IV. AGENT SPECIFIC INFORMATION

EBOLA VIRUS

Overview

Ebola hemorrhagic fever (EHF) is a viral disease that occurs in humans and nonhuman primates. It is fatal in 50% to 90% of clinically ill cases.

EHF is caused by infection with Ebola virus, one of two members of a family of RNA viruses called Filoviridae. (The other known member of this family is Marburg virus.) 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. The fourth, Ebola-Reston, has caused disease in nonhuman primates, but not in humans.

The exact origin and natural habitat (natural reservoir) of Ebola virus remain unknown. However, on the basis of available evidence and the nature of similar viruses, researchers believe that the virus is zoonotic (animal-borne) and that it naturally occurs in an animal that does not get disease and that is native to the African continent. The fruit bat has recently been implicated (Leroy et al. 2005). A similar host is probably associated with Ebola-Reston which was isolated from infected monkeys that were imported into the United States and Italy from the Western Pacific. The virus is not known to be native to other continents, such as North America.

Epidemiology and History

Ebola has appeared sporadically since it was first identified in 1976. According to the World Health Organization, approximately 1,850 cases with over 1,200 deaths have been documented since the Ebola virus was discovered (WHO 2004).

Transmission

Ebola virus can be transmitted through direct contact with blood, body fluids, or tissues of an infected person or animal. This includes contact with objects, such as needles, that have been contaminated with infected secretions. Consequently, medical personnel and family members who care for an infected patient, without using appropriate barrier precautions, are those generally at highest risk for a secondary infection. Patients infected with Ebola virus are not known to be infectious prior to onset of symptoms. There are reports of Ebola virus transmission occurring within a few days after onset of fever; however, the presence of other symptoms in the source patients and the level of exposure to body fluids among secondary cases are unknown in these instances.

Ebola-Reston appeared in a primate research facility in Virginia, where it may have been transmitted from monkey to monkey through the air. While all Ebola virus species have displayed the ability to be spread through airborne particles under research conditions,

this type of spread has not been documented among humans in a real-world setting, such as a hospital or household.

While virus or viral RNA has been found in seminal fluid in patients recovering from Ebola infection (Emond 1977, Rodriguez 9), there is no direct evidence of sexual transmission of Ebola virus (Rodriguez 1999, Rowe 1999). With the closely related Marburg virus, there is one documented case of probable sexual transmission that occurred when the infected individual was well along in convalescence (Martini 1968). Ebola virus has been shown to be present in the genital secretions of convalescents several weeks after illness; however, the potential for transmission of sexual contacts with a recovered case has not been determined (WHO 1997).

Symptoms

The incubation period for EHF ranges from 2 to 21 days. 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 also be present.

Infection usually leads to impairment of cells that maintain the structure of blood vessels and to dysfunction of the clotting system. Consequently the patient may have massive internal bleeding and fluid loss from the circulatory system in all organs. Some patients have died, however, without showing signs of bleeding.

Diagnosis

Clinical diagnosis is based on the constellation of symptoms described above, and suspected exposure to the Ebola virus. Specialized laboratory tests that detect components of the virus can be used to diagnose a case of EHF 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 antibodies. Laboratory tests can be used to diagnose the disease in samples taken from deceased patients.

Treatment

There is no vaccine or antiviral treatment for EHF. Patients receive supportive therapy as standard treatment. This consists of balancing the patient’s fluids and electrolytes, maintaining their oxygen status and blood pressure, and treating them for any complicating infections.

Researchers do not understand why some people are able to recover from EHF and others cannot. However, it is known that patients who die usually have not developed a significant immune response to the virus at the time of death. The search for effective treatments is an active area of research.

Prevention

Transmission of Ebola can be prevented by avoiding contact with blood or secretions of an infected person or animal. This can be accomplished through infection-control measures including using sterilized needles and equipment and wearing protective clothing such as masks, gloves, gowns, and goggles. If a person or animal with EHF dies, it is important to avoid direct contact with the body of the deceased.

Research

Basic research includes examining the mechanism by which the virus enters and infects cells, which may help to identify targets for anti-Ebola virus therapies. Scientists are currently developing vaccines that protect monkeys against Marburg virus before, and sometimes after, exposure. A similar vaccine may work against Ebola. A simple and economical assay has been created that can detect human antibodies to Ebola. Researchers are also investigating the use of monoclonal antibodies as therapies for Ebola infection.

Risk

The risk of an Ebola virus outbreak in the United States is extremely remote for many reasons. Ebola virus is transmitted through contaminated blood and body fluids or materials and objects contaminated with the virus. In the United States, in the unlikely event that a laboratory worker is unknowingly exposed to the Ebola virus and leaves the facility, immediate risks to any members of the public are so low as to be non-existent. During the incubation period (usually 2 to 21 days after exposure), individuals are not infectious to others. In fact, no Ebola infection has been reported in persons whose contact with an infected person occurred only during the incubation period (CDC 2005). This changes once individuals develop clinical symptoms.

The risk for person-to-person transmission of Ebola viruses is greatest during later stages of illness when virus loads are highest. These stages are characterized by vomiting, diarrhea, shock, and, in less than half of infected patients, hemorrhage. These symptoms would necessitate hospitalization and isolation, particularly given the worker's employment history.

