

Viral Hemorrhagic Fevers—Ebola and Marburg

African Hemorrhagic Fever

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Importance

Ebola and Marburg hemorrhagic fevers are severe zoonotic diseases seen in humans and non-human primates. Most species of ebolavirus and the only known species of marburgvirus occur in Africa. Primates are infected sporadically from an unknown source; current evidence suggests that the reservoir hosts are probably bats. Humans seem to become infected directly from bats in caves, as well as when they contact tissues from infected apes and other species. Once the virus has entered the population, it can spread from person to person. Some epidemics affect hundreds of people and decimate entire villages, particularly where hospital facilities and medical supplies are inadequate and nosocomial spread occurs. Although the mortality rate varies, the most pathogenic viruses kill up to 90% of those who become infected. No vaccine is available, and the only treatment is supportive. Epizootics in gorillas and chimpanzees are equally serious, and appear to threaten the survival of these species in the wild. Other wild mammals including duikers also seem to be killed during outbreaks.

One species of ebolavirus, *Reston ebolavirus*, occurs in the Philippines. Until 2008, this virus was known only as an infection of nonhuman primates. It does not appear to be a human pathogen; although some people in contact with this virus have seroconverted, they remained asymptomatic. Between 1989 and 1996, *Reston ebolavirus* was isolated repeatedly at primate quarantine facilities in the U.S. and Italy; in all but one instance, infected monkeys had been imported from a single facility in the Philippines. The source of the virus was never found, but infected monkeys do not seem to have been exported since this facility was closed in 1997. In December 2008, *Reston ebolavirus* was discovered in pigs during an unusually severe outbreak of porcine reproductive and respiratory syndrome (PRRS) in the Philippines. Genetic evidence suggests that the virus may have been circulating in these swine populations since 1989 or earlier. Whether *Reston ebolavirus* can cause disease in swine or is an incidental finding is unknown. Its full host range, reservoir host(s) and geographic range also remain to be discovered.

Etiology

Ebola and Marburg hemorrhagic fever are caused by members of the genera *Ebolavirus* and *Marburgvirus*, respectively. These viruses are the only members of the family Filoviridae. The genus *Ebolavirus* contains four recognized species: *Zaire ebolavirus* (formerly Zaire Ebola virus), *Sudan ebolavirus* (formerly Sudan Ebola virus), *Ivory Coast ebolavirus* (formerly Cote d'Ivoire Ebola virus) and *Reston ebolavirus* (formerly Reston Ebola virus). At least 13 strains of these viruses have been identified. A fifth species, tentatively named *Bundibugyo ebolavirus*, was isolated from a recent outbreak in Uganda. *Marburgvirus* contains a single species, *Lake Victoria marburgvirus* (formerly Marburg virus). Six strains of *Lake Victoria marburgvirus* had been recognized as of 1990; at least nine genetically distinct strains were identified from a more recent outbreak in the Democratic Republic of the Congo.

Geographic Distribution

Zaire ebolavirus, *Sudan ebolavirus*, *Ivory Coast ebolavirus* and *Bundibugyo ebolavirus* are endemic in several African countries south of the Sahara desert. The pattern of outbreaks seems to suggest that each filovirus may have a distinct geographic range. *Ivory Coast ebolavirus* has been reported only from West Africa, while *Sudan ebolavirus* tends to occur in eastern Africa (Sudan and Uganda), and *Zaire ebolavirus* has been seen mainly in the west-central region (Gabon, Republic of the Congo and Democratic Republic of the Congo [formerly Zaire]). *Bundibugyo ebolavirus* was reported from an outbreak in Uganda. However, recent serological surveys suggest that some of these viruses may be more widespread. Antibodies to *Zaire ebolavirus* have been found in nonhuman primates and bats in much of central Africa; seropositive animals were found in some countries, such as Cameroon, where outbreaks of Ebola hemorrhagic fever have never been reported.

Lake Victoria marburgvirus has been found in bats, nonhuman primates and/or humans from eastern Africa to the far western edge of the Congo. This virus has

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caused epidemics in African countries including Angola and Uganda. One case reported from South Africa may have been acquired in Zimbabwe. In 1967, *Lake Victoria marburgvirus* caused an outbreak in Germany and Yugoslavia, when humans were exposed to tissues from imported green (vervet) monkeys (*Cercopithecus aethiops*).

Reston ebolavirus is the only filovirus known to be endemic outside Africa. This virus occurs in the Philippines, but outbreaks have been seen in imported, non-human primates at quarantine facilities in the United States and Italy. In each case, the virus was eradicated.

Transmission

Filoviruses seem to emerge in primates after infection from an outside source. The reservoir hosts have not been definitively identified, but bats are the most likely candidates. Although virus isolation has not yet been successful, RT-PCR and serologic evidence suggest that *Zaire ebolavirus* infections occur in African fruit bats (*Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*), and *Lake Victoria marburgvirus* infections occur in fruit bats (*Rousettus aegyptiacus*) and insectivorous bats (*Rhinolophus eloquens* and *Miniopterus inflatus*). Bats that are experimentally infected with ebolavirus become viremic for up to four weeks but remain asymptomatic. How viruses are transmitted from bats to primates or other mammals is unknown. In addition to bats, there may be other reservoir and/or amplifying hosts.

