The epidemiologic pyramid of bioterrorism

Michael Huerta MD MPH[1] and Alex Leventhal MD MPH[2]

[1] Ministry of Health, Public Health Services, Jerusalem, Israel
[2] Israel Defense Forces Medical Corps, Army Health Branch, Tel Hashomer, Israel

Key words: bioterrorism, anthrax, plague, smallpox, epidemiologic triangle

Abstract

Recent events have drawn world attention to "mythological diseases" – such as anthrax, plague and smallpox – which have been out of the spotlight for some decades. Much of our current knowledge of epidemic intervention and disease prevention was acquired over history through our experience with these diseases, such that the sudden panic over the reemergence of these historically well-known entities is perplexing. Over time, changes in the balance of the epidemiologic triangle have driven each of these disease systems towards a new equilibrium with which we are not familiar. While the pathogens may be similar, these are not the diseases of the past. These new disease systems are insufficiently described by the classic epidemiologic triangle, which lacks a dimension necessary for providing a valid model of the real-world effects of bioterror-related disease. Interactions within the classic epidemiologic triangle are now refracted through the prism of the global environment, where they are mediated, altered, and often amplified. Bioterror-associated diseases must be analyzed through the *epidemiologic pyramid*. The added dimension represents the global environment, which plays an integral part in the effects of the overall disease system. The classic triangle still exists, and continues to function at the base of the new model to describe actual agent transmission, but the overall disease picture should be viewed from the height of the fourth apex of the pyramid. The epidemiologic pyramid also serves as a practical model for guiding effective interventional measures.

IMAJ 2002;4:498–502

As of late 2001, bioterrorism presented itself in the United States, and the rest of the globe is on alert. World attention in general, and specifically that of health professionals, is now directed towards "mythological diseases" such as anthrax, plague and smallpox, which have been out of the mainstream spotlight for some decades. The scope of coverage by the mass media and the high levels of public anxiety that have accompanied the recent anthrax crisis in the USA reflect prevailing concerns over the potential global dissemination of these diseases.

The sudden world panic over ancient diseases historically well known to practitioners of public health is perplexing. Modern public health is, in essence, rooted in the prevention of diseases such as smallpox and plague, and much of what we now know about epidemic intervention and disease prevention, including environmental measures, quarantine and vaccination, we learned over history through our experience in dealing with these very diseases. As early as the twelfth century, ships arriving in the Republic of Venice from the plague-infected Levant were required to sit at anchor for 40 days before landing, in an effort to protect coastal cities from plague epidemics (the Latin root *quadraginta*, meaning "forty," is the source of the modern term "quarantine") [1,2]. By the seventeenth century, port towns in the American colonies had enacted laws forbidding people with smallpox to enter port [3]. In the late 1800s, federal legislation was passed in the United States that established the Division of Quarantine, the agency responsible for quarantine activities, which would merge some 100 years later into today's Centers for Disease Control and Prevention [4].

If these diseases are historically well known to the public health sector, and if experience in preventing their spread has been amassed over time, why are we so surprised by the sudden reality of their existence?

The classic epidemiologic paradigm

When contemplating an infectious disease system, epidemiologists classically refer to the epidemiologic triangle [Figure 1]. According to this model, disease is the product of a unique interaction between the human host, the infectious agent, the environment in which the host's exposure to the agent occurs, and the vector that brokers this exposure [5]. Changes in any one of the apices of this triangle can affect the characteristics of the disease system as a whole. Such disease-altering modifications can be either naturally occurring or man-made. During the twentieth century, for example, pandemics of influenza occurred in 1918, 1957 and 1968 [6,7]. These pandemics were associated with major antigenic changes in the influenza virus itself, which harbored a combination of animal and human viral genes [7,8]. This represents a naturally occurring change in the "agent" apex of the epidemiologic triangle. Contrary to this mechanism, some changes to the balance of the epidemiologic triangle may be induced by humans. For example, forced isolation of infectious persons during an epidemic of a communicable disease alters the forces of the epidemiologic triangle by artificially severing the connection between agent and host.