Initial natural infection in humans – also known as the index case that starts a string of human to human transmission – is presumably acquired from an animal, like other zoonoses. It is noteworthy that Ebola appears to be able to replicate in some rodents without causing disease. An animal model was developed in hamsters but it required many rounds of hamster to hamster infection before any disease was evident. It is likely that in Africa many index cases are the result of handling and/or consuming "bush meat" or other animals infected with the virus, such as rodents or the Red Colobus monkey.

In Africa, where all of the Ebola outbreaks in humans have occurred, ritual preparation of the deceased for burial by family members or other villagers has resulted in infection

through direct exposure to blood, body fluid and other infective tissues. In addition, the larger outbreaks of EHF, such as those that occurred in Zaire in 1976 and 1995, were exacerbated by use and reuse of contaminated needles, syringes, and other medical equipment. Poor hygienic conditions, nursing care provided by unprotected family members, and lack of knowledge regarding the mode of transmission of the disease caused further spread of EHF through hospitals and into villages. Poor nutrition, underlying disease, limited to non-existent medical and supportive care, and many other factors associated with the poorest developing nations all contribute to the high mortality rate associated with EHF in Africa.

Risk Mitigation

The conditions described above that precipitated human outbreaks of EHF in Africa do not exist in the United States. Further, modern infection control practices routinely used as standard precautions in the U.S. and the use of "sharp safe" medical devices should effectively prevent transmission of EHF to healthcare workers and others. These practices are codified in U.S. law as the Occupational Safety and Health Administration (OSHA) Bloodborne Pathogen Standard (29CFR1910.1030) and are routinely applied in healthcare settings in the United States. Techniques include wearing protective clothing such as masks, gloves, gowns, and goggles; using infection-control measures including completely sterilizing equipment and using disposable products where indicated; and isolating EHF patients from contact with unprotected persons (CDC 2005).

Even in Africa where EHF is problematic, spread into the community has been effectively curtailed by implementing infection control measures (CDC/WHO 1998).

As a Select Agent, Ebola virus, is strictly regulated under 42 CFR Part 73, Possession, Use, and Transfer of Select Agents and Toxins; and 7 CFR 331 and 9 CFR 121 from the Department of Agriculture. These regulations specify extensive emergency response plans and reporting requirements. Emergency drills and exercises also help lower risks associated with working with this agent. Further, detailed practices and procedures, and extensive performance standards are compulsory for BSL-4 facilities. (NIH/CDC 2007). In addition, CDC stringently inspects entities that possess this agent for compliance with national standards. Strictly limiting the use of sharp instruments, and glass, and handling only anesthetized animals under BSL-4 operating conditions are also strong risk mitigating practices.

The biology and pathogenesis of Ebola virus coupled with proper planning and adherence to protocols, facility design, appropriate occupational medical support services, and illness reporting mitigate risk to the community to such an extent that it can be considered negligible.

Rationale for Inclusion

Ebola virus was chosen for inclusion in the risk assessments for several reasons. It is one of the more notorious viruses assigned to BSL-4 containment. A high mortality rate

coupled with an unknown disease reservoir; the many books, movies and articles in the popular press; and the outbreaks of severe hemorrhagic disease in African towns and villages have caused fear and concern about EHF.

MONKEYPOX

Overview

Monkeypox is a rare viral disease caused by monkeypox virus, a double-stranded DNA virus that belongs to the orthopoxvirus group of viruses. Other viruses in this group include variola (smallpox), vaccinia (used in smallpox vaccine) and cowpox.

Monkeypox disease occurs predominantly in rodents and non-human primates in Central and Western Africa. Though called monkeypox, the virus has actually been isolated from the African squirrel which may be the natural host (Khodakevich 1987, Sale et al. 2006). Laboratory studies show that monkeypox can also infect rats, mice and rabbits. Accordingly, the disease is "zoonotic" which means it can be transmitted from animal to human.

In studies in Africa, monkeypox was fatal in about 1% to 10% of people infected. This rate may be lower in the United States where nutrition and access to healthcare are higher in many cases (CDC 2003). As a comparison, fatality rates for smallpox which were as high as 30% to 40% before the disease was declared eradicated in 1980 (Damon 2007). Recently, it has become clear that there are at least two strains of monkeypox virus with differing virulence: the strain which is predominant in Western Africa causes less severe disease than the strain which predominates in Central Africa (Likos et al. 2005).

Epidemiology and History

Monkeypox was first identified at the State Serum Institute in Copenhagen in 1958 in captive monkeys (von Magnus et al. 1959). The first human case of monkeypox was observed in 1970 in the Democratic Republic of Congo (formerly Zaire) (Levine 2007). In 2003, an outbreak of the disease in humans occurred in six Midwestern and Central States of the US (IL, IN, KS, MO, OH and WI). This outbreak was subsequently traced to pet prairie dogs that were infected by exotic rodents imported from Africa (CDC 2003). This spread occurred through an extraordinary series of unlikely events which could not be anticipated and consequently for which there was no planning.