Humans often become infected with ebolaviruses after handling the carcasses of animals found in the forest, particularly nonhuman primates and duikers (forest antelope). The virus is thought to enter the body through mucous membranes and broken skin. Filoviruses are probably also transmitted directly from bats to humans. Some marburgviruses infections have been acquired by exposure to primate tissues, while others were associated with transmission within caves, possibly from infected bats. Filoviruses can be spread from person to person. High viral titers occur in blood, which can contaminate the environment during the hemorrhagic stage of the disease. These viruses are also found in many secretions and excretions that are not visibly contaminated with blood, including saliva, tears, breast milk, semen and feces. Urine may be a source of virus; however, *Zaire ebolavirus* was absent from patients' urine during a recent outbreak. Filoviruses disappear from blood and most tissues after the acute stage of the disease, but some body fluids can contain these viruses for a few months. In one patient, *Lake Victoria marburgvirus* was transmitted sexually 13 weeks after the onset of disease. *Zaire ebolavirus* was also isolated from the semen of a convalescent patient up to 82 days after the onset of clinical signs, and detected by RT-PCR up to 91 days. The latter virus was recovered from the breast milk of a convalescing patient, 15 days after the onset of disease.

Filoviruses have been reported to survive for some time in blood and tissues at room temperature. Fomites, particularly those contaminated by blood, can transmit these viruses. Aerosol transmission has been reported in nonhuman primates, but it does not seem to be important during human outbreaks. Arthropod-borne transmission is theoretically possible, but most authors suggest it is unlikely.

Disinfection

Filoviruses can be destroyed by autoclaving. Treatment with sodium hypochlorite (1:100 dilution of household bleach) or standard hospital disinfectants can also be used. Ebolaviruses are reported to be susceptible to 2% sodium hypochlorite, 2% glutaraldehyde, 5% peracetic acid and 1% formalin. These viruses can also be inactivated by ultraviolet light, gamma irradiation, 0.3% betapropiolactone for 30 minutes at 37°C [98.6°F], or heating to 60°C [140°F] for 1 hour. Marburgvirus is susceptible to 1% sodium hypochlorite, 2% glutaraldehyde or formaldehyde, ultraviolet light and heat.

Infections in Humans

Incubation Period

The incubation period for filoviruses can be as short as two days or as long as 21 day; in most cases, symptoms appear in 4 to 10 days.

Clinical Signs

Lake Victoria marburgvirus and the Zaire, Sudan and Ivory Coast species of *ebolavirus* usually cause similar diseases; however, the mortality rate, speed of onset and severity of disease vary with the virus. The symptoms usually appear abruptly; the initial signs may include fever, chills, headache, severe malaise, muscle aches, abdominal pain, nausea, vomiting and diarrhea. Some patients develop conjunctivitis or pharyngitis with a nonproductive cough. A purplish-red, maculopapular rash may also be seen; this rash is especially common on the trunk and shoulders of patients infected with *Zaire ebolavirus*. After a few days, patients may develop mild to severe bleeding tendencies. In mild cases, this may be limited to bruising, bleeding of the gums, epistaxis, petechiae and/or mild oozing from venipuncture sites. In severe cases, patients have hemorrhages from the gastrointestinal tract or other sites, go into shock, and develop multi-organ failure. Although many patients die, some begin to recover after a week or two. Recovery is more likely if the bleeding tendencies were mild. During convalescence, which can be slow, some patients develop joint pain, deafness, orchitis or pericarditis.

Unlike other filoviruses, *Reston ebolavirus* does not seem to be pathogenic for humans. Asymptomatic seroconversion can be seen.

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Communicability

Filoviruses can spread between humans by contact with blood, body fluids and excretions, and tissues. Large quantities of ebolavirus have been found in blood as soon as two days after the onset of symptoms. During the acute stage of the disease, filoviruses are also found in many secretions and excretions that are not visibly contaminated with blood, including saliva, tears, breast milk, semen and feces. Aerosol transmission may be possible, but it does not seem to be a significant route of transmission during between humans.

Some body fluids can contain viruses for up to a few months after recovery. *Zaire ebolavirus* has been isolated from the semen of convalescent patients up to 82 days after the onset of clinical signs, and detected by RT-PCR up to 91 days. In one case, *Lake Victoria marburgvirus* was transmitted sexually 13 weeks after the onset of symptoms. *Zaire ebolavirus* was isolated from the breast milk of a recovering patient, 15 days after the onset of disease, and transmission to a nursing child may be possible. How long filoviruses can be found in milk is unknown. Some authors speculate that filoviruses might also occur within the eye, which is an immunologically privileged site, during convalescence. With these exceptions, filoviruses do not seem to persist after recovery from acute disease, and one study reported that the risk of transmission by casual contact after discharge from the hospital appears to be low.

Diagnostic Tests

Ebola or Marburg hemorrhagic fever can be diagnosed by detecting antigens with an antigen-capture enzyme-linked immunosorbent assay (ELISA) or immunostaining, and by detecting viral RNA with reverse transcription polymerase chain reaction (RT-PCR) assays. Virus isolation is also used. Ebolaviruses and marburgvirus can be recovered in many cell lines, including Vero or Vero E6 cells. In humans, filoviruses are most reliably isolated from the blood during the acute-stage of the disease, but they may also be found in throat washes, urine, semen, anterior eye fluid and other fluids, and in many tissues including the skin. Skin biopsies are often taken at post-mortem for immunohistochemistry. Serology is valuable, particularly in later stages of the disease. Serological assays include ELISA tests that detect IgM and IgG, as well as the indirect immunofluorescence assay (IFA). Neutralization tests are unreliable for filoviruses. Because the consequences of misdiagnosis (including false positive diagnosis) are severe, multiple techniques are used to confirm the infection whenever possible.

The remote location of most epidemics can make the initial diagnosis challenging. Most diagnostic specimens must be sent to BSL-4 laboratories, which are usually unavailable where outbreaks occur. Virus isolation is sometimes unsuccessful because a cold chain cannot be maintained. Diagnostic techniques that can be used in

remote areas without extensive laboratory facilities, including methods that use recombinant antigens, are in development.

