

The Biological Agents Of Concern, Historical Epidemics, And Current Outbreaks: Assessing The Level Of Prior Preparedness In The European Region

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Abstract

The article provides a sequential review of historical epidemics, infectious outbreaks and bio-terror events that significantly transformed not only the global epidemiology but also became the spotlight of medical research. With a special focus on biological agents of major concern that can be used in bio-terrorism, major epidemics, outbreaks that hit Europe are discussed. Epidemiological events that require preparedness like Spanish flu [influenza], Hong Kong Flu, Bubonic Plague, West Nile virus, Diphtheria, Tularemia, and Anthrax during the last century are briefly discussed. Lessons for improving surveillance are derived. Possibilities are highlighted that can add to the current level of preparedness across Europe. Analysing the current control measures and steps taken by the European Commission the authors urge the individual countries to strengthen their biological defence mechanisms to deal effectively with the unexpected internal and external infectious threats. Based on review recommendations are given that can boost up infection control in emergency situation.

INTRODUCTION

The use of biological weapons has been recorded throughout history. Exposure of human beings to deadly biological agents and outbreaks can be traced centuries back. A variety of factors determine the impact of such an event. The type of agent, mode of spread, degree of vulnerability, environmental conditions like temperature, direction of wind, size and doses [if spores or aerosols] and prior preparedness matter most. Low level of suspicion and delay in response can lead to unprecedented loss of human lives. The incident of anthrax in the USA [2001] has increased the fears about the deliberate use of biological agents in the future. The escalating global political tensions since the September 11 attack on the United States have increased the likelihood of such a bio-attack.

Surprisingly, the outbreak of SARS [April, 2003] in China unfolded a herald of increasing public health safety through active epidemiological intelligence, reporting system and the availability of protective measures. Nations of the European Union have already pledged to strengthen preparedness to effectively deal with any infectious emergency situation. However, practical steps are yet to be taken to enhance surveillance, raise public health awareness, and to comply

with the set policies at the individual country level. Growing concerns exist about the capacities of health system where degree of responsiveness greatly vary among Western, central and East European countries. Whether it is an infectious outbreak or a biological attack, prior preparedness is essential in terms of early recognition, prompt management and prophylactic measures.

Reports show that countries in the region are not adequately well equipped to diagnose and contain locally emerging outbreaks. This research particularly focuses on assessing the impact of the key biological agents of concern, provides a retrospective review of major epidemiological emergencies that are relevant to Europe. Furthermore, the intention is to derive specific lessons that can help improve the current network of surveillance and level of preparedness across Europe.

METHODOLOGY

An extensive review of available published and unpublished literature was carried out through the use of multiple search machines. Research materials [in English] were obtained through Pub-Medline technique and Google with the key words e.g., bio-terrorism, biological agents, weaponization,

infectious disease outbreaks in Europe, pandemics in Europe [influenza, anthrax, smallpox, diphtheria, syphilis, plague, tularemia, Ebola, West Nile virus, and preparedness] preparedness for biological terror, and defence against biological attack in Europe. Data on the amenability of European Commission to bio-terrorism were retrieved from the respective websites like Global Infectious Disease surveillance network of the World Health Organization (WHO), United States Centre of Diseases Control [CDC] and Euro-surveillance and European commission. Based on the nature of infectious event and epidemiological parameters [high mortality and morbidity], major incidents in and outside Europe that required specific preparedness of the health system were included in the review. Fifty-one papers were selected and included in the review from the pool of 500 that provided research based information on the biological agents of major public health concern, chronicle of global epidemics, current outbreaks and level of preparedness.

BIO-TERRORISM AND AGENTS OF CONCERN

Bio-terrorism can be described as “the use, or threatened use of biological agents to promote or spread fear or intimidation upon an individual, a specific group, or the population as a whole for religious, political, ideological, financial, or personal purposes”. Through the process of weaponization bio-agents can be enhanced so that their virulence in humans makes them resistant to vaccines and antibiotics. This process enables the agent to mutate or modify its genetic composition and require the ability to procure a virulent strain [e.g., anthrax, tularaemia], culture large amounts of an agent, and process it into a suitable form [e.g., anthrax spores]. Issues like safe handling and storing the agent, dissemination as an aerosol, generation of aerosol particles of the proper size [1-10 u] and the ability to assess climatic effects in order to disseminate agent effectively make it a daunting task. Discerning the use of biological agents as well as appropriate responses to them require a great deal of attention to their known characteristics.