Transmission

Monkeypox is a zoonotic disease. Therefore, human monkeypox infection can occur upon contact with the blood, body fluid or lesions of an infected animal, or via a direct bite or scratch. Transmission among human subjects occurs through large respiratory droplets in prolonged, direct person-to-person contact. It can also be transmitted through contact with the body fluids or lesions of an infected person, or with virus-contaminated objects such as clothing or bedding.

The epidemiology of monkeypox may be changing. Direct transmission of monkeypox to a human host from the animal reservoir was thought to have occurred in about 80% of the

155 cases reported from 1970 to 1983 (Arita et al. 1985). Secondary transmission (among human subjects) accounted for approximately 93 of 338 (28%) reviewed from 1981 to 1986 (Heymann 1988). The low rate of secondary transmission might account for the historical lack of sustained monkeypox outbreaks among human populations.

Symptoms

On average, symptoms of monkeypox begin approximately 12 days after initial infection. Known as the "incubation period", this time between initial exposure and start of symptoms usually ranges from 7 to 17 days. Infected individuals cannot spread the disease to others during this asymptomatic incubation period (Fenner et al. 1988).

The interim case definition for human monkeypox was updated January 2004 (CDC 2004). Initial symptoms of monkeypox may include fever, chills and/or sweats, sore throat, cough, headache, backache, swelling of the lymph nodes, or shortness of breath. Within 1- 3 days of fever onset, the patient develops a papular rash (raised bumps on the skin). This often develops first on the face and periphery and then spreads inward to the trunk. This "centrifugal" type of spread is helpful in making the differential diagnosis from chickenpox in which lesions generally start on the trunk and spread outward. The papules become pustular and the resulting generalized rash is clinically indistinguishable from that of smallpox. The major distinction from smallpox is the presence of swollen lymph nodes (lymphadenopathy). The lesions advance through several stages before crusting over and falling off over the next 2-4 weeks (CDC 2004).

Diagnosis

Initial diagnosis of monkeypox is often suggested by the presence of skin lesions and a history of contact with human or animal cases. Diagnosis is confirmed by laboratory results including: isolation of monkeypox virus in culture; demonstration of monkeypox virus DNA by polymerase chain reaction testing of a clinical specimen; demonstration of virus morphologically consistent with an orthopoxvirus by electron microscopy in the absence of exposure to another orthopoxvirus; or demonstration of presence of orthopoxvirus in tissue using immunohistochemical testing methods in the absence of exposure to another orthopoxvirus (CDC 2004).

Treatment

Currently, there is no known effective treatment for monkeypox although there is a great deal of research in this area. Though broad-spectrum, antiviral agent Cidofovir has been shown to be effective against virtually all DNA viruses including monkeypox *in vitro*, there is no published data on its effectiveness for the treatment of human monkeypox infection. CDC guidelines assert that Cidofovir can be considered for the treatment of severe cases of human monkeypox infection but because Cidofovir has considerable toxicity it should not be used for post-exposure prophylaxis (CDC, 2003). Cidofovir exerts its action by preventing the virus from replicating its DNA.

Recently, two new experimental compounds have been developed and are in Phase I clinical trials. One is a derivative of Cidofovir, HDP-Cidofovir, that is not expected to have Cidofovir's toxicity. The other is a new compound, ST-246, that acts by a different mechanism and prevents the budding of progeny virus. A recent study in ground squirrels showed that ST-246 may be a promising candidate for early treatment of severe orthopoxvirus infection (Sbrana et al. 2007).

Prevention

The most important strategy for reducing community risk from research being conducted with monkeypox virus is vaccination. A licensed, effective vaccine exists and guidance for its administration to laboratory workers is available. Since 1980, this vaccine has been recommended by the Advisory Committee on Immunization Practices to protect laboratory workers from possible infection while working with non-variola orthopoxviruses (e.g., vaccinia and monkeypox) if there are no contraindicating conditions to the vaccine (contraindications to vaccination include infection with HIV, any form of immunosuppression and pregnancy) (CDC 2001). Smallpox vaccination has been reported to reduce the risk of contracting monkeypox. In one study it was estimated that prior smallpox vaccination, defined by the presence of a vaccination scar, conferred about 85% protection against monkeypox (Arita 1985, CDC 2003). In laboratory settings, these vaccinations are recommended for protection against monkeypox.

According to data regarding the persistence of neutralizing antibody after vaccination, persons working with non-highly attenuated vaccinia viruses, recombinant viruses developed from non-highly attenuated vaccinia viruses, or other non-variola (non-smallpox) orthopoxviruses, like monkeypox, should be revaccinated at least every 10 years (McIntosh et al. 1977). To ensure an increased level of protection against more virulent, non-variola orthopoxviruses (e.g., monkeypox), empiric revaccination every 3 years can be considered (Smith et al. 1983). CDC is the only source of this vaccine for civilians and vaccine is provided only to laboratories meeting the criteria for administration to eligible employees and only under the supervision of a physician. The vaccine is shipped directly to physicians responsible for vaccinating at-risk workers. As a further control, laboratories can make vaccination a condition of employment for personnel working with monkeypox.