Treatment

No specific treatment is available. Supportive therapy generally consists of intravenous fluid replacement to maintain blood volume and electrolyte balance, as well as analgesics and standard nursing care. Although more specific treatments have been attempted, most have apparently had little effect on the outcome. Some techniques being tested in laboratory animals are promising when used early in the incubation period, but none have entered human clinical trials. The antiviral drug ribavirin does not seem to be effective. Strict infection control measures and barrier nursing precautions must be used during treatment, to prevent infection of medical staff.

Prevention

In Africa, the index case is often associated with exposure to the tissues of an infected animal during butchering. Most cases have been linked to exposure to chimpanzee, gorilla or duiker carcasses, but one person butchered mandrills shortly before becoming ill. Because the full host range may not be known, all sick and dead wild animals should be avoided. These animals should not be touched, eaten or fed to other animals. To prevent infection from animals that appear healthy but are incubating the disease, good personal hygiene should be used when handling and preparing meat, and the meat should be thoroughly cooked. Meat inspection and testing, where available, also protects consumers. Some filovirus infections have been linked to exposure to caves. Particular care should be taken to avoid areas infested with bats. If contact with bats or caves is unavoidable, personal protective equipment and good hygiene should be used; however, the means of transmission from bats to humans is still unknown. Surveillance for deaths and illness in wild animals, particularly nonhuman primates, may provide an early warning to prevent human epidemics.

Human epidemics can be stopped by isolating patients in facilities with barrier nursing procedures and strict infection control measures. Healthcare workers should use good hygiene and personal protective equipment including gloves, gowns, masks and eye protection to prevent exposure to blood and body fluids. Burial practices should avoid all contact with the body or fomites. In some remote areas of Africa, where disinfectants and routine medical supplies are not readily available, these measures are challenging to achieve. Precautions should also be taken to avoid spreading the disease during convalescence. Sexual transmission is possible during this period, and abstinence should be practiced for at least three months after recovery. If possible, mothers should avoid breastfeeding for a time; ebolavirus may be found in the milk for at least 15 days

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after the onset of disease. No vaccines are currently available for humans, but some promising vaccines are in development.

The *Reston ebolavirus*, which was recently discovered in pigs in the Philippines, is not known to affect humans. However, as a precaution, tissues from infected animals should not be eaten or handled. Good hygiene and appropriate personal protective equipment should be used by individuals who must handle these animals or their tissues.

Morbidity and Mortality

Ebola and Marburg hemorrhagic diseases are most likely to occur in people who butcher carcasses or enter caves and mines. Once infected, people often transmit the disease to family members and others in contact. Healthcare workers are at high risk, as hospital supplies are often limited or nonexistent in areas where filoviral diseases occur. In some cases, hundreds of people may become infected through nosocomial transmission, unsafe self-treatment at home, and other routes. Strict isolation, good infection control measures and barrier nursing can halt the spread of the disease: in some cases, infections have been limited to a few contacts.

Outbreaks of Ebola hemorrhagic fever are reported periodically in Africa. The number of outbreaks has increased in the last ten years, due either to a higher incidence or better recognition of the disease. Marburg hemorrhagic fever was only recently recognized as a serious and recurring problem in humans. *Lake Victoria marburgvirus* was first discovered in Europe in 1967, when laboratory workers were exposed to infected tissues from imported primates. Between 1967 and 1994, only six cases of Marburg were reported, all from Africa; three cases occurred in travelers and three in their contacts. However, in 1998, this virus caused an epidemic that affected hundreds of people in the Democratic Republic of the Congo (DRC). This outbreak was associated with a mine where infected bats were later discovered. Several different strains of *Lake Victoria marburgvirus* were isolated during the epidemic, suggesting that this virus had been introduced repeatedly into the population via infected miners. This outbreak also uncovered a pattern of hemorrhagic disease in the mine dating to 1987 or earlier, and one survivor of an earlier outbreak was found to have antibodies to this virus. In 2004-2005, another large Marburg outbreak was reported in Angola, where *Lake Victoria marburgvirus* was not thought to exist.

In human populations, the African filoviruses usually have high mortality rates. *Zaire ebolavirus* is the most pathogenic virus. The case fatality rate for this infection was 59% to 88% in all outbreaks to 2008; in five of seven epidemics, it was at least 78%. *Sudan ebolavirus* is less virulent, with a case fatality rate of 41-65%. Only one outbreak of *Bundibugyo ebolavirus* has been reported; the case fatality rate was 36%. *Ivory Coast ebolavirus* was only reported once; in 1999, a scientist developed a fatal

hemorrhagic illness after performing an autopsy on a wild chimpanzee that had died from a similar disease. The mortality rate for *Lake Victoria marburgvirus* varies widely. The 1967 outbreak in Europe had a case fatality rate of 22-23%, and three of the six patients reported between 1967 and 1994 died. However, the case fatality rate may have been as high as 83% (56% in laboratory-confirmed cases) during the 1998-2000 outbreak in DRC, and it was 88% during the 2004-2005 outbreak in Angola. It is not known whether the high mortality rates in recent outbreaks are associated with more virulent strains of the virus, higher doses, concurrent malnutrition and disease, or the availability and quality of healthcare. It is also uncertain whether African filoviruses can cause mild or asymptomatic infections. Antibodies have been reported in people who have no history of Ebola or Marburg hemorrhagic disease, but in some cases, the illness may have been misdiagnosed as another disease such as malaria. Cross-reactivity with other viruses may also be a problem. Seroprevalence rates tend to be higher in groups that have more contact with wild animals.

