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Ibrahim Khan, Rashid Chotani, Ulrich Laaser  
Emerging Infections and the Level of  
Preparedness in the European Region

# International Public Health

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# Emerging Infections and the Level of Preparedness in the European Region



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## Acronyms and Abbreviations

BSE	Bovine Spongiform Encephalopathy
CCEE	countries of central and eastern Europe
CDC	Center for disease control and prevention
CISID	Computerized Information System for Infectious Diseases
CSR	Communicable Disease Surveillance and Response
DFID	Department For International Development agency
EC	European Commission
ECID	European Centre for Infectious Diseases
EEE, WEE	Eastern and western equine encephalomyelitis
EISS	European Influenza Surveillance Scheme
ELISA	enzyme-linked immunosorbent assay
EMA	European Agency for the Evaluation of Medicinal Products
EU	European Union
EURO/EMRO	European/ Eastern Mediterranean Region
FETPs	Field Epidemiology Training Programs Network
GOARN	The Global Alert and Response Network
GUM	Genitourinary medicine
ICMM	International Committee on Military Medicine
Ig	Immuno-globulin
IHR	International Health Regulations
IRBA	Intentional Release of Biological Agents
ISS	Informatics Support unit
LVS	Live Vaccine Strain
NCID	National Center for Infectious Diseases
PA	protective antigen
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PH-SEE	Public Health in South Eastern Europe
SARS	Sever Acute Respiratory Sndrome

TEPHINET	Training Programs in Epidemiology and Public Health Interventions Network
VEE	Venezuelan encephalomyelitis
VHF	viral hemorrhagic fever
WHA	World Health assembly act WHA
WHO	World health organization
WHO/EURO	WHO Regional Office for Europe
WHO-HQ	World health organization Head Quarter
WMD	Weapons of Mass destruction
WTO	World trade organization

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## Forward

The book aims at reviewing rapidly emerging infections (both intentional and natural) and assessing the level of preparedness to deal with such emergencies in the European region. The main bulk of the book consists of five chapters. Starting with the introduction of bio-security in the first chapter, a sequential review of historical events that induced deaths, diseases and disabilities on massive scale is given. Coupled with the categories of infectious agents, public health impact of any outbreak or epidemics have been described. Supported by a number of figures, graphics and pictures that elaborate the text and impart comprehensive information about intentional epidemics and infectious outbreaks, have been summarized. This chapter also mentions how biological agents can become a danger for public health.

Chapter two deals with the global epidemiology, and provides a brief assessment of the treatment and prophylactics available for various lethal biological agents that include anthrax, smallpox, tularaemia, plague, and viral hemorrhagic fever.

Chapter three addresses key infectious events that hit Europe in the past till the recent SARS outbreak. Focusing both on naturally occurring infections and intentional epidemics across the Europe, a brief account of infectious emergencies, for instance, Influenza, tularaemia, anthrax, West Nile fever, Syphilis, Smallpox, SARS have been given.

Chapter four illustrates preparedness of both individual EU member states as well as at the European level against intentional and naturally occurring infectious emergencies. An assessment of the network of surveillance, joint preparatory steps and communication channels that currently exist for dealing with the event of intentional release of the biological agents across Europe have been given. Relevant to preparedness the importance of strict implementation of international health regulations in Europe has been emphasized. Steps that European Commission and Member States have taken so far after September 11, 2001 to prepare themselves for the possibility that biological agents may be deliberately released have been thoroughly analysed. The intention here is to provide, not only a pertinent review of infectious events that had hit Europe till now, but also to provide lessons for various components of preparedness and propose recommendation for further improvement. In the light of exiting gaps in the disease surveillance and response mechanisms, specific recommendations are given that can strengthen the networks of epidemiologic intelligence and coping mechanisms for rare indigenous and exotic diseases.

Fifth chapter enlists useful information/Links to research articles (abstracts) and addresses of some key websites that provide in depth vision on activities in Europe. The book provides unique perspectives of the authors on the known and unknown risk of exotic infectious agents and is considered credible source of knowledge for public health researchers, infectious disease experts, program managers and health authorities that deals with infections in Europe.

## CHAPTER ONE

### INTRODUCTION

Biological security has become a public health priority in the recent times (1). In spite of the state of the art technologies and medical advancements, infections can still incapacitate communities and can cause deaths, diseases and disabilities on massive scale if not timely detected and managed. Public health consequences are particularly enormous if any novel or old infection is unfolding in the community without noticing it. The anthrax outbreak in the USA after the September 11, 2001, has revealed that global health security is challenged not only by the naturally and accidentally occurring infectious diseases but also by the intentional release of human and animal pathogens (2,3). As a known fact communicable diseases are considered major sources of disease and death on the planet earth (5-13). Robust and early warning networks are integral for national, regional and global defense. Epidemiological intelligence at all levels serves the basis for prompt disease alert and response mechanisms (2). This is particularly crucial, as primary infections caused by the deliberate release of a biological agent are most likely to be considered a natural event. Such infectious emergencies are complex to manage and pose diagnostic difficulties that are similar to those encountered in natural or accidental infections (13-26). Information of such events stimulate a wide array of planned control and preventive measures that help to protect public health at risk.

Microbes that lead to serious infections are not only complex, dynamic in nature, and constantly evolving but also proliferate rapidly, mutate, and adapt to new environments and hosts. Numerous factors, including those linked to human activities, can accelerate and enhance dissemination and exposure. The impact of non-vigilance and low preparedness for such emergencies can be dramatic in speed. Microbes are quick to exploit new opportunities to spread, adapt, and resist in any population. Infectious diseases have the potential to spread across the globe. In the era where state of art knowledge and technology is available, still there are very few opportunities of treatment and prophylaxis. Protective measures like isolation, quarantine and stringent hygienic protection are still the favored methods. Looking retrospectively the course of human history was frequently changed by epidemics that swept unchecked across continents. With the development of vaccines and the medical discoveries during the last century, potent classes of anti-biotics can prevent and cure many infectious diseases (1-6).

At the rate of approximately one per year newly diagnosed infections are reported from almost all parts of the world. Over the past 25 years more than 30 new infectious diseases have emerged (1,6). Infections like AIDS, tuberculosis, malaria, influenza, anthrax are now threatening global security (1-7). Other emerging diseases, such as Ebola haemorrhagic fever and new variant Creutzfeld-Jakob disease, illustrate the severe damage caused by lethal new agents. In 1997 and 1999, influenza viruses previously confined to animals suddenly appeared now in humans. Apart from the need to cope with the emergence and spread of new diseases, public health infrastructures are further burdened by the dramatic resurgence of older epidemic-prone diseases such as malaria, dengue, tuberculosis, cholera, and yellow fever. The threat of intentional of infectious biological agents/bio-terrorism is probably low in Europe, because of tightened security and many challenges that include those related to obtaining and dispersing biologic agents (9,27). However, it represents one of the greatest long-term threats. A

biological attack on a major city could be as disastrous as an atomic bomb. However, the effects of a biological agent may not be apparent until days after an attack because of the longer incubation period or early non-specific symptoms.

An outbreak anywhere in the world must now be considered a threat everywhere. The recent trend in global travel has given microbes multiple chances to cross all borders in novel ways with unprecedented speed. Microbes can incubate in apparently healthy travelers, hide in food, animals, and cargo. Alone in the UK, 1,128 malaria cases were imported into the country by travelers in 2000 (6,8). Cases of “airport malaria”, in persons who live or work near international airports yet have not traveled, are detected regularly in cities such as London, Paris, Brussels, Geneva, and Oslo as well as in the United States and Canada. Legionellosis and leptospirosis in Australia, Lassa fever, yellow fever, hanta virus, and listeriosis in Europe, and yellow fever, West Nile fever, cryptococcosis, and *E. coli* in the US are just some examples. Taking the example of ongoing outbreak of SARS, the world now faces a situation where unchecked epidemics are again spreading around the globe, but this time at an unprecedented momentum (6).

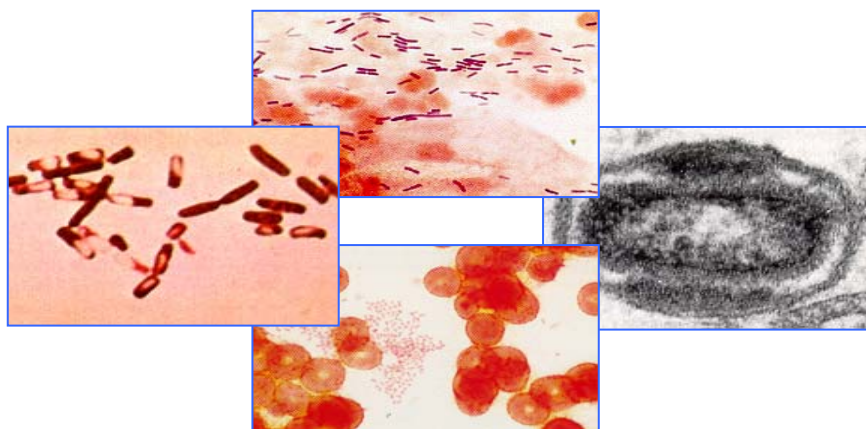
A highly infectious agent, such as small pox, also could spread rapidly in an urban environment, assisted by modern transportation networks. Biological agents can be potentially catastrophic, impacting thousands. Technological advances, access to organisms, and availability of technical information may contribute to the proliferation of biological warfare agents. Preparing for deliberate epidemics involve not only a harmonized policy and sophisticated surveillance networks but also specialized education and training of emergency personnel, specific disaster planning, public education, and local stockpiling of appropriate antidotes. Europe is at a crossroads in terms of readiness to respond to biological terrorism (9,27,28-31). The assistance of European Commission is key to ensure preparedness across all EU nations and focus particularly on those where response and alert mechanism are weak and communities are vulnerable. This book is an attempt to bring specific issues related to the event of deliberate epidemics with special reference to the epidemiology of five key biological agents of concern. The intention is to provide brief account of infectious outbreaks taking place across Europe, and lastly assess the level of preparedness and commitment.

## INTENTIONAL EPIDEMICS/BIO-TERRORISM

It is 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" (1-2). Biological agents include infectious agents of humans, plants, and animals, as well as the toxins that may be produced by microbes and by genetic material potentially hazardous by itself or when introduced into a suitable vector. Biologic agents and infectious substances are closely related terms that are found in the transfer and transportation regulations(2-3). Biological agents may exist as purified and concentrated cultures but may also be present in a variety of materials such as body fluids, tissues, soil samples, etc.

A wide array of biological organisms like bacteria, viruses or any toxic material extracted that can be used for bio-terrorism. The biological agents, with the exception of smallpox virus, are typically found existing in nature in innumerable parts of the world. They can, however, be enhanced so that their virulence in humans make them resistant to vaccines and antibiotics so called "weaponization"(4-6). This usually involves using selective reproduction pressure or recombinant engineering to mutate or modify the genetic composition of the agent. Bio-terrorism agents may be disseminated by various methods, including aerosols, through specific blood-feeding insects, or food and water chain contamination(1-6). The advantages of bio-terror weapons is that their deployment allows terrorists to protect themselves and escape before any effects are detected by people or health authorities. The most attractive feature of bio-weapons may be the tremendous psychological impact that their use, or threatened use, would inflict on the population. Biological weapons have recently attracted the attention of governments, public health authorities and the financial resources of the developed nations(7,8,9). Discerning the nature of the threat of bio-weapons as well as appropriate responses to them requires greater attention to the biological characteristics of these instruments of war and terror. The dominant paradigm of a weapon as a

(Microscopic Picture of Biological Agents-Anthrax, Plague, Smallpox)



nuclear device that explodes or a chemical cloud that is set adrift leaves us ill-equipped conceptually and practically to assess and thus to prevent the potentially devastating effects of bio-terrorism(2,4,6). Strengthening the public health and infectious disease infrastructure is an effective step toward averting the suffering that could be brought by a terrorist's use or any disaster of a biological agent.

Possibilities of intentional epidemics were confined primarily to those in the military, diplomatic, law enforcement, and intelligence communities(1,7-9). Recently have the civilian medical and public health communities begun to be engaged in examining the practical challenges posed by this threat against civilians. Various professional entities have begun to incorporate matter of bio-terrorism in their national priorities. On the international level, the World Health Organization (WHO) decided in 1998 to establish an expert group to review and revise its 1970 landmark document, *Health Aspects of Chemical and Biological Weapons*(1). Evidently, there is increasing fears of bio-terrorism which provoked nascent concern among medical and public health professionals in Europe as much as it is in the USA (1-13). However there is a growing need to understand and equip the communities with knowledge and health system with preventive and curative measures to effectively respond to this problem. In this regard EU nations have remained far behind in terms of public health awareness, precautionary measures, surveillance and preparedness to deal with the emergency of biological disasters.

### **HISTORY OF INTENTIONAL USE OF BIO-AGENTS**

Biological terrorism is not a new phenomenon known to generations. Alone in the past century almost 420 terrorist attacks occurred and 135 of them were of biological nature. In 90 percent of the attacks a white powder was used. A wide array of biological organisms were used in various ways to induce massive casualties. The examples of bio-terror attacks can be traced back to 600 BC when the master tactician Solon used the purgative herb hellebore (skunk cabbage) to poison the water supply during his siege of Krissa. Ancient armies, for instance, tainted water supplies of entire cities with herbs and fungi that gave people horrible diarrhoea and hallucinations. It took a series of calamities inflicted on the Egyptians to finally convince an obstinate pharaoh to liberate the ancient Hebrews, according to the Bible. The history of plague probably date back to about 1300 BC when Nile River water was turned blood-red and undrinkable and caused unprecedented public health miseries in Egypt (2,4-7,10).

History's most serious biological event (anthrax outbreak) was "Black Bane," a terrible epidemic that swept Europe in the 1600s. It killed at least 60,000 people and many more domestic and wild animals. People called it "Black Bane" because many cases involved the cutaneous, or skin, form of anthrax, which involves a blackish sore. Anthrax actually was named from a Greek word that refers to coal and charcoal. Physician Robert Koch discovered how to grow bacteria on gelatin-like material in glass laboratory dishes, and formulated rules to prove that specific bacteria caused specific diseases (2,6-8). In 1876, Koch identified the anthrax bacterium. It led to the development of a vaccine that was first used to immunize livestock in 1880. Other biological agents have roots as almost as ancient as anthrax. In 1797, Napoleon tried to infect residents of a besieged city in Italy with malaria. During the French and Indian War, the British suspected American Indians of siding with the French. In an "act of good will," the British gave the Indians nice, warm blankets -straight from the beds of smallpox victims. The resulting epidemic killed hundreds of Indians (4,7).

In Europe, during the Middles Ages, infected cadavers were catapulted over walls into cities that were under siege. Cadavers and animal carcasses were also used to contaminate enemy water supplies. In World War 1 Germany used *Bacillus anthracis* to infect livestock that would be exported to the Allied forces. Chlorine

and mustard gas were also used extensively by the Germans. Dr. Anton Dilger, a noted German-American physician, established a small biological agent production facility at his Washington, D.C., home in 1915. Using cultures of bacillus anthracis (anthrax) and pseudomonas mallei (glanders) supplied by the German government, Dilger produced an estimated litre or more of the liquid agent. He reportedly passed the agent and a standard inoculation device to dock workers in Baltimore, who used them to infect a reported 3,000 horses, mules and cattle destined for the Allied troops. Several hundred military personnel were infected as well. In 1916, the Bucharest Institute of Bacteriology and Pathology identified B. anthracis in cultures from the German Legation in Romania. Sheep from Romania were to be infected and then exported to Russia. Horses and mules of the French cavalry were also infected (4,7,10,12).

In 1937, Japan began a biological warfare program that included anthrax, and later tested anthrax weapons in China. Biological warfare witnessed further development during World War II when the Japanese conducted biological weapons research on prisoners of war in Manchuria. Unit 731 was the biological weapons research facility where prisoners were infected with B. anthracis, Neisseria meningitidis, Shigella spp, Vibrio cholerae, and Yersinia pestis. The experiments resulted in 1000 deaths. Finally, in 1986, after critics labelled Gruinard "Anthrax Island," the British government decided to clean up the mess. The Japanese conducted large-scale field studies on 11 Chinese cities by contaminating the water supplies and food items with B. anthracis, Shigella spp, V. cholerae, Salmonella spp, and Y. pestis. The Japanese also released fleas that had fed on plague-infected rats to initiate epidemic of plague in the Chinese cities. Such field studies ended in 1942 (4,7).

Many Japanese scientists were granted immunity from war crime prosecution upon disclosure of their test results to the United States. The Allies also developed biological weapons during this time. Japan was the first country in the world to experience a terrorist attack using chemical weapons. On March 20, 1995, Aum Shinrikyo, a religious doomsday cult, released the nerve gas sarin in the Tokyo subway. The diluted form of the gas affected five subway cars during morning rush hour, killing 13 people and injuring a further 6000. More than 600 patients were admitted to St Luke's International Hospital near the affected subway station. The hospital reported that, after three years, many patients still complained of neurological symptoms and fears (4,7).

The attack on the Tokyo subway still has repercussions. The mastermind behind this attack, Chizuo Matsumoto, is still on trial. Aum Shinrikyo is as an organisation, that still exists and is even growing in spite of the fact that its leaders and many of its members have been arrested and sentenced. Aum Shinrikyo is reported to regaining power and is now two thirds of its former size,' Japanese Chief Cabinet Secretary Hiromu Nonaka told reporters in a press conference in 1999 (2,4-6,13).

The United States, Britain and other countries developed anthrax weapons during World War II. The British military in 1942 began testing "anthrax bombs" on Gruinard Island, a 500-acre dot of land off the northwestern coast of Scotland. The Gruinard experiments established the environmental consequences of using anthrax as a weapon of mass destruction. British scientists thought the anthrax spores would quickly die or blow away into the ocean. But the spores lived on.

Huge numbers remained infectious year after year. The British military conducted explosives testing with anthrax spores on Gruinard Island near the coast of Scotland. The spores remained viable for 36 years following the British tests. The contamination of the island with viable anthrax spores was so great that in 1986 it had to be decontaminated with 280 tons of formaldehyde and 2000 tons of seawater. The island is now declared fully decontaminated (2,4,7,13).

In Sverdlovsk, Russia, about 100 people were infected with anthrax, and 64 died in 1979. The Russian government blamed the outbreak on contaminated meat, but the international scientific and intelligence communities suspect the accidental release of anthrax spores from a nearby bio weapons facility. In 1989, Dr. Vladimir Pasechnik, the former director of the Leningrad Institute of Ultrapure Biological Preparations, defects and reveals that the Soviets had an offensive biological weapons program (10). In 1972 a group of American eco-terrorists (college students) named " RISE "made a plan to destroy human race and leave some selected individuals.

They acquired the agents causing typhoid fever, dysentery, diphtheria and meningitis. The plan was aborted when culture was discovered by the police before they implement their ideas and the two of the main perpetrators fled to Cuba. In 1984 a Rajneeshee Cult in the State of Oregon, USA contaminated salad bars with S. typhimurium in order to incapacitate the voters in the election and seize political control. Several people got illnesses and panic afterwards. A 1972 treaty, ratified by 143 countries, banned production, deployment, possession and use of biological weapons. Analysts think that a dozen countries still may have clandestine biological weapons programs (1,13-17).

In 1940s with the advance technology bio-weapon techniques were refined and



made more advanced. Aerosol methods were developed and spray to suspend particles in a mist or spray were developed. Additives were included later to prevent decay and techniques of mass production were developed(1,2,5,8).

(Photo of vessels used for biological agents) The accessibility of microorganisms in the hands of destructive minds apparently seem to pose serious threats by causing massive casualties. The terrorists threaten the world and have now more lethal ways and means of human destruction.

During the 1970s and 80s, most western governments prepared for bombings and hijackings overseas. Today, policymakers are defending attacks against population and critical infrastructure. The worst of these threats confronting policymakers is the terrorist use of Weapons of Mass Destruction (WMD), especially biological or chemical weapons.

The actual probability of a large scale biological or chemical attack remains relatively low compared to others, however, the consequences of a large scale chemical or biological terrorist attack would be so dire that policymakers have been compelled to enact a number of recent initiatives for national domestic preparedness against WMD terrorism. Efforts in preventing and mitigating such attacks has significantly intensified over the past few years following increased incidents and threats of bio-terrorism in the United States (e.g., New York City). Growing concerns exist about the threats that have been received that terrorist will focus on unusual destinations and unexpected locations around Europe (13,14,20).

Additionally, the recent escalation of global tensions underscored the importance of force protection from biological threats. The global biological warfare risks are taken seriously not only by national leaders but mostly by public health authorities. The threat is indeed serious, and the potential for devastating casualties in the future is high for certain biological agents. However with appropriate use of available counter measures the impact of many casualties can be prevented or minimized. There is a growing concern in the West about the possibility of proliferation or enhancement of offensive programs in countries hostile to the western democracies. Without doubt the threat of biological weapons being used against the West is broader and more likely in various geographic scenarios.

## **CATEGORIES OF BIO-AGENTS**

### **Category A**

Based on the nature of virulence and pathogenicity agents in category A are the most lethal one and are of greater concerns in terms of public health casualties. They are high priority agents including organisms that pose a risk to national security because they can be easily disseminated or transmitted person-to-person causing high mortality, with a potential for major public health impact, might cause public panic and social disruption and require special attention for public health preparedness. The organisms included in this category are the following,

- Variola Major (smallpox)
- Bacillus anthrax (anthrax),
- Yersinia pestis (plague),
- Clostridium botulinum toxin (botulism),
- Francisella tularensis (tularemia),
- Filoviruses,
  - Ebola hemorrhagic fever
  - Marburg hemorrhagic fever
- Arenaviruses
  - Lassa (lassa fever)
  - Junin (argentine hemorrhagic fever) and related viruses

### **Category B**

These are the second highest priority agents that are moderately easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of WHO's diagnostic capacity and enhanced disease surveillance. Category B contains Q fever, brucellosis, viral encephalitides, staphylococcal enterotoxin B, food/waterborne (e.g. salmonella). For example the viruses like

alphaviruses (Venezuelan encephalomyelitis (VEE), Eastern and western equine encephalomyelitis (EEE, WEE)), bacteria like *Coxiella burnetii* (Q fever), *Brucella* spp. (brucellosis), *Burkholderia mallei* (glanders) and toxin like *Rhus communis* (caster beans) ricin toxin, *Clostridium perfringens* episolon toxin, *Vibrio cholerae*, *Shigella dysenteriae*, *E. coli* O157:H7, *Cryptosporidium parvum*, etc (1,21-26).

### Category C

This is the third highest priority agents including emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality and major health impact. The category include nipah virus, hantavirus, tickborne hemorrhagic fever, yellow fever and multi-drug resistant TB. Bacteria include multi-drug resistant *Mycobacterium tuberculosis*.

The table given below provides a detailed overview of the mode of transmission and risk associated with some lethal biological agents.

