Public health and bioterrorism: renewed threat of anthrax and smallpox

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Summary. *Bioterrorism is one of the main public health categorical domains. According to sociological analytics, in postmodern society terrorism is one of the real threats of the 21st century. While rare, the use of biological weapons has a long history. Recently, anthrax has been evaluated as one of the most dangerous biological weapons. Naturally occurring anthrax in humans is a disease acquired from contact with anthrax-infected animals or anthrax-contaminated animal products. Usually anthrax infection occurs in humans by three major routes: inhalational, cutaneous, and gastrointestinal. Inhalational anthrax is expected to account for most serious morbidity and most mortality. The clinical presentation of inhalation anthrax has been described as a two-stage illness. Many factors contribute to the pathogenesis of Bacillus anthracis. Antibiotics, anthrax globulin, corticosteroids, mechanical ventilation, vaccine are possible tools of therapy. Smallpox existed in two forms: variola major, which accounted for most morbidity and mortality, and a milder form, variola minor. Smallpox spreads from person to person primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. In the event of limited outbreak with few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration. In larger outbreaks, home isolation and care should be the objective for most patients. Progress in detection, suitable vaccines, postexposure prophylaxis, infection control, and decontamination might be serious tools in fight against the most powerful biological weapon. To assure that the public health and healthcare system can respond to emergencies, the government should direct resources to strengthen the emergency-response system, create medication stockpiles, and improve the public health infrastructure.*

Introduction

"*Biological warfare attacks have often been dismissed as science fiction or as so immoral as to be beyond imagination. The tragic events in the USA on 11 September 2001 show that they are neither, and will force a consideration of international security.*" C. Fraser, M. Dando (Nature Genetics 2001, 29:253-256).

Public health is concerned with four rather broad and different fields: lifestyle, environment, human biology, and the organization of health programs and systems (1). Talking about the public health goals, prevention of epidemics, spread of disease, injuries, environmental hazards, response to disasters, assistance in community recovery, and eventually assurance of the quality of healthcare must be included (2). The main public health categorical domains might be depicted in long nonexhaustive list of examples, as for instance, infectious diseases, injury/trauma, sexually transmitted diseases, environmental health, occupational health, mental health, chronic diseases, consumer product safety, substance abuse, disability, and bioterrorism (1).

As a matter of fact, in 1972 Biological Weapons Convention prohibited the development, production, stockpiling, and transfer of biological agents for use as weapons. Despite it was ratified by more than 100 nations, experts believe that several signatory countries – Iraq, Iran, China, and North Korea – may be violating the convention's terms and developing offensive biological weapons (3). Due to the fact that it is especially difficult to predict, detect, or prevent the possibility of terrorist attack, bioterrorism is among the most feared terrorism scenarios (4).

The aim of this review is to look deeper at the roots

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of newly appearing threat for public health – bioterrorism. Moreover, it is important to analyze sociological prerequisites of it, to discuss most powerful biological weapons, to describe unavoidable sequences and essential response to public health emergencies.

Sociological prerequisites to terrorism

The phenomenon of terrorism is closely related to globalization and the state of postmodernity. The phenomenon of terrorism itself can be defined as "deliberate acts of physical and/or psychological nature perpetrated on select groups of victims" (5). Its intent is to make a change by affecting the psychic state of the group, *i.e.* causing fear, panic, intimidating and coercing, not the elimination of the group itself. It is the way of taking control of the public opinion so that it can pressure the decision-makers in the group. The right-wing writers like to associate terrorism with the culture of the group, committing the terrorist act (for example, religious fanatism as Islamic fundamentalism or catholic separatism) (6), while the left-wing writers tend to see the roots of terrorism in the Western Civilization, its military, cultural, and economic expansion (7). In any case, the keywords used by both sociopolitical schools are postmodernity and globalization, which make the terrorism of contemporary scale possible.

Postmodernity is a condition, "the most profound aspects of which are interconnectedness of international, national, and subnational politics, economy and culture" (8). It is followed by increasing globalization, consumerism and postindustrialism, and the weakening of the nation-state. Beside the nation-state, there are a variety of subnational, regional, and transnational communities and networks not least global corporations that due to the globalized media and communications are no longer under the control of nation-state. Thus, the transnational/cross-border dimension has replaced the national/international. As the events of September 9, Madrid, and London have shown, the state is no longer the owner of the absolute power over defined peoples and territory. Due to modern communication techniques, one might share the culture of the community based on the other side of the globe, or, even more likely, with its headquarters in cyberspace. Thus, the postmodern geopolitical map of the world is no longer divided in nation-states, rather a spider-web of cultures and communities (9).