Reston ebolavirus can infect humans but has never been associated with disease. Seroconversion is possible, but does not seem to be common. In the Philippines, antibodies to this virus were reported in 6 of 141 individuals tested.

Infections in Animals

Species Affected

Bats are the probable reservoir hosts for filoviruses. Viral RNA and antibodies to *Zaire ebolavirus* have been found in three species of arboreal fruit bats: *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata*. *Lake Victoria marburgvirus* RNA and antibodies to this virus have been found in a cave-dwelling fruit bat (*Rousettus aegyptiacus*) and an insectivorous bat (*Rhinolophus eloquens*). RNA alone was detected in an insectivorous bat of the species *Miniopterus inflatus*. Attempts to isolate either virus from wild bats have been unsuccessful, but two genera of bats (*Epomophorus* and *Tadarida*) remained viremic for up to four weeks after intravenous inoculation with *Zaire ebolavirus*. Reservoirs have not been reported for *Sudan ebolavirus*, *Reston ebolavirus* and *Ivory Coast ebolavirus*, but these viruses may also be transmitted by bats. Other reservoir or amplifying hosts may also exist, but there is little evidence to implicate any species. In 1998, *Zaire ebolavirus* RNA was detected in six mice (*Mus setulosus* and *Praomys* sp) and a shrew (*Sylvisorex ollula*). These species were proposed as possible reservoir hosts, but the results have not been confirmed by other groups, and virus isolation was unsuccessful.

Although bats seem to carry filoviruses asymptotically, these viruses are pathogenic in incidental hosts. The African filoviruses (all filoviruses except *Reston ebolavirus*) cause severe disease in both

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humans and nonhuman primates. Domesticated animals do not seem to be affected by these viruses, but wild primates and other wildlife are susceptible. In Africa, Ebola outbreaks have been linked to reports of dead and dying gorillas (*Gorilla gorilla*), chimpanzees (*Pan troglodytes*), mandrills (*Mandrillus* sp.), guenon (*Cercopithecus* sp.) and other monkeys, as well as duikers (a species of forest antelope, *Cephalophus dorsalis*), bush pigs (red river hog, *Potamochoerus porcus*) and other species. Attempts to isolate ebolaviruses or detect viral RNA have been successful only in chimpanzees, gorillas and duikers. It is not known whether other species were affected by Ebola or other diseases. However, antibodies to ebolaviruses have been reported in mandrills, drills (*Mandrillus* sp.), baboons (*Papio* sp.), colobus monkeys (*Colobus badius*) and guenon, as well as chimpanzees and gorillas, suggesting that these species might become infected. One study detected antibodies in dogs, but death or illness has not been reported in this species. Experimental ebolavirus infections have been established in nonhuman primates, newborn mice and guinea pigs, which become ill, and bats, which remain asymptomatic. *Lake Victoria marburgvirus* seems to affect only humans and non-human primates. Antibodies to this virus have been reported in primates including captive vervet monkeys (*Cercopithecus aethiops*) and baboons.

Reston ebolavirus causes hemorrhagic fever in nonhuman primates including cynomolgus macaques (*Macaca fascicularis*). This virus was recently reported in domesticated swine in the Philippines. *Reston ebolavirus* does not seem to be pathogenic for humans, although seroconversion can occur.

Incubation Period

The incubation period varies with the virus and dose. In cynomolgus macaques, inoculation of *Zaire ebolavirus* by the oral or conjunctival route causes clinical signs within 3 to 4 days. The incubation period for *Lake Victoria marburgvirus* or *Zaire ebolavirus* infection in rhesus macaques and vervet monkeys is 3 to 16 days. In guinea pigs, the incubation period is 4 to 10 days.

Clinical Signs

Filoviruses cause hemorrhagic fever in nonhuman primates. Wild chimpanzees and gorillas are often found dead. Clinical signs observed in dying wild animals (of various species) during Ebola outbreaks include vomiting, diarrhea, hair loss and emaciation, as well as bleeding from the nostrils. Whether all of these signs are associated with filovirus infections or some were caused by other diseases is unknown. During the 1989 *Reston ebolavirus* outbreak in Virginia, anorexia was the first sign of disease in cynomolgus monkeys. Some monkeys had swollen eyelids or increased lacrimation. Nasal discharge, coughing and splenomegaly were also seen. Fever, subcutaneous hemorrhages, epistaxis and/or bloody diarrhea were less common signs. In experimentally infected monkeys, the signs of Ebola or Marburg

hemorrhagic fever include fever, anorexia, vomiting, splenomegaly, weight loss and a skin rash. Hemorrhagic signs may include petechiae, bleeding into the gastrointestinal tract, or bleeding from puncture wounds and mucous membranes. Shock and hypothermia are soon followed by death. African species of ebolaviruses are usually more pathogenic than *Reston ebolavirus*; the clinical signs are more severe, hemorrhages are more common, and the mortality rate is higher.

Guinea pigs infected with unpassaged virus from primates usually develop a fever and weight loss but recover; animals infected with serially passaged virus may develop fatal liver disease. No clinical signs have been reported in infected wild bats, and experimentally infected bats remain asymptomatic.

Whether *Reston ebolavirus* causes disease in swine is unknown. This virus was found during an unusually severe outbreak of porcine reproductive and respiratory syndrome caused by an atypical PRRS virus. The clinical signs were consistent with atypical PRRS. These pigs were also infected with porcine circovirus type 2.