Characteristics Of Biological Agents Used in Weapons

Disease	Infection Dose	Incubation	Duration	Mortality
Anthrax **	8000-50,000 spores	1-6 days	3-5 days	High
Smallpox	1-10 organisms	~12 (7-17)	4 wks	Mod-high
Plague **	100-500	2-3d	1-6d	High
Q fever	1-10 organisms	10-40d	2-14d	Very low
Tularemia	10-50 organisms	3-5d	2 wks	moderate
VHF	1-10 organisms	4-21d	7-16d	Mod-high

VHF-viral hemorrhagic fevers, \* Untreated, \*\* Pneumonic form  
Source: Biological Casualties Handbook, US Army Publication, 2001

### ASSOCIATED COMPLEXITIES WITH BIO-AGENTS

Biological agents that can induce disease and death on massive scale include, *Brucella*, *Coxiella burnetii*, Viral hemorrhagic fevers, Smallpox (*Variola*), *Yersinia*



*pestis*, *Francisella tularensis*, and *Bacillus anthracis*. Among the toxins that can be used include Botulinum and ricin (12-19,20). The release could be silent and would almost certainly be undetected. (Figure 2 Culture of *Bacillus anthracis*). The cloud would be invisible, odorless, and tasteless. It would

behave much like a gas in penetrating interior areas. No one would know until days or weeks later that anyone had been infected (depending on the microbe). Then patients would begin appearing in emergency rooms and physicians' offices with symptoms of a strange disease that few physicians had ever seen. Special measures would be needed for patient care and hospitalization, obtaining laboratory confirmation regarding the identity of microbes unknown to most laboratories,

providing vaccine or antibiotics to large portions of the population, and identifying and possibly quarantining patients. Trained epidemiologists and public health experts would be needed to identify where and when infection had occurred, so as to identify how and by whom it may have been spread. Sources of these exotic diseases are several.

The most widely noticed factors that contribute heavily to the emerging state of infectious diseases from high endemic countries to the low endemic countries is international traveling and migration. Global transportation links facilitate the potential for biological terrorist strikes to inflict mass casualties. Urbanization provides terrorists with a wide array of lucrative targets for implementing such options. The diaspora of scientists has increased the danger that rogue states or terrorist groups will accrue the biological expertise needed to mount catastrophic terrorist attacks. The emergence of global, real-time media coverage increases the likelihood that a major biological incident will induce panic. The second source that usually plays a role is exposure to the animals (zoonotic diseases), exposure via travel, leisure pursuits (hunting, camping, fishing), occupation (farming), pets, the availability of and accessibility of terrorist to biological agents in the laboratories and research places(4-6,8,12,18,20,21).

Of the Weapons of Mass destruction (WMD) (biological or nuclear or chemical), the biological ones are the most greatly feared, but the countries in the European region are least prepared to deal with them. Virtually all efforts in strategic planning and training have so far been directed toward crisis management after a chemical release or an explosion. Spills of hazardous materials, explosions, fires, and other civil emergencies are not uncommon events. The expected scenario after release of an aerosol cloud of a biological agent is entirely different. Public health administrators would be challenged to undertake emergency management of a problem alien to their experience and in a public environment where pestilential disease, let alone in epidemic form, has been unknown. First responders to a biological weapons incident (in contrast to an explosion or chemical release) would be emergency room physicians and nurses, family physicians, infectious disease specialists, infection control practitioners, epidemiologists, hospital and public health administrators, and laboratory experts. Surprisingly, to date there has been little involvement of any of these groups in planning for appropriate responses or in training. No recent measures have been observed so far at a national level to address this deficit and to bring experts from all relevant field together.

The WHO handbook dealing with potential biological agents lists 31 infectious agents. Other factors also determine which microbes are of priority concern: specifically, the possibility of further human-to-human spread, the environmental stability of the organism, the size of the infectious dose, and the availability of prophylactic or therapeutic measures. A Russian panel of bio-weapons experts reviewed the microbial agents and concluded that there were 11 that were "very likely to be used." (See Table 2 & Table 3) The top six were smallpox, plague, anthrax, tularemia, viral hemorrhagic fever (VHF) and botulism. Each agent is associated with high case fatality rate when dispersed as an aerosol. Smallpox and anthrax have other advantages in that they can be grown reasonably easily and in large quantities and are sturdy organisms that are resistant to destruction (1,2,4-8).

## **WEAPONIZATION OF BIOLOGICAL AGENTS**

Biological weapons are named as a "poor man's nuclear bomb". It is because they are easy to manufacture, can be deployed without sophisticated delivery systems, and possess the ability to kill or injure thousands of people in a short span of time. In some cases it is passed unnoticed or undetected. Simple devices such as crop dusting airplanes or small perfume atomizers are effective delivery systems for biological agents. In contrast to chemical, conventional, and nuclear weapons that generate immediate effects, biological agents are generally associated with a delay in the onset of illness (hours to days). Moreover, illnesses from biological weapons are likely to be unrecognized in their initial stages (36-45). With highly transmissible agents (e.g., plague and smallpox), the time delay to recognition can result in widespread secondary exposure to others, including health care personnel. Depending on the communicability of the microbe, wide geographic paths can be affected when infected individuals who are asymptomatic travel by airplane to other parts of the country or world.

Events in the past have made the health authorities as well as civilian population to be alert and vigilant. Several fatal biological agents were released against the civilian populations in the past. In 1984 in Oregon, approximately 750 people experienced salmonellosis after bacteria were spread on salad bars in an effort to disrupt local elections. An inadvertent release of anthrax in April 1979 by a military facility in Sverdlovsk, USSR, produced mass infection as distant as 50 km, with 66 documented deaths. Table 1 lists biological agents considered to be the likely candidates for weaponization.

These agents include bacteria, viruses, or preformed toxins, and for most, quantities as small as 1 kg can injure or kill thousands of people (1-7). The Rajneesh Foundation used Salmonella bacteria in 1984 to poison ten restaurant salad bars in the city of Dalles, OR, (USA) intending it would influence an election. A separatist group calling itself 'Republic of Texas' used Botulinum, HIV and rabies in 1998 and 1999 to threaten judges. Three members were later charged with conspiracy to use weapons of mass destruction and the eldest, Johnnie Wise, was sentenced to 24 years in prison. In 1977, Diane Thompson, a nurse from Texas, was sentenced to 20 years for intentionally contaminating doughnuts with Shigella dysenteriae in order to achieve personal revenge (2,3,6,7).

Due to the unique characteristics Ebola is considered suitable for the potential use in biological weapons. They can be disseminated through aerosols and need a low infectious dose to cause high morbidity and mortality. They cause fear and panic in the general public. Effective vaccines are not available or supplies are limited. These pathogens are available and most can be readily produced in large quantities. Research on weaponizing various hemorrhagic fever viruses has been conducted in the past despite the lack of treatment options or protective vaccines. Reports say that several countries have tried in the past to weaponize these viruses.

For example, the Soviet Union (previous USSR) produced weaponized Marburg virus and conducted research on Ebola, Lassa, Rift Valley fever, and yellow fever viruses and New World arenaviruses. The United States conducted biological weapons research on Lassa, Rift Valley fever, and yellow fever viruses and New World arenaviruses. North Korea may have weaponized yellow fever virus. In 2000, CDC published a list of Category A agents (i.e., those that are most likely to

cause mass casualties if deliberately disseminated, can be released as small aerosols, and require broad-based public health preparedness). The list included New World arenaviruses and Ebola, Marburg, and Lassa viruses New World arenaviruses, Machupo (Bolivian hemorrhagic fever), Junin (Argentine hemorrhagic fever), Guanarito (Venezuelan hemorrhagic fever), Sabia (Brazilian hemorrhagic fever), Rift Valley fever virus, Yellow fever virus, Kyasanur Forest disease virus, Omsk hemorrhagic fever virus (1-7,47,49,50,80).

**CHARACTERISTICS OF BIOWARFARE**

The option of selecting biological agents as a tool for terrorizing population and imposing diseases and deaths has some peculiarities. The state of public awareness is already fairly low. Mostly people are vulnerable to contracting diseases and suffer to an unknown extent. Besides the potential for causing massive numbers of casualties, biological agents have the ability to produce lengthy illnesses that require prolonged and intensive care for which health system is never prepared. They are one of a good selection for the destructive minds because of the ability of certain agents to spread via contagion and paucity of adequate detection systems. There exists diminished role for self-aid and buddy aid, thereby increasing sense of helplessness.

Prolonged incubation period enables victims to escape and let the infection disperse widely and disseminate further before it is detected. They have the ability to produce non-specific symptoms and complicating diagnosis. Conditions and diseases induced by biological agents have the ability to mimic endemic infectious diseases, further complicating diagnosis and care (22). Biological weapons have an unmatched destructive potential. Technology for dispersing biologic agents is becoming more sophisticated. Lethal biological agents can be produced easily and cheaply. Biological agents are easier to produce secretly than the chemical or nuclear weapons. Another crucial aspect of bio-terrorism is its cost effectiveness as compared with conventional options. Tables 1 summarizes the estimates of conventional, nuclear and biological weapons in terms of cost of casualties dollar per square kilometer.

Table 1 Cost Effectiveness of Bio-Terrorism

<b>Weapons of Mass Destruction</b>	<b>Cost of casualties Dollar Per Square Kilometer</b>
Conventional (bombs)	2000
Nuclear	800
Nerve Gas	600
Biological Weapon	1

Source: Biologic Casualties Handbook, US Army, 2001

Multiple agents have been classified by the WHO as potential weapons of mass destruction or agents for biologic terrorism. Agents such as smallpox, viral hemorrhagic fever viruses, agents of viral encephalitis, and others are of concern because they are highly infectious and relatively easy to produce. Although dispersion might be difficult, the risk is magnified by the fact that large populations are susceptible to these agents and only limited treatment and vaccination strategies exist. Due to technical difficulties the risk of large-scale bio-terror event using viral agents is small, however public health programs and health care providers must be prepared for this potentially devastating impact on public health.

Table 2 Person-To-Person Acquisition of Biological Agents

<b>Disease</b>	<b>Transmission</b>	<b>Risk</b>
Andes virus	Undefined	<b>Low</b>
Anthrax	Contact with skin lesions	<b>Rare</b>
Ebola, Lassa, Marburg, Congo-Crimean, AHF, BHF	Contact with infective fluid, droplet?	<b>High</b>
Smallpox	Contact, droplet, airborne	<b>High</b>
Plaque (pneumonic)	Droplet	<b>High</b>
Q fever	Contact with infected	<b>Rare</b>

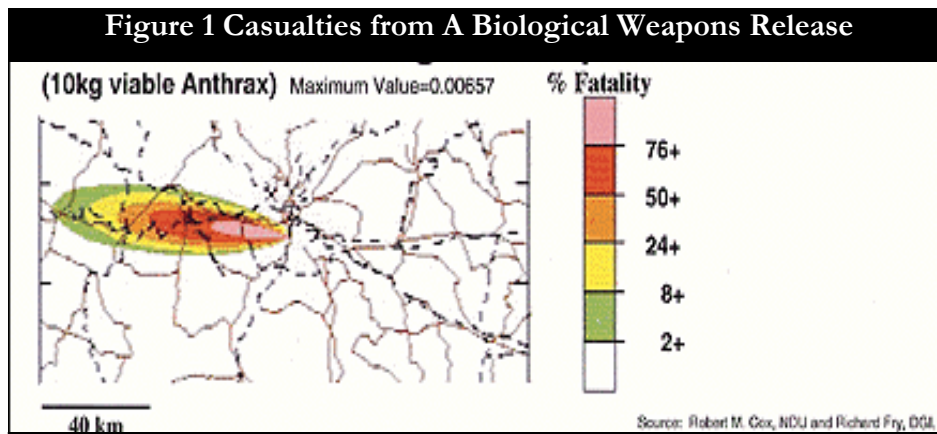
(Source: Viral Hemorrhagic Fever CDC. MMWR 2000;49(RR-4))

The use of biological and chemical weapons as agents of warfare and terrorism has occurred sporadically, but previous attacks overtly demonstrated that the risk exist and the possibility that terrorist groups may use them to fulfil their demands. Historically, most evaluations of the potential risk for biological weaponry have focused on the military, but the recent release of anthrax in the United States demonstrates that civilian populations are also at risk. More likely than not, most bio-terrorism events will be of a small scale; however, agents such as *Bacillus anthracis* and *Yersinia pestis* could leave hundreds of thousands dead or incapacitated.

The impact of the attack will depend on a number of variables, including the agent used, method of dispersal, and the responsiveness of the public health system. With any large-scale event, the public health infrastructure will be called upon to deal with mass casualties and the "worried well." Assessing the impact of biological event is a daunting task however experiences gained from the previous incidents clearly determine that such attempts will have grave consequences in terms of public health. It has direct, indirect, environmental, social, political and economic effects on public health. Its direct impact can be assessed from induced mortality and morbidity as well as disabilities. Indirect consequences include person to person transmission and fomite transmission. The scale of human losses, damage and destruction depend upon the type and nature of biological agent, mode of spread and the degree of vulnerability of population, environmental factors like temperature, direction of wind, size and doses of agents if spores/ aerosols are used. For illustration and public health simplicity here the biological agents are classified into three main categories(1-3,5,6).

### **IMPACT OF INTENTIONAL EPIDEMIC**

The example Siegrist al at 1999 shows in depth assessment of situation in case of bio-terror attack in which anthrax spores are used. Figure 3 shows the impact of a biological attack. High fatalities can be expected in close proximity of the release of biological agent. The events in Florida, USA after September 11, 2001 have drawn world's attention to "mythological diseases" such as anthrax, plague and smallpox which have been out of the spotlight for decades.



Source: David W. Siegrist, EID.Vol. 5, No. 4, July–August,1999.

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. The extent of outbreak basically depend upon the agent used and the mode of induction. Effective triage and surveillance require comprehensive assessment of the situation. Transmission and covert causalities can be prevented promptly once results of the initial assessment are available.

An epidemic resulting from an act of bio-terrorism could be catastrophic. However, if an epidemic can be detected and characterized early on, prompt public health intervention may mitigate its impact. Current surveillance approaches do not perform well in terms of rapid epidemic detection or epidemic monitoring. One reason for this shortcoming is their failure to bring existing knowledge and data to bear on the problem in a coherent manner. Knowledge-based methods can integrate surveillance data and knowledge, and allow for careful evaluation of problem-solving methods. Here an argument for knowledge-based surveillance, describes a prototype of Bio-storm, a system for real-time epidemic surveillance, and shows an initial evaluation of this system applied to a simulated epidemic from a bio-terrorism attack (2).

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.

The thought of an outbreak of disease caused by the intentional release of a pathogen or toxin in an American city was alien just 10 years ago. Many people believed that biological warfare was only in the military's imagination, perhaps to be faced by soldiers on a far-away battlefield, if at all. The "anthrax letters" and the resulting deaths from inhalation anthrax have changed that perception. In contrast to the acute onset and first-responder focus with a chemical attack, in a bio-terrorist attack, the physician and the hospital will be at the center of the fray.

Whether the bio-disaster is a hoax, a small food-borne outbreak, a lethal aerosol cloud moving silently through a area at night, or the introduction of contagious disease, the health care personal who understands threat bio-agent characteristics, diagnostic and treatment options and who thinks like an epidemiologist will have the greatest success in limiting the impact of the bio-terror event. The table 3 in the following depicts the estimation of an event when a 50 kg agent is released by aircraft along a 2 km line upwind of a population center of 500,000.

Table 3 Public Health Impact of biological agents

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

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

There are plenty of biological agents that are highly infectious and have no treatment available yet and have the capability of inducing unprecedented mortality and morbidity (1). However five already mentioned biological agents are of greater concern in terms of their potential and characteristics to be used in bio-terror attack or that can be weaponized will be briefly discussed here. Table 1 in the following provides a detail overview of the mode of transmission and risk associated with some lethal biological agents (1-21). The characteristics and details of some vital biological agents are given in the table 1 and table 2 in the following.

The particular characteristics of biological agents, when used as weapons, are their speedy transmissibility, infectiousness and fatality. An infectious agent can easily spread from the original victim to the close contacts and community. Medical personnel are at special risk that treat victims without knowing what kind of infection they are in contact with. More unpredictable are the number of people and the patterns in which they are affected. The worst-case scenario is a terrorist attack against a major city. One assessment from the World Health Organisation in 1970, asserted 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 clear night could kill between one and three million people (1,2). This is considered as deadly as a one-megaton atomic bomb and lethal impact on the public health varies (mild to the most lethal) depending upon the nature and type of agent used. There have been long fears in the US that terrorists could use crop dusting planes to distribute a biological agent. In an analysis for the US government it was estimated that up to three million people could be killed in one attack (2-8,15).

Toxins derived from biological agents generally have the characteristics of chemical agents, producing illness within hours of exposure. These agents are not infectious. Botulinum toxin, one of the most potent toxins known, can be extracted from the bacterium *Clostridium botulinum*; highly potent, it is 100 000 times more toxic than sarin. Within 1 to 3 days of exposure, victims experience cranial nerve disorders followed by descending paralysis and respiratory failure (12-34).

The enterotoxin of *Staphylococcus aureus* is also incapacitating although not highly lethal, except in those at extremes of age or with chronic illness. Exposure to this toxin can produce severe gastroenteritis that results in marked fluid losses and hypovolumic shock. Ricin and aflatoxin are plant-derived toxins. Inhalation of ricin produces weakness, fever, cough, and pulmonary edema within 24 hours, with death from hypoxemia occurring in 36 to 72 hours. When ingested, ricin produces severe vomiting and diarrhoea, resulting in cardiovascular collapse. Treatment is supportive; there is no antidote (10-28).

Table 4 Person-To-Person Acquisition of Biological Agents

Disease	Transmission	Risk
Andes virus	Undefined	Low
Anthrax	Contact with skin lesions	Rare
Ebola, Lassa, Marburg, Congo-Crimean, AHF, BHF	Contact with infective fluid, droplet?	High
Smallpox	Contact, droplet, airborne	High
Plaque (pneumonic)	Droplet	High
Q fever	Contact with infected	Rare

(Source: Viral Hemorrhagic Fever CDC. MMWR 2000;49(RR-4)

Acts of biological terrorism use various routes of exposure. Inhaled airborne agents may produce toxicity by introducing infection through the respiratory tract (e.g., anthrax, smallpox). Aerosolized agents may also be modified to produce skin injury (e.g., vesicants, corrosives). Finally, aerosolized agents can be designed for absorption through the skin with resulting systemic effects (e.g., VX and other viscous nerve agents). Ingestion of contaminated food or water is another important route of exposure.

Many biological agents are efficiently introduced via this route. For example, as few as 100 bacteria of *Shigella dysenteriae* can produce severe gastro intestinal infection. Early signs and symptoms of illness from biological weapons are often unrecognized by the primary health care professionals. For example, many biological agents initially cause only fever or a flu-like illness. The environmental toll of a biological toxin release can be comparable to that from nuclear explosion. Depending on the agent, local areas can become uninhabitable for days to months.

In the case of anthrax, the ability of the bacterium to sporulate can result in soil contamination by spores that remain viable for a period of thirty years (10,33-45).

The impact depends upon the seasonal prevalence of infection, virulence of strains used, population resistance and prior preparedness (2,3,5,6,8-21). [See table 1] In such a scenario the availability of essential drugs, vaccine, quarantine and trained personal are the first to be checked(27-51). Turning back to the influenza epidemic in early 1970s to mid-1990s, the average number of hospitalizations was 50 per 100,000 Americans per season (27-37). The number of deaths have been substantial during pandemics e.g.; 1918 Spanish flu, 218.4 deaths per 100,000 Americans; 1957 Asian flu, 22 deaths per 100,000 population; 1968 Hong Kong flu, 13.9 deaths per 100,000 population (32,34). Assessing the impact in monetary terms the direct costs [that include hospitalizations, 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 \$(40). Without a mass vaccination campaign, the cost of the next pandemic is projected to about 71.3 to 166.5 billion US \$ in 1995 [inpatient and outpatient care, self-treatment, and lost work days and wages] (27-31,41).

In recent years, wealthy nations have been stunned by outbreaks of food borne disease causing economic losses in the billions of dollars (11,28,36,38). Some experts place losses associated with the emergence of mad cow disease in Europe at close to \$38 billion. In New York in the early 1990s, the emergence of multidrug-resistant tuberculosis, with a death rate of up to 80%, incurred costs associated with the failure to prevent its spread estimated at over \$1 billion. In the Russian Federation, the re-emergence of tuberculosis, including multidrug-resistant forms, is estimated to have cost over \$4 billion in 1999 alone. Initial costs associated with cases of West Nile fever in New York have been placed at almost \$100 million (9,11,28,30,33,36).

## **EXPOSURE OF CHILDREN & ADULTS TO FATAL BIO-AGENTS**

The event of bio-terror attack carries a horrific physical and psychological impact on every individual. The safety of children is of greater concern. The release or exposure or contact of biological agent/ infectious patient would disproportionately affect children through several ways. With aerosolized agents (e.g., anthrax, sarin, or chlorine), the higher number of respirations per minute in children results in exposure to a relatively greater dosage. The high vapor density of gases places the highest concentration in the lower breathing zone of children.

The more permeable skin of newborns and children in conjunction with a larger surface-to-mass ratio results in greater exposure to transdermally absorbed toxicants. Children, because of their relatively larger body surface area, lose heat quickly when showered. Consequently, skin decontamination with water may result in hypothermia unless heating lamps and other warming equipment are used. Having less fluid reserve increases the risk of rapid dehydration or shock after vomiting and diarrhea (8,42,47,50,51,62,80).

Children have significant developmental vulnerabilities. Infants, and young children do not have the motor skills to escape and react from the site of a biological incident. Even if they are able to walk, they may not have the cognitive ability to decide in which direction to flee. The health care facilities responsible for treating children in a biological event could be overwhelmed. This situation differs

markedly from existing hospital disaster alert systems in which victims are triaged in the field and carefully distributed among available resources. Large-scale chemical-biological incidents necessitate the use of alternative health care sites, which requires that pediatric health care resources be dispersed to areas where victims could not receive optimal care. Injuries to health care professionals in both office and in-hospital settings would dramatically diminish available medical resources.

At the community level, planning for biological event begins with the development of local health resources. With chemical releases, unlike biological events, clinical effects can occur within minutes to hours, preventing the use of out-of-state resources (e.g., disaster medical assistance teams). Pediatric health care facilities need to develop protocols for isolation and decontamination of victims, mobilizing additional staff, and potentially using secondary care sites. Because children spend the majority of their day in school, community preparation for the chemical-biological threat should include the local educational system (62).

Plans for rapid evacuation or the identification of in-school shelters should be established. Schools may also become a necessary site for triage and treatment of pediatric casualties, requiring that community planning include this possibility. Decisions to be made after exposure to infectious agents are more difficult than those after exposure to chemical agents or toxins because symptomatic individuals are not likely to present for hours or days after exposure. Many experts suggest personal decontamination if the probability of a true exposure is high, as several infectious agents such as anthrax and smallpox can be transmitted via clothing and direct contact.

Antidotes, antibiotics, vaccines, and other pharmaceuticals have a key role in treatment and prophylaxis after chemical-biological events. Proper doses of many vaccines and antidotes have not been established for children. For many vaccines such as anthrax, efficacy in children are unstudied therefore preferred antibiotic therapies (e.g., tetracycline) generally are not used in children. Information including antidotes and decontamination strategies may be rapidly distributed by poison centers to hospitals, police, and the public. Proper preparation for a biological incident also involves care after the event, including the establishment of teams to evaluate the environment for reinhabitation, for mental health assessment of victims, and long-term epidemiologic assessment.

