parties readily agreed. The program received an overwhelming response and registrations had to be turned down, even after changing the venue to accommodate more delegates. For the first time we were seeing large numbers from all medical and surgical specialties and from specialties like anes-

thesia and radiology in the same room – discussing issues that affected not just their patients but themselves and their families. We were invited by the American Society of Microbiology to conduct the first workshop on bioterrorism at its national meeting on September 26, 2002. We have conducted the workshop every year since in addition to presenting local and regional programs for healthcare providers, hospital executives, and safety engineers.

Last year, I received an invitation from the editor of the second edition of the **Encyclopedia of Molecular Cell Biology and Molecular Medicine** to write a review on "*Preparedness for Bioterrorism*". As I sent the manuscript, I explained to the editor that the material in this chapter was very different from what I expected to see in other chapters of this encyclopedia. Soon after the materials reached the publishers, Wiley–VCH, I received a very gracious note and an invitation to author and edit a book on bioterrorism. Once again, I chose to depend on my colleagues at our institution and this book is another one of our "team projects".

The book *Bioterrorism Preparedness – A Medicine – Public Health – Policy* has been prepared with the hope of being useful to medical students, healthcare providers, infection control practitioners, public health professionals, and legal professionals involved in health policy issues. The first two chapters provide a historical perspective and overview of potential agents of bioterrorism and bioterrorism preparedness. These two chapters will hopefully provide a quick reference to a variety of issues related to bioterrorism. The third chapter, "*Care of Children in the Event of Bioterrorism*", has, in my opinion, a unique quality to it. It emphasizes differences between the approach to bioterrorism-related diseases in adults and children – where they exist and are important. The next six chapters (4 to 9) are dedicated to the Category A agents. Each chapter stands on its own and provides appropriate but not overwhelming detail on all aspects of these diseases. The salient features of Category B and Category C agents are discussed in Chapter 1. The last two chapters on policy issues and legal preparedness written by our colleague in the Department of Medical Humanities have truly broadened the scope of this book. It has been a pleasure for me to interact with this young man and recognize the significance of health policy makers in the overall delivery of health care.

As one ponders over the past, present and future of bioterrorism, it becomes clear that the very advances in technology that have made diagnosis and treatment of many infectious diseases possible have also made it simpler to obtain, cultivate, and use them for bioterror. In particular, the breakthroughs that have come from the genomics revolution may be used to enhance detection, protection, and treatment. These same capabilities might also be misused in the design of bioweapons. The threat of biological agents being used for terrorist activity has given an impetus to research that will enhance our capability to detect, trace, and manage bioterrorism events. A significant example of this is the use of genomics in tracing the origin or source of a microbial agent. Microbial forensics will enable "genetic fingerprinting" of the weapon the same way as it is currently being used on the alleged perpetrators. Such research and future technology will at the same time be useful in detecting and managing natural infectious disease. To quote Albert Einstein, "In the middle of difficulty lies opportunity".

I would like to express my sincere thanks to all my colleagues who have made contributions to this book. I must also thank a long time friend and a colleague in endocrinology and molecular medicine who is known for his encyclopedic knowledge, photographic memory, and constant desire to send me reading materials from sources I generally do not follow. In closing, my gratitude and thanks go to Mrs Nancy Mutzbauer without whose unconditional and constant help much of the book would never have seen the light of day.

Springfield, December 2005 *Nancy Khardori*

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1
Potential Agents of Bioterrorism: Historical Perspective and an Overview

Nancy Khardori

1.1
Historical Perspective – How We Got Here

A quote from Hans Zinser, a bacteriologist and historian during the Great Depression in the United States, puts the concept of "terror associated with biological agents" in the best possible perspective [1]. He said "Infectious disease is one of the great tragedies of living things – the struggle for existence between different forms of life ... incessantly the pitiless war goes on, without quarter or armistice – a nationalism of species against species." What he seemed to convey in this quote is the fact that mankind will never be able to completely protect itself against many of the biological agents coexisting in nature. The interaction between humans and disease-causing pathogens in nature is constant, with one or the other winning at all times and the course of human history has been altered frequently by the capability of infectious agents to spread and cross national borders.

