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between virus names and species names would be to change the current names of virus species into nonlatinized binomial names. Such a system, which has been advocated by plant virologists for many years, consists in replacing the word ‘virus’ appearing at the end of the existing species name by the genus name which also ends in ‘-virus’. Measles virus then becomes Measles morbillivirus, Hepatitis A virus becomes Hepatitis A hepatovirus, and Tobacco mosaic virus becomes Tobacco mosaic tobamovirus. The advantage of such a system, which could be implemented without problems for about 98% of all virus species names, is that inclusion of the genus name in the species name provides additional information about the properties of the virus. A changeover to binomial species names would not affect the common names of viruses in English or other languages since names such as measles virus or ‘virus de la rougeole’ would remain the same. The ICTV is currently debating the possibility of introducing binomial species names and some decision is likely to be made in the near future.

Given that the common names of viruses are used repeatedly in scientific texts there is a need for abbreviating them and the ICTV has published several lists of recommended acronyms for virus names. Since the names of virus species are used only very seldom in publications, there is no need to abbreviate them. If binomial names of virus species were introduced in the future, the abbreviations of common names of viruses will of course not be affected.

See also: Nature of Viruses; Phylogeny of Viruses; Quasispecies; Taxonomy, Classification and Nomenclature of Viruses.

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Viruses and Bioterrorism

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Introduction

Man has known that biological organisms and toxins were useful as weapons of war long before the germ theory of disease was understood. However, as the twentieth century came to a close, the perceived difficulties in production, weaponization, and deployment of these biological weapons as well as a belief that moral restraints would preclude the use of these weapons gave many a false sense of security. Recently, a number of events have served to focus attention on the threat of terrorism and the potential for the use of biological, chemical, or nuclear weapons against the military, civilian populations, or agriculture for the purpose of causing illness, death, or economic loss. This possibility became a reality in October 2001 when someone sent spores of Bacillus anthracis to media companies in New York City and Boca Raton, Florida, resulting in five deaths, considerable panic throughout the United States and other countries, and raised the awareness of our vulnerability.

There are more than 1400 species of infectious organisms that are known to be pathogenic for humans; many additional organisms are capable of causing disease in animals or plants. Realistically, only a few of these infectious agents pose serious problems or are capable of affecting human, animal, or plant health on a large scale. Even fewer of these agents are viruses. Viruses that could be used as weapons against humans, animals, or plants generally possess traits including ease of production and dissemination, transmissibility, environmental stability, and high morbidity and mortality rates.
Definitions

The use of biological agents is often characterized by the manner in which they are used. For the purposes of this article, 'biological warfare' is defined as a special type of warfare conducted by a government against a target; ‘bioterrorism’ is defined as the threat or use of a biological agent (or toxin) against humans, animals, or plants by individuals or groups motivated by political, religious, ecological, or other ideological objectives. Furthermore, terrorists can be distinguished from other types of criminals by their motivation and objective; however, criminals may also be driven by psychological pathologies and may use biological agents. When criminals use biological agents for murder, extortion, or revenge, it is called a ‘biocrime’.

Historical Perspective

The use of viral agents for biological warfare has a long history, which predates their recognition and isolation by culture. Their early use is consistent with what, at the time, was known about infectious diseases, particularly smallpox. In the sixteenth century, the Spanish explorer, Francisco Pizarro, presented the indigenous peoples of South America with variola-contaminated clothing, which resulted in widespread epidemics of smallpox. During the French and Indian War (1745–67), Sir Jeffrey Amherst, commander of the British forces in North America, suggested the deliberate use of smallpox to ‘reduce’ Native American tribes hostile to the British. Captain Ecuyer (one of Amherst’s subordinates), fearing an attack on Ft. Pitt from Native Americans, acquired two variola-contaminated blankets and a handkerchief from a smallpox hospital and, in a gesture of good will, distributed them to the Native Americans. As a result, several outbreaks of smallpox occurred in various tribes in the Ohio River valley. In 1775, during the Revolutionary War, the British attempted to spread smallpox among the Continental forces by inoculating (variolation) civilians fleeing Boston. In the South, there is evidence that the British were going to distribute slaves who had escaped during hostilities, and were sick with smallpox, back to the rebel plantations in order to spread the disease.