Globalization can be roughly defined as global mutual interdependence. According to Nassar, globalization "in the emerging global corporate civilization is consumers, not the human beings that matter. This global setting spawns violence and terrorism, especially when governments become the protectors of corporations rather than people" (7). Globalization has also triggered the counter-globalization movement, in which terrorism is partly a part of in the sense that globalization is by some viewed as the Western civilization's conquest over the rest (7). Ironically, the globalization that is often conceived as the western neo-imperialism by the terrorist groups is also one of the main prerequisites for performing terrorist acts of contemporary scale. At the same time as the multinational organizations and corporal capital flows are making the individual increasingly anonymous and insignificant, a relatively small group of individuals with relatively scarce resources can make an enormous effect on the world politics and economy. This way the global interdependence and deterritorialization has made the world extremely vulnerable.

Several historical facts

Natural epidemics such as smallpox and plague are terrifying enough. However, the notion that these diseases can be used as weapons of war is even more chilling. In the 14th and 15th centuries, little was known about the mechanisms of infectious diseases. Nevertheless, according to medieval medical lore, the stench of rotting bodies was known to transmit infections. Thus, when corpses were used as ammunition, no doubt, they were intended as biological weapons. The second major epidemic of "Black Death" in Europe has started in similar way. While the first true vaccine for smallpox was not invented until 1796, the practice of deliberately inoculating people with a mild form of the disease was established decades earlier. The British military likely employed such deliberate infection to spread smallpox among forces of the Continental Army (10). During the Great War, German scientists and military officials applied microbes in a widespread campaign of biological sabotage. Their target was livestock. The diseases they cultivated as weapons were glanders and anthrax, both known to ravage populations of grazing animals in natural epidemics, when added into their feed (11). In 1925, Geneva Protocol prohibited the use of chemical and biological agents, but not the development of them. The United States signed the Protocol; yet, 50 years passed before the US Senate voted to ratify it. Japan also refused to ratify the agreement in 1925 (12). As a result, in occupied Manchuria, starting around 1936, Japanese scientists used scores of human subjects to test the lethality of various disease agents including anthrax, cholera, typhoid, and plague. It triggered the death of 10 000 people. During the Cold War, the Soviet Union

and the United States explored the use of hundreds of different bacteria, viruses, and biological toxins. Even in 1969, President R. Nixon terminated the offensive biological warfare program and ordered all stockpiled weapons destroyed. So far, in 1979, a rare outbreak of anthrax disease in the city of Sverdlovsk killed nearly 70 people (13). The Soviet government publicly blamed contaminated meat, but US intelligence sources suspected the outbreak was linked to anthrax spores at an army laboratory. In 1991, however, Iraq had weaponized anthrax, botulinum toxin, and aflatoxin and had several other lethal agents in development. Iraq is known to have unleashed chemical weapons in the 1980s. However, there is no evidence that the Iraq state has ever used its biological arsenal (14). Between 1993 and 1995, botulinum toxin and anthrax were spread as many as 10 times in downtown of Tokyo (15).

Recently, due to the genomics revolution, it is possible to enhance the resistance of biological pathogens to antibiotics, to modify their antigenic properties, or to transfer pathogenic properties among them. Such genetic engineering technologies could make them harder to detect, diagnose, and treat; in other words, make them more military useful (14). For more than two decades, bioterrorism experts warned that America might be vulnerable to attack with biological weapons. A week after the terrorist attacks of September 11, letters containing anthrax spores were mailed to different directions. By the end of the year, 18 people had been infected with anthrax, five people had died of the inhaled form of the disease, and hundreds of millions more were struck by anxiety of the unknown (16).

Anthrax and smallpox as biological weapon

Nearly every human microbial pathogen has the potential to be used as bioweapon. US Centers for Disease Control and Prevention has classified potential bioterrorism agents into three priority categories – A, B, and C (17) – on the basis of their ability to cause disease that is easily disseminated or transmitted from person to person; has high mortality, with potential for major public health impact; may result in panic and social disruption; and requires special action for public health preparedness.

Actually, only a few agents are reasonably easy to produce and disperse and can cause serious illness and public panic. Most experts in the field of bioterrorism believe that anthrax and smallpox would be the agents most likely to be used by terrorists.