Pediatricians have an essential role in responding to psychosocial sequelae of a chemical-biological incident. Pediatricians should assist in the development of local critical incident stress management programs for children to manage the psychological effects of a chemical-biological disaster. Pediatricians (through continuing education) and pediatric trainees (through residency) should be educated in issues of pediatric disaster management, including the medical response to chemical-biological events (1-7,42,47,60,80).

## CHAPTER TWO

### ANTHRAX

Anthrax is an acute infectious disease caused by *Bacillus anthracis*, a spore forming, gram-positive bacillus. Anthrax has been widely and frequently used as a biological agent in the terror attacks in different times. The most recent anthrax attack in the USA after September 11, 2001 had 17 confirmed infections, 3 deaths (2 in Washington DC, 1 in Florida), 7 cases of skin anthrax, 7 ill with inhalation anthrax and around 13,300 postal workers took antibiotics as a protective measure. Health authorities speculate that there might be cases that could not be detected. However, the event has made it clear that this agent has gone into the hands of terrorists and future threats of similar attacks are very likely. The figure 2 & 3 show the epidemiology of anthrax in different parts of the world (1-6,10,12,14,20).

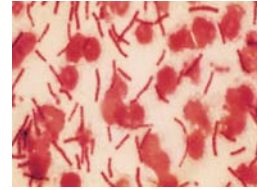
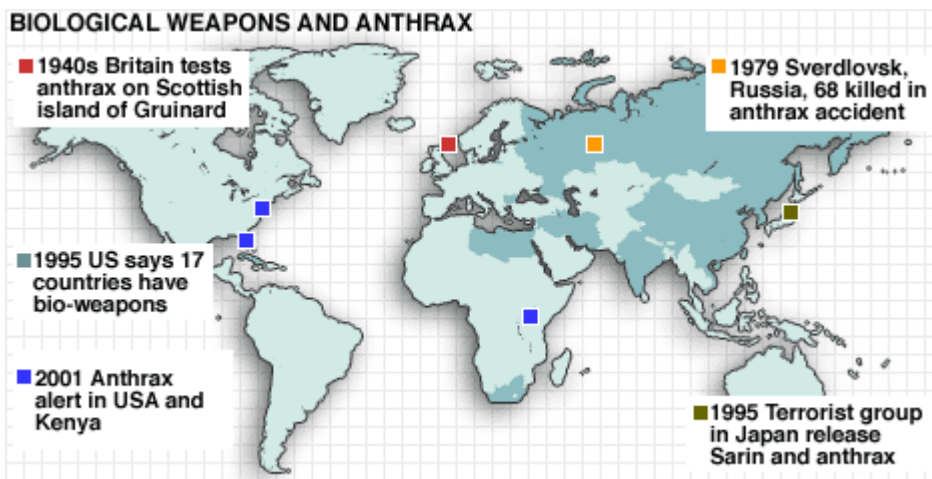
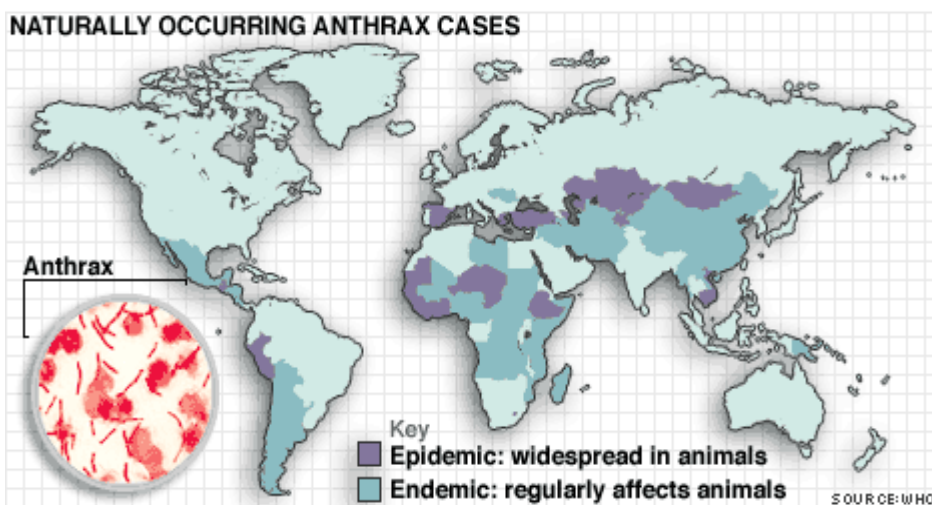


Figure 2 The Epidemiology of Anthrax Used as a Biological Weapon



Source: WHO 2001

Figure 3 The Global Epidemiology Of Anthrax



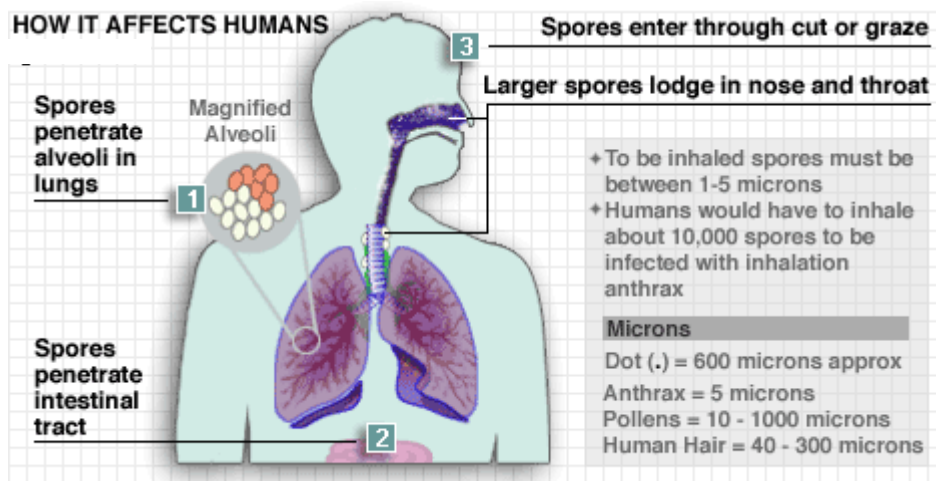
Anthrax associated disease occurs most frequently in sheep, goats, and cattle, which acquire spores through ingestion of contaminated soil. Humans can become

infected through skin contact, ingestion, or inhalation of *B. anthracis* spores from infected animals or animal products. Person-to-person transmission of inhalational disease does not occur. Direct exposure to vesicle secretions of cutaneous anthrax lesions may result in secondary cutaneous infection(1-6). Details of the similar outbreaks in the European region are given in chapter three.

### CLINICAL FEATURES

Human anthrax infection can occur in three forms: pulmonary, cutaneous, or gastrointestinal, depending on the route of exposure. Of these forms, pulmonary anthrax is associated with bioterrorism exposure to aerosolized spores. Clinical features of anthrax for each form vary. In the pulmonary form non-specific prodrome of flu-like symptoms follows inhalation of infectious spores. Two to four days after initial symptoms, abrupt onset of respiratory failure and hemodynamic collapse, possibly accompanied by thoracic edema and a widened mediastinum on chest radiograph suggestive of mediastinal lymphadenopathy and hemorrhagic mediastinitis. Gram-positive bacilli on blood culture, usually after the first two or three days of illness.

Figure 4 The Mechanism of Inhalational Anthrax



Treatable in early prodromal (*An early symptom indicating the onset of an attack or a disease*) stage. Mortality remains extremely high despite antibiotic treatment if it is initiated after onset of respiratory symptoms. Figure 4 illustrates the mechanism of the infection in human respiratory tract (1,2,8,10,12,14,22). In the cutaneous form there is local skin involvement after direct contact with spores or bacilli. Commonly seen on the head, forearms or hands. Localized itching, followed by a papular lesion that turns vesicular, and within 2-6 days develops into a depressed black eschar. Usually non-fatal if treated with antibiotics. In the gastro-intestinal form of anthrax abdominal pain, nausea, vomiting, and fever following ingestion of contaminated food, usually meat is frequently noticed.



There is bloody diarrhea; hematemesis and gram-positive bacilli can be identified on blood culture, usually after the first two or three days of illness. This form is usually fatal after progression to toxemia and sepsis. The spore form of *B. anthracis* is always viable. As a bioterrorism agent, it could be delivered as an aerosol. The modes of transmission for anthrax include inhalation of spores (see Figure 4 and table 3), cutaneous contact with spores or spore-contaminated materials or ingestion of contaminated food(1-6).

## **DIAGNOSIS**

Blood cultures and *B. anthracis*-specific polymerase chain reaction (PCR) of sterile fluids (e.g., blood and pleural fluid) are important in the diagnosis of inhalational anthrax. Serologic testing has also been valuable. An enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulin (Ig) G response to *B. anthracis* protective antigen (PA) is highly sensitive (detects 98.6% of true positives) but is only approximately 80% specific. To improve specificity, a PA-competitive inhibition ELISA is used as a second, confirmatory step. Preliminary studies indicate that specific IgG anti-PA antibody can be detected as early as 10 days, but peak IgG may not be seen until 40 days after onset of symptoms (1-6,40,42-46). Immuno-histochemical examination of pleural fluid or transbronchial biopsy specimens, using antibodies to *B. anthracis* cell wall and capsule, also has an important role in the diagnosis of inhalational anthrax, especially in patients who have received prior antibiotics. Immuno-histochemical examination can detect intact bacilli or *B. anthracis* antigens. The incubation period following exposure to *B. anthracis* ranges from 1day to 8 weeks (average 5days), depending on the exposure route and dose:

- 2-60 days following pulmonary exposure.
- 1-7 days following cutaneous exposure.
- 1-7 days following ingestion.
- Period of communicability

Transmission of anthrax infections from person to person is unlikely. Airborne transmission does not occur, but direct contact with skin lesions may result in cutaneous infection. Prevention is possible if done in time after exposure. Vaccine is available and is routinely administered to military personnel and those at risk. Due to risk of serious complications routine vaccination of civilian populations not recommended. Physical findings are non-specific. A widened mediastinum may be seen on chest x-rays (38,42,45,46).

## **TREATMENT**

Although effectiveness may be limited after symptoms are present, high dose antibiotic treatment with penicillin, ciprofloxacin, or doxycycline should be undertaken. Supportive therapy may be necessary. Treatment recommendations for anthrax infections have been based on historical information and limited data from animals (nonhuman primates), as well as in vitro findings. Susceptibility testing of 65 historical isolates was performed at CDC (40,42-46). In the absence of published guidelines for testing for *B. anthracis*, the standard National Committee for Clinical Laboratory Standards broth microdilution method was used with staphylococcal breakpoints. These 65 isolates and all those associated with the 2001 outbreak were sensitive to quinolones, rifampin, tetracycline, vancomycin, imipenem, meropenem, chloramphenicol, clindamycin, and the aminoglycosides.

The isolates have intermediate-range susceptibility to the macrolides but are resistant to extended-spectrum cephalosporins, including third-generation agents (e.g., ceftriaxone), and to trimethoprim-sulfamethoxazole.

Ciprofloxacin has been recommended on the basis of *in vivo* (animal) findings; other quinolones have not been studied in the primate model. Doxycycline, another first-line agent, should not be used if meningitis is suspected because of its lack of adequate central nervous system penetration. Bacteremic patients are often initially treated with a multidrug regimen. Thus, the recommendation for initial treatment of inhalational anthrax is a multidrug regimen of either ciprofloxacin or doxycycline along with one or more agents to which the organism is typically sensitive. After susceptibility testing and clinical improvement, the regimen may be altered. The drugs of choice for treatment of cutaneous disease are also ciprofloxacin or doxycycline. Amoxicillin or amoxicillin/clavulanic acid may be used to complete the course if susceptibility testing is supportive. Keys to successful management appear to be early induction of antibiotics and aggressive supportive therapy. Steroids have been used to control the oedema of cutaneous disease and have been suggested for the treatment of meningitis or substantial mediastinal edema. Other antitoxin agents investigated *in vitro* include angiotensin-converting enzyme inhibitors, calcium channel blockers, and tumor necrosis factor inhibitors (41-46).

Ciprofloxacin, doxycycline, and penicillin G procaine have been approved by the WHO for prophylaxis of inhalational *Bacillus anthracis* infection. During the recent bioterrorist attacks, interim CDC recommendations for anthrax prophylaxis included ciprofloxacin or doxycycline; amoxicillin (in three daily doses) is an option for children and pregnant or lactating women exposed to strains susceptible to penicillin, to avoid potential toxicity of quinolones and tetracyclines. Amoxicillin is not widely recommended as a first-line prophylactic agent, however, because of lack of WHO approval, lack of data regarding efficacy, and uncertainty about the drug's ability to achieve adequate therapeutic levels at standard doses. Public health officials on the basis of an epidemiologic investigation determine the need for prophylaxis. Prophylaxis is indicated for persons exposed to an airspace contaminated with aerosolized *B. anthracis* (1-6,40-46,49).

### **PROPHYLAXIS AGAINST ANTHRAX**

A licensed vaccine is available. Vaccine schedule is 0.5 ml SC at 0, 2, 4 weeks, then 6, 12, and 18 months for the primary series, followed by annual boosters. Oral ciprofloxacin or doxycycline for known or imminent exposure. Anthrax prophylaxis issues needing further consideration or research include efficacy of additional drugs, optimal duration of prophylaxis, usefulness of a loading dose, safety of prolonged drug use (especially in children and pregnant women), concomitant use of vaccine or antitoxin, level of infectious dose, and definition of high-risk exposure (e.g., according to particle size or degree of environmental contamination). For certain diseases or syndromes (e.g., smallpox and pneumonic plague), additional precautions may be needed to reduce the likelihood for transmission. Standard Precautions prevent direct contact with all body fluids (including blood), secretions, excretions, non-intact skin (including rashes), and mucous membranes. Standard precautions are designed to reduce transmission from both recognized and unrecognized sources of infection in healthcare

facilities, and are recommended for all patients receiving care, regardless of their diagnosis or presumed infection status.

Successful implementation of mass prophylaxis requires vaccination policy, clarity of public health intent and communication, as well as coordination and collaboration. Local health-care providers, employers, and employee organizations should be familiar with the policy. Local or regional task forces may be helpful in planning and communicating public health policy, and resolving jurisdictional issues. Prophylaxis teams should be predesignated to function around the clock. Team members should have contingency plans for personal needs (e.g., child care). Issues for the point of prophylaxis distribution include layout and management of traffic flow; security; availability of medical and office supplies, antibiotic and disease fact sheets, multilingual staff, and mental health counselors; legal needs (e.g., for a physician to write orders); and plans for follow-up, including assessment of adherence, illness, and possible drug adverse effects. Collaboration among health departments, health-care delivery organizations, and clinicians is important. In the 2001 outbreak, some patients with possible drug side effects were refused appointments by their private physicians and were referred back to the health department.

Standard precautions routinely practiced by healthcare providers include: Hands are washed after touching blood, body fluids, excretions, secretions, or items contaminated with such body fluids, whether or not gloves are worn. Hands are washed immediately after gloves are removed, between patient contacts, and as appropriate to avoid transfer of microorganisms to other patients and the environment. Clean, non-sterile gloves are worn when touching blood, body fluids, excretions, secretions, or items contaminated with such body fluids. Clean gloves are put on just before touching mucous membranes and non-intact skin. Gloves are changed between tasks and between procedures on the same patient if contact occurs with contaminated material (38,42,45-47).

Hands are washed promptly after removing gloves and before leaving a patient care area. A mask and eye protection (or face shield) are worn to protect mucous membranes of the eyes, nose, and mouth while performing procedures and patient care activities that may cause splashes of blood, body fluids, excretions, or secretions. A gown is worn to protect skin and prevent soiling of clothing during procedures and patient-care activities that are likely to generate splashes or sprays of blood, body fluids, excretions, or secretions. Selection of gowns and gown materials should be suitable for the activity and amount of body fluid likely to be encountered. Soiled gowns are removed promptly and hands are washed to avoid transfer of microorganisms to other patients and environments.

Principles of Standard Precautions should be generally applied for the management of patient-care equipment and environmental control. Each facility should have in place adequate procedures for the routine care, cleaning, and disinfection of environmental surfaces, beds, bedrails, bedside equipment, and other frequently touched surfaces and equipment, and should ensure that these procedures are being followed. Facility-approved germicidal cleaning agents should be available in patient care areas to use for cleaning spills of contaminated material and disinfecting non-critical equipment. Ideally, patients with bioterrorism-related infections will not be discharged from the facility until they are deemed

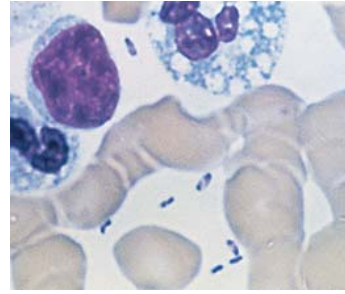
noninfectious. However, consideration should be given to developing home-care instructions in the event that large numbers of persons exposed may preclude admission of all infected patients. Depending on the exposure and illness, home care instructions may include recommendations for the use of appropriate barrier precautions, hand washing, waste management, and cleaning and disinfection of the environment. Triage and management planning for large-scale events may include establishing networks of communication and lines of authority required to coordinate onsite care.

In the post exposure management decontamination of patients and environment is essential. The risk for re-aerosolization of *B. anthracis* spores appears to be extremely low in settings where spores were released intentionally or were present at low or high levels. In situations where the threat of gross exposure to *B. anthracis* spores exists, cleansing of skin and potentially contaminated fomites (e.g. clothing or environmental surfaces) may be considered to reduce the risk for cutaneous and gastrointestinal forms of disease. Decontamination of patient exposed to anthrax include the following:

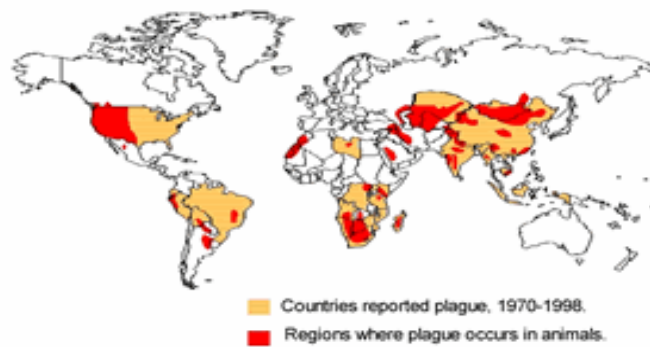
- Instructing patients to remove contaminated clothing and store in labelled, plastic bags. Handling clothing minimally to avoid agitation.
- Instructing patients to shower thoroughly with soap and water (and providing assistance if necessary).
- Instructing personnel regarding Standard Precautions and wearing appropriate barriers (e.g. gloves, gown, and respiratory protection) when handling contaminated clothing or other contaminated fomites.
- Decontaminating environmental surfaces using an EPA-registered, facility-approved sporicidal/germicidal agent or 0.5% hypochlorite solution (one part household bleach added to nine parts water).

## PLAGUE

Plague is an acute bacterial disease caused by the gram-negative bacillus *Yersinia pestis*, which is usually transmitted by infected fleas, resulting in lymphatic and blood infections (bubonic and septicemic plague). A bioterrorism-related outbreak may be expected to be airborne, causing a pulmonary variant, pneumonic plague. The World Health Organization reports globally 1,000 to 3,000 cases of plague every year. Most human cases in the United States occur in two regions of northern New Mexico, northern Arizona, and southern Colorado, and California, southern Oregon, and far western Nevada. Plague also exists in Africa, Asia, and South America (see CDC map (Figure 4) below). In certain areas around the world wild rodents are infected with plague. Outbreaks in people still occur in rural communities or in cities. They are usually associated with infected rats and rat fleas that live in the home. In the United States, the last urban plague epidemic occurred in Los Angeles in 1924-25 (1-6,16,21,22,25).



**Figure 5 Epidemiology of Plague**  
World Distribution of Plague, 1998



Unlike anthrax, pneumonic plague can be highly contagious, quickly infecting families or health care professionals. Untreated, plague carries a mortality as high as 100%.

## CLINICAL FEATURES

Clinical features of pneumonic plague include fever, cough, chest pain, hemoptysis, and muco-purulent or watery sputum with gram-negative rods on gram stain. Radiographic evidence of bronchopneumonia. Plague is normally transmitted from an infected rodent to man by infected fleas (see figure 5). Bioterrorism related outbreaks are likely to be transmitted through dispersion of an aerosol. Person-to-person transmission of pneumonic plague is possible via large aerosol droplets.

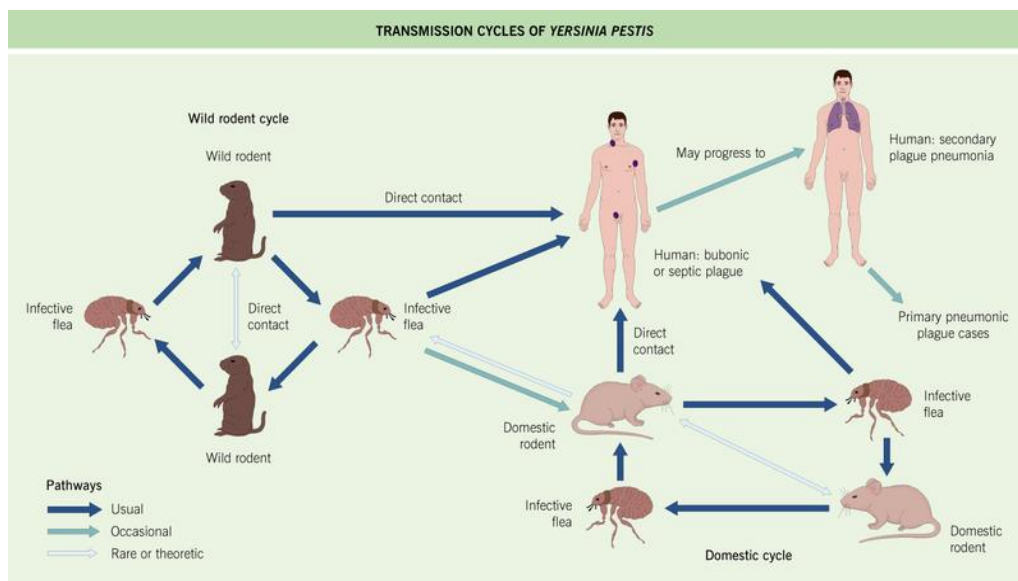


The incubation period for plague is normally 2 – 8 days if due to flea borne transmission. The incubation period may be shorter for pulmonary exposure (1-3 days). Patients with pneumonic plague may have coughs productive of infectious particle droplets. Droplet precautions, including the use of a mask for patient care, should be implemented until the patient has completed 72 hours of antimicrobial therapy (1-6).

### TREATMENT REGIMEN

There are two choices of antimicrobial agent for adults and children. The first contain Doxycycline-100 mg twice daily 5 mg per kg of body mass per day divided into two doses and the second choice contain Ciprofloxacin 500 mg twice daily 20-30 mg per kg of body mass daily, divided into two doses. Pediatric use of tetracyclines and flouroquinolones is associated with adverse effects that must be weighed against the risk of developing a lethal disease. Prophylaxis should continue for 7 days after last known or suspected *Y. pestis* exposure, or until exposure has been excluded. Facilities should ensure that policies are in place to identify and manage health care workers exposed to infectious patients. In general, maintenance of accurate occupational health records will facilitate identification, contact, assessment, and delivery of post-exposure care to potentially exposed healthcare workers (1,6,49).

