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Category C Potential Bioterrorism Agents and Emerging Pathogens

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Category C bioterrorism agents

Infectious agents have been, and in the foreseeable future will remain, potential tools of mass casualties. The intentional use of living organisms or infected materials derived from them has occurred over centuries during war and peacetime by armies, states, groups, and individuals [1–5]. A wide range of microorganisms could be used as biological weapons. Few microorganisms can be used for production of weapons of mass destruction, however. Eligible agents should meet criteria such as availability, ease of dissemination, stability, and potential for high morbidity and mortality to qualify as a weapon of mass destruction [6].

The Centers for Disease Control and Prevention (CDC) has classified critical biologic agents into three major categories [7]. The agents classified as category C by the CDC currently are Nipah virus, Hantavirus, tick-borne hemorrhagic fever viruses, tick-borne encephalitis (TBE) virus complex, yellow fever, and multidrug-resistant tuberculosis (MDR-TB). These agents could be produced, disseminated, and engineered easily for mass exposure in the future. Preparedness for category C agents requires ongoing research to improve disease detection, diagnosis, treatment, and prevention.

Nipah virus

Nipah virus, a zoonotic virus, was discovered in 1999 [8]. The virus is named after the location where it was first detected in Malaysia. Nipah is

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closely related to another zoonotic virus, Hendra virus. Nipah and Hendra are members of the virus family Paramyxoviridae [9]. Nipah virus has caused only a few focal outbreaks [10,11]; however, its capability of causing significant mortality in humans has made this emerging viral infection a public heath concern. In the Malaysian outbreak, a total of 265 people were infected, of whom 105 died. The Singapore outbreak led to 11 cases, with 1 death [12].

Transmission

The risk of transmission of Nipah virus from sick animals to humans is thought to be low, and person-to-person transmission has not been documented yet, even in the context of a large outbreak. In Malaysia and Singapore outbreaks, most of the patients had direct contact with pigs [13]. The mode of transmission from animal to animal and from animal to human is uncertain, but seems to require close contact with contaminated tissue or body fluids from infected animals [14]. It is believed that certain species of fruit bats are the natural hosts for Nipah virus [15]. The bats seem to be susceptible to infection with this virus, but they do not become ill. It is unknown how the virus is transmitted from bats to animals. The role of species other than pigs in transmitting infection to other animals has not yet been determined.

Clinical symptoms

The incubation period of the disease is 4 to 18 days. The infection may be mild or subclinical, and in symptomatic cases, the onset is usually with influenza-like symptoms with high fever and myalgia. The disease may progress to encephalitis with drowsiness, disorientation, convulsions, and coma.

Laboratory diagnosis

Procedures for the laboratory diagnosis of Nipah virus infection include serology, histopathology, immunohistochemistry, electron microscopy, polymerase chain reaction (PCR), and virus isolation [16,17].

Treatment

No drug therapies have been proved to be effective in treating Nipah infection. Treatment relies on providing intensive supportive care. There is some evidence that treatment with the antiviral drug ribavirin may reduce the mortality of acute Nipah encephalitis [18].

Disinfection

Phenolic disinfectants are not effective against Paramyxoviruses, but polar lipophilic solvents, such as chloroform, are effective.

Hantaviruses

Hantaviruses are serologically related members of the family Bunyaviridae [19]. The term *Hantavirus* is derived from the Hantaan River, where the prototype Old World hantavirus (Hantaan virus) was first isolated. The disease associated with the Old World hantaan virus is called Korean hemorrhagic fever or hemorrhagic fever with renal syndrome. Regions especially affected by hemorrhagic fever with renal syndrome include China, the Korean Peninsula, Russia (Hantaan and Seoul viruses), and northern and western Europe (Puumala and Dobrava viruses).

In 1993, a newly recognized species of hantavirus (New World hantavirus) was found to cause the hantavirus pulmonary syndrome in the southwestern United States [20–22]. Hantavirus pulmonary syndrome subsequently was recognized throughout the contiguous United States and the Americas. As of June 6, 2002, a total of 318 cases of hantavirus pulmonary syndrome had been identified in 31 states, with a case-fatality rate of 37% [23]. Several hantaviruses that are pathogenic for humans have been identified in the United States, including New York virus [24], Black Creek Canal virus [25], and Bayou virus [26].