The epidemics and pandemics of infectious diseases caused by communicable agents have swept unchecked across continents claiming more lives and creating more social devastation than wars. Examples include [2]:

1. diseases like smallpox, measles, plague, typhoid, and influenza causing 95% of deaths in pre-Columbian native American populations;
2. the death of 25 million Europeans (a quarter of the population) caused by plague in the 14th century; and
3. more than 21 million deaths because of the influenza pandemic of 1918 and 1919.

Worldwide, naturally occurring infectious diseases remain the major causes of death. In the United States and Western Europe, the impact of several very virulent microbial agents and/or their toxins has been much reduced because of a very accessible health-care system and the public health infrastructure – although a substantial number of people (approximately 170,000) still die each year from

infectious diseases in the United States [3]. The travel and trade necessary for economic globalization, the continued potential for transmission of infectious agents from animals to humans, and large populations living and working in proximity in urban areas of the world enable infectious disease outbreaks to remain a major threat. Recent outbreaks of severe acute respiratory syndrome (SARS) and avian influenza are excellent examples. Until the discovery of preventive measures and anti-infective therapies, for example vaccines and antimicrobial agents, large disease outbreaks were even more common during war times. Infectious diseases caused far more deaths than battle injuries until World War II. Wars led to changes in both the host population of humans and animals and the pathogen population of infectious agents. Humans and animals became more susceptible to disease because of famine and malnutrition and the pathogens found new and vast breeding grounds in decaying organic matter including human and animal corpses. This resulted in pollution of scarce food and water supplies. In addition, vectors, the disease-transmitting agents, for example mosquitoes and flies, multiplied unchecked causing vector-borne diseases for which no preventive measures existed.

It is not surprising that a connection between "disease", "contagion", filth, and foul odor was made much before microbes were discovered. Human ingenuity made use of this association by the crude use of filth, cadavers, and human and animal carcasses as weapons [4]. These avenues of transmitting disease and devastation to armies and civilian populations have been used to contaminate wells, reservoirs, and other water sources since antiquity through the Napoleonic era and into the 20th century. As early as 300 BC, the Greeks polluted the wells and drinking water supplies of their enemies with animal corpses [5]. The same tactics were used later by the Romans and Persians. The bodies of dead soldiers and animals were used to pollute wells during a battle in Italy in 1155. Pollution (poisoning of potable water) was used as an effective and calculated method of gaining advantage in warfare throughout the Classical, Medieval and Renaissance periods. During the Middle Ages military leaders recognized that victims of disease (infections) could themselves become weapons [6]. Gabriel de Mussis, a notary, described how the plague-weakened Tartar forces catapulted victims of plague into the town of Kaffa in 1346 [7]. An epidemic of plague that followed forced a retreat of the Genoese forces. The population under siege may have been at an increased risk of epidemics because of deteriorating sanitation and hygiene. The imported disease continued to spread in Europe. In 1422 bodies of dead soldiers and 2000 cartloads of excrement were hurled into the ranks of the enemy at Carolstein. These two incidents contributed to the 25 million deaths in Europe in the 14th and 15th centuries during the Black Plague. Russian troops battling Swedish forces in Revat resorted to throwing plague victims over the city walls in 1710.

The use of smallpox victims and their fomites as weapons in the new world received similar notoriety. The indigenous people of Central and South America were decimated by measles and smallpox introduced to them by the Spanish conquistadors. They are said to have been presented with smallpox contaminated clothing in the 15th century [6, 8]. Smallpox-laden blankets were provided to the Indians during the French and Indian Wars (1754–1767). This adaptation of the

Trojan Horse use was followed by a smallpox epidemic among native American tribes in the Ohio River Valley. Smallpox epidemics in Native Americans after initial contact with Europeans had, however, been occurring for more than 200 years. Transmission of smallpox by means of respiratory droplets would have been much more efficient than use of fomites. Confederate General Joseph Johnson used the bodies of sheep and pigs in 1863 to pollute drinking water at Vicksburg during the US Civil War. These early attempts (14th to 18th century) at using biological materials to cause disease in the opponent have been referred to as biological warfare even though the nature of the biological agents in these materials was largely unknown. These early incidents also illustrate the complex nature of disease caused by biological agents. Naturally occurring endemic disease is very difficult to differentiate from that caused by deliberate spread of disease. Therefore the concept of "bioterror" should encompass in its spectrum:

1. naturally occurring infectious diseases;
2. acts of biological warfare; and
3. acts of biological terrorism against the civilians in peace and war time.