**Figure 6 Pathways of Plague Transmission**



Source:WHO

### PREVENTION & PROPHYLAXIS

For prevention formalin-killed vaccine exists for bubonic plague, but has not been proven to be effective for pneumonic plague. Immunization is recommended. Routine vaccination requires multiple doses given over several weeks and is not recommended for the general population. Post-exposure immunization has no utility. Symptomatic patients with suspected or confirmed plague should be managed according to WHO guidelines. Recommendations for specific therapy are beyond the scope of this document. (Please See recommended websites). For pneumonic plague, droplet precautions should be used in addition to standard precautions. Droplet precautions are used for patients known or suspected to be infected with microorganisms transmitted by large particle droplets, generally larger

than in size, that can be generated by the infected patient during coughing, sneezing, talking, or during respiratory-care procedures. Droplet precautions require healthcare providers and others to wear a surgical-type mask when within 3 feet of the infected patient. Based on local policy, some healthcare facilities require a mask be worn to enter the room of a patient on Droplet

Droplet Precautions should be maintained until patient has completed 72 hours of antimicrobial therapy. Patients suspected or confirmed to have pneumonic plague require Droplet Precautions. Infected patient should be kept in a private room. Cohort in symptomatic patients with similar symptoms and the same presumptive diagnosis (i.e., pneumonic plague) when private rooms are not available. Maintaining spatial separation of at least 3 feet between infected patients and others when cohorting is not achievable. Avoiding placement of patient requiring Droplet Precautions in the same room with an immuno-compromised patient. Cleaning, disinfection, and sterilization of equipment and environment Principles of Standard Precautions should be generally applied to the management of patient-care equipment and for environmental control (1-6,51).

Generally, patients with pneumonic plague would not be discharged from a healthcare facility until no longer infectious (completion of 72 hours of antimicrobial therapy) and would require no special discharge instructions. In the event of a large bioterrorism exposure with patients receiving care in their homes, home care providers should be taught to use standard and droplet Precautions for all patient care. In situations where there may have been gross exposure to *Y. pestis*, decontamination of skin and potentially contaminated fomites (e.g. clothing or environmental surfaces) may be considered to reduce the risk for cutaneous or bubonic forms of the disease. While decontaminating patients should be instructed to remove contaminated clothing and store it in labeled plastic bags. Instructing patients to shower thoroughly with soap and water (and providing assistance if necessary).

Advance planning should include identification of sources for appropriate masks to facilitate adherence to Droplet Precautions for potentially large numbers of patients and staff. Instruction and reiteration of requirements for Droplet Precautions (as opposed to Airborne Precautions) will be necessary to promote compliance and minimize fear and panic related to an aerosol exposure. Laboratory confirmation of plague is by standard microbiologic culture, but slow growth and misidentification in automated systems are likely to delay diagnosis. In diagnostic samples serum for capsular antigen testing, blood cultures and sputum or tracheal aspirates for Gram's, Wayson's, and fluorescent antibody staining is done (40-44).

## SMALLPOX

Smallpox is highly fatal and transmissible infection and, is one of the most serious bioterrorist threats to the civilian population (1-3,6,17,18). Smallpox was once worldwide in scope; before vaccination was practiced almost everyone eventually contracted the disease. The epidemiology of smallpox can be traced back to 1754-1767 when it was used as a biological weapon during the French-Indian wars in the United States. British soldiers gave the Indians blankets that had been used by smallpox patients (60). Covert attempts and programs to weaponize various biological agents in various countries across the globe came under debate of international community. In 1972, more than 140 countries signed the Biological and Toxin Weapons Convention, which called for cessation of offensive biological weapons research and development followed by the destruction of existing biological stocks. Despite participating in the 1972 convention, the former Soviet Union continued to expand its biological-weapons program. During that time, the Soviet Union reportedly developed weaponized variola virus that could be mounted in intercontinental ballistic missiles and bombs for strategic use (53,56,59).



*(New Yorkers queue up outside the Morrisania Hospital in the Bronx, awaiting vaccination. During a smallpox outbreak in the city in 1947, some six million New Yorkers were vaccinated)*

A recent report from the Center for Nonproliferation Studies suggests that a 1971 outbreak of smallpox in Kazakhstan involving 10 people (three of whom died) may have resulted from an open-air test of a Soviet smallpox biological weapon on Vozrozhdeniye Island in the Aral Sea (a top-secret Soviet bioweapons testing site) (43). Currently, variola virus is known to be stored in two facilities (at the CDC in Atlanta and at the Russian State Centre for Research on Virology and Biotechnology, Koltsovo, Novosibirsk Region, Russian Federation).

In the early 1980s, WHO recommended that all existing stocks of variola virus held in other countries be either destroyed or shipped to one of the two WHO-approved collaborating centers. However, there has been no systematic way to assure that all countries actually did comply with the WHO recommendations (Henderson 2001). Also, there is no way to be certain that the virus has not fallen into the hands of rogue nations or potential terrorists (53,56,60,61). On several occasions, WHO has recommended that the remaining stores of variola virus be destroyed (56). Smallpox is of concern as a biological weapon for several reasons as world's population is susceptible to infection, the virus carries a high rate of morbidity and mortality, vaccine is not yet available for general use, and past experience has demonstrated that introduction of the virus creates a great deal of

havoc and panic (50,58). Looking smallpox in the historical perspectives the first efforts at smallpox vaccination involved a process called variolation, which was the deliberate cutaneous inoculation of variola virus via infectious material obtained from smallpox pustules of a patient with active disease. Variolation was practiced as early as 1000 AD in China and gradually spread around the globe. Variolation generally resulted in a severe localized reaction, a generalized rash, and constitutional symptoms. The case-fatality rate following variolation was much lower than that following natural smallpox (about 0.5% to 2% and 20% to 30%, respectively) and, therefore, this practice was widely implemented (1-3,6,17,18,50,53,58).

### **SUSCEPTIBILITY TO SMALLPOX**

Children are no longer being immunized and more than 80% of the adult population and 100% of children are susceptible to the virus. Smallpox produces a characteristic centrifugal rash consisting of vesicles with umbilicated centers. The rash, once familiar to clinicians, is now unlikely to be recognized quickly and can be mistaken for varicella. Reported mortality from smallpox ranges from 3% to 30%, respectively, in individuals who have or have not been immunized. In 1980, the World Health Assembly announced that smallpox had been eradicated and recommended that all countries cease vaccination. An aerosol release of smallpox virus would disseminate readily given its considerable stability in aerosol form and epidemiological evidence suggesting the infectious dose is very small. Even as few as 50-100 cases would likely generate widespread concern or panic and a need to invoke large-scale, perhaps national emergency control measures. Several factors fuel the concern: the disease has historically been feared as one of the most serious of all pestilential diseases; it is physically disfiguring and there is no treatment; it is communicable from person to person (44,49,51,56,57). (See manifestations below)



### **CLINICAL MANIFESTATION**

Acute clinical symptoms of smallpox resemble other acute viral illnesses, such as influenza. Skin lesions appear (rash), quickly progressing from macules to papules to vesicles. Other clinical symptoms to aid in identification of smallpox include: 2-4 day, non-specific prodrome of fever, myalgias. The rash most prominent on face and extremities (including palms and soles) in contrast to the truncal distribution of varicella. rash scabs over in 1-2 weeks. In contrast to the rash of varicella, which arises in “crops,” variola rash has a synchronous onset. Transmission is possible via

both large and small respiratory droplets. Patient-to-patient transmission is likely from airborne and droplet exposure, and by contact with skin lesions or secretions. Patients are considered more infectious if coughing or if they have a hemorrhagic form of smallpox. The incubation period for smallpox is 7-17 days; the average is 12 days. Period of communicability. Unlike varicella, which is contagious before the rash is apparent, patients with smallpox become infectious at the onset of the rash and remain infectious until their scabs separate (approximately 3 weeks).

## TREATMENT

Treatment for smallpox largely consisted of general supportive measures which include Adequate fluid intake (difficult because of the enanthem) Alleviation of pain and fever. Keeping the skin lesions clean to prevent bacterial superinfection. No specific antiviral treatment of demonstrated effectiveness was available in the pre-eradication era. In recent years, 274 antiviral compounds have been screened for therapeutic activity against variola virus and other orthopoxviruses (57). Cidofovir as well as 27 other compounds have demonstrated activity against orthopoxviruses, including variola. In advanced clinical testing for other viral infections, cidofovir, adefovir dipivoxil, cyclic cidofovir, and ribavirin have shown significant in vitro activity (54). All promising compounds will be further evaluated in animal models.

## PROPHYLAXIS

Edward Jenner a British physician, in the late 1700s, successfully used cowpox virus to vaccinate people against smallpox. As this practice was safer and effective, it rapidly gained wide acceptance and replaced variolation as the primary method of conferring protection against smallpox. Over time, vaccinia virus gradually replaced cowpox virus as the agent used in smallpox vaccine. Vaccinia virus is genetically distinct from cowpox virus, although its origin remains unknown. It may have been derived from cowpox virus initially and modified over time through serial passage in laboratory cultures, or it may represent another orthopoxvirus that is now extinct in nature (CDC). A live-virus intradermal vaccination is available for the prevention of smallpox. Vaccination against smallpox does not reliably provide lifelong immunity and previously vaccinated persons are considered susceptible to infection again.



For patients with suspected or confirmed smallpox, both Airborne and contact precautions should be used in addition to standard precautions. Airborne precautions are used for patients known or suspected to be infected with microorganisms transmitted by airborne droplet nuclei (small particle residue, smaller in size) of evaporated droplets containing microorganisms that can remain suspended in air and can be widely dispersed by air currents. Airborne Precautions require healthcare providers and others to wear respiratory protection when entering the patient room. Contact Precautions are used for patients known or suspected to be infected or colonized with epidemiologically important organisms

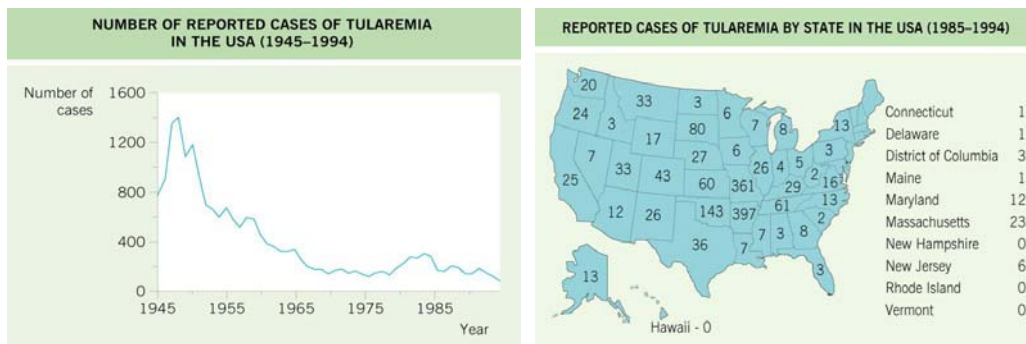
that can be transmitted by direct contact with the patient or indirect contact with potentially contaminated surfaces in the patient's care area. Contact precautions require healthcare providers and others to wear clean gloves upon entry into patient room. Wear gown for all patient contact and for all contact with the patient's environment. Gown must be removed before leaving the patient's room. Wash hands using an antimicrobial agent.

Patients suspected or confirmed with smallpox require placement in rooms that meet the ventilation and engineering requirements for Airborne Precautions, which include: Monitored negative air pressure in relation to the corridor and surrounding areas. 6 – 12 air exchanges per hour. Appropriate discharge of air to the outdoors, or monitored high efficiency filtration of air prior to circulation to other areas in the healthcare facility. A door that must remain closed. Healthcare facilities without patient rooms appropriate for the isolation and care required for Airborne Precautions should have a plan for transfer of suspected or confirmed smallpox patients to neighboring facilities with appropriate isolation rooms. Patient placement in a private room is preferred. However, in the event of a large outbreak, patients who have active infections with the same disease (i.e., smallpox) may be cohorted in rooms that meet appropriate ventilation and airflow requirements for Airborne.

Limit the movement and transport of patients with suspected or confirmed smallpox to essential medical purposes only. When transport is necessary, minimize the dispersal of respiratory droplets by placing a mask on the patient, if possible. Cleaning, disinfection, and sterilization of equipment and environment. A component of Contact Precautions is careful management of potentially contaminated equipment and environmental surfaces. Post-exposure immunization with smallpox vaccine (vaccinia virus) is available and effective. Vaccination alone is recommended if given within 3 days of exposure. Passive immunization is also available in the form of vaccinia immune-globulin (VIG) (0.6ml/kg IM). If greater than 3 days has elapsed since exposure, both vaccination and VIG are recommended. Vaccination is generally contraindicated in pregnant women, and persons with immunosuppression, HIV-infection, and eczema, who are at risk for disseminated vaccinia disease. However, the risk of smallpox vaccination should be weighed against the likelihood for developing smallpox following a known exposure (54,57,62-65).

## TULEREMIA

*Francisella tularensis*, is the organism that causes tularemia. It is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to cause disease (19). *Francisella tularensis* is a hardy non-spore forming organism that is capable of surviving for weeks at low temperatures in water, moist soil, hay, straw or decaying animal carcasses. *F. tularensis* has been divided into two subspecies: *F. tularensis* biovar *tularensis* (type A), which is the most common biovar (*A group of infra-sub specific of bacterial strains distinguishable from other strains of the same species on the basis of physiological characters. Formerly called biotype*) isolated in North America and may be highly virulent in humans and animals; *F. tularensis* biovar *palearctica* (type B) which is relatively avirulent and thought to be the cause of all human tularemia in Europe and Asia. Tularemia is a zoonosis. Natural reservoirs include small mammals such as voles, mice, water rats, squirrels, rabbits and hares. Naturally acquired human infection occurs through a variety of mechanisms such as: bites of infected arthropods; handling infectious animal tissues or fluids; direct contact or ingestion of contaminated water, food, or soil; and inhalation of infective aerosols. *F. tularensis* is so infective that examining an open culture plate can cause infection (19). (see epidemiological-maps below). Description on recent outbreaks of tularemia in Europe is given in chapter 3.



## EPIDEMIOLOGY OF TULEREMIA

Tularemia was first described as a plague like disease of rodents in 1911 and, shortly thereafter, was recognized as a potentially severe and fatal illness in humans. Tularemia's epidemic potential became apparent in the 1930s and 1940s, when large waterborne outbreaks occurred in Europe and the Soviet Union and epizootic-associated cases occurred in the United States. As well, *F. tularensis* quickly gained notoriety as a virulent laboratory hazard. Public health concerns impelled substantial early investigations into tularemia's ecology, microbiology, pathogenicity, and prevention. *Francisella tularensis* has long been considered a potential biological weapon. It was one of a number of agents studied at Japanese germ warfare research units operating in Manchuria between 1932 and 1945; it was also examined for military purposes in the West. A former Soviet Union biological weapons scientist, Ken Alibek, has suggested that tularemia outbreaks affecting tens of thousands of Soviet and German soldiers on the eastern European front during World War II may have been the result of intentional use (1-7,19,25,47,54,58).

Following the war, there were continuing military studies of tularemia. In the 1950s and 1960s, the US military developed weapons that would disseminate *F. tularensis* aerosols; concurrently, it conducted research to better understand the

pathophysiology of tularemia and to develop vaccines and antibiotic prophylaxis and treatment regimens. In some studies, volunteers were infected with *F tularensis* by direct aerosol delivery systems and by exposures in an aerosol chamber. By the late 1960s, *F tularensis* was one of several biological weapons stockpiled by the US military. According to Alibek, a large parallel effort by the Soviet Union continued into the early 1990s and resulted in weapons production of *F tularensis* strains engineered to be resistant to antibiotics and vaccines.

In 1969, a World Health Organization expert committee estimated that an aerosol dispersal of 50 kg of virulent *F tularensis* over a metropolitan area with 5 million inhabitants would result in 250 000 incapacitating casualties, including 19 000 deaths. Illness would be expected to persist for several weeks and disease relapses to occur during the ensuing weeks or months. It was assumed that vaccinated individuals would be only partially protected against an aerosol exposure. Referring to this model, the Centre for Disease Control and Prevention (CDC) recently examined the expected economic impact of bioterrorist attacks and estimated the total base costs to society of a *F tularensis* aerosol attack to be \$5.4 billion for every 100 000 persons exposed (19,47,58).

The largest recorded airborne tularemia outbreak occurred in 1966-1967 in an extensive farming area of Sweden (5,7,14). This outbreak involved more than 600 patients infected with strains of the milder European biovar of *F tularensis* (*F tularensis* biovar *palaeartica*) [type B]), most of whom acquired infection while doing farm work that created contaminated aerosols. In the aforementioned Swedish outbreak, conjunctivitis was reported in 26% of the 140 confirmed cases and an infected ulcer of the skin was reported in nearly 12%; pharyngitis was reported in 31% and oral ulcers in about 9% of the cases; and 32% of these patients had various exanthemas, such as erythema multiforme and erythema nodosum. Tularemia outbreaks arising from similar agricultural exposures have been reported from Finland, mostly presenting with general constitutional symptoms rather than specific manifestations of pneumonia; enlargement of hilar nodes was the principal radiographic finding in these cases. The most recent outbreak of tularemia was recorded in Kosova in 1999-2000 (68). Details given in chapter 3.

It is considered to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death. During World War II, the potential of *F. tularensis* as a biological weapon, was studied by the Japanese as well as by the US and its allies. Tularemia was one of several biological weapons that were stockpiled by the US military in the late 1960's, all of which were destroyed by 1973(6,19,47,54,58). The Soviet Union continued weapons production of antibiotic and vaccine resistant strains into the early 1990s. A large outbreak of tularemia occurred in Kosovo in the early postwar period, 1999-2000. Epidemiological and environmental investigations were conducted to identify sources of infection, modes of transmission, and household risk factors. A total of 327 serologically confirmed cases of tularemia pharyngitis and cervical lymphadenitis were identified in 21 of 29 Kosovo municipalities. Weaponized by the United States military during the biologic offensive program in the 1950s-1960s. Aerosolized *F. tularensis* would cause typhoidal tularemia (a nonspecific, febrile illness), with high mortality rates (30-60%) if untreated. During

an act of bioterrorism, release of an aerosol will be the most likely route of transmission with typhoidal tularemia the most likely clinical presentation.

### CLINICAL MANIFESTATION

There are several different classification systems for clinical tularemia. The most straightforward classifies tularemia into ulceroglandular (75% of patients) and typhoidal (25% of patients). Ulceroglandular disease involves lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 cm, or both. In typhoidal tularemia, the lymph nodes are usually smaller than 1 cm and no skin or mucous membrane lesions are present. This form is more commonly associated with pneumonia and has a higher mortality rate. In the natural setting, tularemia is noted to be a predominately rural disease with clinical presentations including ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal and septic forms(19,47,58).



Aerosol dissemination of *F. tularensis* in a populated area would be expected to result in the abrupt onset of large numbers of cases of acute, non-specific febrile illness beginning 3 to 5 days later (incubation range, 1-14 days), with pleuropneumonitis developing in a significant proportion of cases over the ensuing days and weeks. Without antibiotic treatment, the clinical course could progress to respiratory failure, shock and death. The overall mortality rate for severe Type A strains has been 5-15%, but in pulmonic or septicemic cases of tularemia without antibiotics treatment the mortality rate has been as high as 30-60%. An illness characterized by several distinct forms, including the following:

- Ulceroglandular (cutaneous ulcer with regional lymphadenopathy)
- Glandular (regional lymphadenopathy with no ulcer)
- Oculoglandular (conjunctivitis with preauricular lymphadenopathy)
- Oropharyngeal (*stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy*)
- Intestinal (intestinal pain, vomiting, and diarrhea)
- Pneumonic (primary pleuropulmonary disease)
- Typhoidal (febrile illness without early localizing signs and symptoms)

People can get tularemia in many different ways, such as through the bite of an infected insect or other arthropod (usually a tick or deerfly), handling infected animal carcasses, eating or drinking contaminated food or water, or breathing in *F. tularensis*. Symptoms of tularemia could include sudden fever, chills, headaches, muscle aches, joint pain, dry cough, progressive weakness, and pneumonia. Persons with pneumonia can develop chest pain and bloody spit and can have trouble breathing or can sometimes stop breathing. Other symptoms of tularemia depend on how a person was exposed to the tularemia bacteria. These symptoms can include ulcers on the skin or mouth, swollen and painful lymph glands, swollen and painful eyes, and a sore throat.

People who have been exposed to *F. tularensis* should be treated as soon as possible. The disease can be fatal if it is not treated with the appropriate antibiotics.

Clinical diagnosis is supported by evidence or history of a tick or deerfly bite, exposure to tissues of a mammalian host of *Francisella tularensis*, or exposure to potentially contaminated water. Laboratory criterion for diagnosis is elevated serum antibody titer(s) to *F. tularensis* antigen (without documented fourfold or greater change) in a patient with no history of tularemia vaccination or detection of *F. tularensis* in a clinical specimen by fluorescent assay, confirmatory, isolation of *F. tularensis* in a clinical specimen and fourfold or greater change in serum antibody titre to *F. tularensis* antigen.

### **TREATMENT OPTIONS**

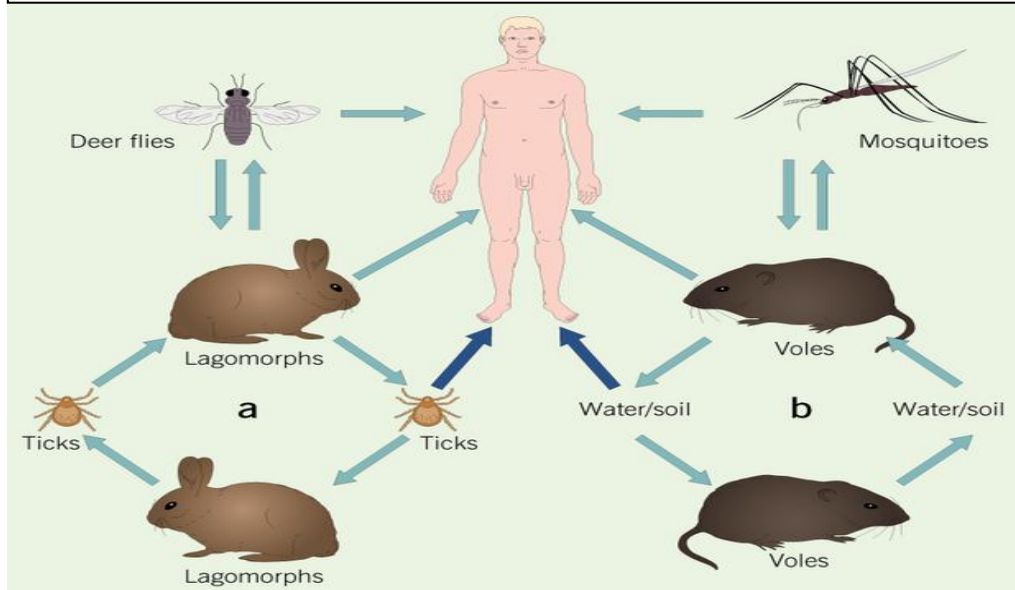
The treatment of choice for all forms of tularemia except meningitis is streptomycin; gentamicin is an acceptable alternative. For both drugs, dosages must be adjusted for renal insufficiency. Gentamicin is safe during pregnancy; avoid streptomycin due to its association with irreversible deafness in children exposed in utero. Streptomycin: Adult dosage is 0.5-1.0 gm (7.5 mg/kg) intramuscularly every 12 hours for 10-14 days. In very sick patients, streptomycin may be given with a dose of 15 mg/kg intramuscularly every 12 hours for 10-14 days. Pediatric dose is 15 mg/kg intramuscularly every 12 hours for 10-14 days. Among the alternatives are the antibiotics is Gentamicin which is given 3-5 mg/kg/day intravenously or intramuscularly in three divided doses, with a peak serum level of at least 5 ug/ml desirable. Continue for 10-14 days. Tetracycline and chloramphenicol are bacteriostatic and associated with high relapse rates. These agents must be continued for a minimum of 14 days. 2 grams /day IV of Tetracycline or orally in four divided doses or doxycycline 100 mg IV or orally twice a day for at least 14 days. With treatment, the most recent mortality rates in the US have been 2%. Aminoglycosides, macrolides, chloramphenicol and fluoroquinolones have each been used with success in the treatment of tularemia (1-7,19,25,47,54,58).