Biological agents include a wide array of infectious agents of humans, plants, and animals, as well as the toxins that may be produced by microbes. For illustration the biological agents are classified into three main categories. Based on the nature of virulence and pathogenicity the agents in category A are the most lethal ones. Included in this category are the organisms of variola major [smallpox], bacillus anthrax [anthrax], yersinia pestis [plague], clostridium botulinum

toxin [botulism], francisella tularensis [tularaemia], filoviruses, ebola hemorrhagic fever, marburg hemorrhagic fever, and lassa [lassa fever] etc. They pose high risk to the human health and are easily disseminated from person-to-person. The agents of category B are moderately lethal in nature and can cause moderate morbidity and low mortality. Viruses like alpha viruses [Venezuelan encephalomyelitis [VEE], Eastern and western equine encephalomyelitis [EEE, WEE]], bacteria like coxiella burnetii [Q fever], brucella spp. [brucellosis], burkholderia mallei [glanders], Vibrio cholerae, Shigella dysenteriae, E. coli, staphylococcal enterotoxin B, food/waterborne [e.g. salmonella] etc. are worth mentioning. They require specific diagnostics and methods of surveillance. Agents of category C have also high potential for morbidity and mortality and include pathogens that could be engineered for mass dissemination e.g., nipah virus, hantavirus, tickborne hemorrhagic fever, yellow fever and multi-drug resistant mycobacterium tuberculosis. Table 1 highlights lethal aspects of some biological agents. Estimations reflected here are taken from a scenario when a 50-kg agent is released by aircraft along a 2-km line upwind of a population centre of 500,000.

Figure 1

Table 1: Public Health Impact of biological agents

Agent	Downwind reach, km	Number of dead	Number of incapacitated
Rift valley fever	1	400	35000
Tick born	1	9500	35000
Typhus	5	19000	85000
Brucellosis	10	500	125000
Q fever	>20	150	125000
Tularaemia	>20	30000	125000
Anthrax	>20	95000	125000

Source: Christopher et al., JAMA 278; 1997: 412.

An assessment of the World Health Organization in 1970, concluded that a dissemination of 50 kg of Yersinia pestis over a city of five million might result in 150 000 cases of pneumonic plague and 36 000 deaths. Another estimation showed that 100 Kg of anthrax over a large city on a clear night could kill between one and three million people. This is considered as deadly as a one-megaton atomic bomb and lethal impact on the public health. Botulinum toxin is considered one of the most lethal toxins known, that can be extracted from the Clostridium botulinum. Within 1 to 3 days of exposure, victims experience cranial nerve disorders followed by descending paralysis and respiratory failure.

KEY EPIDEMIOLOGICAL EVENTS IN

HISTORICAL PERSPECTIVES

The chronology of massive infectious events is fairly long. Alone in the past century almost 420 terrorist attacks occurred in which 135 were of biological nature. Unprecedented epidemics, outbreaks and bio-terrorism attacks that shaped global epidemiology provide pertinent clues for future preparedness. The master tactician Solon used the purgative herb hellebore [skunk cabbage] to poison the water supply during his siege of Krissa in 600 BC. Armies in the ancient times, tainted water supplies of entire cities with herbs and fungi that induced fatal diarrhoea and hallucinations. According to the Bible a series of biological calamities were inflicted on the Egyptians to convince an obstinate pharaoh to liberate the ancient Hebrews.

THE CAUSALITIES OF INFLUENZA

History suggests that the influenza pandemics have occurred three times i.e., in 1918, 1957, and 1968. The unforgettable Spanish Flu [1918-1919], made almost 1 billion people sick and killed 21 to 40 million. Influenza virus began a global campaign, producing a moderate outbreak among US military recruits before moving into the civilian population. The virus invaded Europe and by the end of summer, the first wave had encircled the world and earned the name Spanish flu after receiving much publicity in Spain. The epidemics of this unprecedented lethality had broken out in ports of China [Hong Kong], France [Brest], the United States [Boston], and Sierra Leone [Freetown]. The transmission was facilitated by ship, railroad, and war-induced migrations of civilians and military personnel. Europe was never an influenza free zone and was engulfed by widely known Asian Flu [1957], Hong Kong Flu [1968], Swine Flu [1976], and Russian Flu [1977]. Large numbers of frightened, critically ill people overwhelmed the health system. The swiftness of the outbreak was a long mystery and an inadequate reporting greatly obscured the effectiveness of containment. Due to the unique characteristics of the virus, epidemiologists predict enormous disease burden in the future. Outbreaks of influenza are highly unpredictable and can rapidly turn into pandemics keeping in view the risk of air travel, global tourism, migration and the population expansion of current times.