Transmission

Hantaviruses are rodent-borne, and no arthropod vector has been implicated in the transmission of any of them. Hantaviruses do not cause overt illness in their reservoir hosts [27]. Transmission to humans is believed to be via aerosols of infected excreta of rodents [28]. No person-to-person transmission has been reported with the Old World hantavirus or in the United states [23]. All hantaviruses known to cause hantavirus pulmonary syndrome are carried by the New World rats and mice, family Muridae, subfamily Sigmodontinae [23].

Clinical features

Hemorrhagic fever with renal syndrome is characterized by fever and myalgia, which develop days or weeks (incubation period 5–42 days) after exposure to rodents. The disease progresses to hemorrhage and hemodynamic instability, occasionally progressing to shock. The disease enters a second phase affecting the kidneys characterized at first by oliguria then polyuria, hypertension, bleeding of the mucous membranes, and edema of the lungs. Mortality is usually from shock or hemorrhage. The fatality rate is 1% to 3% for Puumala virus, 7% for Hantaan virus, and 5% to 15% for Dobrava virus.

Hantavirus pulmonary syndrome is characterized by fever, chills, and severe myalgia, which progress to variably severe respiratory compromise and hemodynamic instability. Thrombocytopenia is common, and hemoconcentration and other hematologic abnormalities occur commonly in severe cases.

Laboratory diagnosis

The diagnosis of hantaviruses is based on history of any possible contact with rodents, the clinical findings, and serology results. In the early phase of the illness, the infection cannot be differentiated from other viral fevers. Direct detection of antigen, for early diagnosis of the disease, also has been used. The virus antigen can be shown in the blood or urine. Isolation of the virus from urine is successful early in the illness, whereas isolation of the virus from the blood is less consistent.

Treatment

Ribavirin is effective against Hantaan virus and was made available for postexposure prophylaxis to soldiers in Operation Desert Shield/Storm. Supportive care, such as dialysis support of the kidneys and maintenance of blood volume, also is important.

Decontamination

The viruses can be killed by sodium hypochlorite (1%), glutaraldehyde (2%), and ethanol (70%).

Yellow fever virus

Yellow fever is a viral hemorrhagic fever transmitted by infected mosquitoes. Infection causes a wide spectrum of disease, from mild symptoms to severe illness and death. The *yellow* in the name stands for the jaundice that affects some patients. Yellow fever occurs only in Africa and South America [29]. The World Health Organization has estimated that 200,000 cases of yellow fever occur each year [30].

Sylvatic (jungle), intermediate, and urban are the three cycles of infection of the yellow fever virus [31]. Jungle yellow fever is a disease of monkeys. It is a rare disease that occurs mainly in individuals who are exposed to tropical rain forests and are bitten by mosquitoes that have been infected by monkeys. The intermediate cycle of yellow fever occurs only in humid or semihumid savannahs of Africa and in small-scale epidemics in rural areas. Semidomestic mosquitoes infect monkey and human hosts. Urban yellow fever is a disease of humans. It is spread by *Aedes aegypti* mosquitoes that have been infected by other people. These mosquitoes have adapted to living among humans in cities, towns, and villages. Urban yellow fever is the cause of most yellow fever outbreaks and epidemics.

Transmission

The mosquito takes a blood meal from an infected monkey or human (urban), then bites a human. It injects saliva containing the virus into the bite to prevent blood clotting and infects the human.

Clinical features

The clinical spectrum of yellow fever ranges from subclinical infection to overwhelming multisystem disease [32]. Symptoms occur after 3 to 6 days of infection and usually include fever, prostration, headache, photophobia, lumbosacral pain, extremity pain (including knee joints), epigastric pain, anorexia, and vomiting. The second phase involves the liver and kidneys, and hemorrhagic symptoms and signs caused by thrombocytopenia and abnormal coagulation can occur. The fatality rate of severe yellow fever is approximately 20% [29].