In any and all of these roles, biological agents have been, and will remain, potential tools of mass casualties.

1.2 Development of Modern Biological Weapons

Bacillus anthracis was the first specific biological agent attributed to human disease when Robert Koch confirmed his own "postulates" concerning this organism in 1877. The subsequent development of the science of bacteriology in the 19th century expanded the scope of biological agents as weapons of mass destruction. This occurred concomitantly with understanding of the pathogenicity of microbes, host–pathogen interactions, and advances in the prevention and treatment of infectious diseases. Modern microbiology intended primarily for diagnosis and treatment of infectious diseases also afforded the capability to isolate and produce stacks of specific pathogens. Germany developed an ambitious biological warfare program during World War I. Covert operations to infect livestock and contaminate animal feed to be exported to the allied forces were conducted in neutral trading partners [9]. *Bacillus anthracis* and *Burkholderia mallei*, causative agents of anthrax and glanders, respectively, were prepared for use to infect Romanian sheep for export to Russia. These cultures were identified at the Bucharest Institute of Bacteriology and Pathology after being confiscated from the German Legation in Romania in 1916. Between 1917 and 1918, livestock in Mesopotamia and Argentina intended for export to Allied Forces were infected with *B. anthracis* and *B. mallei*. During World War I the horror of chemical warfare clearly superceded the impact of biological agents. International diplomatic efforts were directed at limiting the proliferation and use of weapons of mass destruction culminating in the 1925 Geneva Protocol prohibiting the use in war of asphyxiation, poisons, or other gases

and of biological methods of warfare [10]. Many of the parties that ratified the Geneva Protocol began research programs to develop biological weapons after World War I. These included Belgium, Canada, France, Great Britain, Italy, the Netherlands, Poland, and the Soviet Union. The United States began an offensive biological program in 1942. Japan conducted twelve large-scale field trials of biological weapons during World War II. This operation was conducted largely under the auspices of Unit 731, a biological warfare research facility. Pathogens used in these experiments included *B. anthracis, Neisseria meningitidis, Shigella* spp. *Vibrio cholera*, and *Yersinia pestis* [11]. During the Japanese program between 1932 and 1945 an estimated 10,000 prisoners died as a result of experimental infection or execution after experimentation. Biological agents were used by Japan to attack 11 Chinese cities. The avenues used included contamination of water supplies and food items, tossing of cultures into homes, and spraying of cultures from aircraft. Pure cultures of *B. anthracis*, V. *cholerae*, Shigella spp., Salmonella spp., and *Y. pestis* were used. Japan was alleged to have used *Y. pestis* as a biological weapon by feeding laboratory bred fleas on plague-infected rats and releasing them over Chinese cities from aircraft. Large numbers of fleas, as many as 15 million, were used per attack to initiate plague epidemics. Rigorous epidemiological and bacteriological data from these experiments are not available. It is estimated that Japan killed 260,000 people in China with biological weapons, primarily plague. Japanese troops suffered approximately 10,000 biological casualties and 1700 deaths, mostly from cholera, in 1941 because they had not been adequately trained or equipped for the hazards of biological weapons. The success of the Japanese attacks attest to the simplicity and diversity with which biological agents can be used to cause death and devastation.

Although the German offensive biological weapons threat during World War II never materialized [12], experiments with *Rickettsia prowazekii, Rickettsia mooseri*, hepatitis A virus and Plasmodia spp. were conducted on Nazi concentration camp prisoners to study pathogenesis and to develop vaccines. As the Weil Felix Test using a cross-reaction immunological method (with Proteus OX19) became available, it was used by the German army to avoid areas with epidemic typhus. As a defense against deportation of people in occupied areas of Poland, physicians used Proteus OX-19 as a vaccine to induce false positivity for typhus. An example of biological weapons being used in a defensive role was created.