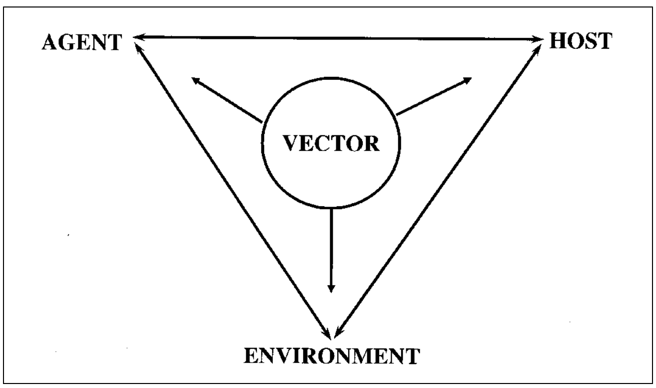

Figure 1. Classic epidemiologic triangle

When we consider the diseases currently thought to be the most likely to be encountered in the context of a bioterror attack, namely anthrax, smallpox and plague (anthrax, of course, is no longer a threat but a fact), it becomes apparent that changes have occurred over time in all three apices of the epidemiologic triangle, leaving today's population at an unprecedentedly high level of risk for disease. The alteration of checks and balances within the epidemiologic triangle has the potential to drive each disease system towards a new equilibrium, one with which we are not familiar and have not experienced in the past.

The most obvious modern transformation of the elements of the classic epidemiologic triangle has been to the vectors of disease. The traditional paradigm has dealt with naturally occurring, unintentional vectors such as fleas and mosquitos; it did not factor malice into the equation of disease. Today's vectors, however, are both artificial – such as mailed envelopes, aircraft and suicide bombers – and intentional, in that they are specifically designed and engineered for malicious agent delivery. The shift from *innocent vector* to *intentional vector* has the potential for vastly improving the effectiveness and efficiency of the agent delivery system, leading to an amplified disease milieu. Furthermore, today's rapid transportation and international air travel add a global dimension to pathogen communication. Whereas disease spread was once limited by the barriers of time and distance, these barriers are all but non-existent today.

In addition to the universal evolution of new vectors as described above, changes have occurred over time in the various apices of the respective epidemiologic triangles for each of the infectious diseases discussed here. We will consider each entity individually, noting the changes that have led to the potential emergence of these "new" diseases.

Anthrax

Anthrax has been traditionally limited to occupationally exposed individuals, with the vast majority of cases occurring in the cutaneous form. Criminal use of anthrax, however, disturbs the balance of this disease's epidemiologic triangle, resulting in a new disease picture.

- ***Agent***

Weaponization of anthrax, or the production of a finely ground preparation of anthrax spores to facilitate effective aerosol delivery, provides new and unprecedented advantages to the agent. The clinical presentation of intentionally released anthrax is likely to be inhalational rather than cutaneous, as it was in half of the 22 recently reported cases in the U.S. [9]. Additionally, although the anthrax strains isolated to date in the recent bout of exposures have not been found to have unusual antibiotic resistance patterns [10], available technology permits bioengineering of the infectious agent, potentially rendering it less susceptible to antibiotic therapy [11]. Finally, while zoonotic anthrax involves transmission of vegetative bacteria, spores, rather than vegetative forms, are disseminated in bioterror-related disease. Anthrax spores, unlike vegetative bacteria, are extraordinarily durable and retain prolonged infective ability under adverse environmental conditions [12,13].

- ***Environment***

Changes have taken place in the environmental apex of the anthrax epidemiologic triangle. While the environment of exposure was once the workshop or the abattoir, the current environment is the office building or the postal facility. Interestingly, the recent bioterrorism-associated anthrax cases were predominantly occupational, with the majority of inhalational disease occurring among postal workers and mail handlers [14]. Further changes in the methods and environment of spread, however, may continue to amplify the population of potential susceptibles. With the bypassing of the traditional occupational setting, greater numbers of persons are now at risk for exposure, and new environmental factors such as central air-conditioning systems may potentially provide an ecologic advantage for the agent, facilitating airborne spread among susceptible hosts.

- ***Host***

There are no natural defenses against inhalational exposure to anthrax. A vaccine against anthrax does exist, but it is in use only among those at occupational risk for exposure, including laboratory workers, U.S. military personnel, and persons exposed to potentially infected animal carcasses [15]. There have been no real changes in the host apex of the anthrax epidemiologic triangle, but the host is now at a relative disadvantage of infection due to the recent dynamics in agent, vector and environment for this disease system.

- ***Vector***

In classic anthrax, the infected herbivore serves as a vector to humans, transmitting vegetative bacteria to the human host through incidental contact. The nature of this restricted transmission limits the scope of human infection. In intentionally released anthrax, however, there is no need for a living vector due to the employment of spores rather than vegetative forms. Thus, anthrax in the bioterror setting is free of the limits and constraints of a living vector, amplifying its ability to cause disease among human hosts.

Plague

The current cause for concern about the use of *Yersinia pestis* in the context of biowarfare stems from modification of the epidemiologic triangle of this disease system, resulting in a shift from classic bubonic plague to epidemic pneumonic plague.