THE EPIDEMIC OF TULARAEMIA

Tularaemia is a fatal illness caused by *Francisella tularensis*. Tularaemia's epidemic became apparent in the 1930s and 1940s, when large waterborne outbreaks occurred in Europe

and in the Soviet Union. It has long been considered a potential biological weapon and was one of the agents studied at the Japanese germ warfare research units operating in Manchuria between 1932 and 1945. According to a former Soviet Union biological warfare scientist, Ken Alibek, tularemia outbreaks affecting tens and thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use. The largest airborne tularaemia outbreak occurred in 1966-1967 in an extensive farming area of Sweden. More than 600 patients were infected with strains of the milder European biovar of *F. tularensis*, and most of whom acquired infection during farm work that created contaminated aerosols. Such outbreaks from similar agricultural exposures have also been reported from Finland.

ANTHRAX

Anthrax caused the most serious biological outbreak named "Black Bane" that swept Europe in the 1600s. It killed at least 60,000 people and many more domestic and wild animals. The horror continued till World War I when Germans used *Bacillus anthracis* to infect livestock for exportation to the allied forces. Dr. Anton Dilger, a noted German-American physician, established a production facility in Washington, D.C., in 1915. Cultures of *bacillus anthracis* [anthrax] and *pseudomonas mallei* [glanders] were used to produce liquid agent to infect military personnel of the Allied troops in Baltimore. In 1916, the Bucharest institute of bacteriology identified *b. anthracis* in cultures from the German Legation in Romania. The mysterious anthrax outbreak of April, 1979 in the Soviet city of Sverdlovsk [now called Ekaterinburg] created a great panic. Apart from its physical effects the event had grave effects on the psyche of people of all ages. The reported figures showed that at least 64 were killed and more than 94 people were affected. It was later disclosed publicly that the outbreak occurred due to the release of anthrax spores from a suspected Soviet biological weapons facility located in the city. The spores *B. anthracis* mailed in the US added more to the aftermath of September 11, 2001. The incident caused 23 cases of confirmed anthrax. Perpetrators remained still unidentified, and the risk of future exposure through unconventional means still exists.

PLAQUE

Known as a "Black Death" plague was the earliest epidemic in Athens in 430 B.C. that succumbed an estimated 25% to 50% of the population. The epidemic spread widely across

Europe in 1334 and killed three quarters of the European population and Asia in less than 20 years. By 1349 it swept across Hungary, Italy, Spain, France, Germany and England. Followed by the sporadic outbreaks of bubonic plague throughout the three centuries plague returned to Holland in 1663, and to London in 1665. However, it has never gone away, and the possibility still exists that it may, once again, turn into a deadly scourge.

OUTBREAKS IN CENTRAL AND EASTERN EUROPE

In spite of modern surveillance several localized outbreaks have been witnessed in the European region. The presence of West Nile virus was initially indicated in 1958, from two Albanians. Afterwards the virus was isolated in 1963 from patients and mosquitoes. Subsequently in 1970s, 1980s, and 1990s West Nile virus was also isolated in Portugal, Belarus, Western Ukraine, Slovakia, Moldavia, Ukraine, Hungary, Romania, Czech land, southern France, southern Russia, Spain and Italy. The incidence of West Nile fever in Europe is largely unknown and it is believed that virus causes sporadic human cases, clusters, or outbreaks.

Environmental factors that include human activities enhance vector population densities. Especially irrigation, heavy rains & floods, and higher temperature climate create massive breeding places for mosquitoes, which facilitate the transmission of infection. In the Eastern block, the resurgence of drug resistant tuberculosis and syphilis are also widely reported. Between 1990 and 1996, syphilis rates increased 68-fold among Russians teenagers. Since 1990 similar peaks have also been seen in Belarus, Moldova and Ukraine. Coupled with HIV/AIDS, syphilis epidemic is closely associated with hepatitis B and C infection in the region. In the Netherlands, the last diphtheria epidemic occurred during World War II that affected 220,000 people between 1940 to 1946. Till recently the increasing number of diphtheria cases have posed an additional threat for the already vulnerable population. Evidence has proved that the inadequate herd immunity to diphtheria can lead to outbreaks. According to the recent Bulletin of EuroGROG several outbreaks of influenza have been reported from the schools around Europe particularly from Finland, Greece, Ireland, Russia and Serbia. It is stated that the morbidity rates due to the influenza-like illness (ILI) reached to 951 cases in Belgium and 136 cases per 100 000 population in the Netherlands. Whether this trend continues to be the case during the forthcoming influenza season, remains to be seen.