Laboratory diagnosis

Definitive diagnosis is made by viral culture from blood or tissue specimens. It also is made by identification of yellow fever virus antigen or nucleic acid in tissues using immunohistochemistry, enzyme-linked immunosorbent assay (ELISA), or PCR tests [33]. Detection of IgM antibody by capture ELISA with confirmation of fourfold or greater increase in neutralizing antibody titers between acute-phase and convalescent-phase serum samples also is diagnostic [29].

Treatment

Live attenuated virus preparation made from the 17D yellow fever virus strain is available [34]. It is provides immunity for about 10 years. No effective specific antiviral therapy for yellow fever has been identified. Treatment consists of providing general supportive care and varies depending on which organs are involved.

Decontamination

The yellow fever virus is killed by 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde, and 70% ethanol. It also is killed by heating at 60°C for 10 minutes.

Tick-borne encephalitis complex

TBE is a human viral infectious disease involving predominantly the central nervous system. It is one of the most dangerous human infections occurring in Europe and many parts of Asia. TBE is caused by members of the TBE virus complex of the Flaviviridae [35]. TBE virus is believed to cause at least 14,000 human cases of encephalitis in Europe annually [36]. Other viruses within the same group, including louping ill virus, Langat virus, and Powassan virus, also are known to cause human encephalitis, but rarely on an epidemic scale [36].

Transmission

TBE virus is spread by the bite of ticks of the genus *Ixodes,* and it can be spread through consumption of contaminated raw milk [37]. Ticks act as the vector and reservoir for TBE virus, small rodents are the main host, and humans are accidental hosts [38]. TBE cases occur during the period of highest tick activity (April–November), when humans are infected in rural areas through tick bites [38].

Clinical features

After an incubation period of 4 to 14 days, patients develop typical flulike symptoms that resolve in about 1 week. After a remission of a few days to a few weeks, about a quarter of patients develop severe symptoms, including meningitis or meningoencephalitis [39]. In severe cases (no more than a quarter of cases), a partial paralysis may be seen. Although most patients recover from the disease, about a third are believed to have long-lasting neurologic problems, including problems with cognition, balance, and coordination [40].

Laboratory diagnosis

The diagnosis is based on confirmed exposure to ticks in a high-risk area, a tick bite within the previous 3 weeks, clinical symptoms, infected cerebrospinal fluid, and IgM and IgG antibodies in the serum [37].

Treatment

A vaccine of killed virus is available in Europe. No specific therapies are available, and supportive care is used to treat symptoms as necessary.

Decontamination

The virus is killed by 1% sodium hypochlorite, 2% glutaraldehyde, formaldehyde, and 70% ethanol. It also is killed by heating at 60°C for 10 minutes.

Tick-borne hemorrhagic fever viruses

Tick-borne hemorrhagic fever viruses include Crimean-Congo hemorrhagic fever (CCHF), Omsk hemorrhagic fever, Kyasanur Forest disease, and Alkhurma viruses [36]. CCHF virus is a tick-borne virus of the genus *Nairovirus* within the family Bunyaviridae [41]. The disease was first characterized in the Crimea in 1944, then later recognized in 1969 as the cause of illness in the Congo, resulting in the current name of the disease [42]. The virus is widespread and has been found in Africa, Asia, the Middle

East, and eastern Europe. The *Nairovirus* genus includes 32 members, all of which are transmitted by argasid or ixodid ticks, but only 3 have been implicated as causes of human disease: the Dugbe and Nairobi sheep viruses and CCHF, which is the most important human pathogen among them [43].

Transmission

The virus is transmitted by the bite of an infective adult tick of the genus *Hyalomma* [41]. Nosocomial outbreaks also have occurred as a result of exposure to blood and secretions [44,45]. Transmission also can occur by drinking raw milk or slaughtering infected animals [41,46].