Communicability

Blood, secretions and excretions, and tissues may contain infectious virus; filoviruses can probably be found almost anywhere in the body. Aerosol transmission has been reported in experimentally infected primates. The extent of transmission between animals in the wild depends on the interactions between members of the population, as well as the infectivity of body fluids and carcasses. Gorilla to gorilla transmission probably occurs, but the extent to which is responsible for the spread of disease is controversial. Unpublished data suggests that carcasses decomposing in the African forests are infectious for only three or four days after death.

Post Mortem Lesions

At necropsy, petechiae, ecchymoses and frank hemorrhages may be present. Hemorrhages can occur in any organ, but they are particularly common in the gastrointestinal tract, kidneys, and pleural, pericardial and peritoneal spaces. The liver and spleen may be swollen and friable, and the liver may be severely reticulated and discolored. Other potential lesions include interstitial pneumonia, nephritis and a maculopapular rash, as well as necrosis of the liver, lymphoid tissue, adrenal cortex or pulmonary epithelium.

Diagnostic Tests

Filovirus infections can be diagnosed by detecting antigens with an antigen-capture ELISA or immunostaining, and by detecting viral RNA with RT-PCR. Virus isolation is also used: ebolaviruses and marburgvirus can be recovered in many cell lines, including Vero or Vero E6 cells. Electron microscopy can identify virus particles in tissues: filoviruses are pleomorphic, long and filamentous and may be branched. Some may be U-shaped, b-shaped or circular. In primates,

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filoviruses are found in high concentrations in the liver, spleen, lungs and lymph nodes. Skin biopsies collected into formalin may be helpful; large amounts of ebolavirus antigens have been found in skin. In bats, filoviruses have been found in liver and spleen. For surveillance in wild animals by RT-PCR, liver, spleen, muscle and skin have been taken from animals in good condition. RT-PCR can sometimes detect ebolavirus RNA in the bones of decomposed carcasses. Virus isolation is more difficult: unpublished data suggests that carcasses decomposing in the African forests may contain infectious virus for only 3 to 4 days after death.

Serologic tests include IFA and ELISAs. Immunoblotting may be used in research. Neutralization tests are unreliable for filoviruses. Paired serum samples should be tested if possible; low IFA titers in single samples are difficult to interpret. Cross-reactions can occur, and the significance of antibody titers in asymptomatic primates is controversial.

Treatment

No specific therapy is available. Because most filovirus infections are highly fatal in both humans and nonhuman primates, infected animals are usually euthanized.

Prevention

Quarantine of nonhuman primates during importation protects humans and healthy nonhuman primates from exposure. To prevent the exportation of *Reston ebolavirus*, the government of the Philippines has banned wild-caught monkeys from export and established a 45-day quarantine. During outbreaks, suspects and exposed animals should be isolated, and euthanized after confirmation of the disease. Strict infection control procedures are necessary to prevent virus transmission on fomites. Prevention of human exposure is vital. No vaccine is commercially available, but some vaccines being tested in nonhuman primates have been promising.

Measures to prevent infection of swine with *Reston ebolavirus* have not yet been established, but normal biosecurity measures including the prevention of contact with bats or nonhuman primates are appropriate. Eradication procedures including quarantines, testing and culling are being established in infected pigs, and exports have been suspended from affected areas.

Morbidity and Mortality

In Africa, high mortality rates have been reported in gorilla, chimpanzee and duiker populations during human ebolavirus epidemics. Among wild animals, outbreaks occur suddenly and may cause widespread mortality on one area while having little or no impact on other regions. The effect on local populations can be severe. In one preserve, gorilla and duiker numbers fell an estimated 50% and chimpanzee populations decreased by 88% during one outbreak. Another study estimated 90-95% mortality (5000 animals) in a population of gorillas.

Experimental inoculation of gorillas or chimpanzees is not done, but infection of other nonhuman primates is often fatal. The mortality rate varies with the dose and virus. Nearly all macaques inoculated with *Zaire ebolavirus* die, but many animals inoculated with *Sudan ebolavirus* survive. Antibodies have been reported in some wild primate populations, suggesting that some animals may recover or are resistant to disease. In one survey, none of 145 captive-born mandrills and chimpanzees had antibodies to ebolavirus, but 13% of wild-born chimpanzees, 3% of mandrills, 7% of gorillas, 4% of baboons, and 1% of guenon were seropositive. In chimpanzees, the seroprevalence rate varied from 4% to 18%, depending on the area. Ebolavirus outbreaks in Africa have also been linked to reports of other dead and dying primates including mandrills and guenon, as well as bush pigs and possibly other species. Because filoviruses have not been demonstrated in these species, whether they died of Ebola or other diseases is unknown. Few species other than nonhuman primates have been successfully inoculated with filoviruses. Experimentally infected bats remain asymptomatic.

Reston ebolavirus has been reported only in captive nonhuman primates and domesticated pigs; this virus has never been isolated from wild animals. *Reston ebolavirus* spreads rapidly among susceptible primates. During the first outbreak to be recognized, 82% of the cynomolgus monkeys (*Macaca fascicularis*) at a quarantine facility in Reston, Virginia died. (This outbreak was complicated by the discovery of simian hemorrhagic fever virus, which is also pathogenic for this species, in the same population.) Experimental infection of cynomolgus monkeys resulted in a mortality rate greater than 80%. Although control measures were established in the Philippines, *Reston ebolavirus* outbreaks recurred at primate quarantine facilities in the U.S. in 1989, 1990 and 1996, and in Italy in 1992. Although some monkeys in the 1989 outbreaks came from an illegal exporter, most incidents were linked to the one breeding facility in the Philippines. In 1996, a study found viral antigens in 32% of dead or moribund monkeys and 4% of healthy monkeys at this facility. The mortality rate was 14%, significantly higher than the 2% average mortality reported at other sites. The source of the infection was not found, but *Reston ebolavirus* was not reported in imported primates after this facility was closed in 1997. In December 2008, *Reston ebolavirus* was detected in domesticated pigs investigated during an outbreak of PRRS in the Philippines. Although high morbidity and mortality were reported in populations infected with both *Reston ebolavirus* and PRRS virus, the contribution of the ebolavirus (if any) has not yet been determined.