THE IMPACT OF AN INFECTIOUS EVENT

The impact of previous events in terms of physical, mental and psychological effects is highly complex to assess. It depends upon seasonal prevalence of infection, virulence of strains, population resistance and prior preparedness.[See table 1] In such a scenario the availability of essential drugs, vaccine, quarantine and trained personnel are first to be checked. Turning back to the influenza epidemic in the early 1970s to mid-1990s, the average number of hospitalisations was 50 per 100,000 Americans per season. The number of deaths had been substantial during the following pandemics e.g.; 1918 Spanish flu, 218.4 deaths per 100,000 Americans; 1957 Asian flu, 22 deaths per 100,000 population; and 1968 Hong Kong flu, 13.9 deaths per 100,000 population. Assessing the impact in monetary terms the direct costs [that include hospitalisations, medical fees, drugs, tests, and equipment] estimated in 1986 were about 1 billion US \$ annually while the indirect costs ranged from 2 to 4 billion US \$. Without a mass vaccination campaign, the cost of the next pandemic is projected to be 71.3 to 166.5 billion US \$ in 1995 [inpatient and outpatient care, self-treatment, and lost work days and wages].

PREPAREDNESS AT THE EUROPEAN UNION (EU) LEVEL

Surveillance for emerging infectious diseases and preparedness for intentionally-caused outbreaks are closely related. Effective preparedness both require improving the sensitivity of national and international public health surveillance as well as improving coordination and communication between the medical and public health sectors, and other sectors such as civil defence, animal health, the military and the law-enforcement community at all levels. Preparations at the EU level are underway that will provide significant protection and reduce the risk of exposure to infection. The European Union has taken proactive stance on the issue of bio-terrorism.

The European Commission has set up a close network of collaboration with the WHO and the "G7+" states [USA, Canada, UK, France, Germany, Italy, Japan and Mexico] to ensure an optimal and co-ordinated level of preparedness. The meeting in Ottawa on the 7th of November 2001 was a milestone in this regard. Agreement was made to take concerted global actions to strengthen the public health response to the threat of international biological, chemical and radio-nuclear emergencies. Among the other several strides taken by the EU Commission the establishment of a

communicable diseases network was a fundamental initiative in this direction. It plays a key role in early warning and response system [EWRS], making public health authorities in the Member States as well as the Commission to timely alert. Launching Global Alliance [2002] between the EU and WHO that fights against communicable diseases, and other potential threats have further intensified these efforts. Preparedness began since WHO urged every nation to make a pandemic plan [influenza] for the first global outbreak of the 21st century.

European Influenza Surveillance Scheme [EISS] was established in 1996 that helps to reduce and abolish the burden of influenza across Europe. The conference on "Preparedness and planning for Influenza in the EU" [2001] in Brussels strengthened the roots of European action plan to pandemic influenza outbreaks by the end of 2002. This plan intended to identify the most urgent actions and approaches undertaken by the Member States and the EU.

DISCUSSION

This review provides strong clues on how to beef up the preparedness to respond effectively to the threats of infectious agents either emerging naturally or intentionally released in a population. Unprecedented fatalities were noticed in various historical epidemiological events where level of preparedness was low. No incident of bio-terrorism has been detected so far, however; infectious outbreaks have been largely hitting Europe. Understanding the nature of infectious agents and recognising the scope of bio-terrorist events are considered vital before designing any intervention.

Outbreaks and epidemics provide some pertinent indications for upgrading the preparatory activities in the region. The impact of such an event in current times will be disastrous if infection is not promptly contained in populations where the potential of frailty is known. Generally it has been observed that poor reporting and surveillance can bring fatal delays to timely respond. The most vivid example is the recent SARS outbreak in China. Rapid means of transportation has let the deadly virus cross the international borders of at least 17 countries including Europe. According to the WHO investigation the delay in detection and reporting in China is mainly to blame. Preoccupied with vast patient loads, health care providers are unable to register cases quickly and prevent further spread. It is hard to judge the efficacy of interventions, to fairly allocate human and financial resources and ensure public safety. An effective response would count on the capacity to accurately estimate cases and

deaths, measure the success of infection controls, and communicate frequently with the public to alleviate panic.