### **PROPHYLAXIS**

A live attenuated vaccine was developed that partially protected against respiratory and intracutaneous challenges with the virulent SCHU S-4 strain of *F. tularensis*, and various regimens of streptomycin, tetracyclines, and chloramphenicol were found to be effective in prophylaxis and treatment. In the United States, a live-attenuated vaccine derived from the avirulent Live Vaccine Strain (LVS) has been used to protect laboratory personnel routinely working with *F. tularensis*. Given the short incubation period of tularemia and incomplete protection of current vaccines against inhalational tularemia, vaccination is not recommended for post-exposure prophylaxis. Given the lack of human-to-human transmission, isolation is not recommended for tularemia patients. Simple, rapid and reliable diagnostic tests that could be used to identify persons infected with *F. tularensis* in the mass exposure setting need to be developed. Research is also needed to develop accurate and reliable procedures to rapidly detect *F. tularensis* in environmental samples. The diagnosis of tularemia requires a high index of suspicion since the disease often presents with very nonspecific symptoms. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings and pharyngeal exudates. Since the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis.

The bacteria grow slowly; some strains may require up to 2-3 weeks to develop visible colonies. Antibody detection assays include tube agglutination, microagglutination and ELISA. A single titre (by tube agglutination) of > 1:160 is a presumptive positive; a four-fold rise is required for a definitive serologic diagnosis. ELISA and micro agglutination tests may be more sensitive than tube agglutination. Serology testing is available through national reference laboratories. Tularemia is the third most commonly reported laboratory-associated bacterial infection. Cases have occurred among clinical laboratory technicians working with bacterial cultures. Laboratory staff handling specimens from persons who are suspected of having tularemia must wear facemasks with eye protection, surgical gloves, protective gowns, and shoe covers especially when working with pure bacterial cultures. Laboratory tests (*such as serological examinations and staining of impression smears*) can be performed in high biological safety .

**Figure 7 Life Cycles of Francisella Tularensis** (Source:WHO)

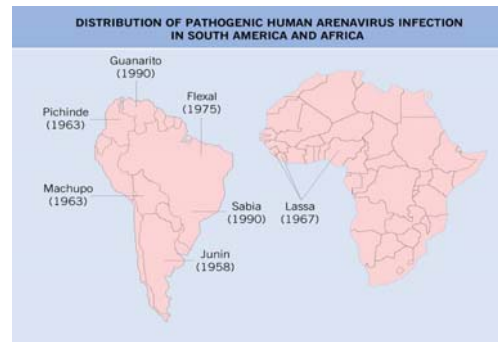


Tularemia is not transmissible from person-to-person. Standard precautions should be followed for all patients. Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as *F. tularensis* can be isolated from such lesions for one month or longer. There is no vaccine for tularemia. The best way to protect yourself is to avoid tick-infested areas and contact with potentially infected animals. You may reduce your risk of tularemia by taking the following precautionary measures: Avoid areas where ticks are likely to be found. The type of tick most likely to carry the tularemia germ is the common dog tick. Ticks cling to vegetation and are most numerous in brushy, wooded or grassy habitats.

They are not found on open sandy beaches, but may be found in grassy dune areas. Isolation is not recommended for tularemia patients, given the lack of human-to-human transmission. In hospitals, standard precautions are recommended by the working group for treatment of patients with tularemia. Microbiology laboratory personnel should be alerted when tularemia is clinically suspected. Routine diagnostic procedures can be performed in biological safety conditions. Examination of cultures in which *F. tularensis* is suspected should be carried out in a biological safety cabinet (19,54,55).

## HEMORRHAGIC FEVER VIRUS

Ebola haemorrhagic fever (EHF) is one of the most virulent viral diseases known to humankind, causing death in 50-90% of all clinically ill cases. Ebola hemorrhagic fever (Ebola HF) is a severe, often-fatal disease in humans sporadically since its initial recognition in 1976 (1-7). The disease is caused by infection with Ebola virus, named after a river in the Democratic Republic of the



Congo (formerly Zaire) in Africa, where it was first recognized. The virus is one of two members of a family of RNA viruses called the Filoviridae. There are four identified subtypes of Ebola virus. Three of the four have caused disease in humans: Ebola-Zaire, Ebola-Sudan, and Ebola-Ivory Coast (1,6,21,2344,47,50). The fourth, Ebola-Reston, has caused disease in nonhuman primates, but not in humans. Hemorrhagic fever viruses (HFVs) are a diverse group of organisms, each of which belong to one of four distinct families:

1. Filoviridae: Ebola and Marburg viruses
2. Arenaviridae: Lassa fever virus and a group of viruses referred to as the New World arenaviruses
3. Bunyaviridae: Crimean Congo hemorrhagic fever virus, Rift Valley fever virus, and a group of viruses known as the 'agents of hemorrhagic fever with renal syndrome'
4. Flaviviridae: dengue, yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease virus.

The natural reservoir of the Ebola virus seems to reside in the rain forests of Africa and Asia, but has not yet been identified. Different hypotheses have been developed to try to explain the origin of Ebola outbreaks. Initially, rodents were suspected, as is the case with Lassa fever whose reservoir is a wild rodent (*Mastomys*). Another hypothesis is that a plant virus may have caused the infection of vertebrates. Laboratory observation has shown that bats experimentally infected with Ebola do not die and this has raised speculation that these mammals may play a role in maintaining the virus in the tropical forest. The Ebola virus was first identified in a western equatorial province of Sudan and in a nearby region of Zaire (now Democratic Republic of the Congo) in 1976 after significant epidemics in Yambuku, northern Zaire, and Nzara, southern Sudan (54).

Hemorrhagic fever viruses are all capable of causing a clinical diseases associated with fever and bleeding disorder, classically referred to as viral hemorrhagic fever (VHF). None of these viruses occurs naturally in the United States. Risk factors for these diseases include travel to certain geographic areas where these diseases may naturally occur (such as certain areas of Africa, Asia, the Middle East, and South America), handling of animal carcasses, contact with sick animals or people with the disease, and arthropod bites. The subset of these viruses pose particularly serious threats as biological weapons, based on, among other characteristics, their infectious properties, morbidity and mortality, transmissibility by way of aerosol dissemination, and prior research and development as biological weapons (1-7).

Between June and November 1976 the Ebola virus infected 284 people in Sudan, with 117 deaths. In Zaire, there were 318 cases and 280 deaths in September and October. An isolated case occurred in Zaire in 1977, a second outbreak in Sudan in 1979. In 1989 and 1990, a filovirus, named Ebola-Reston, was isolated in monkeys being held in quarantine in laboratories in Reston (Virginia), Alice (Texas) and Pennsylvania, United States of America. In the Philippines, Ebola-Reston infections occurred in the quarantine area for monkeys intended for exportation, near Manila(1-7,54).



(Electron micrograph of Ebola virus)

Ebola-related filoviruses were isolated from cynomolgus monkeys (*Macacca fascicularis*) imported into the United States of America from the Philippines in 1989. A number of the monkeys died and at least four persons were infected, although none of them suffered clinical illness. A large epidemic occurred in Kikwit, Zaire in 1995 with 315 cases, 244 of which had fatal outcomes. One human case of Ebola haemorrhagic fever and several cases in chimpanzees were confirmed in Côte d'Ivoire in 1994-95. In Gabon, Ebola haemorrhagic fever was first documented in 1994 and outbreaks occurred in February 1996 and July 1996. Ebola virus infections were not reported again until the autumn of 2000 when an outbreak occurred in northern Uganda. Excluding the most recent outbreak, approximately 1,500 cases with slightly over 1,000 deaths have been documented since the virus was discovered (1-7,23,50,54).

Several different forms of Ebola virus have been identified and may be associated with other clinical expressions, on which further research is required. The incubation period is from 2 to 21 days. The Ebola virus is transmitted by direct contact with the blood, secretions, organs or semen of infected persons. Transmission through semen may occur up to seven weeks after clinical recovery, as with Marburg haemorrhagic fever. (80). Health care workers have frequently been infected while attending patients. In the 1976 epidemic in Zaire, every Ebola case caused by contaminated syringes and needles died (23,44,47,50).

### **CLINICAL MANIFESTATION & DIAGNOSIS**

The onset of illness is abrupt and is characterized by fever, headache, joint and muscle aches, sore throat, and weakness, followed by diarrhea, vomiting, and stomach pain. A rash, red eyes, hiccups and internal and external bleeding may be seen in some patients. Researchers do not understand why some people are able to recover from Ebola HF and others are not. However, it is known that patients who die usually have not developed a significant immune response to the virus at the time of death. Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, IgM ELISA, polymerase chain reaction (PCR), and virus isolation can be

used to diagnose a case of Ebola HF within a few days of the onset of symptoms. Persons tested later in the course of the disease or after recovery can be tested for IgM and IgG antibodies; the disease can also be diagnosed retrospectively in deceased patients by using immunohistochemistry testing, virus isolation, or PCR. These tests present an extreme biohazard and are only conducted under maximum biological containment conditions. No specific treatment or vaccine exists for Ebola haemorrhagic fever. Severe cases require intensive supportive care, as patients are frequently dehydrated and in need of intravenous fluids. Experimental studies involving the use of hyper-immune sera on animals demonstrated no long-term protection against the disease after interruption of therapy (1-7,21,44,47,50,54,80).

Suspected cases should be isolated from other patients and strict barrier nursing techniques practiced. All hospital personnel should be briefed on the nature of the disease and its routes of transmission. Particular emphasis should be placed on ensuring that high-risk procedures such as the placing of intravenous lines and the handling of blood, secretions, catheters and suction devices are carried out under barrier nursing conditions. Hospital staff should have individual gowns, gloves and masks. Gloves and masks must not be reused unless disinfected. Patients who die from the disease should be promptly buried or cremated.

As the primary mode of person-to-person transmission is contact with contaminated blood, secretions or body fluids, any person who has had close physical contact with patients should be kept under strict surveillance, i.e. body temperature checks twice a day, with immediate hospitalization and strict isolation recommended in case of temperatures above 38.3°C (101°F). Casual contacts should be placed on alert and asked to report any fever. Surveillance of suspected cases should continue for three weeks after the date of their last contact. Hospital personnel who come into close contact with patients or contaminated materials without barrier nursing attire must be considered exposed and put under close supervised surveillance (1-7,21,44,47,50,54,80).

## CHAPTER THREE

### MAJOR EPIDEMIOLOGICAL EVENTS IN EUROPE

Coupled with conventional burden of infectious diseases Europe has widely witnessed a number of newly emerging diseases in the past. Ranging from the rapidly emerging resistant myco-bacterium to the recent exotic diseases like SARS, influenza and tularemia a brief account of these infectious diseases is given in the following. Various theories exist which appeared to have contribution to this reemerging state of rare diseases, which include climate changes, human manipulation of plant and animal food and genetics, increasing travel of humans and some animals (especially animals used for food), as well as deliberate introduction as in the case of bio-terrorism. In most imported infectious diseases the origin or the source of initial infection is not known as not every country in the EU has the standardized facilities to prevent, mitigate, and to develop prompt response to any biological emergencies (9,27-31,65-73).

### INFLUENZA

History suggests that influenza pandemics have occurred three times i.e., in 1918, 1957, and 1968 (1-7,32,33-37). The unforgettable Spanish Flu [1918-1919], made almost 1 billion people sick and killed 21 to 40 million (18,32,37). 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 (1-7). Europe was never a influenza free zone and was engulfed repeatedly 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 health system. The swiftness of the outbreak was long a 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 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 population expansion of current times.

In 1997, avian influenzavirus was shown to infect humans directly when an influenza virus A/H5N1 infected 18 people in Hong Kong; of those, six died (75,76). After this event, experts predicted that another influenza pandemic is highly likely, if not inevitable (77,78). The impact of a pandemic depends on factors such as the virulence of the pandemic virus and the availability of a vaccine. Because development is time-consuming, the vaccine would likely not be available in the early stages of a pandemic, and a major vaccine shortage would be expected (6). An influenza virus pandemic would likely cause substantial social disruption because of high rates of illness, sick leave, hospitalization, and death. Therefore, pandemic planning is essential to minimize influenza-related illness, death, and social disruption (79,80).

The economic effects of an influenza pandemic have been estimated (37). Meltzer et al. examined the possible effects of influenza vaccine-based interventions in terms of outpatient visits, hospitalizations, deaths, and related costs during a pandemic in the United States. More recently, different strategies for the control of inter-pandemic influenza for the elderly population in three European countries (England and Wales, France, and Germany) have been evaluated (81). 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 (27-37,44,47,67,73). It is stated that the morbidity rates due to the influenza-like illness (ILI) reached to 951 cases in Belgium and 136 cases of per 100 000 population in the Netherlands. Whether this trend continues to be the case during the forthcoming influenza season, remains to be seen (82,83).

### **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 (1-7,9). It has long been considered a potential biological weapon and was one of agents studied at the Japanese germ warfare research units operating in Manchuria between 1932 and 1945 (19,47,50,54,58,68). 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 (1-7,9,19,50). 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 (19,47,50,54,58,68).

A large outbreak of tularemia occurred in Kosovo in the early postwar period, 1999-2000 (68). Epidemiologic and environmental investigations were conducted to identify sources of infection, modes of transmission, and household risk factors. Case and control status was verified by enzyme-linked immunosorbent assay, Western blot, and microagglutination assay. A total of 327 serologically confirmed cases of tularemia pharyngitis and cervical lymphadenitis were identified in 21 of 29 Kosovo municipalities. Matched analysis of 46 case and 76 control households suggested that infection was transmitted through contaminated food or water and that the source of infection was rodents. Environmental circumstances in war-torn Kosovo led to epizootic rodent tularemia and its spread to resettled rural populations living under circumstances of substandard housing, hygiene, and sanitation (68).

### **ANTHRAX**

Anthrax caused the most serious biological outbreak named "Black Bane" that swept Europe in the 1600s (1-7,12,20,38,40). It killed at least 60,000 people and many more domestic and wild animals. The horror continued till the World War 1 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 (10). 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 (10). 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 (20,21,38-46).

## **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 (1-7,16,21,22,25). Millions of people in Europe died from plague in the Middle Ages, when human homes and places of work were inhabited by flea-infested rats. Today, modern antibiotics are effective against plague, but if an infected person is not treated promptly, the disease is likely to cause illness or death. The plague 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 (40-44,49,51).

## **WEST NILE VIRUS & DIPHTHERIA**

In spite of modern surveillance several localized outbreaks have been witnessed in the European region (9,27,28). 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 (6,27,28,82). Environmental factors that include human activities enhance vector population densities. Conditions like irrigation, heavy rains & floods, and higher temperature climate create massive breeding places for mosquitoes, which facilitate the transmission of infection (98-100). 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 (98). Evidence has proved that the inadequate herd immunity to diphtheria can lead to outbreaks (98).

## **SYPHILIS OUTBREAKS**

In the Eastern European block, the resurgence of drug resistant syphilis associated with tuberculosis is widely reported (6,66,67,72,82-84,100). 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 the HIV/AIDS, syphilis epidemic is closely associated with hepatitis B and C infection

in the region (6). Localised by several outbreaks the number of cases of infectious syphilis in England were more than doubled between 1998 and 2000. These outbreaks reflect unsafe sexual practices in England and signify also the altered immunity status, changes in sexual behaviour, the level and effectiveness of intervention, or random fluctuations in the composition of the population(84). They also emphasise the importance of sustained multidisciplinary public health action in this area, according to research published (66,67,72,82-84,100).

Four other outbreaks of infectious syphilis were witnessed in Bristol, Manchester, Brighton, and the area including Peterborough and North Cambridgeshire between January 1997 and January 2002. The investigation and control of the outbreaks included enhanced surveillance of patients at clinics for genitourinary medicine (GUM), notification of partners, increased efforts to raise awareness, communication with health professionals, increased level of GUM services, and targeted promotion of sexual health to groups identified as at risk. The importance of identifying and investigating sexual networks and involving local voluntary agencies in the delivery of targeted health promotion was emphasised.

The diagnosis was made on the basis of clinical symptoms, by finding *Treponema pallidum* in material from syphilitic lesions in dark field microscopy, and serological testing. Such outbreaks are difficult to detect as the timescales within which outbreaks may be detected, investigated, and controlled may be longer than those for other outbreaks. To speed up the process, access to clinic services needs to be improved and partner notification is essential. In this context, a new pilot initiative recently funded by the European Commission (European Surveillance of Sexually Transmitted Infections, ESSTI) aims to work towards achieving coordinated STI surveillance across Europe through setting up a network of collaborating countries.

The project is being carried out by the PHLS Communicable Disease Surveillance Centre with the Institut de Veille Sanitaire (InVS) in France, Smittskyddsinstitutet (the Swedish Institute for Infectious Disease Control, SMI), and epidemiology and microbiology collaborators from 11 other European Union (EU) member states and Norway. The establishment of ESSTI may help to improve our understanding of the distribution and determinants of this resurgence. The proposed ESSTI early warning system will also help to identify similar outbreaks in hitherto unaffected areas. Ultimately, surveillance data must inform public health action and the ESSTI network should play a key role in increasing dialogue and avoiding duplication of resources and efforts across EU states (84).

### **SMALLPOX IN SWEDEN**

Sweden-Stockholm was declared a smallpox infected area on 16<sup>th</sup> May, 1963. (85). The outbreak was recognized on May 13 when the diagnosis of smallpox was first suspected. The disease was sufficiently mild in nature that medical care was not sought. The only fatality to date occurred in the second patient who apparently suffered an acute hemorrhagic form of the disease, diagnosed as smallpox in retrospect. This outbreak is of unique interest in that it represents one of the few epidemics in Western nations in recent years not evidencing a predominant spread among hospital contacts. Immunization campaign among hospital personnel presumably have changed the pattern of hospital spread observed in other recent outbreaks. Four additional cases of smallpox had been identified in Stockholm

with onsets of illness on May 18. All four presumably acquired their disease as a result of hospital contact. The outbreak (85) affecting total 16 cases, with three generations of transmission following the importation of smallpox by a seaman who presumably acquired his disease in transit through Southeast Asia.

Sweden was the first major country to eliminate indigenous smallpox, a distinction it achieved in 1895 (62). This outbreak was the first appearance of imported smallpox there since 1932, except for a single case in 1945 (63). Infecting 25 persons over six indigenous generations of transmission, this was one of the largest such outbreaks in Europe (which had two other imported outbreaks in 1963, four in 1962, and 10 in 1961, for example) after 1958 (64). Despite Sweden's active vaccination efforts among hospital personnel, eight of the indigenous cases were acquired by hospital staff or patients; most of the remainder were infected by face-to-face contact in the homes of case-patients. However, the versatile virus apparently also spread in this one outbreak from a corpse, from laundry of another case-patient, and by remote airborne exposure, and its clinical presentation ranged from six cases (among persons with old vaccinations) who did not develop a rash at all to at least one hemorrhagic case.

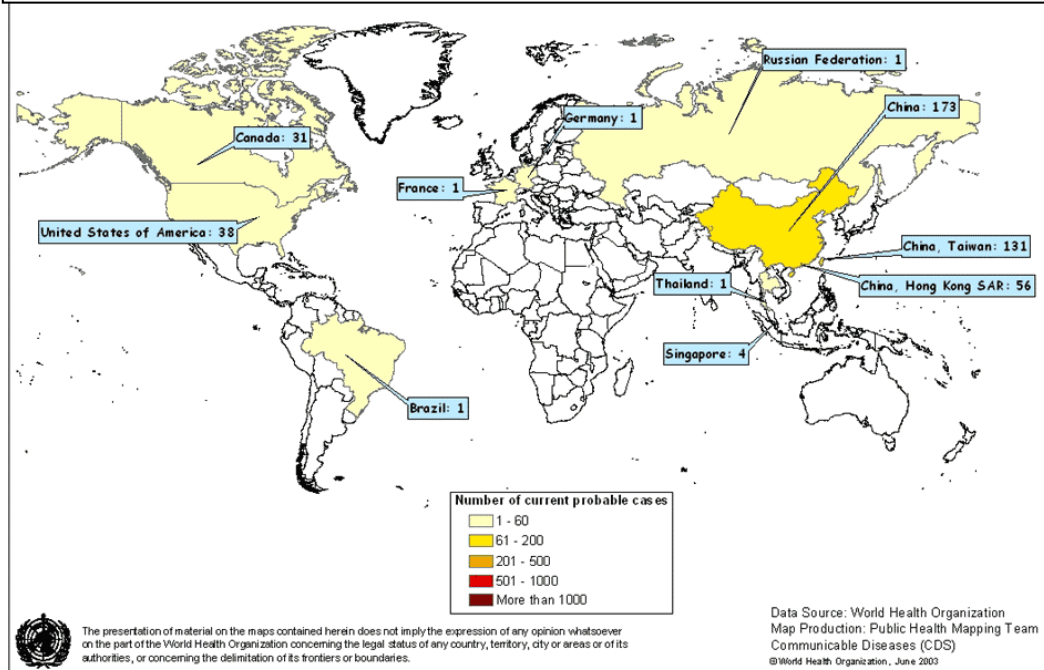
This outbreak also highlighted the potential danger posed to all other humans as long as smallpox existed anywhere on the planet. Even discounting the unknown, apparently chance encounter by which the index patient in this outbreak came to be infected, the capricious nature of many of the subsequent encounters that resulted in indigenous cases in Sweden is breathtaking. The painful lesson was not lost on Sweden, which contributed almost \$16 million to the global Smallpox Eradication Program, beginning in 1967, making it the second largest donor after the United States (64). Sweden's generosity was especially important during the final battles against smallpox in India, Bangladesh, and Somalia (65).

### **SEVER ACUTE RESPIRATORY SINDROME (SARS)**

SARS is a newly emerged and poorly understood respiratory syndrome with high fatality and high transmission rate. Reported to WHO in late February, 2003, the deadly SARS virus (corona virus) primarily detected in Guangdong-China, has rapidly become an international public health threat. SARS cases were reported along the routes of international travelling. Still currently in progress SARS has crossed the borders of 30 countries on five continents in a fairly short period of time and caused cumulative 8461 cases and more than 804 deaths since the index case.