- ***Agent***

As pointed out for anthrax above, bioengineering of the agent is technically possible, potentially imparting it with antibiotic resistance and increased virulence. In fact, scientists who defected from the Russian Biopreperat network claimed during their debriefing in the West that Russia had developed a form of *Yersinia pestis* that was resistant to 16 different antibiotics [11].

- ***Environment***

Whereas traditional plague outbreaks have often been limited to geographic foci characterized by poor living conditions and a high level of rodent infestation in the local environment, weaponized pneumonic plague is not governed by these limitations. High speed travel will most likely facilitate widespread dissemination of the disease over vast discontiguous geographic areas within a short time, making it difficult to identify the place, time and source of infection.

- ***Host***

Host susceptibility is general, and while active immunization confers some protection against bubonic plague, it does not confer immunity against primary pneumonic plague [16].

- ***Vector***

While naturally occurring plague is transmitted primarily by infected fleas, resulting in the bubonic form, weaponized plague will most probably be distributed in aerosol form. This will remove the flea vector from the disease matrix and will result almost exclusively in the highly contagious and highly fatal pneumonic form [15]. The diseased host himself becomes the new vector, spreading the agent among his contacts via airborne droplet infection.

Smallpox

Global eradication of smallpox was certified by the World Health Organization in 1979, and no cases of the disease have been reported since then. The variola virus no longer exists in the wild, and all known stocks of the virus are stored at the Centers for Disease Control and Prevention in Atlanta, Georgia, and at the State Research Centre of Virology and Biotechnology in Novosibirsk, Russia [15]. Concern has been expressed, however, that amidst financial difficulties, lax security and the departure of a substantial number of scientists to unknown locations in the wake of the collapse of the former Soviet Union, quantities of the virus may have "leaked" from the Russian facility to other countries [17]. Thus, a great deal of uncertainty surrounds the existence of clandestine stocks of the agent. The viral samples known to exist, stored until now for research purposes, were designated for destruction in 2002. But in a recent decision the U.S., in light of the emerging threat of the use of this agent as a biologic weapon, has resolved to delay destruction of the remaining virus indefinitely until further research into smallpox vaccines and treatments is completed [18].

- ***Agent***

There is concern that bioweapons research programs may have succeded in inducing changes in the virus through hybridization of viral strains or DNA shuffling [11]. If this is so, the possibility exists that bioterror-related smallpox may be far more virulent than naturally occuring strains.

- ***Environment***

Modern urbanization will contribute significantly to the spread of disease should smallpox be released today. The concentration of susceptible persons within cities and the formation of crowds at work, travel, recreation and commerce are more pronounced today than in the past. There are fewer physical boundaries in place, and economic forces have opened geopolitical borders between countries.

- ***Host***

In the past, many people were immune to variola, either through natural exposure to the virus, or as a result of mass global immunization with vaccinia virus. Vaccine programs have for the most part, however, been inactive for nearly 20 years in light of the global eradication of the disease. In the absence of wild virus circulation and naturally occurring disease, vaccination provided no benefit to the population. The inherent risks and side effects associated with vaccination became unacceptable in the absence of disease prevention, and vaccination efforts were terminated. Today, it is clear that nearly everyone is susceptible to this extremely infectious disease, and the current immune status of persons vaccinated in the distant past remains unclear [19,20]. If the agent does, in fact, lie in hands that may release it in an act of bioterror, it will find upon its release a globe of hosts susceptible to the disease.

- ***Vector***

There is no known animal vector for smallpox virus. Infected humans are the source of infective virus for other susceptible persons, and there is no evidence that any changes have taken place that would alter this.

While the agent-host-environment interactions are unique to each of the diseases discussed above, there are a number of factors common to all three. Their use in an act of bioterrorism is unnatural and dissimilar to well-known patterns of disease; they will most likely be delivered via the inhalational route; we have no real clinical or epidemiologic experience with the unusual disease patterns expected in the context of bioterrorism; and all are identified in the collective global historical memory as feared killers.