The use of viruses other than Variola major is a more recent phenomenon and reflects an increased knowledge of how to grow and stabilize viruses for delivery purposes. Allegations have been made by the government of Cuba that the CIA was responsible for the massive outbreaks of swine fever in 1971 and dengue fever in 1980 that ravaged the country. However, subsequent investigations have failed to find substantive proof of CIA involvement in these outbreaks. The Aum Shinrikyo, a religious cult responsible for the 1995 release of sarin gas in the Tokyo subway system, was also involved in biological warfare activity and sent a team of 40 people to Zaire to acquire Ebola virus. Fortunately, they were unsuccessful in this endeavor. In 1997, unknown farmers in New Zealand deliberately and illegally introduced rabbit hemorrhagic disease virus (a calicivirus) onto the south island as an animal control tool to kill feral rabbits.

Over the past two decades, the human immuno-deficiency virus (HIV) has been involved in a number of biocrimes. This most likely reflects the availability of HIV-contaminated blood as a source of this virus. For example, in 1990, Graham Farlow, an asymptomatic HIV-positive inmate at a prison in New South Wales, Australia, injected a guard with HIV-contaminated blood. The guard became infected with HIV; Farlow subsequently died of AIDS. In 1992, Brian T. Stewart, a phlebotomist at a St. Louis, MO hospital, injected his 11-month-old son with HIV-contaminated blood during a fight over payment of child support. In 1993, Iwan E. injected his former girlfriend with 2.5 ml of HIV-contaminated blood after she broke up with him. In 1994, Dr. Richard J. Schmidt, a married Louisiana gastroenterologist, injected a former lover with HIV-contaminated blood. Molecular typing of the HIV strains demonstrated that she contracted the same strain of HIV as found in one of Dr. Schmidt’s patients. In perhaps the most famous case, Dr. David Acer, a Florida dentist infected with HIV, transmitted the disease to six of his patients between 1987 and 1990. The intentional infection of these patients is a possibility although there is no direct evidence. In spite of these incidents, HIV has not been included on lists of threat agents for public health bioterrorism preparedness. However, some contend that HIV has great weapon potential if the goal is to destabilize a society.

Viruses have also been involved in suspected incidents or hoaxes. In 1999, an article appeared suggesting that the CIA was investigating whether Iraq was responsible for causing the outbreak of West Nile fever in the New York City area. The story relied heavily on a previous story written by an Iraqi defector, claiming that Saddam Hussein planned to use West Nile virus strain SV 1417 to mount an attack. The investigation indicated that there was no known evidence of bioterrorism involved in the spread of West Nile virus. A fictional ‘virus’ was also involved in one of the largest bioterrorism hoaxes in 2000. According to e-mail messages widely circulated on the Internet, an organization known as the Klingerman Foundation was mailing blue envelopes containing sponges contaminated with a fictional pathogen called the ‘Klingerman virus’. According to the e-mail alert, 23 people had been infected with the virus, including 7 who died.

Viruses as Bioweapons

Advances in viral culture and virus stabilization made during the second half of the twentieth century facilitated
large-scale production of viral agents for aerosol dissemination. A report for the United Nations on chemical and biological weapons and the effects of their possible use gave estimates on the numbers of casualties produced by a hypothetical biological attack (Table 1). Three viruses (Rift Valley fever virus, Tick-borne encephalitis virus, and Venezuelan Equine Encephalomyelitis (VEE) virus) were evaluated in a scenario in which 50 kg of the agent was released by aircraft along a 2 km line upwind of a population center of 500 000. The viral agents produced fewer casualties and impacted a smaller area when compared with the bacterial agents used in this hypothetical model. Of note, smallpox was apparently not evaluated because it had not yet been eradicated and level of vaccine-induced immunity in the population was high.

Viral agents were part of the biological weapons arsenal of both the Soviet Union and the United States (Table 2). VEE virus was stockpiled by both countries as an incapacitating agent; Variola major and Marburg viruses were stockpiled as lethal agents by the Soviet Union. The Soviet Union reportedly conducted a live field test of Variola major virus on Vozrozhdeniye Island in the Aral Sea in the 1970s, in which 400 g of the virus was released into the atmosphere by explosion. Unfortunately, a laboratory technician who was collecting plankton samples from an oceanographic research vessel 15 km from the island became infected. It was reported that after returning home to Aralsk, she transmitted the infection to several people including children. All those infected died. A number of other viruses that infect humans (e.g., Ebola virus, Lassa fever virus, enterovirus 70) or livestock (e.g., foot and mouth disease virus, rinderpest, Newcastle disease virus) have also been studied for their offensive capabilities or for the development of medical and veterinary countermeasures.