During the Outbreak WHO-Europe office on SARS alert provides regular updates that include both the results of WHO conducted investigations as well as those reported to the global outbreak alert and response network. According to the latest WHO reports large number of SARS cases were detected widely across Europe. Prompt containment and stringent public health measures of the European commission and individual countries greatly helped to limit the spread of infection. However, trans-rapid international traveling and covert local transmission have brought the virus to several European countries like Germany (10), France (7), Finland (1), Italy (9), Ireland (1), Spain (1), Romania (1), Sweden (3), Switzerland (1), UK (4), and Bulgaria (1) have reported SARS cases (86). (See epidemiology of SARS below)

Figure 8 Epidemiology of SARS (June, 2003, source: WHO)



## CHAPTER FOUR

### **PREPAREDNESS AGAINST INTENTIONAL EPIDEMICS**

Preparedness is integral for an effective response and establishing control interventions and has several related vital dimensions. Preparedness envisages entire health system from physician's preparedness, hospital preparedness, laboratory and diagnostics preparedness to the public health preparedness. Network of communication and media utilisation is considered an important element to make all operations successful in case of any infectious emergency. Adequate epidemiological intelligence on the natural behavior of infectious diseases facilitate identifying of an unusual event and greatly contribute in determining whether suspicions of a intentional cause should be traced (2,6,9,20,27-32).

In such instances public health system will be at the front line throughout the response in first to detect infective cases and alert the community. Preparedness for the intentional use of a bio-agent requires collaboration of the intelligence community, law enforcement agencies, public health professionals, and the biomedical sciences. Surveillance pertains to routine vigilance on monitoring diseases with a high burden, tracing outbreaks of epidemic-prone diseases, and detecting newly emerging diseases(4,6).

There is a low risk that bio-agents will be used deliberately to induce diseases and deaths in the European region(9,27,32). However, the consequences are potentially so great as to make it prudent for health authorities to prepare how to address such an emergency in their national response to other challenges to public health. Preparedness measures can reassure public safety and reduce panic in the event of a intentional biological release. Historical precedent further suggests that the risk of a deliberate release is considerably reduced by the existence of an effective ability to respond to and manage an incident.

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 co-ordination and communication between the medical and public health sectors at all levels. Preparedness plans should, therefore, be developed using risk-management principles. The relative priority of these threat should be accorded by comparing them with others public health risks. The preparedness to deliberate releases can be greatly increased by strengthening the public health infrastructure.

The targeting by countries in their preparation of a limited but well chosen group of agents will help facilitate coordinated planning efforts involving national and local emergency response and public health services. There is the need, therefore, to develop objective criteria for selecting these agents in order to identify priorities. In response to increasing requests from Member States for technical advice on how to improve preparedness to possible releases of biological and chemical weapons to cause harm, WHO has been strengthening its activities in this field: information on these actions is available at the following Web address: [http://www.who.int/emc/deliberate\\_epi.html](http://www.who.int/emc/deliberate_epi.html) (1,2,6)

## **PREPAREDNESS MILE STONES IN THE EUROPEAN REGION**

The WHO Regional Office for Europe, in close coordination with the EU has begun to negotiate and implement activities for preparedness against the natural, accidental and deliberate release of biological, chemical and radiological agents. These programs work in close collaboration with a variety of national and international organizations. To harmonize regional plans for enhanced surveillance and preparedness, a consensus meeting was held in Grottaferrata, Italy, in April 2000. Twenty-eight Member States from central and eastern Europe and the former Soviet Union made 36 recommendations for long-term investments in the strengthening of communicable disease surveillance (9).

A second regional meeting, described in this report, held on 6-8 February 2000 in Lyon, France, was jointly organized by the WHO Regional Office for Europe and the WHO Communicable Disease Surveillance and Response Office in Lyon (73,74,87). The Meeting on "Natural and Intentional Epidemic Risks in Europe: Strengthening Alert Mechanisms" allowed countries that attended the first regional meeting in 2000 to review progress. It also allowed discussions on ways to strengthen national and international capacities for early detection and response to health threats, including those due to deliberate use of biological agents.

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 intentional epidemics or 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(9,72-74,82). The meeting in Ottawa on the 7<sup>th</sup> 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 (7,27-28,31,72,73,74). Preparedness began since WHO urged every nation to make a pandemic plan [influenza] for the first global outbreak of the 21<sup>st</sup> century (31,32). European Influenza Surveillance Scheme [EISS] was established in 1996 that helps to reduce and abolish the burden of influenza across Europe (31,32). 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 (71-74).

Prior preparedness of health system is crucial to respond effectively to the threats of infectious agents either emerging naturally or intentionally released in the European continent. Unprecedented fatalities were evident from the previous outbreaks and epidemics 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 a bio-terrorist events are considered vital before designing any intervention (1-7). Outbreaks and epidemics provided 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 (5,6,8). Generally it has been observed that poor reporting and surveillance can bring fatal delays to timely respond.

The most vivid example in this regard 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 (86). Preoccupied with vast patient loads, health care providers are unable to register cases quickly and prevent further spread (1-7,18,20). 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 the 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 lasts several days (2,13,20,29). 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 "died" and the disease had spread throughout the United States and to other countries (29).

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 co-ordinated. The facilities for vaccine production exist in only a limited number of Member States (9,27-28,32,69-74).

## **COUNTRY SPECIFIC INFECTION ALERT OPERATIONS**

There are some country specific progresses made in establishing a routine infection alert operations across Europe. Over the last two years the European Regional Office has played a significant role in bringing more and more European experts together towards a common goal. With regard to September 11, 2001 anthrax event and threats on the intentional use of biological agents the European Regional office has undertaken several activities to both analyse and respond to such risk to the health of the The Grottaferrata Meeting held in April 2000 set the scene for strengthening national surveillance, early warning, epidemic preparedness and response in the European Region. The objectives were to develop a common language for an integrated, action oriented, surveillance system, streamline support to national surveillance and response, and promote communication, cooperation and coordination between countries.

The meeting particularly recommended five areas for strengthening; surveillance and early warning, epidemic preparedness and response, capacity building, networking, and partnerships among the member states. Kyrgyzstan, Moldova, Romania have taken steps to reform their epidemic surveillance network, so that more cost-effective prevention and control programmes can be launched. Follow-up missions to all the three countries have been carried out with a view to the development of a national plan of action. These countries are in the process of revising the national guidelines and case definitions based on WHO criteria. Several preparatory courses and knowledge transfere workshops have been carried out, notably second-generation surveillance for HIV-AIDS-STI, on the role of laboratories in infectious disease surveillance (87).

The Regional Office of Europe (WHO/EURO) has developed a Computerized Information System for Infectious Diseases (CISID), which is their first database that can be accessed through the Internet both for data entry and data queries. Collaboration and coordination with other regional and international organizations has improved, notably a joint consultation of WHO-HQ on BSE and with WTO on revision of the international health regulations. WHO-European office has formualted an inter-departmental Task Force on Biological, Chemical and Nuclear Warfare to effectively coordinate and respond to the Member States in case of an emergency and also to improve early warning system (72-74,82,87).

WHO has cooperated with a number of countries in outbreak response, especially in Kosovo (tularaemia), Tajikistan (control of rodents), and an international outbreak of leptospirosis involving cases from several countries, diphtheria outbreak in Latvia, among others. WHO/EURO has coordinated an informal international consultation on ways to explore partnership and technical guidance for the development of opportunities in applied epidemiology training and increase the pool of international experts from Member States.

During 2001 a surveillance network, comprising 17 Central, Southern and Eastern European countries, as well countries from the Baltic states (CCEE-Baltic) was created. These countries have agreed to form an electronic network to reinforce mutual collaboration, coordination and communication on infectious disease surveillance and control. Partnership has been strengthened with a number of other partners, notably the United States Agency for International Development (USAID)for HIV, TB control and vaccination programs, the World Bank,

Department For International Development agency (DFID) from the United Kingdom as well as the Open Society Institute of the Soros Foundation. WHO/EURO has a partnership and cooperation with the Task Force for control of infectious diseases in the Baltic Region, a project created by the Nordic Council of Ministers among the nine Nordic and Baltic countries and the North-West of the Russian Federation.

In November 2001, a WHO consultation on Prevention and Management of Substance Terrorism against Water Services was attended by over 30 specialists in this area. A final report will be available in the near future. During 13–14 December 2001 the Second Futures Forum for High Level Decision Makers took place in WHO's Regional Office in Copenhagen. Focus of the meeting was to discuss the cooperation against terrorism and to assess the risks associated with a biological attack and to identify the necessary planning, service and communication arrangements required to ensure timely and adequate response (87).

The EU has carried out a survey on the preparedness of countries for bioterrorism. Bioterrorist threats in Europe were hoaxes and should be considered as a “preparedness exercise” from which three lessons can be drawn; because of inadequate preparedness planning and funding arrangements, Europe was not ready in October 2001 to respond to bioterrorism. Although European institutes quickly reacted and adapted their priorities to a new type of threat, they need an adequate and sustained support from national governments to maintain their overall capacity. The recent crisis demonstrated the need for an increased investment in epidemiology training programs and the establishment of a technical coordination unit for international surveillance and outbreak response with the European Union. Governments need to invest in European public health institutes to maintain sustained capacity.

### **France**

The Lyon meeting for the first time highlighted issues like level of preparedness and individual progress made by each country in the region. Country,s experts and representatives presented their current situation, discussed gaps and shortcomings of the health system. As depicted by the reform of the surveillance system adaptation of national surveillance systems in France to meet European Union requirements need some legal, organizational, and structural transformations. The European network for surveillance is coordinated by the European Commission Directorate General SANCO through a network committee constituted of two members per country.

There is a need to further strengthen coordination within the EU, as well as with other agencies and institutions such as WHO, and projects such as the International Health Regulations revision and implementation. France is one of several countries that have stocks of smallpox virus and can produce the vaccine. In October 2001, the French Ministry of Health asked the Institut de Veille Sanitaire (InVS) for its recommendations to setting up a plan to fight the event of an intentional release of biological agents by taking into consideration the epidemic risk and the side effects of the vaccine on various vaccination scenarios. A benefit/risk assessment of various vaccination scenarios, including vaccination of the whole French population, was carried out to evaluate the severity of a terrorist action threat.

The analysis concluded that at the stage where no specific threat exists, vaccination campaign did not seem to be justified. Even in the case of a real threat, the vaccination of frontline healthcare personnel, and in particular of contacts of cases, must be given priority. While planning vaccination the estimates of the incidence of side effects should be considered carefully, because of diverging data in the literature on the frequency of post-vaccination complications, reflection of different methods, and quality of surveys. Massive preventive vaccination without any significant recognised threat is not recommended. Even in the case of a recognised threat, large scale vaccination, which is likely to be demanded, would lead to the occurrence of severe side effects in populations at no special risk of exposure. Moreover, it would raise the concern of vaccine shortage, stocks of which could be insufficient for targeted vaccination around suspected or confirmed cases, in the event of ongoing transmission. Vaccination of contacts of a case constitutes the most efficacious and efficient vaccination strategy considered, provided it is implemented rapidly (88).

### **Kyrgyzstan**

The World Bank has been playing a key role in strengthening surveillance efforts in countries like Kyrgyzstan. As a matter of fact bioterrorism is a threat that requires strong national surveillance and early warning systems. Laboratory systems need to be harmonised to correspond to those in the EU. Priorities identified so far in Kyrgyzstan include the improvement of existing surveillance and response systems, improving networks, and elaboration of standards for surveillance and control, strengthening of quality controlled laboratory, and regulatory documents.

### **Moldova**

After evaluating the national surveillance system, identified gaps in disease prioritisation for early warning and routine surveillance, lack of standards for surveillance, outdated laboratory methods and inadequate capacity. A task force of experts has been created to determine priorities, develop standard protocols and guidelines, integrated forms, and assignment of roles and responsibilities for each level.

### **Romania**

After and in-depth evaluation supported by WHO/EURO, WHO/HQ and partners, have identified development of standards, strengthening of the Early Warning Systems, and sharing of information and comparable data as priorities. Elaboration of a national plan of action bringing together key players in the country from various levels is envisaged.

### **Germany**

The creation of a new law on surveillance systems in Germany has resulted in a reduction in the number of reported diseases, clearly identified laboratory reported diseases, and regulated fast track reporting. Diseases are immediately reported to the EU network and WHO. The Robert Koch Institute has developed the "SurvNet" surveillance software for data management. The new surveillance system is more responsive for early warning of diseases. For massive prophylactic measures Germany has stockpiled about six million doses of smallpox vaccine in 2001 that will be ready for the use in case of an outbreak. The stockpile enables to vaccinate less than 10% of its citizens in an emergency situation(89).

## **Poland**

In Poland, a special group for IRBA has been formed. This group examines the preparedness of the country in terms of the capacity of hospitals to accommodate massive infectious disease casualties, the laboratory capacity to diagnose potential agents for bioterrorism, coordination of services, vaccines and stockpiles, as well as border issues. Recommendations have been made with regards to the characterisation of agents, procedures in case of IRBA management of suspected mail, notification and cooperation systems, reference laboratories, and safety procedures.

## **The Russian Federation**

The Russian Federation has laws relating to bio-terrorism with a federal commission, replicated at regional and local levels. Public Health and medical response is enhanced through epidemiological capacity building for outbreak investigation including those of unknown origin, laboratory capacity, medical management, training and education and information and communication.

## **Sweden**

In Sweden three basic steps for preparedness to bio-emergencies have been implemented. First, build on existing structures for surveillance and control, second, emergency planning integrated into ordinary, everyday systems, third, Cooperation between sectors with different areas of responsibility. All sectors involved in routine surveillance and control of infectious diseases also have clearly defined responsibilities in emergencies. Just as in routine mode, response to emergencies is coordinated by the National Board of Health and Welfare. A special centre for microbiological preparedness was created two years ago, with four main areas of work, notably, the development of diagnostics, epidemiology database and response team, research into molecular virology, and high-isolation patient care.

## **Turkey**

Except military plans and teams, there is no official national specific preparedness for intentional release biological agent and response plan in Turkey. In case of a threat or actual event, based within the Ministry of Health, temporary teams are established. These teams cover 24 hours, 7 days a week, with 12 hour shifts. They are responsible for central coordination/supervision of provincial health authorities and mobile teams, data collection, daily analysis, reporting and response. From the recent experiences in Turkey, lessons learnt include the need for a flexible multi-sectoral national response plan, a central crisis response team, and a number of well trained and well equipped, mobile field teams.

## **NETWORK OF SURVEILLANCE IN THE BALTIC STATES (CCEE)**

It was WHO's main aim to create a global surveillance system that has been facilitating the development of a "network of networks" by linking together existing local, regional, national and international networks of laboratories and medical or surveillance centres into a super surveillance network. In the European Region, 51 Member States need to be connected in the future, but for the time being only one sub-regional network actually works in a systematic manner. Since December 2000, the countries of central and eastern Europe (CCEE) and the Baltic States have met and reiterated to communicate surveillance data on infectious disease within the 17 country participants. To date, two specific

networks have been proposed by the CCEE-Baltics collaboration: an early warning and response system, and a surveillance network for measles elimination, including a weekly reporting system.

To improve information sharing and monitoring of communicable diseases, the Communicable Disease Surveillance and Response (CSR) Programme and the Informatics Support unit (ISS) of the WHO Regional Office for Europe have developed the Computerized Information System for Infectious Diseases (CISID–<http://cisid.who.dk>). CISID eventually aims to monitor some infectious diseases by first (and in some cases, second) administrative level within the European Region, and provide a detailed description of clusters of cases by time, place and person. The WHO Regional Office for Europe acts as secretariat to the CCEE-Baltics Network, supports the Network meetings, and gives technical assistance towards realization of an Internet-based solution (87).

This system enables to communicate information of potential threats to public health to other network members in a secure and unofficial forum. The content of messages posted to the network are stored in the secure area of the CCEE-Baltics Network on the CISID Server located at the WHO Regional Office for Europe in Copenhagen, Denmark. All messages and replies are accessible only by registered members. Members of the CCEE-Baltics network are entitled to freely post messages to the network or reply to messages posted by others. The EU has currently put in place mechanisms to cooperate with the CCEE and NIS member States in developing effective programmes to combat communicable diseases. PHARE is able to provide financial assistance to partner countries until they reach the stage where they assume the obligations of membership. Priorities are economic infrastructure, social infrastructure and services, institution building, strengthening of democratic institutions and public administration.

### **EARLY WARNING AND RESPONSE MEASURES**

A global response and early alert system facilitates rapid and rational responses in the event of intentionally induced outbreak or epidemic. Such networks exist now at Global level (WHO) as well as at the regional or country level (WHO-EU). This network ensures that the necessary laboratory and epidemiological skills are on alert, since the call-out for natural outbreaks at the global level is almost daily. It provides the mechanisms for sharing experiences, available facilities, and staff. In responding to the threat of deliberately caused outbreaks, a global system of surveillance and response helps to ensure how to collaborate in managing a shared threat.

This network disseminates the news of international concern and are communicated to the international community as the event unfolds, enhancing vigilance for similar cases elsewhere. Investigating rumours, verifying genuine events, and providing assistance in a systematic fashion. The Global Alert and Response Network (GOARN) was established in 1999 (90). It is a technical partnership representing the pooled resources of 72 institutions and existing networks, focused on rapid identification, characterisation and containment of epidemic threats. The network ensures coordinated mechanisms for outbreak alert and response, complements and strengthens existing networks and relationships. WHO has long been concerned for the public health consequences of biological.

The Global Outbreak Alert and Response Network under development since 1997 interlinks over 100 existing networks (90). Together, these possess much of the data, expertise, and skills needed to keep the international community constantly alert and ready to respond. The network, which was formalized in April 2000, is supported by several new mechanisms and a computer driven tool for real-time gathering of disease intelligence. This tool, the Global Public Health Intelligence Network, heightens vigilance by systematically crawling web sites, news wires, local online newspapers, public health email services, and electronic discussion groups for rumours of outbreaks.

In this way, WHO is able to scan the world for informal news that gives cause for suspecting an unusual event. Formal sources of information, linked together in the network, include government and university centres, ministries of health, academic institutions, other UN agencies, networks of overseas military laboratories, and nongovernmental organizations having a strong presence in epidemic-prone countries. Information from all these sources is assessed and verified on a daily basis. Validated information is made public via the WHO web site (90).

Beefing up surveillance and early warning channels has become a priority of the day in the European region. In order for the public health systems of Member States to be able to address the increasing challenges posed by intentionally caused epidemics there is an urgent need for a strong political commitment at the highest national and international levels matched by the provision of adequate resources. In addition, the need for close collaboration and coordination among countries is essential to meet these challenges. No country can ever guarantee the total security of its population against a biological attack, especially when a contagious agent is used.

As seen with naturally caused outbreaks of SARS, the harm is delivered by invisible, highly mobile, microscopic agents that easily cross borders, placing all countries at risk (86). The consequences whether in the form of cases of disease or waves of panic can quickly spread in a highly mobile, interconnected, and electronically linked world. As some recently published scenarios indicate, the deliberate release of variola virus in a single country would be followed by the spread of the virus, incubating in travellers, to other countries days or even weeks before suspicions of an outbreak are aroused. The 22 infections and 5 deaths caused by the deliberate distribution of anthrax in the US resulted in the prescribing of antibiotics to over 32 000 persons, while rumours and hoaxes occupied emergency and law enforcement services throughout the world.

In collaboration with countries and partners, WHO has developed a four-phased model for strengthening national surveillance, early warning and response systems. This model views all communicable disease surveillance and response systems in countries as being part of a national surveillance system, and as such promotes strengthening in an integrated manner for greater effectiveness and efficiency.

This model for integrated disease surveillance consists of carrying out a critical review of the capacity of existing surveillance and response systems to effectively and efficiently achieve their objectives, and promotes the rational use of resources between systems. The second phase consists of developing a national plan of action to deal with gaps identified, address priority reform needs and design

efficient surveillance systems. The third phase is the implementation of reforms, through strengthening of the core functions of surveillance (data collection, confirmation, transmission, analysis and interpretation and use) providing standards, strengthening communication systems, laboratory strengthening, training and disease specific interventions.

The last phase of this model is monitoring and evaluation of the implementation of the reform. The CSR/Lyon office supports biosafety activities in countries that are building their laboratory capacity and epidemiological training. Its main activities focus on laboratory and epidemiology strengthening. The laboratory capacity building has so far focused on 7 countries in the African Region and currently on 7 countries in the Eastern Mediterranean region. The next cohort would be from Eastern European Countries. Support to the Training Programs in Epidemiology and Public Health Interventions Network (TEPHINET), and to the Field Epidemiology Training Programs (FETPs) are also endorsed by Lyon (101, 102).

## **COMMITMENT OF THE EUROPEAN COMMISSION TO BIO-EMERGENCY**

### **PH-SEE Curriculum On Bioterrorism**

Public Health in South Eastern Europe (PH-SEE) is a consortium for training and Research in Public Health(91). PH-SEE has the objective of establishing a formal agreement between the members of the Public Health in South Eastern Europe (PH-SEE) Network, developing the academic programmes for training and research in public health. This Network, formed in 2000 within the framework of Stability Pact collaboration, recognizes the need for sustainable collaboration and strongly supports the reconstruction of postgraduate public health training and research based on regional specificities and following international standards in public health education. This Consortium Agreement has been signed by the Directors of the participating Universities, Schools and Institutions of the 15 member countries to remained adhered, to maintain continuity of collaboration and cooperation for the future.

The curriculum support and improve the quality of postgraduate training in public health based on specific health and training needs in South Eastern European countries, using a Pan-European context. This Curriculum consists of ten *Units*, each comprising a number of related *Topics*. For each topic, one or more training *modules* of varying length will be available during a continuous development process. These modules can be used in postgraduate training programme and/or continuing education for public health professionals. Modules are prepared in such a way that each lecturer in the PH-SEE Network can use them in his/her own teaching practice. The Internet Platform provides an opportunity for continuous development of the Curriculum contents. This is a step ahead in the direction of European preparedness to deal with all major public health issues including deliberate epidemics or bioterrorism (91).

Two comprehensive modules has been put on the website. The first one provides essential knowledge on the issue of intentional epidemics or bioterrorism, explains the phenomena and related aspects, while the second one provides epidemiological perspectives on five biological agents that have the potential to be used in intentional epidemics. Given in the following other areas of collaboration and conditions of this agreement are identified:

1. Each member of the PH-SEE Network will foster cooperation and exchange in postgraduate and continuing education - including far distance learning - and research in public health.
2. Each member of the PH-SEE Network will advise, counsel and support any other member institution on request on how to develop and improve public health training for practice and research, especially with regard to capacity building of institutionalized Schools of Public Health.
3. Each member of the PH-SEE Network will contribute in development, implementation and evaluation of mutual training materials on the common, copyright protected Internet-Platform (Public Health Curriculum- training modules).
4. Each member of the PH-SEE Network will stimulate and make professional and financial efforts to exchange lecturers and researchers, and support mobility of postgraduate students for scientific and/or field work. Visiting academic staff will be accorded the status of Visiting Fellow (or equivalent).
5. Each member will assist lecturers and students participating in this Regional Exchange Programme to find accommodation. Each institution will offer the library, research and other facilities normally available to its own students and staff.
6. Tuition fees for foreign students within the framework of the Regional Exchange Programme must not exceed those ones for nationals.
7. Participants in the Regional Exchange Programme will be subject to the rules, regulations and discipline of the host institution. Students will be chosen on the basis of academic excellence. They must meet the entry or scientific requirements of the host institution and possess suitable language and other skills for the pursuit of their programme of study. Each host institution reserves the right to reject candidates.
8. The granting of credit for any course, study or diploma undertaken at the foreign university will be at the discretion of the home institution. Each member of the PH-SEE Network will make efforts to provide their own certification for students who successfully pass the training modules prepared, offered and organized by the other PH-SEE Network member institutions. This training programme should be a component in any prescribed scheme of studies leading to the award of Diploma or degree in Public Health.
9. Each member of the PH-SEE Network will support development in joint public health research and identification of common priorities based on bilateral and multilateral collaboration.
10. Each member of the PH-SEE Network will have a representative (or representatives) who will be the contact person(s) responsible for development of mutual collaboration.