Anthrax is one of the greatest infectious diseases in our days as well as of antiquity. The fifth and sixth plagues in the Bible's book of Exodus may have been outbreaks of anthrax in cattle and humans. The "Black Bane," a disease that passed in Europe in the 1600s, causing plethora of human and animal deaths, was something like anthrax.

In 1970, the World Health Organization and in 1993 the Office of Technology Assessment analyzed the potential scope of larger attacks. In 1970, the World Health Organization estimated that 50 kg of *B. anthracis* released over a population of 5 million would sicken 125 000 and kill 95 000. A US Congressional Office of Technology assessment analysis from 1993 estimated that 130 000 to 3 000 000 deaths would follow the release of 100 kg of *B. anthracis*, a lethality matching that of a hydrogen bomb. Moreover, it has been estimated that an aerial spray of anthrax along a 100-km line under ideal meteorological conditions could produce 50% lethality rates as far as 160 km downwind (18).

Naturally occurring anthrax in humans is a disease acquired from contact with anthrax-infected animals or anthrax-contaminated animal products. By the way, anthrax killed 1 million sheep in Iran in 1945 (19).

Usually anthrax infection occurs in humans by three major routes: inhalational, cutaneous, and gastrointestinal. Eighteen cases of inhalational anthrax were reported in the USA from 1900 to 1976 (20).

Cutaneous anthrax is the most common type, with an estimated 2000 cases reported annually worldwide. The largest epidemic occurred in Zimbabwe in 1979–1985, when more than 10 000 human cases of anthrax were reported (20).

Gastrointestinal anthrax is uncommon, and outbreaks, induced by it, are continually reported mostly in Africa and Asia, following ingestion of insufficiently cooked contaminated meat.

Inhalational anthrax is expected to account for most serious morbidity and most mortality (20).

Pathogenesis and clinical manifestations

B. anthracis is derived from the Greek word for coal, *anthrakis*, because of the black skin lesions it causes. It is an aerobic, gram-positive, spore-forming, nonmotile *Bacillus* species. Moreover, *B. anthracis* spores can survive for decades in ambient conditions (19).

Inhalational anthrax follows the deposition of spore-bearing particles into alveolar spaces. Then macrophages ingest the spores, some of which are lysed and destroyed. Surviving spores are transported via lymphatics to mediastinal lymph nodes. Replicating bacilli release toxins that lead to hemorrhage, edema,

and eventually necrosis. Dose sufficient to kill 50% of persons exposed to is 200–55 000 inhaled spores (21, 22).

The clinical presentation of inhalational anthrax has been described as a two-stage illness. Patients developed a broad spectrum of nonspecific symptoms including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, *etc*. This stage lasted from hours to a few days. The second stage was reported to have developed abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Up to half of patients developed hemorrhagic meningitis, delirium. Cyanosis and hypotension progressed rapidly; death sometimes occurred within hours (23). During the 20th century, the mortality rate of occupationally acquired inhalation anthrax was 89% (20).

It is of interest to note that some field studies concluded that there was no significant threat to personnel in areas contaminated by 1 million spores per square meter either from traffic on asphalt-paved roads or from a runway used by helicopters (23). In the areas of ground contaminated with 20 million spores per square meter, a soldier exercising actively for a 3-hour period would inhale between 1000 and 15 000 spores. It is important to note that spores persist and remain viable for 36 years (24).

Smallpox is caused by *Orthopoxvirus*, variola virus. Variola is infectious only for humans. Smallpox was declared eradicated in 1980 by the World Health Organization. Following global eradication, the smallpox virus has been retained under strict security in two World Health Organization collaborating centers: the Centers for Disease Control and Prevention, USA, and the Laboratory for Applied Microbiology at Koltsovo in Novosibirsk region, Russian Federation. Smallpox existed in two forms: variola major, which accounted for most morbidity and mortality, and a milder form, variola minor. Typical variola major epidemics such as those that occurred in Asia resulted in case-fatality rates of 30% or higher among the unvaccinated, whereas variola minor case-fatality rates were customarily 1% or less. Smallpox spreads from person to person, primarily by droplet nuclei or aerosols expelled from the oropharynx of infected persons and by direct contact. Contaminated clothing or bed linens can also spread the virus (25). The incubation period of smallpox is 12–14 days (range 7–17). Persons cannot infect others during incubation period. They are considered infectious from the time of development of the eruptive exanthema until all scabs separate. The frequency of infection is highest after face-to-face contact with patient once fever has begun and during the first week of rash, when virus is released via the respiratory tract. Smallpox is transmitted from person to person by infected aerosols, and air droplets spread in face-to-face contact with an infected person after fever has begun (26).