Today, with the increased level of concern, a number of viruses have been cited as possible weapons for use against humans or animals (Table 2). The requirements for an ideal biological warfare agent include availability, ease of production, stability after production, a susceptible population, absence of specific treatment, ability to incapacitate or kill the host, appropriate particle size in aerosol so that the virus can be carried long distances by prevailing winds and inhaled deeply into the lungs of unsuspecting victims, ability to be disseminated via food or water, and the availability of a vaccine to protect certain groups. Other factors such as the economic and psychological impact of an attack on animal agriculture with a viral agent must also be considered.

Variola major is considered to be the major viral threat agent for humans. Thus, considerable effort has been expended toward preparing the public health and medical communities for the possibility that this agent will be employed by a terrorist. Variola major is considered to be an ideal terrorist weapon because it is highly transmissible by the aerosol route from infected to susceptible persons; the civilian populations of most countries contain a high proportion of susceptible persons; the disease is associated with a high morbidity and about 30% mortality; initially, the diagnosis of a disease that has not been seen for almost 30 years would be difficult; and, other than the vaccine, which may be effective in the first few days post infection, there is no proven treatment available.

Alphaviruses (Table 2) are also of concern because they can be produced in large amounts in inexpensive and unsophisticated systems; they are relatively stable and highly infectious for humans as aerosols, and strains are available that produce incapacitating (e.g., VEE) or lethal infections (EEE case fatality rates range from 50–75%). Furthermore, the existence of multiple serotypes of VEE and EEE viruses, as well as the inherent difficulties of inducing efficient mucosal immunity, make defensive vaccine development difficult.

The filoviruses and arenaviruses that cause hemorrhagic fever have also been considered as agents that might be used by terrorists because of their high virulence and capacity for causing fear and anxiety. The filoviruses, Ebola and Marburg, can also be highly infectious by the airborne route. Humans are generally susceptible to infection with these viruses with fatality rates greater than 80%, and infection can be transmitted between humans through direct contact with virus-containing body fluids. There are five species of arenaviruses (Lassa fever, Junin, Machupo, Guanarito, and Sabia) that can cause viral hemorrhagic fevers with a case fatality rate of about 20%. Large quantities of these viruses can be produced by propagation in cell culture. Infection occurs via the respiratory pathway suggesting that dissemination via aerosol might be used by a terrorist. Human to human transmission has also been reported with aerosol transmission the most likely route for at least some of the secondary cases. The filoviruses and arenaviruses discussed above are BSL-4.

### Table 1 Estimates of casualties produced by hypothetical biological attack

| Agent                      | Downwind | Reach (km) | Dead   | Incapacitated |
|----------------------------|----------|------------|--------|---------------|
| Rift Valley fever virus    | Upwind   | 1          | 400    | 35 000        |
| Tick-borne encephalitis    | Upwind   | 1          | 9 500  | 35 000        |
| VEE                        | Upwind   | 1          | 200    | 19 800        |
| Franciscella tularensis    | >20      | 30 000     | 125 000|
| Bacillus anthracis         | >20      | 95 000     | 125 000|

Note. These estimates are based on the following scenario: release of 50 kg of agent by aircraft along a 2 km line upwind of a population center of 500 000.
agents and diagnostic capacities for infections caused by these viruses are limited.

**Impact of Biotechnology**

Because the nucleic acid of many viruses, including some that are currently not threats, can be manipulated in the laboratory, the potential for genetic engineering remains a serious threat. Biotechnology, which has had a tremendous impact on the development of medicines, vaccines, and in the technologies needed to counter the threat of naturally occurring disease, can also be used to modify viruses with unintended consequences or even for the development of novel biological agents. Several examples involving viruses are presented below.