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Internet Resources

Centers for Disease Control and Prevention (CDC).

Ebola Hemorrhagic Fever

<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/ebola.htm>

CDC. Marburg Hemorrhagic Fever

<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/marburg.htm>

Ebola Virus Haemorrhagic Fever. Proceedings of an international colloquium on Ebola virus infection and other hemorrhagic fevers held in Antwerp, Belgium, 6-8 December, 1977

<http://www.itg.be/ebola/>

Medical Microbiology

<http://www.gsbs.utmb.edu/microbook>

Public Health Agency of Canada. Material Safety Data Sheets (MSDS)

<http://www.phac-aspc.gc.ca/msds-ftss/index.html>

Wisconsin Primate Research Center. Primate Info Net.

<http://www.primate.wisc.edu/pin/>

World Health Organization (WHO).

Ebola Haemorrhagic Fever.

<http://www.who.int/csr/disease/ebola/en/>

WHO. Marburg Haemorrhagic Fever.

<http://www.who.int/csr/disease/marburg/en/>

References

Allela L, Boury O, Pouillot R, Délicat A, Yaba P, Kumulungui B, Rouquet P, Gonzalez JP, Leroy EM. Ebola virus antibody prevalence in dogs and human risk. *Emerg Infect Dis*. 2005;11:385-90.

Ascenzi P, Bocedi A, Heptonstall J, Capobianchi MR, Di Caro A, Mastrangelo E, Bolognesi M, Ippolito G. Ebolavirus and Marburgvirus: insight the Filoviridae family. *Mol Aspects Med*. 2008;29:151-85.

Barrette RW, Metwally SA, Rowland JM, Xu L, Zaki SR, Nichol ST, Rollin PE, Towner JS, Shieh WJ, Batten B, Sealy TK, Carrillo C, Moran KE, Bracht AJ, Mayr GA, Sirios-Cruz M, Catbagan DP, Lautner EA, Ksiazek TG, White WR, McIntosh MT. Discovery of swine as a host for the Reston ebolavirus. *Science*. 2009;325(5937):204-6.

Baskin GB. Pathology of nonhuman primates. *Primate Info Net*. Wisconsin Primate Research Center; 2002. Feb. Available at: <http://www.primate.wisc.edu/pin/pola6-99.html>. * Accessed 23 Oct 2002.

Bausch DG, Nichol ST, Muyembe-Tamfum JJ, Borchert M, Rollin PE, Sleurs H, Campbell P, Tshioko FK, Roth C, Colebunders R, Pirard P, Mardel S, Olinda LA, Zeller H, Tshomba A, Kulidri A, Libande ML, Mulangu S, Formenty P, Grein T, Leirs H, Braack L, Ksiazek T, Zaki S, Bowen MD, Smit SB, Leman PA, Burt FJ, Kemp A, Swanepoel R; International Scientific and Technical Committee for Marburg Hemorrhagic Fever Control in the Democratic Republic of the Congo. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med*. 2006;355:909-19.

Bausch DG, Towner JS, Dowell SF, Kaducu F, Lukwiya M, Sanchez A, Nichol ST, Ksiazek TG, Rollin PE. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. *J Infect Dis*. 2007;196:S142-7.

Bermejo M, Rodríguez-Teijeiro JD, Illera G, Barroso A, Vilà C, Walsh PD. Ebola outbreak killed 5000 gorillas. *Science*. 2006 8;314:1564.

Bowen ET, Platt GS, Simpson DI, McArdell LB, Raymond RT. Ebola haemorrhagic fever: experimental infection of monkeys. *Trans R Soc Trop Med Hyg*. 1978;72:188-91.

Bray M, Murphy FA. Filovirus research: knowledge expands to meet a growing threat. *J Infect Dis*. 2007;196:S438-43.

Chepurinov AA, Dadaeva AA, Kolesnikov SI. Study of the pathogenesis of Ebola fever in laboratory animals with different sensitivity to the virus. *Bull Exp Biol Med*. 2001;132:1182-6.

Dalgard DW, Hardy RJ, Pearson SL, Pucak GJ, Quander RV, Zack PM, Peters CJ, Jahrling PB. Combined simian hemorrhagic fever and Ebola virus infection in cynomolgus monkeys. *J Am Assoc Lab Anim Sci*. 1992;42:152-157.

Drosten C, Gottig S, Schilling S, Asper M, Panning M, Schmitz H, Gunther S. Rapid detection and quantification of RNA of Ebola and Marburg viruses, Lassa virus, Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, dengue virus, and yellow fever virus by real-time reverse transcription-PCR. *J Clin Microbiol*. 2002;40:2323-30.

Enserink M. Infectious diseases. A puzzling outbreak of Marburg disease. *Science*. 2005;308:31-3.

Feldmann H, Klenk HD. Filoviruses. In: Baron S, editor. *Medical microbiology* [online]. 4th ed. New York: Churchill Livingstone; 1996. Available at: <http://www.gsbs.utmb.edu/microbook/ch072.htm>. Accessed 11 Oct 2002.

Feldmann H, Jones SM, Daddario-DiCaprio KM, Geisbert JB, Ströher U, Grolla A, Bray M, Fritz EA, Fernando L, Feldmann F, Hensley LE, Geisbert TW. Effective post-exposure treatment of Ebola infection. *PLoS Pathog*. 2007;3:e2.