Clinical features

The incubation period is about 2 to 7 days and has not been recorded as longer than 12 days. Illness begins abruptly with high fever, myalgia, headache, vomiting, and pain in the epigastrium, lower back, and thighs. Loose stools, dry cough, and relative bradycardia may be present. After 3 to 5 days, hemorrhage begins and is seen as a red or purple discoloration of the skin and the development of nosebleeds. In about half of all cases, the liver is enlarged. Blood is found in saliva, urine, black skin patches, and vomit. Bleeding leads to shock, vascular collapse, and death about 10 days after the onset of symptoms. Fatality rates in hospitalized patients range from 9% to 50% [42].

Laboratory diagnosis

Rapid diagnosis of CCHF virus is made by classic reverse transcriptase (RT)-PCR methods [47,48]. IgG and IgM antibodies can be detected with ELISA and indirect immunofluorescence tests from about day 7 of illness [41].

Treatment

No vaccine is available for CCHF. Intensive supportive management is required at an early stage and sometimes for prolonged periods. Convalescence is often slow, with debility lasting for some weeks after recovery. There is evidence that CCHF responds to treatment with ribavirin [49].

Decontamination

The virus is killed by common disinfectants and by dry heat at 56°C for 30 minutes.

Multidrug-resistant tuberculosis

MDR-TB is caused by *Mycobacterium tuberculosis,* which is resistant to at least isoniazide and rifampicin. MDR-TB has emerged as a serious problem in many areas of the world. The World Health Organization [50] estimates that one third of the world's population is infected with *M tuberculosis,* and that MDR-TB prevalence is greater than 4% among new tuberculosis cases in eastern Europe, Latin America, Africa, and Asia. In 2003, the CDC reported that 7.7% of tuberculosis cases in the United States were resistant to isoniazid, whereas 1.3% were resistant to isoniazid and rifampicin [51]. With the difficulty of treatment and its ability to disseminate by aerosol, MDR-TB might be used as a biological weapon in the future [6].

Emerging pathogens with potential for bioterrorism

In the early twenty-first century and with advances in technology, one may think that major infectious diseases threats would be conquered, but the world is connected through massive and easy international travel, politics, trade, economics, and culture, which makes possible the potential global spread of pathogens of the microbial world that previously might have been confined to a remote, local area. Novel infectious diseases agents keep getting discovered because they continue to emerge and re-emerge, have expanded their geographic range, have the potential of genetic manipulation and bioweaponization, and pose substantial threat throughout the world. Infectious diseases presenting significant challenges as emerging and re-emerging threats include severe acute respiratory syndrome (SARS), West Nile virus (WNV) infection, pandemic influenza, and monkey poxvirus infection.

Pandemic and avian influenza

Historically, the twentieth century saw three pandemics of influenza. The influenza pandemic of 1918 caused at least 500,000 US deaths and 50 million deaths worldwide. The 1957 influenza pandemic caused at least 70,000 US deaths and 1 to 2 million deaths worldwide. The 1968 influenza pandemic caused about 34,000 US deaths and about 700,000 deaths worldwide. The influenza virus responsible for the 1918 pandemic remains uncertain. In the 1957 and 1968 pandemics, the new virus contained components of previous human and avian influenza viruses.

A pandemic occurs when a mutant influenza virus emerges as a virus that exhibits more radical changes (antigenic shift) than the changes occurring continuously in influenza viruses (antigenic drift) and that is more virulent and pathogenic [52]. Although avian influenza viruses generally replicate inefficiently in humans, some subtypes of avian influenza can replicate within the respiratory tract of humans to cause disease. Since 2003, the highly pathogenic H5N1 strain of avian influenza A has spread to poultry in 17

countries in Asia and eastern Europe and now is considered endemic in some of these countries [53]. At the time of writing, this strain has caused about 160 human cases and 85 deaths so far in countries including Cambodia, China, Indonesia, Thailand, and Vietnam [54].