**Mousepox Virus**

An Australian research group was investigating virally vectorised immunocontraceptive vaccines based on ectromelia virus, the causative agent of the disease termed mousepox. They created a recombinant virus, which expressed the mouse cytokine IL-4 in order to enhance the antibody-mediated response to other recombinant antigens carried on the virus vector. Instead, the ectromelia virus vector expressing IL-4 altered the host’s immune response to this virus resulting in lethal infections in normally genetically

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**Table 2**  Classification of viral agents that are considered to be of concern for bioterrorism and biowarfare and those that have been weaponized or studied for offensive or defensive purposes as part of former or current national biological weapons programs

| Nucleic acid                  | Family          | Genus                | Species                                                                 |
|-------------------------------|-----------------|----------------------|-------------------------------------------------------------------------|
| Negative-sense single-stranded RNA | Arenaviridae    | Arenaviruses         | Lassa fever[^a,b]
|                                |                 |                      | Junin[^a,b]
|                                |                 |                      | Machupo[^a,b]
|                                |                 |                      | Sabia
|                                |                 |                      | Guanarito
| Bunyaviridae                  | Phlebovirus     | Rift Valley fever[^b]
|                                | Nairobi virus   | Crimean-Congo HF     |
|                                | Hantavirus      | Hantaan and related viruses[^b] |
|                                |                 | Sin Nombre           |
| Orthomyxoviridae              | Influenzaviruses| Influenza A[^i]      |
| Filoviridae                   | Filovirus       | Ebola[^a]
|                                |                 | Marburg[^a]           |
| Paramyxoviridae               | Henipavirus     | Nipah virus          |
|                                | Morbillivirus   | Rinderpest[^a,b,d,e,f]|
|                                | Avulavirus      | Newcastle disease virus[^b] |
| Positive-sense single-stranded RNA | Flaviviridae    | Flavivirus           | Yellow fever[^a,b,d] |
|                                |                 |                      | Dengue[^b] |
|                                |                 |                      | Tick-borne encephalitis virus[^a] |
|                                |                 |                      | Japanese encephalitis virus[^a] |
|                                |                 |                      | Omsk hemorrhagic fever virus |
| Togaviridae                   | Alphavirus      | Venezuelan equine encephalomyelitis virus[^c,g] |
|                                |                 |                      | Eastern equine encephalomyelitis virus[^b] |
|                                |                 |                      | Western equine encephalomyelitis virus[^b] |
|                                |                 |                      | Chikungunya virus[^a] |
| Picornaviridae                | Enterovirus     | Enterovirus 70[^a]   |
|                                | Hepatovirus     | Hepatitis A virus    |
|                                | Aphthovirus     | Foot and mouth disease virus[^d] |
| Double-stranded DNA           | Poxviridae      | Orthopoxivirus       | Variola major[^c,b,i] |
|                                |                 |                      | Camelpox[^a] |
|                                | Asfarviridae    | Asfivirus            | African swine fever virus[^a] |

[^a]: Studied by the Soviet Union BW program.
[^b]: Studied by the U.S. BW program.
[^c]: Weaponized by the Soviet Union BW program.
[^d]: Studied by the Canada BW program.
[^e]: Studied by the France BW program.
[^f]: Studied by the Germany BW program.
[^g]: Weaponized by the U.S. BW program.
[^h]: Studied by the Iraq BW program.
[^i]: Studied by the Iran BW program.
[^j]: Studied by the North Korea BW program.
resistant mice (e.g., C57BL/6). Additionally, this virus also caused lethal infections in mice previously immunized against infection with ectromelia virus. The creation of this ‘supermousepox’ virus led to speculation that similar genetic engineering could be performed on Variola major leading to a biological weapon that would be effective against an immunized population.

**Pandemic Influenza**

The influenza pandemic of 1918–19, which followed World War I, was uniquely severe, causing an estimated 20–40 million deaths globally. This pandemic happened before the advent of viral culture and very little was known about the virus until the discovery of the polymerase chain reaction (PCR). Recently, the complete coding sequences of all eight viral RNA segments has been determined by using reverse transcription-PCR (RT-PCR) to amplify the viral RNA sequences from formalin-fixed and frozen tissue samples from individuals who died during this pandemic in an effort to shed light on both the reasons for its extraordinary virulence and evolutionary origin. More recently, researchers reconstructed the 1918 Spanish influenza pandemic virus using reverse genetics and observed that this reconstructed virus exhibited exceptional virulence in the model systems examined and that the 1918 hemagglutinin and polymerase genes were essential for optimal virulence.

**Synthetic Genomes**

A full-length poliovirus complementary DNA (cDNA) (c. 7500 bp) has been synthesized in the laboratory by assembling oligonucleotides of plus- and minus-strand polarity. The synthetic poliovirus cDNA was transcribed by RNA polymerase into viral RNA, which translated and replicated in a cytoplasmic extract of uninfected HeLa S3 cells, resulting in the de novo synthesis of infectious poliovirus. The publication of this research raised concerns that more complicated viruses (e.g., Variola major or Ebola) could be synthesized fromscratch based on publicly available sequences, or that viruses could be created that do not exist in the wild.