The allies developed biological weapon programs for potential retaliatory use in response to German biological attacks. Bomb experiments involving weaponized spores of *B. anthracis* conducted on Gruinard Island near the coast of Scotland, revealed the extensive longevity of viable anthrax spores in the environment. The island was decontaminated with formaldehyde and seawater during 1986 [13]. The United States offensive biological program was begun in 1942 under the direction of a civilian agency, the War Reserve Service [4]. The program weaponized lethal agents such as *B. anthracis*, Botulinum toxin, *Francisella tularensis*, and incapacitating agents such as *Brucella suis, Coxiella burnetii*, Staphylococcus enterotoxin B, and Venezuelan equine encephalitis virus. Anticrop agents such as rice blast, rye stem rust, and wheat stem rust were stockpiled but not weaponized. Cities like New York and San Francisco were surreptitiously used as laboratories to test aerosolization

and dispersal methods for simulants. An outbreak of urinary tract infection caused by *Serratia marcescens* occurred at Stanford University Hospital after covert experiments using *S. marcescens* as a stimulant. When the Washington Post reported these covert experiments much later (in 1976) public interest was aroused. The US program was expanded during the Korean War (1950–1953), but the US denied using biological weapons against North Korea and China. The US offensive biological weapons program was terminated after President Nixon's executive orders in 1969 and 1970. Three months later, he extended the ban to include toxins. The US Army Medical Research Institute for Infectious Disease (USAMRIID) at Fort Detrick, Maryland was established to conduct unclassified research on protection against potential agents of bioterrorism.

The origin of the Biological Weapons Program of the former Soviet Union dates back to the statements made by Lenin. Although experimental work was started in the nineteen-twenties, the modern era was ushered in only with the post World War II military building programs [14]. Despite the wide availability of technology for producing and weaponizing biological agents, the direct use of crude fomites against humans continued. One of the examples is the smearing of pungi sticks with excrement by the Vietcong in the early sixties [15]. In 1973 the Soviet Politburo formed the organization known most recently as the Biopreparat to conduct offensive biological weapons programs concealed behind civil biotechnology research [14]. In January 1991 the first ever visit to Biopreparat facilities was undertaken by a joint United Kingdom and United States technical team. By the mid nineteen-nineties substantial changes occurred within the Biopreparat and a concerted effort is in progress to help the Russians civilianize these former biological weapons research and development establishments. The current capability of the old Russian Ministry of Defense sites remains largely unknown. The status of one of Russia's largest and most sophisticated former bioweapons facilities called Vector in Koltsovo, Novosibirsk, is of concern. The facility housed the smallpox virus and work on Ebola, Marburg, and the hemorrhagic fever viruses (e.g. Machupo and Crimean-Congo) [16, 17]. A visit in 1997 found a half-empty facility protected by a handful of guards. No one is clear where the scientists have gone. Confidence is lacking that this is the only storage site for smallpox outside the Centers for Disease Control and Prevention.

Iraq's biological weapons program dates back to at least 1974, started after the Biological and Toxin Weapons Convention had been signed. In 1995, Iraq confirmed that it had produced and deployed bombs, rockets, and aircraft spray tanks containing *Bacillus anthracis* and botulinum toxin [18]. Unfortunately, the number of countries engaged in biological weapons experimentation grew from four in the nineteen-sixties to eleven in the nineties [19]. It is estimated that at least ten nations and possibly seventeen possess biological warfare agents [20]. Of the seven countries listed by the United States Department of State as sponsoring international terrorism, at least five are suspected of having biological warfare programs [21–23]. Nations and dissident groups have the access to skills needed to selectively cultivate some of the most dangerous pathogens and to deploy them as agents of biological terrorism and warfare.

As the technology for cultivating and transporting microorganisms became easier and cheaper, dissident groups and well-financed organizations used biological agents in attacks and threats to accomplish political goals [24, 25]. Some examples of these attempts between 1979 and 2001 are summarized in Table 1.1.

Tab. 1.1
Examples of political attempts at bioterrorism. (Adapted with minor modifications from Ref. [26].)