The role for post-exposure vaccination is less clear. Vaccinia immunization after exposure to smallpox is reported to be effective in preventing or ameliorating disease. The CDC currently recommends vaccination with the smallpox vaccine within 4 days of initial direct exposure to monkeypox, and consideration of vaccination for those who are within 2 weeks of most recent exposure.

Research

The declaration of the global eradication of smallpox by the World Health Assembly in 1980, led to the concern that variola (the smallpox virus) and other orthopoxviruses (e.g., monkeypox) might be used in bioterrorist activities. By international treaty, there are just two laboratories worldwide that are allowed to have viable samples of variola virus. However, monkeypox viruses exist naturally in Western and Central Africa, increasing the likelihood that monkeypox could be used intentionally to cause public health or societal harm. Hence, there is an increasing need to develop novel vaccines, and antiviral agents, directed against the orthopoxviruses (Sliva et al. 2007, Parrino et al. 2006).

Because monkeypox is closely related to smallpox and other orthopoxviruses, research advances in one orthopoxvirus species can often be generalized to other orthopoxvirus species. One example of research includes understanding the virus, from the basic molecular and cellular biology through expression of recombinant proteins for evaluation as candidate vaccine agents (Heraud et al. 2006, Fogg et al. 2007). Another example of this type of basic research is using the genome sequence of monkeypox and other related viruses to examine factors that influence virus spread and virulence. Understanding how the human immune system fights infection is another important aspect of research on monkeypox. For these studies an understanding of innate immunity, the body's first line of defense against disease, is crucial.

Diagnosing, preventing and treating the monkeypox virus are other key areas of research. Simple, rapid and inexpensive tests for orthopoxviruses are essential for detecting and responding to disease outbreaks. Scientists are currently working on developing safer, next-generation vaccines that will be helpful in protection from monkeypox infection. Researchers are working to develop treatments for people infected with monkeypox virus. Second generation antiviral agents are currently being evaluated and many compounds have been screened for antiviral activity against orthopoxviruses. As previously mentioned, the already licensed antiviral drug Cidofovir protects against the smallpox virus in animal model systems (Stittelaar et al. 2006).

Risk

Any possible risk to the community would come from direct contact with either an infected animal or person. The monkeypox virus is not as infectious as the smallpox virus. Moreover, the monkeypox virus is not a direct ancestor of the variola virus (or vice versa), and variola virus cannot be readily "derived" from the monkeypox virus.

Direct contact with infected animals poses a considerable risk as demonstrated by the recent outbreak of monkeypox in six states in the US. Of the 72 human monkeypox cases under investigation, 18 (i.e., 25%) were in veterinarians or veterinary staff who had contact with pet prairie dogs infected with the virus (CDC 2003).

Non-human primates have been infected with aerosolized virus in the laboratory for the study of monkeypox pathology (Zaucha et al. 2001). Hence, the aerosol route

theoretically could pose an infection risk for laboratory personnel. Therefore it is prudent for healthcare workers exposed to patients infected with monkeypox to use respiratory protection to avoid exposure to potentially aerosolized monkeypox virus. The CDC recommends the use of a NIOSH-certified N95 (or comparable) disposable respirator that has been fit-tested. Surgical masks can be used to protect against transmission through large droplets in cases where a N95 or comparable respirator is not available.

Risk Mitigation

When laboratory workers are adequately vaccinated, the risk of transmitting monkeypox virus from the laboratory, as a result of a laboratory-acquired infection, is virtually eliminated. The CDC recommends pre-exposure smallpox vaccination for veterinarians, animal-control personnel, field investigators, and healthcare workers who are investigating, or caring for, individuals suspected of having monkeypox, provided they have shown no prior contraindications to vaccination. Persons who are immunocompromised (e.g., those persons with HIV/AIDS or those who are receiving treatment with drugs that suppress the immune system) and pregnant women should not be given the smallpox vaccination, or should wait until the contraindicating condition has resolved.

Monkeypox is often handled in BSL-3 laboratories particularly if there is a potential for aerosolization of the virus. If the virus is not intentionally aerosolized, vaccinated personnel may conduct research in a BSL-2 laboratory following BSL-3 practices and procedures (DHHS 2007). In any case rigorous adherence to appropriate biocontainment practices must be observed. Needle stick injuries, direct contact with the specimen or aerosols generated by laboratory procedures are the most common cause of laboratory exposure to poxviruses. To limit the possibility of cutaneous or mucosal exposure to monkeypox, “Veterinary Standard Precautions” (animals), and “Standard (or Universal) Precautions” associated with blood borne pathogens (humans) are warranted. These precautions assume, respectively, that zoonotic disease prevention is best accomplished through good veterinary practices and that all bodily fluids are potentially infectious.

Monkeypox virus is considered a Select Agent and its possession, use and transfer is strictly regulated and laboratories are routinely inspected by the CDC for compliance. Many States and localities have enacted laws regulating Select Agents, as well. Combined with practices and procedures described in the BMBL for work with monkeypox virus; laboratory specific operating procedures; and most importantly, good hand hygiene; the risk of transmission of monkeypox virus into the community is eliminated.