Andrija Stampar School of Public Health, Medical School, University of Zagreb, Croatia, is the PH-SEE Network Coordinating Center, sharing responsibilities for its developments. All specific annual activities, including certification of training modules is prepared and added in the *Annual Annex*. This unique public health consortium has successfully completed three years of its inception and has generated scientifically credible knowledge that has empowered millions of people across Europe with vision of their public health interest. Additional training and teaching materials for public health preparedness, health system preparedness,

hospital preparedness, physician,s preparedness are expected to be put on the website soon.

Health care systems in South Eastern Europe are characterized by a predominantly curative orientation. During the last decade, public health became insufficient due to war as well as economic and political changes. Today, there is a lack of competence in public health, above all in health management and strategy development but also in the fields of health surveillance and prevention. It is recognized that there is a need for sustainable collaboration and support in advanced training and continuing education of qualified professionals to reach the required competence levels. The main aim of the program is to improve and support collaboration of teaching and research institutions within SEE countries in public health training and research programs related to regional specificities and needs.

- Establishment of the public health professionals network among SEE countries
- Collaborative development of postgraduate and continuing training materials in public-health
- Development of a common Internet platform for implementation and evaluation of training programs through common workshops
- Identification of priorities and stimulation of national and joint public health research projects in SEE countries his Curriculum
- Prepared for an Internet-based platform

### **THE EUROSURVEILLANCE PROJECT**

The Eurosurveillance Project is funded by the European Commission with the aim to promote the diffusion and exchange of information on communicable diseases (73,74,82). It is an incredible step ahead and includes a monthly publication Eurosurveillance, and a weekly bulletin Eurosurveillance Weekly. Eurosurveillance (monthly) is a peer-reviewed journal on communicable disease surveillance, prevention and control. It publishes original articles on the epidemiology of communicable diseases, surveillance reports from national and European programmes, comparisons between the national public health policies in Europe, and outbreaks investigation reports. Some articles extracted from national epidemiological bulletins published in EU Member States are also indexed.

Eurosurveillance is published in a print bilingual format (English/French), which is distributed to more than 10000 subscribers throughout Europe. In addition, the bulletin is available in electronic formats at [www.eurosurveillance.org](http://www.eurosurveillance.org), with an average of 23000 internet users' sessions per month. Translations in Italian, Portuguese and Spanish are also available at this website. Articles published in Eurosurveillance monthly are indexed by Medline/Index Medicus. Eurosurveillance Weekly is an electronic bulletin for epidemic alerts, updates, and responses. It publishes news related to infectious diseases, surveillance data as soon as they are published. The Weekly is e-mailed to thousands of subscribers across the region. Information published comes from our network of public health centers based in Europe and beyond. The two editorial teams are hosted by the Institut de veille sanitaire (InVS, Public Health Institute, Saint-Maurtice, France) for Eurosurveillance, and the Health Protection Agency Communicable Disease Surveillance Centre, London, England for Eurosurveillance Weekly. The joint

editorial committee includes representatives from the members states of the European Union, plus Norway since 1999 and Estonia since 2001.

### **THE ROLE OF INTERNATIONAL HEALTH REGULATION (IHR)**

The world is rapidly transforming. Mostly fatal public health risks cross the international borders without noticing. Coupled with the increase in the global traffic and trade, novel microbes have appeared and old diseases have re-surfaced even in areas where stringent health care facilities are available. The guiding principle for the IHR is to prevent international disease spread by early detection of events that threaten public health. This demands an early detection of exotic disease events through a vigilant surveillance system. International coordination is an essential node in the chain of an effective response to public health emergencies of international concern. IHR aim to ensure the maximum security against the international spread of diseases with minimum interference with world traffic.

Its origins date back to the mid-19th century when cholera epidemics overran Europe between 1830 and 1847. These epidemics were catalysts for intensive infectious disease diplomacy and multilateral cooperation in public health, starting with the first International Sanitary Conference in Paris in 1851. Between 1851 and the end of the century, eight conventions on the spread of infectious diseases across national boundaries were negotiated. The beginning of the 20th century saw multilateral institutions established to enforce these conventions, including the precursor of the present Pan American Health Organization (PAHO). In 1948, the WHO constitution came into force and in 1951 WHO Member States adopted the International Sanitary Regulations, which were renamed the International Health Regulations in 1969. The regulations were modified in 1973 and 1981 (92). The IHR were originally intended to help monitor and control six serious infectious diseases: cholera, plague, yellow fever, smallpox, relapsing fever and typhus. Today, only cholera, plague and yellow fever are notifiable diseases.

New needs created by the resurgence of the infectious disease threat are the main driving force behind revisions of the *International Health Regulations* (92). As one of several new features, the revised regulations will identify the core surveillance capacities required at national level in order for a country to fully participate in the new requirement to report public health emergencies of international concern. It is anticipated that this core capacity will become a benchmark for national surveillance systems and contribute to their strengthening by providing a clear, internationally recognized target.

The need now is for European integration and unity. In this regard, initiatives that swiftly followed the Ottawa Plan provide good evidence of both the willingness to collaborate internationally and the many advantages of doing so. Strengthened public health capacity for disease surveillance and response may not be able to predict or pre-empt another bioterrorist attack. But it can do much to mitigate the effects.

The European Regional Office has made progress in developing national and regional surveillance systems over the last two years. In April 2000 the European Region held, a consensus meeting in Grottaferrata, Italy (69-73). Twenty-eight member states from former Soviet Union and Central Europe developed 36 recommendations for long term investments on strengthening of infectious disease

surveillance. This included enhancing surveillance systems, outbreak preparedness, capacity building, creation of networks and international collaboration as well as building partnerships.

Recent international events have made clear that the international community must address the Intentional Release of Biological Agents (IRBA) as a public health priority. The WHO Executive Board agreed in Florence on 13th of November on critical areas for development of activities such as strengthening of surveillance systems, early warning of health events caused by natural or deliberate use of biological agents. The current IHRs first introduced to help monitor and control four serious diseases which had significant potential to spread between countries involve:

- i. Notification of cases: WHO Member States are obliged to notify WHO for a single case of cholera, plague or yellow fever, occurring in humans in their territories, and give further notification when an area is free from infection. These notifications are reported in WHO's Weekly Epidemiological Record.
- ii. Health-related rules for international trade and travel.
- iii. Health organization: Measures for deratting, disinfecting, and disinfecting international conveyances (ships, aircraft, etc.) are to be implemented at points of arrival and departure (ports, airports and frontier posts). The health measures called for are the maximum measures that a state may apply for the protection of its territory against cholera, plague and yellow fever.
- iv. Health documents required: Requirements are included for health and vaccination certificates for travelers from infected to non-infected areas etc.

Building an international consensus Regional and country workshops has been one of the priority of the EU. The idea of IHR workshops is to update the Member States on the revision process and changes proposed, and, most importantly, to stimulate critical comments and feedback on both the existing regulations and the revision proposals. Some workshops are worth mentioning here which were conducted throughout 2002 with Slovenia, CCEE-Baltic States Communicable Disease Network.

Others took place in Oslo-Norway (22-23 July 2002) in the Baltic States, Russia, Poland, Norway, Sweden, Finland St. Petersburg, Russian Federation (13-14 August 2002), and an Inter-regional EURO/EMRO Mediterranean basin workshop in Rome- Italy (20-21 January 2003). It included 12 Mediterranean basin countries. Therefore, it is evident that, in the European region, there is a need to identify ways to strengthen national and international capacities to early detect and respond to health threats that have emerged in this new context. Further participation and willingness of the European region to strengthen preparedness in the European nations is considered vital (73,74,82,92).

#### **GAPS AND SHORTCOMINGS IN DISEASE RECONNAISANCE**

In 1998, the EU created a network for epidemiological surveillance (decision 2119/98), and in 1999, the Early Warning and response system. A new public health strategy was developed in the year 2000. The EU surveillance system

consists of a network of networks and coordinating structures, an early warning and response network, disease specific networks and basic building blocks, notably the European Programme for Intervention Epidemiology Training (93), Euro-surveillance and Inventory of resources or infectious diseases in Europe (94). The purpose of the EU rapid response is the enhancing of existing EU expertise, support to member states, facilitation of the organization of investigations, addressing of rapidly emerging epidemiological problems, identification of risks, proposing prevention and control measures.

Many public health issues could be identified: lack of adequate resources at national level to address EU activities, the need to improve laboratory capacity, and for rapid response. There is need for a coherent approach, and a service function in public health. There is a need for national capacity building and trust building. With relation to bioterrorism, well functioning communicable disease surveillance and outbreak investigation capacity provides the basis for detection and management of biohazardous events, and collaborating with and between other authorities is necessary. EU laboratory capacity is crucial. There is an urgent need for a strong technical coordination unit at the EU level, building EU expertise and permanent EU financing mechanisms.

To assess preparedness a survey was conducted to document the response of 18 European public health institutes in 16 countries to the anthrax release through mail after September 11<sup>th</sup> and to identify the gaps that need to be addressed. Three key lessons were drawn. 1) Inadequate preparedness planning and funding arrangements, Europe was not ready in October 2001 to respond to an intentional outbreak. 2) Although European institutes reacted quickly and adapted their priorities to a new type of threat, they need adequate and sustained support from national governments to maintain their overall capacity. 3) The bio-event reflected the need for increased investment in epidemiology training programmes and the establishment of a technical coordination unit for international surveillance and outbreak response in the European Union.

The experiences of this event had considerable consequences in Europe. Such events event signify the role of the healthcare sector in surveillance and response to deliberate overt but also to covert releases. This requires early recognition followed by prompt activation of an effective multisector response, and health services have a crucial role. The following key elements are essential. Surveillance for clinical syndromes. Cases of disease arising due to covert deliberate releases of any biological agent will first appear as unusual clinical syndromes or unexpected patterns of occurrence of more common syndromes.

Examples include rapid onset of severe sepsis with respiratory failure in the case of inhalation anthrax, plague or tularaemia; typical skin lesions in cutaneous anthrax; rapidly descending, afebrile, symmetrical, flaccid paralysis in botulism; and clusters of severe systemic illness with vesicular rash in smallpox (95).

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 (9,28,31,32,72,74,81,83).

Protection of the vulnerable communities and technical assistance to the poorly prepared countries of the South-eastern and Central Europe has not been adequately addressed (9,72-74,87,91,95). Contact or exposure to any biological hazard or infectious agent has grave affects on children. With respect to the 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] published recently treatment guidelines for the use against smallpox emergency (96). 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 a 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.<sup>21</sup> 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.

The covert release of a biological agent in most cases, take several days to manifest itself. Prompt detection depends on the vigilance, alertness to clusters of unusual symptoms and immediate reporting to the appropriate authorities. Most health personnel will have little or no experience of several of the illnesses that could be deliberately caused. Training is mandatory for the recognition and initial management of casualties, and for a rapid communication. It is a firm belief that not all the countries in the EU region have the surge capacity, in staff and facilities, to manage either a very large and lethal outbreak or simultaneous attacks with different agents.

To detect suspicious events clinical alert mechanisms and syndrome-based surveillance systems need to be incorporated into routine practices. With respect to a robust preparedness, special attention is required to beef up surveillance and alert system in the following areas,

- 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, Patient presenting a rare disease and has bio-terrorism potential [e.g., inhalational anthrax, tularaemia, or plague]

### **LABORATORY SUPPORT AND INFORMATION TECHNOLOGY**

Consideration was given to the laboratory and the data derived from routine diagnostic and reference work. Private laboratories were considered and the issues of interaction with the public laboratories, as well as the poor contribution of many private laboratories to local and national surveillance. There may be a need to require private laboratories to report certain results to public health authorities for surveillance purposes, perhaps as part of their accreditation processes and for licensing. There are several levels of laboratory services ranging from local to reference laboratories. The periodicity of obtaining data from the different levels and the degree of urgency for obtaining data, equipment and reagents, standardization of methods and quality assurance issues, were considered. The need to establish a close working relationship between epidemiologists and laboratory personnel was also discussed.

### **HUMAN RESOURCE DEVELOPMENT**

Review and further definition of training programmes may be required in many countries. Basic epidemiology is taught in medical school, but the curriculum may need attention. Specialisation exists in some countries. Long-term intervention epidemiology capacity is needed in much of the Region. Skills of intervention field epidemiologist should include the ability to plan, design and run surveillance systems; use laboratory data for surveillance, outbreak investigation and research. In addition to the methodological capabilities, epidemiologists should have good management and communication skills.

Training needs a multi-disciplinary approach, and should be task oriented, with learning by doing aspects, with a snowball effect, and training of trainers. The international input is a key factor of any programme developed. There is a need to associate general epidemiology as well as communicable diseases, including the deliberate release of biological weapons. Many existing national and international resources and experiences can be used. Challenges include linking training with communicable disease surveillance and control programmes, and the selection of appropriate specific case studies and teaching examples. Success will be dependent on each country becoming the owner of the initiative. Old diseases are re-emerging, new diseases appear and the intentional use of biological, chemical and nuclear agents is a threat to the regional health security. It was acknowledged that surveillance and response systems and laboratory capacity to address these threats is deficient in many countries.

Progress has been made during the last 22 months after the Grottaferrata meeting of April 2000 and especially in the area of integrated databases, network building between national surveillance institutes, review of national programs, development of training opportunities for intervention epidemiology both at national and international level. It must be recognized that the WHO European Regional Office has limited financial resources to implement all the recommendations of the Grottaferrata meeting and additional work will be needed to increase the funding of the regional programme so that more progress can be made during the next 2 years. In view of these financial limitations, coordination is even more critical.

Network initiatives such as the CCEE-Baltics Network collaboration on early warning and measles surveillance offer economical solutions to sharing data, information, experience and can contribute to strengthen national surveillance systems. Other specific networks could be created to exchange information on legislation, reform of surveillance systems, training curricula or disease specific and relevant for a number of partners in such networks. WHO should stimulate and facilitate this process, including the promotion of a network for Russian speaking Member States. Member States and WHO are encouraged to establish and develop computer-based information systems for national laboratory and epidemiology programmes (87-91,96).

#### **RECOMMENDATIONS FOR THE EU MEMBER STATES**

Member States should review the strengths and weakness as well as the needs for the improvements of the current national surveillance systems. Countries should be encouraged to share information and guidelines that have recently been developed on surveillance methods, evaluation, standards and response to particular disease or bioterrorist threats. The use of the World Wide Web or reporting through the WHO Regional Office, would be ways of disseminating this information. In many countries the collaboration between microbiologists and epidemiologists is suboptimal and not a routine practice. Countries are urged to elaborate strategies for developing closer working relationships between these two public health disciplines.

Member States are encouraged to strengthen cooperation and collaboration between human and veterinary diagnostic laboratories as well as medical and veterinary epidemiologists. All countries should identify potential threats and review the preparedness to those. This assessment should not only include the health sector but also those such as police, civil defence, military among others. Preparedness plans should focus on improving coordination between different sectors and agencies that would be involved in emergency response. Countries should advocate for public health as a priority for funding opportunities from EU funded Aid Programmes.

Clear benefits have been demonstrated from collaborations between countries through the establishment of networks, such as the disease specific networks in the European Union. They have provided the means for earlier detection of health threats and warnings, including earlier recognition of international outbreaks when there are just small number of cases in several Member States. Networks have been shown to be very effective when an international coordinated health response is required. Countries are encouraged to identify national institutes that could be

partners of the Global Outbreak Alert and Response Network (GOARN) coordinated by WHO/EURO. Emergency plans and early warning systems both for natural or intentionally caused outbreaks should be integrated with already existing surveillance systems rather than building new systems.

Relevant documentation on preparedness and response to disease outbreaks or intentional release of biological agents, at least in English and in European languages should be made available. Further support is required for a systematic review of surveillance and response functions within the existing structures of countries' surveillance systems. WHO should assist in the process of standardization of public health laboratory procedures, so that both quality and comparability will be improved. WHO is currently working with 7 countries to strengthen their laboratory surveillance. WHO is urged to set up a two to three week international training course for intervention epidemiology as soon as possible. Countries are encouraged to reserve funds for such training both from national budgets and to seek additional resources such as from the European Commission, UNICEF and other funding agencies. Involving public health laboratories is crucial to effective surveillance.

Physician's preparedness, hospital preparedness, laboratory preparedness and above all public preparedness with stringent protective measures are the essential for a prompt response. Multidisciplinary response to threats i.e., police and security services lead team that work together and share information when a deliberate release is suspected. After the release of anthrax spore (2001) in the UK, when suspicious packages were identified, the police undertook the initial threat assessment and categorised the threat as "credible" and "non-credible." The role of health services is to provide support for instance, to decontaminate exposed persons and ensure rapid management with prophylactics as the threat is considered credible. Security response mechanism may not always be used to dealing with deliberate attacks and may need to collect expertise urgently.

Good local, regional, and national planning between the relevant services are key to an adequate response. In the event of covert infectious emergency close interdisciplinary collaboration among clinicians, microbiologists, toxicologists, epidemiologists, communicable disease control physicians, and radiation biologists and physicists enhance the magnitude, appropriateness and effect of the response. Surge capacity is considered an essential component of preparedness and must be taken into account while planning for biological event. Additional support need to be provided for diagnosis and management of cases, laboratory and epidemiological investigations, and public health actions. This requires sharing of ideas, experience, laboratory facilities, and personnel across Europe as well as building expertise within countries. Linking laboratories into a network like the PHLS in the UK is helpful as well as trainees, experts from Europe can provide vital additional support if properly supervised.

WHO coordinates a large number of electronic "detective" systems and databases for keeping experts alert to changes in the volatile infectious disease situation. These networks, most of which now operate in real time, keep watch over disease-related events ranging from new strains of influenza virus, through outbreaks of salmonellosis and dengue, to the emergence of drug-resistant pathogens. Most of these networks also include quality assurance and training components to ensure

that data submitted from all parts of the world are comparable and conform to established standards. The oldest of these, FluNet, was established over 50 years ago and has served as the prototype for the design and implementation of subsequent systems. It now draws support from 110 collaborating laboratories in 84 countries.

The sensitivity of FluNet (97) has recently proved vital in the early detection of cases where influenza virus strains have crossed the species barrier from animals, such as swine and poultry, to infect humans. These surveillance networks all operate within the framework of the International Health Regulations, which provide the only international legally-binding instrument, implemented by WHO, governing the reporting of epidemic-prone diseases and the application of measures to prevent their spread. To be prepared to respond to a terrorist attack, the EU must address critical areas in national strategy: preparedness, response, and research, which will require leadership from Federal state, and local governments; the medical and health communities, and the public. Develop specific strategies for responding to all potential weapons of mass destruction.

1. Strengthen the public health infrastructure. Many diseases have been eradicated in the United States, and over time, the nation's public health system has eroded and has become less effective for tracking and reporting diseases.
2. Train emergency health care personnel to recognize rapidly and treat victims of chemical and biological terrorism and to report such incidents.
3. Maintain stockpiles of antibiotics, antidotes, and vaccines for use in the event of an attack, along with medical equipment and supplies.
4. Designate and give adequate authority to a Federal central office that can integrate the various agencies at the Federal, state, and local levels involved in emergency response.
5. Establish, strengthen, and expand sophisticated detection and analysis surveillance systems focused on all forms of biologic agents. Ensure their integration with public health systems and the nation's emergency departments.
6. Establish and sustain educational programs for health care workers and the public. Involve emergency physicians who are responsible for establishing policies and protocols for the nation's Emergency Medical Services systems.
7. Conduct research focused on improving detection, investigation, diagnosis, and treatment for these threats. Improvement of established disaster management methods will require the integration of data from research and experience.
8. Ensure that local communities have comprehensive disaster response plans that integrate all the required responders, including medical, law enforcement, fire, EMS, and government.

#### **EUROPEAN CENTER OF DISEASE PREVENTION**

The idea of launching a European centre till 2005 to respond to deliberately released biological agents and naturally occurring infections is long under debate

(69-73). Postal delivery of anthrax spores in the USA have increased the suspicion of Europeans to such threats. Several other infectious emergencies in Europe (see chapter three) have increased the need for a centralized structure that can help to share epidemiological information and actively combine advanced research, surveillance, control, and training in the member states. The example of US National Center for Infectious Diseases (NCID) which is considered an integral part of the Centers for Disease Control and Prevention (CDC).

An organization analogous to the NCID a European Centre for Infectious Diseases (ECID) is direly needed (69-71). Tibayrenc1 M has already formulated the conceptual framework and principle in order to set up a central structure with walls, which, like its American counterpart, would coordinate advanced research, surveillance and professional training. The European CID would not be limited to the European Union, and would include countries such as Switzerland, as well as those of Eastern Europe and with strong links with developing countries. This will help to disrupt cross border transmissions (69-71). Unprepared and uncoordinated health systems offer a strategic advantage for causing havoc in the event of infectious outbreaks.

Recently European Commissioner for Health and Consumer Protection David Byrne has pledged for the establishment of European centre for disease control by 2005. The intended centre will bring together the expertise in member states and will act as a reference and coordination point both in routine and crises situations. The EU Commission also plans to establish a health portal for online information by 2004. In the context of a widening European Union (EU), whose citizens are aware of the increasing influence that EU and global events have on health systems of individual states, combating major health challenges of communicable diseases, ensuring the safety of sensitive products, such as foodstuffs or blood, and the functioning of health systems within the single market has become an ultimate priority (72,73,74).

## **EPIDEMICS AND MILITARY HEALTH INSTITUTIONS**

The use of biological weapons are not the only health threat in war. War and disease have accounted for a major proportion of human sufferings in the past. Disease was and is a bigger enemy than the army in the battlefield. Despite the advances in both medicine and weapons technology throughout the 20th century, infectious diseases have continued to be the most formidable enemy, at least for the civilian population. Armed conflict always amplifies factors that lead to increased incidence of infectious diseases among civilians. Exodus, increasing population density, lack of access to clean water, poor sanitation, lack of shelter, and poor nutritional status all increase the population's vulnerability to disease.

In addition, the collapse of public health infrastructure and the lack of health services hampers control programs such as vaccination or vector control. Disease surveillance and control has direct civilian advantages, as it improves protection against all infectious agents that can incapacitate individuals and communities in a relative short period of time irrespective of the cause. Taking the example of anthrax or smallpox which can create a great panic among populations in times of an emergency. Similarly malaria, cholera and dysentery, AIDS, measles, respiratory infections like are SARS are also serious enemies wherever there is conflict. The approaches and methods we use to respond to biological agents are not different

than those of ordinary disease outbreaks. War history has shown that the use of bio- agents on the battlefield mainly affected combatants, but in the recent past willingness exist to induce fatal agents to target civilians. To prepare for and respond to such use is considerably more complex and difficult than to protect military personnel.