Year	Group	Attempt	Outcome
1970	Weather Underground	A. US revolutionary group intended to obtain agents from Fort Detrick by blackmail and to temporarily incapacitate US cities to demonstrate the "impotence of the federal government"	Report originated with a US Customs informant. The case later seemed to be apocryphal.
1972	R.I.S.E.	A group of college students influenced by ecoterrorist ideology and 1960 s drug culture planned to use agents of typhoid fever, diphtheria, dysentery, and meningitis, initially to target the entire world population but later narrowed the plan to five cities near Chicago	The attack was aborted and cultures were discarded
1978	Unknown	Bulgarian defector Georgi Markov was assassinated in London when a spring-loaded device disguised in an umbrella was used to implant a ricin-filled pellet in his thigh.	A similar device used against a second defector in the same area was unsuccessful.
1979	Accidental	Accidental release of anthrax spores from a bioweapons facility in Sverdlovsk, Russia, caused an epidemic of inhalational anthrax.	At least 77 cases and 60 deaths.
1980	Red Army Faction	Members of a Marxist revolutionary ideology group allegedly cultivated botulinum toxin in a safe-house in Paris and planned attacks against at least nine German officials and civilian leaders	This was probably an erroneous report, later repudiated by the German government.
1984	Rajneeshee Cult	An Indian religious cult headed by Rajneesh plotted to contaminate a restaurant salad bar in Dalles, Oregon, with *Salmonella typhimurium*. The motivation was to incapacitate voters, win local elections, and seize political control of the county.	The incident resulted in a large community outbreak of salmonellosis involving 751 patients and at least 45 hospitalizations. The plot was revealed when the cult collapsed and members turned informants.

Year	Group	Attempt	Outcome
1991	Minnesota Patriots Council	A right-wing "Patriot" movement obtained ricin extracted from castor beans by mail order. They planned to deliver ricin through the skin with dimethyl sulfoxide and aloe vera or as dry aerosol against Internal Revenue Service officials, US Deputy Marshals, and local law enforcement officials	The group was infiltrated by Federal Bureau of Investigation informants.
1995	Aum Shinrikyo	A new age doomsday cult seeking to establish a theocratic state in Japan attempted at least ten times to use anthrax spore, botulinum toxin, Q fever agent, and Ebola virus in aerosol form.	Multiple chemical weapon attacks with sarin, Vx, and hydrogen cyanide in Matsumator, Tokyo, and assassination campaigns were conducted. All attempts to use biological weapons failed. The nerve gas sarin killed 12 and injured 5,500 in a Tokyo subway.
1997	Disgruntled employee in Texas	Intentional contamination of muffins and donuts with laboratory cultures of *Shigella dysenteriae*.	Caused gastroenteritis in 45 laboratory workers, four of whom were hospitalized.
2001	Unknown	Intentional dissemination of anthrax spores through the US Postal System led to the deaths of five people, infection of 22 others, and contamination of several government buildings.	Investigation into the attacks so far has not reached a conclusion.

Although most such events do not warrant national or international response and security, they can have substantial public health consequences and therefore require resources and preparedness at the local level. Active surveillance and rapid response at the local level are the cornerstones for preparedness against all types of bioterrorism – "think locally, act globally."

Incidents involving intentional use of microbial agents by small groups or individuals with limited targets are highly likely but the public health consequences are far less. An example is the well publicized arrest on February 18, 1998 of Larry Wayne Harris, a microbiologist who allegedly threatened to release "military grade anthrax" in Las Vegas, Nevada. He had obtained the plague and veterinary vaccine strains of anthrax and reportedly isolated several other bacteria. He made vague threats against US officials on behalf of Christian identity and white supremacists groups. He was arrested when he talked openly about the use of biological agents in terrorist activities. The sensational media coverage appears, however, to have had the unintended effect popularizing anthrax as a potential agent of terrorism among potential perpetrators. The first wave of anthrax hoaxes

followed the report of this event. The ease with which he had obtained the cultures prompted new legislation to ensure legitimate medical and scientific purposes for transfer of biological agents.

1.3 Biological Weapons Systems

Acquisition, storage, and transport of biological weapons is much easier than for chemical and nuclear weapons. A biological weapons system comprises:

1. a payload – the biological material consisting of an infectious agent or a toxin produced by bacteria, plants, or animals;
2. munitions that carry and keep the pathogens virulent during delivery;
3. a delivery system, which can be a missile, a vehicle (aircraft, boat, automobile, or truck), an artillery shell, or even an expendable soldier or martyr or conventional mail;
4. a dispersion system that enables dissemination of the payload, in a virulent form, among the susceptible target population [27, 28].