Rationale for Inclusion

Monkeypox was included in the risk assessments because the disease caused so closely resembles smallpox: scientists use it as a surrogate to study the characteristics of smallpox; it is communicable from person to person; and an outbreak was caused in the United States when pet prairie dogs became infected from an African rodent imported as

an exotic pet. As a result, disease was caused in humans, both adults and children, in six States (CDC/MMWR 2003). The U.S. outbreak in 2003 and public fear that smallpox or other orthopoxviruses could possibly be used as a bioterrorist threat are additional reasons why monkeypox was included in the risk assessment.

SABIA VIRUS (BRAZILIAN HEMORRHAGIC FEVER)

Overview

Sabia Virus (SABV), the causal agent of Brazilian Hemorrhagic Fever (BrHF), is a single-stranded RNA virus that is the newest member of a family of viruses known as the arenaviruses. Since 1956, a new arenavirus has been discovered every three to five years, and many are capable of producing severe disease in humans. Of the 23 species of arenaviruses, five cause viral hemorrhagic fevers (VHF), which are severe multisystem syndromes in which the vascular (blood vessel) system of the body is damaged and which can be rapidly fatal. The five VHF-causing arenaviruses, Junin, Machupo, Guanarito, Lassa and the Sabia virus, are included in the Category A Pathogen List established by the US Centers for Disease Control and Prevention that includes agents with the greatest potential for adverse public health impact if encountered through natural outbreaks or acts of bioterrorism. The diseases caused by these five pathogens have an average case fatality rate of about 20%, (Charrel and Lamballerie 2003).

Diseases caused by arenaviruses are known as “zoonoses,” which are infections of animals that are naturally transmissible to humans. Humans acquire viral zoonotic infections when they have contact with animal species that carry the virus. Some of these animal species are known as “reservoirs” of disease, meaning that these species are natural hosts to the virus, and sometimes do not even show overt symptoms of illness when infected. Some members of the arenavirus family are thought to have rodents as reservoir species.

Epidemiology and History

Sabia virus was first recognized in 1990 in Sabia, a small village outside San Paulo, Brazil (Dyal and Fohner 2005). Only three human cases of Sabia virus infection have been reported since it was first detected in 1990. The index case was a 25-year old woman in Sabia, Brazil (PAHO 2003). This infection was naturally acquired, but the other two known infections that followed were laboratory acquired. The second case surfaced in a 39-year old laboratory technician who was working to identify the infectious agent isolated from the first case (Coimbra et al. 1994). A third case occurred in 1994 in a virologist at Yale University working in a BSL-3 facility to characterize the newly discovered virus (MMWR 1994). Exposure apparently resulted when a centrifuge bottle containing infected cell culture fluid cracked and leaked into the spinning centrifuge, releasing aerosolized virus particles into the air. While Sabia was lethal in the first patient, both of the latter two patients recovered (Coimbra et al. 1994, MMWR 1994). Although it is not known how the initial patient contracted the virus, a rodent endemic to the area surrounding Sabia has been implicated (Dyal and Fohner 2005), suggesting that rodents may be possible reservoir species for Sabia virus.

Transmission

The low number of identified cases makes it difficult to define modes of transmission. However, natural infection with other arenaviruses tends to occur through exposure to dried urine or feces from infected host rodents. These exposures may be through inhalation (contaminated dust or bedding), ingestion (contaminated food or water) or though direct contact with broken skin or with mucous membranes, such as those of the mouth or nose (Borio et al. 2002). Natural infection by SABV is thought to occur in a similar manner. Inhalation of aerosol particles was the most likely route of exposure for the two documented laboratory acquired Sabia infections, especially in the instance of the Yale researcher and the cracked centrifuge cups (MMWR 1994).

Person-to-person secondary transmission of some viral hemorrhagic fevers is known to have occurred via direct contact with bodily secretions (Borio et al. 2002) or contact with contaminated objects such as syringes and needles. No cases of secondary transmission of Sabia virus have been documented to date. In the case of the Yale researcher who contracted Sabia virus infection, none of the 142 persons he had contact with following his exposure were infected, which is a 0% secondary transmission rate (Armstrong et al. 1999).

Symptoms

While not known specifically for Sabia, most viral hemorrhagic fevers have an incubation time of 7-10 days, but it may be as few as 5 and as many as 21 days depending on the agent and the individual. Symptoms of Sabia infection can include high fever, headache, muscle pain, nausea, vomiting and generalized weakness. The progression of the disease can be severe, resulting in fluid accumulation in the lungs, blood vessel damage resulting in leakage of the blood into the organs and membranes and bleeding, liver damage, coma and death (APHA 2004).

Diagnosis

The diagnosis of any New World arenavirus is critical, since death can occur swiftly, even before antibodies against the disease are detectable (Dyal and Fohner 2005). However, Sabia can be difficult to diagnose, due to its rarity and to several endemic diseases that present a similar clinical picture. The early symptoms can be mistaken for flu, and the later stages may look like Yellow Fever or even Dengue Hemorrhagic Fever (Coimbra et al. 1994). Similarly, in the case of the Yale researcher, initial symptoms were thought to be caused by a recurrence of a previous *Plasmodium vivax* malarial infection (MMWR 1994). Antigen capture ELISA, which detects specific components of the virus, is a preferred method of diagnosis (Dyal and Fohner 2005), but definitive diagnosis relies upon the isolation and identification of whole virus particles from patient specimens (PAHO 2003). In addition, polymerase chain reaction (PCR) methods are being developed to provide rapid detection and diagnosis of arenaviruses in humans and in animal reservoirs (Charrel et al. 2005).