There is concern that the currently circulating H5N1 strain of avian influenza will evolve into a pandemic strain by adapting to humans through genetic mutation or reassortment with human influenza strains. It has been noted that pig's trachea contains receptors for avian and human influenza viruses and supports the growth of viruses of human and avian origin. Genetic reassortment between human and avian influenza viruses may occur in pigs leading to a novel strain against which there would be little or no population immunity and that would be highly pathogenic, capable of human-to-human transmission and having pandemic potential. The currently circulating strain of H5N1 avian influenza A also has potential as a bioterrorism agent because of the aforementioned properties and ease of propagation, lack of vaccine, environmental stability of the virus, and emerging resistance to the antiviral agent oseltamivir.

Transmission

For human influenza A (H5N1) infections, evidence is consistent with bird-to-human and possibly environment-to-human transmission. There is limited, nonsustained human-to-human transmission to date [55], although it has been suggested in several household clusters [56] and is apparent in one case of child-to-mother transmission [57].

The virus causing avian influenza in poultry has spread to humans as a result of contact with infected poultry by airborne spread from their secretions or by contamination during food preparation. Undercooked poultry also has been implicated. Human-to-human transmission of influenza virus occurs by inhalation of infectious droplets and droplet nuclei caused by coughing and sneezing, by direct contact, and by indirect (fomite) contact.

Clinical features

The incubation period of H5N1 ranges from 2 to 8 days (median 4 days). Initial symptoms of H5N1 influenza A in humans include fever, cough, sore throat, muscle aches, and pneumonia. Diarrhea, vomiting, abdominal pain, pleuritic pain, and bleeding from the nose and gums also have been reported early in the course of illness [58,59]. Progression to respiratory failure has been associated with acute respiratory distress syndrome. Other complications, such as renal dysfunction, cardiac failure, and multiorgan failure, have been reported [58–60].

Laboratory diagnosis

Rapid antigen testing kits cannot differentiate between various subtypes of influenza A virus. Diagnosis of H5N1 can be made by virus isolation through viral culture or by detection of H5-specific RNA by RT-PCR.

Treatment

Early initiation of antiviral agents seems to be beneficial. Avian influenza virus is susceptible in vitro to the neuraminidase inhibitors oseltamivir and zanamivir [61,62]. Oral oseltamivir and inhaled zanamivir are active in animal models of H5N1, but inhaled zanamivir has not been studied in cases of H5N1 in humans.

Mechanistically, neuraminidase molecular rearrangement occurs to create a pocket to which oseltamivir attaches. Viral resistance to oseltamivir results from the substitution of a single amino acid resulting in H274Y, R292K, or N294S mutation. Any of these mutations causes inhibition of neuraminidase molecule active site changes to create a pocket for oseltamivir [63]. None of these mutations prevents the binding of zanamivir, and that is why no virus resistant to zanamivir has yet been isolated [63]. There have been case reports of neuraminidase conferring high-level resistance to oseltamivir in two Vietnamese patients during oseltamivir treatment [64].

Prevention

At present, there is no licensed vaccine available against avian influenza for humans, but several candidate vaccines are under study. Chemoprophylaxis with 75 mg of oseltamivir by mouth every 24 hours for prevention for 7 to 10 days is recommended for individuals who have had a possible unprotected exposure and for household contacts [65,66].

Severe acute respiratory syndrome

SARS is a respiratory viral illness caused by the newly discovered coronavirus [67], SARS-associated coronavirus (SARS-CoV) [68]. SARS first appeared in southern China in November 2002. Over the next few months, the illness spread to more than 24 countries in North America, South America, Europe, and Asia, and it was recognized as a global threat in March 2003. This major outbreak was contained by July 2003. The most recent human cases of SARS were reported from China in April 2004 in an outbreak that was caused by laboratory-acquired infections [69]. At the time of this writing, there is no known SARS transmission in the world [70]. SARS is a potential agent for bioterrorism. Rapid and easy transmissibility of this agent by respiratory droplet and airborne spread and short incubation period add to its threat.

SARS-CoV-like viruses were isolated from Himalayan palm civets and a raccoon dog in an animal market in southern China, which suggests that SARS-CoV may have originated from these or other wild animals [71]. Considering the possibility that these wild animals or a human reservoir of SARS-CoV still may exist, there is a concern that SARS may return [72].