Tracing the source of covert releases would require data from all institutions. An efficient multi-sector response needs to be organised on carefully tested plans and appropriate modelling that takes into account geographic and epidemiological characteristics. Conducting a large-scale exercise to assess how local, state, and national emergency systems respond to infectious emergencies in major EU cities is considered a useful tool. Such exploratory practices have already provided credible hints. For example, in May 2000 the capacities and responsiveness towards a biologic attack were assessed in three mid-size U.S. cities. The large-scale exercise lasted several days. The biological attack scenario, played out, showed that most local and regional authorities, even those who had been specially trained, were under-prepared to deal with a large communicable disease outbreak and were overwhelmed by the complex coordination, decision making, and management needed to contain and control the spread of disease. When the scenario ended [after four days], between 950 and 2,000 people had potentially "died" and the disease had spread throughout the United States and to other countries.

It has been seen that in emergency situations, hospitals face acute shortages of staff, beds, equipment, and measures of standard precautions. It is anticipated that a novel virulent strains of virus can bring major disruption, if the level of preparedness is not up to the mark to deal with a nominal upswing. Like the smallpox, the influenza virus requires high degree of preparedness both at the national and at the community levels. Vaccination is one of the most challenging response measures. However, in the event of sudden need, vaccine shortage is most probable. In many European countries the availability of vaccine and anti-viral drugs are nationally determined and access to them is not coordinated. The facilities for vaccine production exist in only a limited number of Member States.

With respect to the current preparedness there are more challenges lying ahead. For instance, there is a strong need for strategies to enhance capabilities of early detection; improve readiness and decrease time required to mount a response; identify important gaps in existing research; identify key resources for launching a large scale response; developing a flexible contingency plan for insuring availability of vaccines and antiviral agents. More assistance of the state and local officials is required in developing state

and local preparedness plans and to collaborate actively with the EISS. Protection of vulnerable communities and technical assistance to poorly prepared countries of South-eastern and Central Europe has not been adequately addressed. Contact or exposure to any biological hazard or infectious agent has grave affects on children. With respect to increasing number of influenza, diphtheria and syphilis among children across the EU, no stringent safety precautions at schools have been adopted so far. In future Tularaemia, Q-fever and smallpox have already been prioritised for various interventions by the European Union of communicable disease surveillance network.

The European Agency for the Evaluation of Medicinal Products [EMA] recently published treatment guidelines for use against smallpox emergency. However there is no agreement to the need for a community level stockpile of any medicines at the present time. In addition, there is no common understanding on sharing national stockpiles. With regard to an EU consortium for the procurement of vaccines or other medicines, such as antibiotics, too few Member States are interested in participating in such an exercise. Most member States hold national stockpiles of first generation vaccines. Despite the fact that these old vaccines do not meet current quality standards for the manufacture of vaccines, few States appear to be planning to buy a second-generation vaccine when it becomes available.

Efforts are needed to galvanise security measures around research laboratories and institutions where biological agents are handled or worked with. In a border-free region where products, services and people move without hindrance, it has become imperative to share up to date local and national data on unusual infections [internal as well external outbreaks] with the WHO Global outbreak alert and response network. Reconnaissance system at borders needs to be highly vigilant to such threats. Furthermore, screening facilities will be an ideal step where the entry of virulent strains of virus or an infectious agent through animal, plant or other channel can be promptly spotted. To detect suspicious events clinical alert mechanisms and syndrome-based surveillance systems need to be incorporated into routine practices.

Review of various events have shown that the following set of criteria can help in establishing a robust alert system to the suspicion of an infectious agent. They include, for example:

- Rapid increase in the incidence of disease [e.g.,

within hours or days] in a normally stable population;

- Rises and falls in an epidemic curve during a short period of time;
- Unusual increase in the number of people seeking care, especially with fever, respiratory, or gastrointestinal manifestations;
- Endemic diseases emerge rapidly at an uncharacteristic time or in an unusual manner;
- Lower attack rates among people who had been indoors, especially in areas with filtered air or closed ventilation systems, compared with people who had been outdoors;
- An unusual temporal or geographic clustering of disease;
- Large numbers of rapidly fatal cases; and
- Patient presenting a rare disease and has bio-terrorism potential [e.g., inhalational anthrax, tularaemia, or plague]

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