Viral Hemorrhagic Fevers-Ebola and Marburg

- Food and Agriculture Organization of the United Nations [FAO]. Animal Production and Health Division [AGA]. Ebola-Reston virus in pigs. FAO AGA; 11 Dec 2008. Available at: http://www.fao.org/ag/againfo/home/en/news_archive/2008_ebola.html. Accessed 16 Dec 2008.
- Geisbert TW, Daddario-DiCaprio KM, Geisbert JB, Young HA, Formenty P, Fritz EA, Larsen T, Hensley LE. Marburg virus Angola infection of rhesus macaques: pathogenesis and treatment with recombinant nematode anticoagulant protein c2. *J Infect Dis.* 2007;196:S372-81.
- Groseth A, Feldmann H, Strong JE. The ecology of Ebola virus. *Trends Microbiol.* 2007;15:408-16.
- Hensley LE, Jones SM, Feldmann H, Jahrling PB, Geisbert TW. Ebola and Marburg viruses: pathogenesis and development of countermeasures. *Curr Mol Med.* 2005;5:761-72.
- Hoenen T, Groseth A, Falzarano D, Feldmann H. Ebola virus: unravelling pathogenesis to combat a deadly disease. *Trends Mol Med.* 2006;12:206-15.
- International Committee on Taxonomy of Viruses Universal Virus Database [ICTVdB] Management. 01.025.0.02. *Ebolavirus*. In: Büchen-Osmond C, editor. ICTVdB - The universal virus database, version 4 [online]. New York: Columbia University; 2006. Available at: <http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdb>. Accessed 16 Dec 2008.
- International Committee on Taxonomy of Viruses Universal Virus Database [ICTVdB] Management. 01.025.0.01. *Marburgvirus*. In: Büchen-Osmond C, editor. ICTVdB - The universal virus database, version 4 [online]. New York: Columbia University; 2006. Available at: <http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdb>. Accessed 16 Dec 2008.
- Johnson BK, Gitau LG, Gichogo A, Tukei PM, Else JG, Suleman MA, Kimani R, Sayer PD. Marburg, Ebola and Rift Valley fever virus antibodies in East African primates. *Trans R Soc Trop Med Hyg.* 1982;76: 307-10.
- Johnson ED, Johnson BK, Silverstein D, Tukei P, Geisbert TW, Sanchez AN, Jahrling PB. Characterization of a new Marburg virus isolated from a 1987 fatal case in Kenya. *Arch Virol Suppl.* 1996;11:101-14.
- Klenk H-D, Slenczka W, Feldmann H. Marburg and Ebola viruses. In: Webster RG, Granoff A, editors. *Encyclopedia of Virology*. Academic Press Ltd; 1995. Available at: <http://www.bocklabs.wisc.edu/eov-ebola.html>. * Accessed 15 Oct 2002.
- Kortepeter M, Christopher G, Cieslak T, Culpepper R, Darling R, Pavlin J, Rowe J, McKee K, Eitzen E, editors. *Medical management of biological casualties handbook* [online]. 4th ed. United States Department of Defense; 2001. Viral hemorrhagic fevers. Available at: <http://www.vnh.org/BIOCASU/15.html>. * Accessed 24 Oct 2002.
- Ksiazek TG, West CP, Rollin PE, Jahrling JB, Peters CJ. ELISA for the detection of antibodies to Ebola viruses. *J Infect Dis.* 1999;179:S192-8.
- Kurosaki Y, Takada A, Ebihara H, Grolla A, Kamo N, Feldmann H, Kawaoka Y, Yasuda J. Rapid and simple detection of Ebola virus by reverse transcription-loop-mediated isothermal amplification. *J Virol Methods.* 2007;141:78-83.
- Lahm SA, Kombila M, Swanepoel R, Barnes RF. Morbidity and mortality of wild animals in relation to outbreaks of Ebola haemorrhagic fever in Gabon, 1994-2003. *Trans R Soc Trop Med Hyg.* 2007;101:64-78.
- Leffel EK, Reed DS. Marburg and Ebola viruses as aerosol threats. *Biosecur Bioterror.* 2004;2:186-91.
- Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassanin A, Yaba P, Délicat A, Paweska JT, Gonzalez JP, Swanepoel R. Fruit bats as reservoirs of Ebola virus/ *Nature.* 2005;438:575-6.
- Leroy EM, Rouquet P, Formenty P, Souquière S, Kilbourne A, Froment JM, Bermejo M, Smit S, Karesh W, Swanepoel R, Zaki SR, Rollin PE. Multiple Ebola virus transmission events and rapid decline of central African wildlife. *Science.* 2004;303:387-90.
- Leroy EM, Telfer P, Kumulungui B, Yaba P, Rouquet P, Roques P, Gonzalez JP, Ksiazek TG, Rollin PE, Nerrienet E. A serological survey of Ebola virus infection in central African nonhuman primates. *J Infect Dis.* 2004;190:1895-9.
- Lucht A, Formenty P, Feldmann H, Gotz M, Leroy E, Bataboukila P, Grolla A, Feldmann F, Wittmann T, Campbell P, Atsangandoko C, Boumandoki P, Finke EJ, Mieth P, Becker S, Grunow R. Development of an immunofiltration-based antigen-detection assay for rapid diagnosis of Ebola virus infection. *J Infect Dis.* 2007;196:2:S184-92.
- Public Health Agency of Canada. Material Safety Data Sheet – Ebola virus. Office of Laboratory Security; 2002 Nov. Available at: <http://www.phac-aspc.gc.ca/msds-ftss/msds53e-eng.php>. Accessed 16 Dec 2008.
- Public Health Agency of Canada. Material Safety Data Sheet – Marburg virus. Office of Laboratory Security; 1996. Available at: <http://www.phac-aspc.gc.ca/msds-ftss/msds98e-eng.php>. Accessed 16 Dec 2008.
- Mahanty S, Bray M. Pathogenesis of filoviral haemorrhagic fevers. *Lancet Infect Dis.* 2004;4:487-98.
- Miranda ME, Ksiazek TG, Retuya TJ, Khan AS, Sanchez A, Fulhorst CF, Rollin PE, Calao AB, Manalo DL, Roces MC, Dayrit MM, Peters CJ. Epidemiology of Ebola (subtype Reston) virus in the Philippines, 1996. *J Infect Dis.* 1999;179:S115-9.
- Morikawa S, Saijo M, Kurane I. Current knowledge on lower virulence of Reston Ebola virus. *Comp Immunol Microbiol Infect Dis.* 2007;30:391-8.