Transmission

SARS is transmitted from person to person by respiratory droplet and airborne spread [73,74]. SARS-CoV has been isolated from sputum, nasal

secretions, serum, feces, and bronchial washing specimens, however, which suggests that alternate modes of transmission may exist. Strict adherence to contact and droplet precautions with added airborne precautions can prevent SARS transmission in most cases. Use of surgical or N95 masks significantly reduces the transmission [75].

Clinical features

The incubation period typically is 2 to 10 days, but it may be prolonged. Initial symptoms include a prodrome of fever usually accompanied by dry cough, headache, myalgias, and other nonspecific symptoms, which usually is followed by development of pneumonia with worsening of respiratory symptoms.

Laboratory diagnosis

Diagnosis of SARS should be confirmed by SARS-CoV-specific microbiologic and serologic studies, including viral culture and RT-PCR from clinical specimens and antibody testing using enzyme immunoassay. Sensitive and specific tests that can yield results within hours are needed, especially in the setting of an outbreak. Real-time nested PCR has the potential for increased sensitivity and early diagnosis of SARS [76].

Treatment

Several antiviral and anti-inflammatory agents have been evaluated for treatment of SARS, including ribavirin, oseltamivir, ritonavir-lopinavir, interferon alfa, and corticosteroids [77–81]. Sufficient evidence to recommend any specific therapy is lacking, and the mainstay of treatment remains supportive care.

West Nile virus

WNV, a single-stranded RNA arbovirus, is in the family Flaviviridae. WNV was first isolated from Uganda in 1937 and subsequently was reported from Africa, Europe, Asia, Israel, and Egypt. WNV represents a potential and effective biological weapon because of persistent animal reservoir, seasonal predilection, relatively short incubation period, broad spectrum of clinical illness, and lack of vaccination.

In August 1999, WNV was detected for the first time in North America by causing an outbreak in New York City [82–84]. The WNV strain from the United States is closely related genetically to a strain from Israel from 1998, which supports the hypothesis that the WNV outbreak in the United States originated from introduction of a strain circulating in Israel [85,86]. There is no evidence, however, that WNV was introduced in the United States deliberately. It is possible that the virus was imported to North America through infected birds, infected mosquitoes, or viremic humans [85,87]. WNV is now a seasonal epidemic in the United States lasting from summer through fall.

Transmission

WNV is maintained in nature by a cycle involving mosquitoes and birds. Birds usually develop high levels of prolonged viremia and serve as amplifying hosts. Humans, horses, and dogs serve as incidental hosts. Human WNV infection can result from a mosquito bite (usually of the *Culex* spp.), infected blood products [88,89], and transplanted organs from infected donors [90].

Pathogenesis

WNV initially replicates at the site of inoculation after a mosquito bite. Virus may infect fibroblasts and vascular endothelial cells and subsequently spread to lymph nodes and bloodstream [91]. Central nervous system infection may occur as a result of viremia.

Clinical features

The incubation period for infection ranges from 2 to 14 days, but it may be prolonged. Most human infections are asymptomatic. Individuals in whom symptoms develop present with a self-limited febrile illness characterized by fever, headache, fatigue, malaise, myalgias, and gastrointestinal symptoms.

Neuroinvasive disease occurs in less than 1% of infected patients as meningitis or encephalitis, which can be complicated by acute asymmetric flaccid paralysis. Paralysis also can occur without overt meningitis or encephalitis, however [92]. Flaccid paralysis results from involvement of anterior horn cells by WNV and is similar to that seen with poliomyelitis.

Laboratory diagnosis

The most commonly used method of diagnosis is detection of IgM antibody to WNV in serum or cerebrospinal fluid, which provides strong evidence of recent WNV infection. WNV also can be detected from cerebrospinal fluid, blood, or tissue by isolation or nucleic acid amplification tests. RT-PCR and nucleic acid sequence-based amplification techniques are more sensitive than culture to detect WNV infection [93].

Treatment

Treatment is mainly supportive care. Trials of interferon alfa and intravenous immunoglobulin for treatment of WNV infection are currently ongoing. Currently no human vaccine is available for WNV infection.