The dispersion system can be aerosol sprays, explosives, and food and water [29]. Aerosol sprays are the most effective means of widespread dissemination and therefore would be the most likely. The factors that can alter the effectiveness of a given dispersion system include the particle size of the agent, stability of the agent under desiccating conditions and ultra violet light, wind speed, wind direction, and atmospheric stability. Optimum conditions and/or the use of hardy organisms would enable clouds of infectious material to travel several hundred kilometers and be delivered to the terminal airways when inhaled. The natural lag time provided by the organism's incubation period (3 to 7 days for most pathogens) would enable safe escape for terrorists before recognition of the attack. Because heat and physical stress inactivate biological activity, explosives are not very effective in disseminating infectious or toxic materials, although the explosion itself and the threat of biological weapons would still create panic, terror, and civil disruption. Effective contamination of large water supplies would usually require an unrealistically large amount of the biological agent. Potable water would be an ineffective dispersion system unless the agent is introduced into smaller reservoirs or into the water supply after it passes through the purification facility. Contamination of food immediately before consumption is easier and more effective in transmitting infectious agents. Unfortunately, an outbreak associated with intentional contamination of food may be recognized late because of difficulty differentiating it from a naturally occurring event. The use of the US Postal service to disseminate anthrax spores carried on pieces of mail has revealed the potential of novel delivery and dispersal systems. Direct delivery of biological agents as pellets and flechettes has also been used. Biological agents can also be used in combination with conventional weapons to create fear and panic, further increasing the potential of mass casualties.

A successful bioterrorism event depends on several factors. For the most optimum outcome:

1. The microbial agents used should have the specific characteristics required of a bioweapon [30, 31]:
   - Most importantly, they must be suitable for mass production, storage, and "weaponization". Transforming microbial agents into bioweapons means they must be able to be packaged and distributed in a manner that disseminates them over a broad area without damaging the pathogenicity, and remain stable during dissemination. Covert release in an urban civilian setting may affect individuals in widely dispersed areas. Although they get the same illness, a common source of infection may not be considered early, because of use of different healthcare providers.
   - They should consistently produce the desired effects of disease and death. These outcomes would be magnified by the fact that both lethal and incapacitating agents would have an adverse impact on civilian health care delivery systems. In a military context, the incapacitation agents may better serve the perpetrator's purpose because the unit will not be able to perform their mission and affected soldiers will consume scarce medical and evacuation resources.
   - They should be highly contagious and infective in low doses. The person-to-person or vector-borne transmission would further increase the number of people affected and enhance the mass casualty effect.
   - They should have a known short and predictable incubation time. This knowledge would favor the terrorists by giving them the lead time and make clinical diagnosis difficult because of multiple possibilities.
   - The disease caused by the agent(s) should be difficult to identify in the target population because of multiplicity of clinical presentation and overlap with common and/or endemic infections. Lack of or low persistence in the environment after delivery would add to the difficulty in determining a "point-source" origin of the disease.
2. The target population should be highly susceptible based on lack of natural or acquired immunity. The lack of herd immunity after infection would lead to ongoing infection as long as the pathogen is around. If no treatment or immunization is available or readily accessible, the disease burden and deaths will increase.
3. The aggressors should have means to protect or treat themselves and their own forces and populations. The presence of partial or full immunity to an agent in the aggressor's population would also be favorable to them.

Biological weapons used in the form of aerosols are invisible, silent, odorless, tasteless and are dispersed relatively easily [32]. They cost 600 to 2000 times less than other weapons of mass destruction. It is estimated that approximately 0.05 % of the cost of a conventional weapon used for biological agents would produce similar numbers of mass casualties per square kilometer [28]. The economic

impact of a bioterrorism attack has been estimated to be from $477.7 million per 100 000 persons exposed (brucellosis scenario) to $26.2 billion per 100 000 persons exposed (anthrax scenario) [33].