Treatment

Like other arenaviruses, Sabia virus appeared to be responsive to treatment with the antiviral drug ribavirin in the case of the Yale researcher who contracted the disease and was given intravenous ribavarin and recovered (PAHO 2003, Dyal and Fohner 2005). Ribavirin, a nucleoside analog, is not approved by the FDA for use against viral hemorrhagic fever (Borio et al. 2002). However, it has been shown to be effective in treating some early stage arenavirus and bunyavirus infections (Bossi 2004, Borio et al. 2002). For prevention of disease following exposure to the virus, ribavirin administered orally at 2 g/day in four divided doses is recommended (Bossi 2004, Borio et al. 2002). Ribavirin is not recommended for children, and individuals receiving treatment should avoid conceiving for six months due to the risk of birth defects, which were observed in animal testing of the drug. Ordinarily, the use of ribavirin would be discouraged in pregnant patients, but in certain cases, the seriousness of this disease may warrant consideration of the costs and benefits of this route of therapy (Bossi 2004, Borio et al. 2002)

Additionally, isolation and supportive therapy to treat symptoms related to dehydration and bleeding would be needed. Hemorrhage (bleeding) is most often the primary concern, meaning that fluid intake should be monitored carefully to compensate for vascular leaking and tissue swelling. Hydration may be an option, but this must be closely monitored since the fluid leakage that occurs with hemorrhagic fevers can lead to fluid buildup in the lungs and rapid congestive heart failure (Bossi 2004). In cases of hemorrhage, blood transfusions may be helpful in supporting clotting. Artificial ventilation, kidney dialysis and anti-seizure medication may be required, but intra-muscular injections, aspirin and nonsteroidal anti-inflammatory drugs should not be used (Borio et al. 2002).

Prevention

There is currently no licensed vaccine for Sabia virus or for any other arenavirus. There is an experimental vaccine for Junin virus (the cause of Argentine hemorrhagic fever) that has an investigational new drug (IND) status from the US Food and Drug Administration (FDA) for high-risk populations (Nierengarten and Lutwick 2002). The Junin live attenuated vaccine (also known as candid #1) is the only one that has been developed for protection against an arenaviral hemorrhagic fever. Evaluation of over 200,000 volunteers who participated in clinical trials between 1992 and 1999 showed that the vaccine stimulated an immune response in about 98% of persons tested (Maiztegui JI et al. 1998, Ambrosio et al. 2006). In animal models, the vaccine seems to provide cross protection against Machupo virus (Bolivian hemorrhagic fever), but not against Guanarito virus (Venezuelan hemorrhagic fever). It has not been tested against Sabia virus in an animal model (Nierengarten and Lutwick 2002).

Research

The recent identification of cellular receptors for several arenaviruses that are related to Sabia provides some new possible targets for drug and vaccine design. These receptors enable the virus to penetrate a cell and start an infection (Radoshitzky et al. 2007, Rojek et al. 2006, Spiropoulou et al. 2002).

Risk

Based on the very small number of known human cases of Sabia, the calculated case fatality rate of one in three (33%) may not accurately reflect the actual risk of severe illness or death posed by infection by this virus. Without additional information, the assumption must be made that the virus has a high morbidity and mortality, and that, like some other arenaviruses, it is spread through airborne/aerosolized particles. Secondary transmission of Sabia virus has not been documented to date, though secondary transmission of other arenaviruses has been reported (Briggiler et al. 1987).

The small number of Sabia cases, only one of which was caused by a natural exposure, suggests that there may be factors that have, up until the present time, prevented the Sabia virus from causing major outbreaks of disease in human populations. These factors may include limited contact between humans and the host species, rarity of the virus in nature or low transmissibility to humans or among humans. Because so little is known about this virus, the reasons that Sabia has not caused larger numbers of severe human cases are not known.

Based on what is known about other members of the arenavirus family and known symptoms of human infection with Sabia, Sabia was placed in on the CDC Category A list of pathogens, and BSL-4 facilities are required for handling of this pathogen. However, it may be reassuring that the only known death from this virus occurred from a natural exposure and that both persons infected as a result of a laboratory accident survived.

Risk Mitigation

Within the confines of a BSL-4 rated facility, the real risk of accidental aerosol-transmitted disease associated with Sabia virus research is greatly diminished by simple laboratory techniques and good microbiological practice; use of proper safety equipment (e.g., safety centrifuge cups/rotor, biological safety cabinet, etc.); and personal protective equipment such as the one-piece, positive pressure supplied air suit used at BSL-4. Multiple levels of safety procedures and equipment used in a BSL-4 facility protect laboratory workers from accidental exposure, and thus greatly reduce the risk to the surrounding community. An entire series of procedural and/or equipment failures or errors would be required in order for a biological agent to be released from a BSL-4 laboratory facility.