Viral Hemorrhagic Fevers-Ebola and Marburg

- Murphy FA. Pathology of Ebola virus infection. In: Proceedings of an international colloquium on Ebola virus infection and other hemorrhagic fevers; 1977 Dec 6-8: Antwerp, Belgium. Available at: <http://www.itg.be/ebola/ebola-17.htm>. Accessed 28 Oct 2002.
- Onyango CO, Opoka ML, Ksiazek TG, Formenty P, Ahmed A, Tukei PM, Sang RC, Ofula VO, Konongoi SL, Coldren RL, Grein T, Legros D, Bell M, De Cock KM, Bellini WJ, Towner JS, Nichol ST, Rollin PE. Laboratory diagnosis of Ebola hemorrhagic fever during an outbreak in Yambio, Sudan, 2004. *J Infect Dis*. 2007;196:S193-8.
- Peters CJ, LeDue JW. An introduction to Ebola: the virus and the disease. *J Infect Dis*. 1999;179:ix-xvi.
- Pourrut X, Délicat A, Rollin PE, Ksiazek TG, Gonzalez JP, Leroy EM. Spatial and temporal patterns of Zaire ebolavirus antibody prevalence in the possible reservoir bat species. *J Infect Dis*. 2007;196:S176-83.
- Pourrut X, Kumulungui B, Wittmann T, Moussavou G, Délicat A, Yaba P, Nkoghe D, Gonzalez JP, Leroy EM. The natural history of Ebola virus in Africa. *Microbes Infect*. 2005;7:1005-14.
- Promed Mail. Ebola-Reston, porcine – Philippines. Dec 11, 2008. Archive Number 20081211.3896. Available at <http://www.promedmail.org>. Accessed 15 Jan 2008.
- Promed Mail. Ebola-Reston, porcine – Philippines. Dec 12, 2008. Archive Number 20081212.3910. Available at <http://www.promedmail.org>. Accessed 15 Jan 2008.
- Promed Mail. Ebola-Reston, porcine – Philippines. Dec 14, 2008. Archive Number 20081214.3932. Available at <http://www.promedmail.org>. Accessed 15 Jan 2008.
- Rouquet P, Froment JM, Bermejo M, Yaba P, Délicat A, Rollin PE, Leroy EM. Wild animal mortality monitoring and human Ebola outbreaks, Gabon and Republic of Congo, 2001-2003. *Emerg Infect Dis*. 2005;11:283-90.
- Saijo M, Niikura M, Ikegami T, Kurane I, Kurata T, Morikawa S. Laboratory diagnostic systems for Ebola and Marburg hemorrhagic fevers developed with recombinant proteins. *Clin Vaccine Immunol*. 2006;13:444-51.
- Spence IM, Gear JH. Marburg virus disease--an indicator case in South Africa. *S Afr Med J*. 1982;62:796.
- Swanepoel R, Leman PA, Burt FJ, Zachariades NA, Braack LE, Ksiazek TG, Rollin PE, Zaki SR, Peters CJ. Experimental inoculation of plants and animals with Ebola virus. *Emerg Infect Dis*. 1996;2:321-5.
- Swanepoel R, Smit SB, Rollin PE, Formenty P, Leman PA, Kemp A, Burt FJ, Grobbelaar AA, Croft J, Bausch DG, Zeller H, Leirs H, Braack LE, Libande ML, Zaki S, Nichol ST, Ksiazek TG, Paweska JT; International Scientific and Technical Committee for Marburg Hemorrhagic Fever Control in the Democratic Republic of Congo. Studies of reservoir hosts for Marburg virus. *Emerg Infect Dis*. 2007;13:1847-51.
- Towner JS, Pourrut X, Albariño CG, Nkoghe CN, Bird BH, Grard G, Ksiazek TG, Gonzalez JP, Nichol ST, Leroy EM. Marburg virus infection detected in a common African bat. *PLoS ONE*. 2007;2:e764.
- Towner JS, Sealy TK, Khristova ML, Albariño CG, Conlan S, Reeder SA, Quan PL, Lipkin WI, Downing R, Tappero JW, Okware S, Lutwama J, Bakamutumaho B, Kayiwa J, Comer JA, Rollin PE, Ksiazek TG, Nichol ST. Newly discovered ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog*. 2008;4:e1000212.
- World Organization for Animal Health (OIE). Immediate notification report. Porcine reproductive and respiratory syndrome. Ref OIE: 7596. Report Date: 10/12/2008 , Country: Philippines. Available at: http://www.oie.int/wahis/reports/en_imm_0000007596_20081210_125559.pdf. Accessed 16 Dec 2008.

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