The new epidemiologic paradigm

As we have seen, the classic paradigm for understanding infectious disease systems refers to the triangle of agent, host, and environment, and their interaction with the vector that connects them. Major changes have occurred over time within the various components of the epidemiologic triangle for the diseases related to bioterror. The pathogens are old, but they now represent new disease entities, and the diseases they cause are no longer limited to the physical body of the host but rather play out on a much wider field. In fact, the main objective of terrorists who intentionally release these agents may not be the causation of physical disease. Instead, they aspire to disrupt commerce and travel, inflict economic damage, induce mistrust of government, and propogate fear, anxiety, uncertainty and depression within the population. Paradoxically, terrorists need not actually release any biologic agents to achieve some of these goals, such that the actual physical illness induced by a bioevent may be secondary if not altogether marginal. The mere threat of releasing a dreaded disease on an unprotected population has much of the same effect as the act itself. The recent release of anthrax in the U.S. resulted in 22 clinical cases and 5 deaths, while at the same time nearly 32,000 people were under antibiotic prophylaxis, the severity of the disease system having been greatly amplified by forces external to the physical environment in which the actual infection occurred. These new disease systems of bioterror are insufficiently described by the classic epidemiologic triangle. The triangle is lacking a certain dimension necessary for providing a valid model of the real-world effects of disease.

Today's environment extends well beyond the immediate geographic area in which the exposure to the agent occurs. Disease processes are now interpreted in a series of environments external to the arena of agent transmission. In today's world of broadcast media, the internet and the "global village," local occurrences take on worldwide meaning at a pace and in a way never before experienced. We now interpret the real, or "tangible," environment as it is filtered through a series of intangible "global environments" that surround us – the psychological environment, the political environment, the social environment, the economic environment, and the broadcast media. These environments are the dimension missing from our current paradigm. Events that may seem trivial in the tangible local environment can become distorted and misinterpreted as they pass through the virtual global environment to the ears of the public. Interactions within the classic epidemiologic triangle are refracted through the prism of the global environment, where they are mediated, altered, and often amplified. The terrorist understands this, and utilizes this very amplification to achieve his goals. Inasmuch, he is one step ahead of us.

We propose that bioterror-associated diseases must be analyzed using a new epidemiologic paradigm, namely the *epidemiologic pyramid* [Figure 2]. This paradigm shift moves us from two-dimensional triangular thinking to three-dimensional pyramidal thinking. The added dimension represents the new forces in play. The classic triangle still exists, and continues to function at the base of the new model to describe agent transmission. But the overall disease picture is now viewed from the height of the fourth apex of the pyramid, namely the global environment. The pyramid demonstrates that the "virtual" global environment – fear, anxiety, mistrust, politics and communication – plays an integral part in the overall comprehension of bioterror-related disease in today's society.

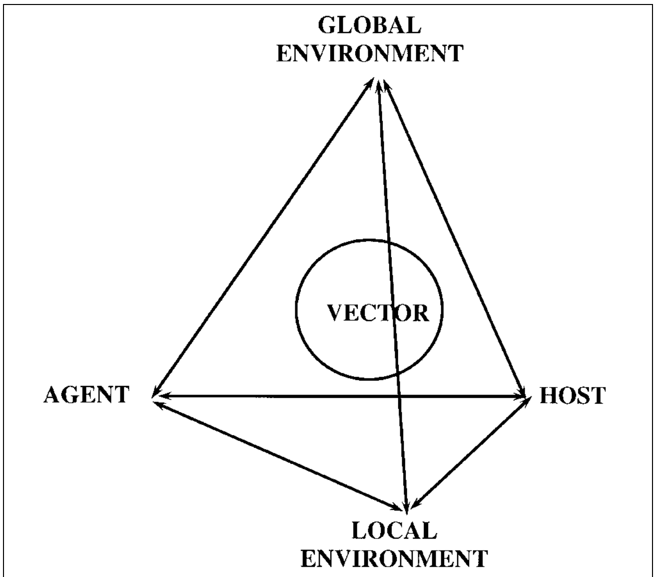

Figure 2. Newly evolved epidemiologic pyramid

The epidemiologic pyramid is not merely a theoretic model to help in understanding the impact of disease, but also a practical model for guiding intervention. Classically, intervention in disease systems in an effort to prevent or disrupt disease transmission called for interruption of the epidemiologic triangle and detachment of one or more of its components from the others. For example, vaccination eliminates susceptible hosts, insect control eliminates vectors, and eradication eliminates the agent. In the same manner, we can interrupt the continuity of the epidemiologic pyramid and minimize the overall impact of a bioterror-related disease system by implementing measures aimed directly at factors that are part of the global environment.

Communication

The world has become dependent on the mass media for its information on global events. Media "spin" and the amount of airtime allocated for coverage will directly affect the percieved severity of a bioevent. The ability to productively channel the energies of the media in order to control the public reponse to disease is a crucial tool in public health. Effective control of bioterror-related disease requires active, timely and transparent intervention in the broadcast media and internet coverage. These are skills that must be developed, learned and integrated into the interventional plan for disease control.