A suspected case of smallpox is a public health emergency. Local and state public health authorities, the hospital epidemiologist, and other members of a hospital response team for biologic emergencies should be notified immediately.

As soon as the diagnosis of smallpox is made, all individuals in whom smallpox is suspected should be isolated immediately, and all household and other face-to-face contacts should be vaccinated and placed under surveillance. Because the widespread dissemination of smallpox virus by aerosol poses a serious threat in hospitals, patients should be isolated in the home or other nonhospital facility whenever possible. Home care for most patients is a reasonable approach, given the fact that little can be done for a patient other than to offer supportive therapy. In the event of an aerosol release of smallpox and a subsequent outbreak, the rationale for vaccinating patients suspected to have smallpox at this time is to ensure that some with the mistaken diagnosis are not placed at risk of acquiring smallpox. Vaccination administered within the first few days after exposure and perhaps as late as 4 days may prevent or significantly ameliorate subsequent illness. An emergency vaccination program is also indicated that would include all health care workers at clinics or hospitals that might receive patients; all other essential disaster response personnel, such as police, firefighters, transit workers, public health staff, and emergency management staff; and mortuary staff who might have to handle bodies. All such personnel for whom vaccination is not contraindicated should be vaccinated immediately irrespective of prior vaccination status. Vaccination administered within 4 days of first exposure has been shown to offer some protection against acquiring infection and significant protection against a fatal outcome. Those who have been vaccinated at some time in the past will normally exhibit an accelerated immune response. Thus, it would be prudent, when possible, to assign those who had been previously vaccinated to duties involving close patient contact. It is important that discretion would be used in identifying contacts of patients to ensure, to the extent that is possible, that vaccination and adequate surveillance measures are focused on those at greatest risk. Specifically, it is recommended that contacts would be defined as persons who have been in the same household as the infected individual or who have been in face-to-face contact with the patient after the onset

of fever. Experience during the smallpox global eradication program showed that patients did not transmit infection until after the prodromal fever had given way to the rash stage of illness. Isolation of all contacts of exposed patients would be logistically difficult and, in practice, should not be necessary. Because contacts, even if infected, are not contagious until onset of rash, a practical strategy calls for all contacts to have temperatures checked at least once each day, preferably in the evening. Any increase in temperature higher than 38°C during the 18-day period following last exposure to the case would suggest the possible development of smallpox and be cause for isolating the patient immediately, preferably at home, until it could be determined clinically and/or by laboratory examination whether the contact had smallpox. All close contacts of the patients should be promptly vaccinated. If it is not feasible to vaccinate contacts, they should be placed on daily watch, which should continue up to 18 days from the last day contact with the case. If these contacts have two consecutive readings of 38°C or above, they should be isolated (25, 26).

In the event of limited outbreak with a few cases, patients should be admitted to the hospital and confined to rooms that are under negative pressure and equipped with high-efficiency particulate air filtration. In larger outbreaks, home isolation and care should be the objective for most patients. However, not all will be able to be so accommodated and, to limit nosocomial infections, authorities should consider the possibility of designating a specific hospital or hospitals for smallpox care. All persons isolated as such and those caring for them should be immediately vaccinated. Employees for whom vaccination is contraindicated should be furloughed. Standard precautions using gloves, gowns, and masks should be observed. All laundry and waste should be placed in biohazard bags and autoclaved before being laundered or incinerated (25).

Emergency response to an attack

To assure that the public health and healthcare system can respond to emergencies, the government should direct resources to strengthen the emergency-response system, create medication stockpiles, and improve the public health infrastructure. The larger portion of this preparedness budget should be allocated to measures that enhance rapid response to an attack. These measures would include developing and maintaining laboratory capabilities for both clinical diagnostic testing and environmental sampling, developing and maintaining drug stockpiles, and developing and practicing response plans at the local level (27, 28). The early recognition of a bioterrorist event is essential in ensuring effective containment and reduction of causalities. Surveillance for illness resulting from biological terrorism should be integrated into disease surveillance systems. Rapid detection of a bioterrorist act will require enhanced disease surveillance activities using active surveillance methods. Education of the local health care providers, emergency medical staff is essential for the successful surveillance activities and medical response.

For clinicians, the response to a bioterrorism attack is in many ways the same as the response to naturally occurring outbreaks of communicable disease. Both situations typically require early identification of ill or exposed persons, rapid implementation of preventive therapy, special infection control considerations, and collaboration or communication with the public health system (29).