In the new global orders the use of massive military power, involvement of military institutions and peace keeping missions has brought new public health dimensions to the international health regulations. Due to the growing global public health concerns WHO and other similar organization are counting more on relations with military health institutions. Although military health institutions are non-traditional partners for WHO, the organization has been mandated to collaborate with "all potential technical partners in the area of epidemic alert and response". In many outbreak settings, particularly those associated with complex humanitarian emergencies, the military can be central to epidemic alert and response.

WHO has been engaging military health assets for public health by establishing collaborating center relationships with military laboratories in developing countries and bringing military health assets in the use for epidemic response and alert operations. A civil military liaison activity to facilitate military contributions to the epidemic alert and response activities has been set up. WHO has been seriously engaged in building in official link with the International Committee on Military Medicine (ICMM) which is the largest intergovernmental military medical organization involving some 110 Member States. There is strong urge for Planning and to look for a window of opportunity for further partnership with the Committee in order to obtain technical expertise on epidemic alert and response to epidemics, has been put on the agenda.

WHO will also examine the development of new tools, within our mandate to contain or mitigate the effects of natural occurrence, accidental release or deliberate use of biological, chemical agents and radio nuclear material. Such tools could include modeling of possible scenarios of natural occurrence, accidental release or deliberate use of such agents and collective mechanisms concerning the global public health response. WHO member states have pledged to put in place national disease-surveillance plans which are complementary to regional and global disease-surveillance operations, and to collaborate in the rapid analysis and sharing of surveillance data of international humanitarian concern.

A strong commitment has been also shown to collaborate and provide mutual support in order to enhance national capacity in field epidemiology, laboratory diagnoses, toxicology and case management. This is important, since the capacity for both surveillance and response obviously varies tremendously between countries. Countries have agreed to share expertise, supplies and resources in order to contain promptly the infection and mitigate its effects in the event of a global public health threat (1-7,87,90,80).

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(<http://www.cdc.gov/epo/dih/fetp.html>)

## LIST OF RECOMMENDED ARTICLES (ABSTRACTS) & WEBSITES

### **Planning against Biological Terrorism: Lessons from Outbreak Investigations**

David A. Ashford, Robyn M. Kaiser, Michael E. Bales, Kathleen Shutt, Ameer Patrawalla, Andre McShan, Jordan W. Tappero, Bradley A. Perkins, and Andrew L. Dannenberg

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We examined outbreak investigations conducted around the world from 1988 to 1999 by the Centers for Disease Control and Prevention's Epidemic Intelligence Service. In 44 (4.0%) of 1,099 investigations, identified causative agents had bioterrorism potential. In six investigations, intentional use of infectious agents was considered. Healthcare providers reported 270 (24.6%) outbreaks and infection control practitioners reported 129 (11.7%); together they reported 399 (36.3%) of the outbreaks. Health departments reported 335 (30.5%) outbreaks. For six outbreaks in which bioterrorism or intentional contamination was possible, reporting was delayed for up to 26 days. We confirmed that the most critical component for bioterrorism outbreak detection and reporting is the frontline healthcare profession and the local health departments. Bioterrorism preparedness should emphasize education and support of this frontline as well as methods to shorten the time between outbreak and reporting. (EID-CDC. Vol. 9, No. 5. May 2003) (<http://www.cdc.gov/ncidod/eid/vol9no5/02-0388.htm>)

### **Pandemic Influenza and Healthcare Demand in the Netherlands: Scenario Analysis** **Marianne L.L. van Genugten,\* Marie-Louise A. Heijnen,\* and Johannes C. Jager\***

\*National Institute for Public Health and the Environment, Bilthoven, the Netherlands

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In accordance with World Health Organization guidelines, the Dutch Ministry of Health, Welfare and Sports designed a national plan to minimize effects of pandemic influenza. Within the scope of the Dutch pandemic preparedness plan, we were asked to estimate the magnitude of the problem in terms of the number of hospitalizations and deaths during an influenza pandemic. Using scenario analysis, we also examined the potential effects of intervention options. We describe and compare the scenarios developed to understand the potential impact of a pandemic (i.e., illness, hospitalizations, deaths), various interventions, and critical model parameters. Scenario analysis is a helpful tool for making policy decisions about the design and planning of outbreak control management on a national, regional, or local level. (EID-CDC. Vol. 9, No. 5. May 2003). (<http://www.cdc.gov/ncidod/eid/vol9no5/02-0388.htm>)

### **[CDC - Viral Gastroenteritis Outbreaks in Europe, 1995-2000](#) [find more like this...](#)**

Summary: Ben Lopman,\* Mark Reacher,\* Yvonne van Duynhoven, François-Xavier Hanon, David Brown, and Marion Koopmans \*Public Health Laboratory Service Communicable Disease Surveillance Centre, London, England; Central Public Health Laboratory, London, England. <http://www.cdc.gov/ncidod/EID/vol9no1/02-0184-G1.htm> , 10042 bytes, updated 03-20-03

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### **[CDC - Viral Gastroenteritis Outbreaks in Europe, 1995-2000](#) [find more like this...](#)**

Summary: Figure 3. Setting of viral gastroenteritis outbreaks, European surveillance, 2000. SE, Sweden; FI, Finland; SI, Slovenia; E&W, England and Wales; NL, the Netherlands; DK, Denmark; DE, Germany; ES, Spain; FR, France; IT, Italy. \*Includes restaurants, <http://www.cdc.gov/ncidod/EID/vol9no1/02-0184-G3.htm> , 10254 bytes, updated 03-20-03

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[CDC - Viral Gastroenteritis Outbreaks in Europe, 1995-2000](#) [find more like this...](#)

Summary: Figure 2. Completeness of epidemiologic and viral characterization information on viral gastroenteritis outbreaks, European surveillance, 2000. SE, Sweden; FI, Finland; SI, Slovenia; E&W, England and Wales; NL, the Netherlands; DK, Denmark; DE, Germa. <http://www.cdc.gov/ncidod/EID/vol9no1/02-0184-G2.htm> , 10363 bytes, updated 03-20-03

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[CDC - EID Past Issue](#) [find more like this...](#)

Summary: First Isolation of Rickettsia slovaca from a Patient, France, C. Cazorla Enteropathogenic Klebsiella pneumoniae in HIV-Infected Adults, P.L. Nguyen Thi Granulomatous Lymphadenitis as a Manifestation of Q Fever, P. Tattevin Has Coxiella burnetii (Q Fever). [http://www.cdc.gov/ncidod/EID/vol9no1/contents\\_v9n1.htm](http://www.cdc.gov/ncidod/EID/vol9no1/contents_v9n1.htm) , 31788 bytes, updated 03-20-03

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[Bovine Spongiform Encephalopathy: Main Index, CDC](#) [find more like this...](#)

Summary: Since 1996, evidence has been increasing for a causal relationship between ongoing outbreaks in Europe of a disease in cattle, called bovine spongiform encephalopathy (BSE, or "mad cow disease"), and a disease in humans, called variant Creutzfeldt-Jakob d. <http://www.cdc.gov/ncidod/diseases/cjd/cjd.htm> , 29319 bytes, updated 05-23-03

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[CDC - Ahead-of-Print](#) [find more like this...](#)

Summary: Linked articles are published online ahead of print. Volume 9, Number 8- August 2003 Perspectives Porcine Reproductive and Respiratory Syndrome Virus: Origin Hypothesis, P.G.W. Plageman Detecting Bioterror Attack by Screening Blood Donors: Best-Case Anal. <http://www.cdc.gov/ncidod/EID/upcoming.htm> , 41343 bytes, updated 06-27-03

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<http://www.cdc.gov/ncidod/eid/vol5no4/pdf/henderson2.pdf> [find more like this...](#)

Summary: 537 Vol 5 No 4 JulyAugust 1999 Emerging Infectious Diseases Special Issue Clinical and Epidemiologic Characteristics of Smallpox Smallpox is a viral disease unique to humans To sustain itself the virus must pass from person to person in a continuing chain <http://www.cdc.gov/ncidod/eid/vol5no4/pdf/henderson2.pdf> , 257890 bytes, updated 11-08-02

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[CDC Travelers' Health Information on Bovine Spongiform Encephalopathy and New Variant Creutzfeldt-Jakob Disease](#) [find more like this...](#)

Summary: Since 1996, evidence has been increasing for a causal relationship between ongoing outbreaks in Europe of a disease in cattle called bovine spongiform encephalopathy (BSE, or "mad cow disease") and a disease in humans called new variant Cruetzfeldt-Jakob. <http://www.cdc.gov/travel/madcow.htm> , 28090 bytes, updated 06-05-03

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[CDC - Viral Gastroenteritis Outbreaks in Europe, 1995-2000](#) [find more like this...](#)

Summary: To gain understanding of surveillance and epidemiology of viral gastroenteritis outbreaks in Europe, we compiled data from 10 surveillance systems in the Foodborne Viruses in Europe network. However, the absolute number and population-based rates of vira <http://www.cdc.gov/ncidod/EID/vol9no1/02-0184.htm> , 106683 bytes, updated 05-21-03

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[Smallpox: Clinical and Epidemiologic Features](#) [find more like this...](#)

Summary: Subscribe To Subscribe to the EID Listserv to receive email notifications of Journal updates please click here. The disease most commonly confused with smallpox is chickenpox, and during the first 2 to 3 days of rash, it may be all but impossible to dis <http://www.cdc.gov/ncidod/EID/vol5no4/henderson.htm> , 36714 bytes, updated 02-21-03

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[Bovine Spongiform Encephalopathy and New Variant Creutzfeldt-Jakob Disease, CDC](#) [find more like this...](#)

Summary: Regardless, as of July 2002, cattle remain the only known food animal species with disease caused by the BSE agent. The spread of the BSE agent from the United Kingdom or potentially from other countries with BSE was most likely through the importation of.. [http://www.cdc.gov/ncidod/diseases/cjd/bse\\_cjd.htm](http://www.cdc.gov/ncidod/diseases/cjd/bse_cjd.htm) , 29414 bytes, updated 05-21-03

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[Trichinellosis Outbreaks -- Northrhine-Westfalia, Germany, 1998-1999](#) [find more like this...](#)

Summary: This report summarizes the investigation of these cases, which indicated the existence of two simultaneous outbreaks--one caused by contaminated ground meat and the other by a commercially prepared raw smoked sausage. Among the eight case-patients and 28.. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4823a2.htm> , 21323 bytes, updated 08-11-01

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13 0.77 [Trichinellosis Outbreaks -- Northrhine-Westfalia, Germany, 1998-1999](#) [find more like this...](#)

Summary: From November 1998 through January 1999, 52 cases of trichinellosis were identified by the public health surveillance systems in 11 cities and districts of the state of Northrhine-Westfalia (NRW), Germany. Preliminary investigations indicated that 22 of <http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/mm4823a2.htm> , 13616 bytes, updated 09-29-01

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[Probable Locally Acquired Mosquito-Transmitted Plasmodium vivax Infection -- Georgia, 1996](#) [find more like this...](#)

Summary: that this case probably was acquired through the bite of a locally infected Anopheles sp. mosquito, although a probable source of infection for mosquitoes was not confirmed. Two potential sources of mosquito infection were considered: persons who recent.. <http://www.cdc.gov/mmwr/preview/mmwrhtml/00047001.htm> , 22370 bytes, updated 08-11-01

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[Probable Locally Acquired Mosquito-Transmitted Plasmodium vivax ...](#) [find more like this...](#)

Summary: that this case probably was acquired through the bite of a locally infected Anopheles sp. mosquito, although a probable source of infection for mosquitoes was not confirmed. Two potential sources of mosquito infection were considered: persons who recent ..<http://www.cdc.gov/epo/mmwr/preview/mmwrhtml/00047001.htm> , 14821 bytes, updated 09-29-01

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<http://www.cdc.gov/ncidod/eid/vol6no2/ascii/buchholz.txt> [find more like this...](#)

Summary: Haff disease, identified in Europe in 1924, is unexplained rhabdomyolysis in a person who ate fish in the 24 hours before onset of illness. Although Haff disease is traditionally an epidemic foodborne illness, these six cases occurred in two clusters and

<http://www.cdc.gov/ncidod/eid/vol6no2/ascii/buchholz.txt> , 14038 bytes, updated 11-08-02

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**[Haff Disease: From the Baltic Sea to the U.S. Shore](#)** [find more like this...](#)

Summary: Haff disease, identified in Europe in 1924, is unexplained rhabdomyolysis in a person who ate fish in the 24 hours before onset of illness. From March through August 1997, two clusters of Haff disease cases occurred in Los Angeles, California, and St. Lo <http://www.cdc.gov/ncidod/eid/vol6no2/buchholtz.htm> , 46333 bytes, updated 02-21-03


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**[CDC - Human Pathogens in Body and Head Lice](#)** [find more like this...](#)

Summary: Suggested citation for this article: Fournier P-E, Ndihokubwayo J-B, Guidran J, Kelly PJ, Raoult D. Human pathogens in body and head lice. Using polymerase chain reaction and sequencing, we investigated the prevalence of Rickettsia prowazekii, Bartonella..<http://www.cdc.gov/ncidod/EID/vol8no12/02-0111.htm> , 69755 bytes, updated 03-21-03

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**[Draft Smallpox Decontamination](#)** [find more like this...](#)

Summary: Guide FEnvironmental Control of Smallpox Virus A Purpose This document provides general guidance on environmental infection control and decontamination for use in any setting where care is given to smallpox patients This information will be beneficial to  <http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.pdf> , 231912 bytes, updated 04-30-03

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**[Draft Smallpox Decontamination](#)** [find more like this...](#)

Summary: Healthcare workers, Housekeeping and laundry personnel, Mortuary personnel and morticians, Public health officials, Emergency responders in handling cases of smallpox, and Persons who manage the treatment and disposal of regulated medical waste. Smallpox.. <http://www.bt.cdc.gov/agent/smallpox/response-plan/files/guide-f.doc> , 72704 bytes, updated 04-30-03

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**[International Notes -- Quarantine Measures Smallpox -- Stockholm, Sweden, 1963](#)** [find more like this...](#)

Summary: Reprinted below is the entire series of reports published during May-July 1963 about a smallpox outbreak in Sweden. Recent immunization programs among hospital personnel presumably have altered the pattern of hospital spread observed in other recent outb..<http://www.cdc.gov/mmwr/preview/mmwrhtml/00042757.htm> , 34933 bytes, updated 08-11-01

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**[Botulism in Norway](#)** Botulism is a severe neuroparalytic disease caused by toxin produced by Clostridium botulinum, an anaerobic spore-forming bacillus. Physicians in Norway are required to notify the National Institute of Public Health (NIPH) of cases of botulism immediately... *year : 1999 | size : 11,2 Kb.countries : Norwaysubject : BOTULISM*

**[Eurosurveillance Weekly 1999;3 \(19\): 06/05/1999](#)** Vaccine research: new vaccines and evidence of vaccine safety | Unvaccinated child dies of Haemophilus influenzae type b infection | Fall in AIDS incidence in Europe in 1998 | Sexually transmitted diseases in the Newly Independent States | Does prophy... *year : 1999 | size : 20,7 Kb*  
*countries : England, Europe, United Kingdom, World*  
*subject : BOVINE SPONGIFORM ENCEPHALOPATHY, CREUTZFELDT-JAKOB DISEASE, Haemophilus influenzae, HIV/AIDS, IMMUNISATION, Pneumocystis carinii, SEXUALLY TRANSMITTED DISEASES*

[Eurosurveillance Weekly 2002;6 \(43\): 24/10/2002](#) New programme of Community action in the field of public health (2003-2008) | United States smallpox response plans: a commentary from the Bioterrorism Taskforce (BICHAT) perspective | First case of variant Creutzfeldt-Jakob disease reported in a United S... *year : 2002 | size : 35 Kb*  
*countries : Canada, England, Europe, France, United Kingdom, United States*  
*subject : Bioterrorism, BOVINE SPONGIFORM ENCEPHALOPATHY, CREUTZFELDT-JAKOB DISEASE, EUROPEAN PROJECTS, FOOD POISONING, Foodborne disease, FOODBORNE INFECTIONS, HOSPITAL-ACQUIRED INFECTIONS, IMMUNISATION, Infectious disease, MENINGOCOCCAL DISEASE, NOSOCOMIAL INFECTION, Salmonella, SALMONELLOSIS, Smallpox, Vaccine preventable diseases*

[Outbreak of trichinellosis in Cáceres, Spain, December 2001—February 2002](#) An outbreak of trichinellosis by T. britovi occurred in Cáceres, Spain, between 18 December 2001 and 11 February 2002, following the consumption of insufficiently cooked meat from a domestic pig. Among the 56 people exposed, 26 cases of trichinellosis were... *year : 2002 | size : 17,2 Kb*  
*countries : Spain, subject : TRICHINELLOSIS*

[Influenza pandemic preparedness and response planning at community level](#) In November 2001 the European Commission invited experts from all over Europe to express their views on ways to improve preparedness for an influenza pandemic at the European Community level. The conference was well attended and key actions to be addressed... *year : 2002 | size : 13,5 K, countries : Europe, subject : INFLUENZA*

[Eurosurveillance Weekly 2002;6 \(41\): 10/10/2002](#) Yellow fever epidemic in Senegal | Outbreak of legionnaires' disease associated with visits to Belgium - update | Outbreak of Salmonella Enteritidis PT 14b in the United Kingdom - update | Workshop on communicable disease surveillance in Europe: Is there ... *year : 2002 | size : 33,3 K, countries : Belgium, Denmark, Europe, Italy, Senegal, United Kingdom, subject : ANTIMICROBIAL RESISTANCE, HIV/AIDS, Legionella, LEGIONELLOSIS, PERTUSSIS, Salmonella, SALMONELLOSIS, SEXUALLY TRANSMITTED DISEASES, SEXUALLY TRANSMITTED INFECTIONS, Yellow fever*

[Eurosurveillance Weekly 2002;6 \(40\): 03/10/2002](#) European Commissioner again pledges European centre for disease control by 2005 | Outbreak of legionnaires' disease associated with visits to Belgium | Outbreak of Salmonella Enteritidis PT 14b in the United Kingdom | First case of variant Creutzfeldt-Jak... *year : 2002 | size : 26,7 Kb*  
*countries : Austria, Belgium, England, Europe, France, Italy, United Kingdom*  
*subject : Bat rabies, CREUTZFELDT-JAKOB DISEASE, EUROPEAN PROJECTS, Legionella, LEGIONELLOSIS, Rabies, Salmonella, Zoonoses, Zoonotic diseases*

[Eurosurveillance Weekly 2002;6 \(39\): 26/09/2002](#) New chairs named at first meeting of European Food Safety Authority | West Nile virus: spread to new regions, association with poliomyelitis-like syndrome and transmission through organ donation and blood transfusion | DengueNet – WHO's internet based sys... *year : 2002 | size : 32,5 Kb*  
*countries : Europe, United Kingdom, United States, World*  
*subject : abnormal prion protein, Blood borne virus, Bloodborne diseases, CREUTZFELDT-JAKOB DISEASE, Dengue fever, Food Safety Authority, Haemorrhagic fever, POLIOMYELITIS, SEXUALLY TRANSMITTED INFECTIONS, West Nile virus*

[Eurosurveillance Weekly 2002;6 \(38\): 19/09/2002](#) Outbreaks of infectious intestinal disease among coach tour passengers, Ireland | Outbreak of acute neurological disease due

to Nipah virus infection in Bangladesh in 2001 | 100 years of infectious disease prevention and control at Denmark's Statens Serum... *year : 2002 | size : 15 K, countries : Bangladesh, Denmark, Ireland, subject : Infectious disease, Intestinal disease, neurological*

[\*\*Eurosurveillance Weekly 2002;6 \(33\): 15/08/2002\*\*](#) Cluster of shigellosis in men in Berlin in 2001 | Genital chlamydia now the most commonly diagnosed sexually transmitted infection in England, Wales, and Northern Ireland | Legionnaires' disease outbreak in England – update | Variant Creutzfeldt-Jakob dis... *year : 2002.*

[\*\*Eurosurveillance Weekly 2002;6 \(32\): 08/08/2002\*\*](#) Improving surveillance of varicella in Europe in response to increasing availability of varicella vaccine | Legionnaires' disease outbreak in England | Spread of gonorrhoea from the Barents and Baltic Sea regions to the Nordic countries?... *year : 2002 | size : 20,9 K, countries : Europe, United Kingdom subject : Gonorrhoea, Legionella, LEGIONELLOSIS, SEXUALLY TRANSMITTED DISEASES, SEXUALLY TRANSMITTED INFECTIONS, Varicella*

[\*\*Eurosurveillance Weekly 2002;6 \(30\): 25/07/2002\*\*](#) Rates of syphilis in England are rising | Incidence trends and short term predictions for variant Creutzfeldt-Jakob disease in the United Kingdom – update... *year : 2002 | size : 24,4 K, countries : England, United Kingdom subject : CREUTZFELDT-JAKOB DISEASE, ESSTI, EUROPEAN PROJECTS, SEXUALLY TRANSMITTED DISEASES, SEXUALLY TRANSMITTED INFECTIONS, SYPHILIS*

[\*\*Eurosurveillance Weekly 2002;6 \(29\): 18/07/2002\*\*](#) Reported synthesis of poliovirus and implications for polio eradication and bioterrorism | Rising incidence of Creutzfeldt-Jakob disease in Switzerland | Substantial impact of the HIV pandemic on migrant populations in Europe | Sexually transmitted infect... *year : 2002 | size : 28,4 K, countries : Europe, Switzerland, World, subject : Bioterrorism, CREUTZFELDT-JAKOB DISEASE, Gonorrhoea, Herpes B, HIV/AIDS, Injecting drug users, MENINGOCOCCAL DISEASE, POLIOMYELITIS, SEXUALLY TRANSMITTED DISEASES, SEXUALLY TRANSMITTED INFECTIONS, SURVEILLANCE, SYPHILIS*

[\*\*Eurosurveillance Weekly 2002;6 \(27\): 04/07/2002\*\*](#) Launch of new European guidelines for control and prevention of travel associated legionnaires' disease | A community cluster of legionnaires' disease among pilgrims to San Giovanni Rotondo, Puglia, Italy | HIV infection in Europe: endemic in the west, ep... *year : 2002 | countries : Africa, Asia, Azerbaijan, Botswana, Brazil, Cambodia, China, Estonia, Europe, France, Italy, Kyrgyzstan, Latvia, Poland, Russia, Ukraine, World, subject : EUROPEAN PROJECTS, EWGLI, HIV/AIDS, Legionella, LEGIONELLOSIS, Listeria, Listeriosis, MEASLES, POLIOMYELITIS, SURVEILLANCE*

[\*\*Eurosurveillance Weekly 2002;6 \(25\): 20/06/2002\*\*](#) Tuberculosis control in Europe needs expanded DOTS, linked HIV/TB control, and improved surveillance | Suspected acute haemorrhagic fever syndrome in the Republic of Congo | Rapid reporting EU surveillance system for *Neisseria meningitidis* W135: 2a: P1.2,... *year : 2002 | size : 19,1 Kb countries : Africa, Asia, Congo, Europe, Gabon, Netherlands, Saudi Arabia subject : Haemorrhagic fever, MENINGITIS, TUBERCULOSIS*

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