Civil liberties

The western world holds in high regard the values of individual autonomy, freedom of choice and freedom of movement. Effective intervention in a bioterror epidemic, such as smallpox, may involve measures that are at odds with these values, such as mandatory vaccination and large-scale isolation and quarantine. Such measures will be ineffective if carried out in the plane of the epidemiologic triangle alone, without proper simultaneous interventions within the arena of global public and political percption. These additional interventions must be aimed at defusing public skepticism and building the foundations for public acceptance of controversial steps that will save lives at the cost of infringing on certain individual liberties.

Global reservoirs

In natural disease systems the reservoir is often an animal phase of a zoonosis or an aymptomatic human carrier. In the case of bioterrorism, unlike natural disease, the reservoir is the terrorist's laboratory. This is where the agent lives until it is intentionally released on the public by the sophisticated human and mechanical vectors described earlier. Control and containment of disease requires a unified international effort to seek out and destroy these reservoirs that pose a collective global threat.

Conclusion

Malaria, as its name indicates, was once thought to be caused by the inhalation of "bad air." It was only after the introduction of the epidemiologic triangle concept that the interactions between agent, host, environment and vector were appreciated [21] and effective interventions developed to promote disease control. We are currently in a similar initial phase of learning about the overall impact of bioterror-related disease. We require a paradigm shift in our understanding of disease, one that will factor in components of the global environment. We propose a three-dimensional epidemiologic model, the epidemiologic pyramid, which views the classic triangle as it is refracted through the prism of the global environment. With this concept we can better understand the global impact of bioterror-related disease, and we can design and implement measures aimed at containing disease within the global arena.

References

1. Clemow FG. The Origin of "Quarantine". *Br Med J* 1929;1:122–3.
2. Merriam Webster's Collegiate Dictionary, 10th edn. Springfield, MA: International Thomson Publishing, 1998.
3. Hoehling AA. The Great Epidemic. Boston: Little, Brown & Co., 1961.
4. National Center for Infectious Diseases, Centers for Disease Control and Prevention. DQ illustrates intra agency cooperation. *Focus* 1997;6(3):1–2.
5. Gordis L. Epidemiology. 2nd edn. Philadelphia: WB Saunders, 2000:14.
6. De Jong JC, Rimmelzwaan GF, Fouchier RA, Osterhaus AD. Influenza virus: a master of metamorphosis. *J Infect* 2000;40(3):218–28.
7. Kilbourne ED. Perspectives on pandemics: a research agenda. *J Infect Dis* 1997;176(Suppl 1):S29–31.
8. Horimoto T, Kawaoka Y. Pandemic threat posed by avian influenza A viruses. *Clin Microbiol Rev* 2001;14(1):129–49.
9. Update: Investigation of bioterrorism-related anthrax Connecticut, 2001. *MMWR* 2001;50(48):1077–9
10. Update: Investigation of bioterrorism-related anthrax and interim guidelines for clinical evaluation of persons with possible anthrax. *MMWR* 2001;50(43):941–8.
11. Dennis C. The bugs of war. *Nature* 2001;411:232–5
12. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979. *Science* 1994;266:1202–8.
13. Khan AS, Swerdlow DL, Juranek DD. Precautions against biological and chemical terrorism directed at food and water supplies. *Public Health Rep* 2001;116:3–14.
14. Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* [serial online] 2001;7(6). Available online at: http://www.cdc.gov/ncidod/eid/index.htm .
15. Chin J, ed. Control of Communicable Diseases Manual. 17th edn. American Public Health Association, Washington DC, 2000.
16. Titball RW, Williamson ED. Vaccination against bubonic and pneumonic plague. *Vaccine* 2001;19(30):4175–84.
17. Henderson DA. The looming threat of bioterrorism. *Science* 1999;283: 1279–82.
18. Miller J. U.S. Set to Retain Smallpox Stocks. *New York Times* [serial online], 16 Nov 2001. Online at: http://www.nytimes.com/2001/11/16/international/16germ.html.
19. Tudor V. Smallpox, Cholera. Tunbridge Wells, UK: Abaccus Press, 1977.
20. Christie AB. Infectious Diseases, Epidemiology and Clinical Practice. Baltimore: Williams & Wilkinson, 1969.
21. Fantini B. Unum facere et alterum non omittere: antimalarial strategies in Italy, 1880-1930. *Parasitologia* 1998;40(1-2):91–101.

Correspondence: Dr. A. Leventhal, Director of Public Health Services, Ministry of Health, 20 King David St., P.O. Box 1176, Jerusalem 91010, Israel.
Phone: (972-2) 622-8802
Fax: (972-2) 623-3058
email: alex.leventhal@moh.health.gov.il