Once a potential outbreak or significant cluster or event has been detected, prompt consultation with appropriate medical specialists and public health authorities is indicated. All clinicians should know how to contact their local or state public health institutions 24 hours a day to report suspicious or otherwise immediately notifiable cases or for consultation.

Given the rarity of anthrax infection and the possibility that early cases are a harbinger of a larger epidemic, the first suspicion of an anthrax illness must lead to immediate notification of the local or state public health institution, local hospital epidemiologist, and local or state health laboratory.

There are no data to suggest that patient-to-patient transmission of anthrax occurs. Standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection; the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated. There is no need to immunize or provide prophylaxis to patient contacts (*e.g.,* household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol at the time of the attack (30). Ciprofloxacin and doxycycline are recommended as first-line agents for prophylaxis in persons exposed to inhalational anthrax. *In vivo* data suggest that other fluoroquinolone antibiotics would have efficacy equivalent to that of ciprofloxacin. High-dose amoxicillin is an option when ciprofloxacin or doxycycline is contraindicated. Postexposure prophylaxis should continue for at least 60 days (31). In addition to immediate notification of the hospital epidemiologist and local public health institution, the local hospital

microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken. A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids. Proper burial or cremation of humans and animals that have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. If autopsies are performed, all related instruments and materials should be autoclaved or incinerated. Animal transmission might occur if infected animal remains are not cremated or buried (30).

Conclusions

The phenomenon of terrorism in our days is closely related to globalization and the state of postmodernity. A great variety of biological agents could potentially be used for biological warfare, but anthrax and smallpox would be the agents most likely to be used by terrorists. The public health infrastructure must be prepared to prevent illness resulting from biological terrorism. Early detection and control biological attacks depend on strong and flexible public health system. We need a high degree of cooperation between scientists and national and international agencies of public health. Countries should improve their capabilities to respond to a renewed threat of anthrax and smallpox epidemics.

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Visuomenės sveikata ir bioterorizmas – nauja juodligės ir raupų grėsmė

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Raktažodžiai: visuomenės sveikata, bioterorizmas, biologinis ginklas, juodligė, raupai.

Santrauka. Bioterorizmas yra viena svarbiausių visuomenės sveikatos sričių. Terorizmo fenomenas yra glaudžiai susijęs su globalizacija ir išlieka viena realių 21-ojo amžiaus grėsmių. Nors naudojamas retai, tačiau biologinis ginklas buvo seniai žinomas ir turi ilgą istoriją. Dabar pasaulyje juodligė (angl. *anthrax*) įvardijama kaip vienas iš pavojingiausių biologinių ginklų. Natūraliai žmogus šia liga užsikrečia kontaktuodamas su sergančiais gyvūnais. Juodligės infekcija gali būti perduodama trimis būdais: per kvėpavimo takus, odą ir virškinimo sistemą. Užsikrėtus per kvėpavimo takus, išsivysto sunkiausios juodligės klinikinės formos ir dažniausiai liga baigiasi mirtimi. *Bacillus anthracis* patogenezę sąlygoja įvairūs veiksniai. Svarbiausios gydymo priemonės yra antibiotikai, juodligės imunoglobulinas, kortikosteroidai, mechaninė ventiliacija.

Raupai egzistuoja dviejų formų: *variola major*, kuri sąlygoja didžiausią sergamumą ir mirštamumą ir lengvesnė forma – *variola minor*. Raupai iš infekuoto žmogaus nosiaryklės kitam žmogui perduodami oro-lašiniu būdu ir tiesioginiu kontaktu. Kilus nedideliam raupų protrūkiui, ligoniai turi būti hospitalizuojami ir izoliuojami neigiamo slėgio palatose su oro filtrais. Kilus dideliam protrūkiui, dauguma ligonių izoliuojami ir gydomi namuose. Laiku neužfiksuotas bioterorizmas, tinkami skiepai, poekspozicinės profilaktikos, infekcijų kontrolės ir dekontaminacijos priemonių sukūrimas galėtų būti ypač veiksmingos priemonės biologinio ginklo pasekmių kontrolei. Siekiant užtikrinti visuomenės sveikatos ir asmens sveikatos sistemų atsaką visų šalių vyriausybės turi skirti lėšų kritinių situacijų valdymo sistemoms stiprinti, medicininėms atsargoms sudaryti ir visuomenės sveikatos infrastruktūrai tobulinti.

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