In the Sabia risk scenario (see Section VII), laboratory workers are infected when they obtain a mislabeled sample that is stored in a BSL-2 freezer and proceed to work with the sample (which is actually Sabia virus) under BSL-2 laboratory conditions, which provide insufficient protection against exposure. In reality, in a BSL-4 laboratory, even a mislabeled sample would be handled within that setting under multiple levels of BSL-4 procedures, equipment and precautions, which would greatly limit the possibility that a laboratory worker could be infected and subsequently expose the community to this agent.

In its designation as a CDC Select Agent, Sabia virus is stringently regulated by the Department of Health and Human Services under 42 CFR Part 73, Possession, Use, and Transfer of Select Agents and Toxins. Required under these regulations are extensive emergency response plans, reporting requirements; emergency drills and exercises that help lower the already minute risks to the community from the science conducted with this agent. Further, extensive performance standards concerning BSL-4 practices and procedures are provided in the CDC/NIH publication entitled *Biosafety in Microbiological and Biomedical Laboratories – Fifth Edition* (BMBL) and the CDC routinely inspects institutions possessing or working with this agent for compliance with these national standards.

Rationale for Inclusion

Sabia virus was included for risk assessment study as a representative of the Arenavirus family for which there are two known human cases that originated in a laboratory setting. Sabia virus causes hemorrhagic disease and there is documented aerosol transmission in the laboratory (MMWR 1994). Two of the three reported cases of Sabia virus infection have been laboratory-acquired and were most likely associated with the inhalation of laboratory-generated aerosols (Peters 2002).

RIFT VALLEY FEVER

Overview

Rift Valley Fever (RVF) is an emerging mosquito-borne viral disease of humans and domestic animals. Many associate RVF with epidemics, in areas that experience heavy rainfall. RVF is a viral hemorrhagic fever, belonging to the family *Bunyaviridae* (Mathews 1982). RVF is generally found in regions of eastern and southern Africa where sheep and cattle are raised, but the virus also exists in most countries of sub-Saharan Africa and in Madagascar.

Epidemiology and History

RVF was first described in 1931 near Naivasha in the Rift Valley of Kenya (Daubney et al. 1931). Since then, outbreaks have been reported in East and South Africa (Flick and Bouloy 2005) and currently in East Africa (CDC 2007). Human and epizootic (outbreak in animals) cases have also been reported outside the continent of Africa. One of the largest and most significant outbreaks occurred in Egypt in 1977 (Meegan 1979). Other outbreaks have extended into Saudi Arabia and subsequently Yemen in September 2000 (Madani et al. 2003, Ahmad 2000).

Transmission

RVF is most often transmitted by mosquitoes of the genera *Aedes* and *Culex* (McIntosh 1972) and sometimes by sandflies. Epidemics/epizootics most often occur while constructing dams or after periods of heavy rainfall. Water is an important factor for insect vector breeding (Flick and Bouloy 2005) as it aids the propagation of mosquitoes. One of the first epidemics in West Africa in 1987 was associated with the Senegal River Project. This construction caused flooding and altered interactions between humans and animals there, transmitting the RVF virus to humans. RVF outbreaks also have been shown to be closely coupled with climate anomalies (Davies et al. 1985). Epizootics in East Africa are correlated with heavy rainfall associated with warm El Niño–Southern Oscillation (ENSO) events (Linthicum et al. 1999) but not in West Africa (Chevalier et. al. 2004). Transovarian transmission which occurs in mosquitoes is presumed to permit the maintenance of a low level of the virus in nature in between epizootics. The horizontal (animal to animal; insect to animal) transmission from mosquitoes infects vertebrate hosts (sheep, goats, cattle, camels, and buffalo) which then infect other mosquitoes. Virus amplification occurs in these vertebrate hosts (McIntosh 1972). The densities of domestic ungulates appear to be critical for zoonotic outbreaks. Human infections contribute little to the maintenance of RVF virus transmission.

In endemic regions, much of the RVF transmission from animals to humans occurs directly through human contact with infected animal materials such as carcasses. Presumably the mechanism is aerosol transmission. Transmission of RVF to humans can also use a bridge vector that bites both domestic animals and humans. Many common

species of mosquitoes may serve this purpose. Scientists have determined that several North American mosquito species are also potential vectors of RVF virus should the virus be introduced to the continent. For this reason and the potential to cause both human and animal disease, RVF is considered a potential agent of both bio- and agro-terrorism. Significant economic losses would be incurred should RVF virus be introduced into agricultural animals in the United States.

Symptoms

In livestock, newborn calves, lambs and kid goats are the most susceptible (Olaleye 1996, Ksiazek 1989). The incubation period of 24 hours is followed by fever, loss of appetite and abnormal breathing; 90 percent mortality is seen in calves, lambs and kid goats 3 days after exposure. The symptoms of acute disease are bloody stools and/or nasal discharge. Among flocks and herds, abortion is often the first indication of the disease. The disease in adult animals ranges from unapparent to acute.