**Recognition, Response, and Deterrence**

An effective defense requires a comprehensive approach that includes: prevention of access to viral stocks; improved means of detecting deliberately induced disease outbreaks; rapid medical recognition of specific syndromes (e.g., hemorrhagic fever syndrome); rapid laboratory identification of viruses in patient specimens; prevention of person–person transmission; reliable decontamination procedures; development of effective vaccines; and development of effective antiviral therapy.

Rapid and accurate detection of biological threat agents is the basis of an effective public health response to bioterrorism. In order to address this issue, CDC in collaboration with other partners established a national network of laboratories called the Laboratory Response Network (LRN), which was provided with the tools to accomplish this mission. Rapid assays utilizing advanced molecular and immunological technologies for detection of agents such as variola virus, as well as emerging public health threats such as SARS coronavirus and H5N1 influenza virus, were distributed to member laboratories. Equipment, training, and proficiency testing are elements of the LRN and contribute to a uniform operational plan. The importance of high-quality standardized testing for detection of these agents is exemplified by the rapid need for medical countermeasures to protect or treat civilian populations. Accurate laboratory analysis is a major element in the decision process for deployment of the Federal Government’s Strategic National Stockpile (SNS) of medical countermeasures.

As part of the effort to deter biological terrorism and strengthen the law enforcement response to such an act, the US recently established a microbial forensic laboratory known as the National Bioforensics Analysis Center that operates in partnership with the Federal Bureau of Investigation. Scientists are already developing methods for the forensic investigation of incidents involving viruses.

**Summary**

For the terrorist, the use of a viral agent would pose a challenge due to problems associated with acquisition, cultivation, and dissemination. The target for an attack with a viral agent can range from humans to animals and plants. Therefore, agricultural targets are also a major concern. Nature has provided many challenges to combating viral diseases. Viral agents are much more prone to genetic variation and mutation, and can be manipulated or created in the laboratory to take on desired characteristics. Differentiating between natural and intentional viral disease outbreaks can be challenging. Unlike bacterial diseases, many of which are treatable, there are fewer medical countermeasures to employ when dealing with viral infections. Laboratory diagnostic methods and reagents must continuously be refined to account for genetic changes and variants. Thus, the challenge of developing bioterrorism countermeasures is significant. Fortunately, this effort contributes to combating natural disease events more effectively, which has global benefits.

See also: AIDS: Disease Manifestation; AIDS: Global Epidemiology; AIDS: Vaccine Development.
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Glossary

Alkaliphilic Having a requirement for an environment with a high pH.

Burst size The number of infectious virus particles released per cell.

Carrier state Persistent infection of a host cell by a virus, with the surviving host persistently carrying and continually producing virus without entering a lysogenic state.

Circular permutation A change in the sequence of the linear DNA termini that does not alter the relative sequence (e.g., circular permutation of ABCDEFGH could generate BCDEFGHA, CDEFGHAB, etc).

Concatamer Two or more DNA molecules that are linked together to form a long, linear DNA molecule.

Cured A host cell that was once a lysogen, but no longer carries viral DNA in any form.

Halophilic Having a requirement for an environment with a high salt concentration.

Headful packaging The mechanism of packaging viral DNA based on the size of the virus head, rather than the length of the viral genome.

Hyperthermophile Having a requirement for an environment with a high temperature (>80 °C).

Insertion sequences Repetitive sequences of DNA that can move from one site to another within the viral DNA.

Integrase/recombinase An enzyme which can integrate viral DNA into the genome of its host cell.

Lysogen A host cell that has been infected by a virus that remains dormant, despite the presence of viral DNA.

Lytic virus A virus that is able to infect a host, replicate, and subsequently leave the host cell by rupturing (lysing) the host cell.

Methanogenic Having the ability to produce methane.

Monovalent A virus that has a host range limited to one species.

Prophage A virus that is dormant within the host cell.

Protein-primed replication Replication of DNA via the interaction of the DNA polymerase with specific proteins, rather than DNA or RNA primers.

Temperate virus A virus that is able to infect a host, but remain dormant within the host cell.

Terminal redundancy Linear DNA with the same sequence at each end.

Transduction The transfer of host DNA from one host cell to another by a virus.

Transfection The introduction of pure viral genomic DNA into a host cell, producing viable virus.