1.4 Potential Bioterrorism Agents – Categorization and Prioritization

Many potential biological agents are capable of causing human disease. Although bioterrorism attacks could be caused by virtually any pathogenic microorganism, the list of agents that could cause mass casualties by the aerosol route of exposure is very small. Among the diseases caused by agents capable of being "weaponized" are some that are incapacitating while others cause mass casualties. Examples of the latter include anthrax, plague, and smallpox [26]. A North Atlantic Treaty Organization handbook dealing with biological warfare defense lists 39 agents including bacteria, viruses, rickettsia, and toxins as potential agents [34]. The relationship between aerosol infectivity and toxicity versus quantity of agent determine the potential for equivalent effects and narrows the spectrum of possible agents capable of causing mass casualties [23]. For example, only kilogram quantities of anthrax would be needed to cover a 100-km^2 area and cause 50% lethality compared with 8 metric tons of a "highly toxic" toxin such as ricin for similar results. The potential impact on a given area can be determined by the effectiveness of an aerosol in producing downward casualties. In a World Health Organization (WHO) model of a hypothetical dissemination of 50 kg of agent along a 2 km line upwind of a large population center, anthrax and tularemia were shown to cause the highest level of disease and death and the greatest downward spread. Before 1969 both the former Soviet Union and the Untied States spent years determining which pathogens and toxins had strategic and tactical capability. A working group organized by the Johns Hopkins Center for Civilian Biodefense evaluated potential bioterrorism agents to determine 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 disruption, panic, and overwhelming of the civilian health-care resources in addition to large loss of life.

Several events in the nineteen-nineties led the US Government to re-embark on a civilian biodefense program [35]. Congress designated Centers for Disease Control and Prevention (CDC) as the lead agency to enhance the nation's epidemiology and laboratory system. A national pharmaceutical stockpile was also established to assist the National Disaster Medical System to manage mass casualties. In addition to its traditional partners (i.e. local and state health departments and laboratories), CDC added the Department of Defense and law-enforcement agencies as its new partners. A Bioterrorism Preparedness and Response Office was established. For initial preparedness five areas were targeted:

1. planning;
2. improved surveillance and epidemiological capabilities;

3. rapid laboratory diagnostics;
4. enhanced communications; and
5. medical therapeutic stockpiling [36, 37].

The biological agents toward which the efforts should be targeted needed to be formally identified and prioritized. A meeting of national experts including academic infectious diseases experts, national public health experts, Department of Health and Human Services representatives, civilian and military intelligence experts and law enforcement officials was convened in June, 1999. Under review were lists of previously identified biological threat agents and potential general criteria for selecting the biological agents that pose the greatest threat to civilians. The lists of potential biological threat agents reviewed included the Select Agent Rule List, Australian Group List for Biological Agents for Export Control, unclassified military list of biological warfare agents, Biological Weapons Convention List and the WHO Biological Weapons List. The general criteria used were:

1. public health impact based on illness and death;
2. delivery potential to large populations based on ability to mass produce and distribute an agent, its stability and potential for person-to-person transmission;
3. public perception of the disease caused by the agent as related to fear and potential civil disruption; and
4. special public health preparedness needs pertaining to stockpiling requirements, diagnostic needs and enhanced surveillance.

Discussions were held to identify agents that were felt to have the potential for high impact based on subjective assessment in these four general categories. After the meeting, CDC personnel tried to identify objective indicators in each category that could be used to further define and prioritize the identified high-impact agents. Rating schemes were used to evaluate agents in each of the general areas according to objective criteria. A risk-matrix analysis process was used to evaluate and categorize potential biological threat agents [37]. The agents were placed in one of three priority categories (A, B, or C) for initial public health preparedness efforts (Table 1.2).

Category A, highest priority agents, include organisms that pose a risk to national security because they:

1. can be easily disseminated or transmitted person-to-person;
2. cause high mortality with potential for major public health impact;
3. might cause public panic and social disruption; and
4. require special action for public health preparedness.

The bacteria, viruses, and toxins listed in CDC Category B are the second highest priority agents; these:

1. are moderately easy to disseminate;
2. cause moderate morbidity and low mortality; and
3. require specific enhancement of CDC's diagnostic capacity and enhanced disease surveillance.