Though RVF is primarily a veterinary public health problem on the African continent, humans, including veterinarians and livestock industry personnel (through slaughtering or handling of infected animals) are also highly susceptible to infection. Laboratory-acquired infections of RVF through inhalation of infective aerosols have often been recorded (Sabin and Blumberg 1947, Harding and Byer 2006) as have infections caused by direct contact with infectious animal tissues.

Disease in humans usually presents with mild clinical manifestations ranging from headache, fever and muscle ache but may be more serious and include hepatitis and conjunctival injection (red eye) (Peters and Meegan 1981). A small percentage (<1%) develop hemorrhagic disease, or encephalitis and those who survive may have ocular sequelae (primary retinal vasculitis) (Wilson 1994, Gerald et al. 2000) often resulting in blindness. Of those individuals exhibiting hemorrhagic disease, approximately 50 percent die.

Diagnosis

There is currently no licensed diagnostic assay available for RVF in humans. Those who work in high risk professions in RVF-endemic areas are at an increased risk of contracting this disease from animals. Though some patients could develop more severe illness, including hemorrhagic fever, encephalitis, or ocular disease, most human illness resolves two days to one week after onset of illness.

Treatment

Treatment for those infected with RVF virus has yet to be well defined. However, the antiviral ribavirin has been observed in studies in monkeys and other animals to be a promising drug that may be used in the future in humans. Additional studies suggest that interferon, immune modulators, and convalescent-phase plasma may also help in the treatment of patients with RVF.

Prevention

Mosquito repellants and bed nets are two ways to decrease contact with mosquitoes and other bloodsucking insects. Additionally, avoiding exposure to animals infected with the virus is another important preventive measure for those working in RVF-endemic areas.

An animal vaccination program is critical in preventing the disease, especially in endemic areas. The live vaccine produces life long immunity, but may cause abortion if given to pregnant animals. Animals in the U.S. are not vaccinated against RVF virus because the virus does not exist on the North American continent. The killed vaccine does not harm the fetus. An inactivated vaccine for humans, that is not available commercially, has been used under an investigational new drug (IND) application in the U.S. to protect laboratory workers from RVF.

Research

Scientists have made one more step forward in developing alternative animal models for RVF that can be studied in lower level biocontainment facilities. Using two less pathogenic viruses, it was determined in hamster models that infections with Punta Toro (PT) and Gabek Forest (GF) viruses resembled RVF in pathologic changes and illness.

Antiviral research is another area critical to controlling and treating this disease. Researchers have conducted therapeutic studies with a similar virus, PT, that does not require the same high level of biocontainment as RVF. They found that liposomes complexed to noncoding plasmid DNA given before or after PT virus challenge overwhelmingly protected animals in the study. The data obtained from this study may suggest prevention and treatment of RVF is possible through these approaches. In addition, a live attenuated vaccine is being studied and is in Phase I clinical studies.

Continuing research efforts in RVF research focus on advancing development of vaccine and drug candidates; monitoring RVF infection in animal and human populations; and understanding the role of transmission in RVF disease.

Risk

The actual risks to the public of acquiring RVF as a result of a laboratory accident, infected worker or insect, or other mishap is exceedingly small and are greatly reduced by simple laboratory techniques and good microbiological practice; use of proper safety equipment (e.g., safety-sealed centrifuge cups/rotor, biological safety cabinet, etc.); and personal protective equipment including respiratory protection. There is no known human-to-human transmission. While there is no licensed vaccine for use in humans, there are effective licensed vaccines for use in animals. Immunization of animals against RVF drastically lowers the incidence of disease in humans by removing a susceptible host in which the virus can replicate. This helps reduce both vector-borne and occupational illness in humans. In Africa during epidemics, bans on slaughtering animals

and sale of meat from potentially infected species of animals may be instituted as a public health measure.

Risk Mitigation

RVF virus is a Select Agent regulated by the Department of Agriculture under 7 CFR Part 331 and 9 CFR 121; and by the Department of Health and Human Services under 42 CFR Part 73, Possession, Use and Transfer of Select Agents and Toxins. In healthcare settings, modern infection control practices routinely used as standard precautions in the U.S. and the use of "sharp safe" medical devices effectively prevent transmission of RVF to healthcare workers. As RVF virus is a pathogen of serious agricultural concern and is highly infectious for humans, stringent safety practices and procedures are practiced in laboratories working with this virus (DHHS 2007). CDC routinely inspects institutions in possession of or working with this select agent to comply with national standards.

Rationale for Inclusion

Rift Valley Fever was included for risk assessment study as there is an ongoing epizootic (epidemic in animals) of RVF in cattle and sheep in east Africa (Kenya, Somalia, and Tanzania) that, as of May 1, 2007, has caused at least 1065 confirmed human cases and 315 deaths. Humans are highly susceptible. RVF has caused laboratory-acquired infections through the respiratory and bloodborne routes. There have been 103 laboratory-acquired infections, resulting in four deaths, published in the scientific literature (Paragas and Endy 2006). Because of the aggressive nature of RVF-transmitting mosquitoes through human and animal biting, scientists worry that RVF could reach the U.S. from the African continent (Becker 2004), thereby impacting human and animal health and the U.S. economy.