Monkeypox virus

Human monkeypox is caused by monkeypox virus, a member of the family Poxviridae and genus *Orthopoxvirus*. Other important viruses in this group include variola virus (virus that causes smallpox) and vaccinia virus (virus used in smallpox vaccine). The first human cases of monkeypox

were reported in 1970 in the Democratic Republic of Congo (formerly the Republic of Zaire) [94,95]. Since then, the disease has been endemic in Congo basin countries of Africa.

Since the discontinuation of routine smallpox vaccination and resulting lack of immunity in the population, there are concerns about the potential use of monkeypox virus as a bioterrorism agent. The risk also includes recombination between various pox viruses and genetically engineered manipulation of monkeypox virus to exhibit greater virulence and transmissibility. In 2003, monkeypox virus emerged for the first time in the Western Hemisphere when an outbreak of human monkeypox occurred in the midwestern United States [96–98]. Most of the patients got sick by having direct contact with pet prairie dogs that became infected after being housed with rodents imported from Ghana in western Africa [96,97]. In contrast to African patients, most US patients with mild self-limited illness.

Transmission

Monkeypox is transmitted to humans by direct contact or during handling of infected animals. Human-to-human transmission can occur by large respiratory droplets during prolonged face-to-face contact [99] or by touching body fluids of a sick person.

Clinical features

The incubation period is 10 to 14 days. Prodromal symptoms include fever, malaise, and lymphadenopathy. Most clinical features of human monkeypox disease resemble those of ordinary smallpox, but lymphadenopathy is considered a distinguishing feature of human monkeypox. Rash is distributed mainly on the trunk, but it can spread in a peripheral fashion toward the palms and soles. The clinical course can be complicated by secondary skin and soft tissue infections, pneumonitis, encephalitis, and ocular complications [100].

Laboratory diagnosis

Various laboratory tests for diagnosis of monkeypox virus include PCR, electron microscopy, IgM and IgG ELISA, immunofluorescent antibody assay, and histopathology, but many of these tests cannot differentiate between different orthopoxviruses. Virus isolation using cell culture or chick chorioallantoic membrane in conjunction with DNA-based assay is considered to be a definitive test for identification of monkeypox virus [101].

Treatment and prevention

Cidofovir is a broad-spectrum antiviral drug that has in vitro activity against monkeypox virus [102], but because of its relative toxicity, it can be considered only in severe cases of human monkeypox virus infection. No data are currently available on effectiveness of vaccinia immunoglobulin for treating human monkeypox virus infection or its complications.

Vaccination with vaccinia virus is protective against infection with monkeypox virus [103,104].

Genetically engineered biological weapons

Biologic threats now are categorized as conventional or genetically modified agents. Traditional biological weapons include naturally occurring organisms or toxins characterized by their ease of production, toxicity, stability, and modes of transmission. The dangers associated with conventional agents can be enhanced by genetic modification. Examples of potential genetic modifications include increased virulence, antibiotic resistance, toxin production, enhanced aerosol stability, and improved survival of the biologic agents.

Continuous development and advances in biotechnology have tremendous potential to revolutionize present and future biologic threats by facilitating an entirely new class of fully engineered agents, referred to as advanced biological warfare agents. Advanced biological warfare agents are specifically engineered to target specific organ system (eg, cardiovascular, gastrointestinal, neurologic) or specific biologic processes (eg, incapacitation, neurologic impairment, death) [105].

Summary

The threat of using weaponized forms of certain biologic agents against civilian populations through bioterrorism attacks has emerged over the past few years. With advances in biotechnology, category C bioterrorism agents and emerging pathogens may become attractive weapons for bioterrorists. For bioterrorists, category C bioterrorism agents and emerging pathogens have many advantages over conventional weapons and other biologic agents listed under categories A and B, including their relatively low costs; their relative accessibility; and the relative ease with which they could be produced, be delivered, and avoid detection. Their use, or even threatened use, is potentially capable of producing widespread social disruption. Although biotechnology is a tool by which bioterrorists could develop weapons of mass destruction, it also should be used to improve the methods of fighting such weapons.

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