Ebolavirus and Marburgvirus Infections

Ebola and Marburg Virus Disease, Ebola and Marburg Hemorrhagic Fever, African Hemorrhagic Fever

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Importance

Ebolaviruses and marburgviruses are incompletely understood pathogens that cause severe, often fatal, illnesses in humans and non-human primates. These diseases have been known as Ebola and Marburg hemorrhagic fevers, respectively, after the most dramatic symptoms in severe cases. The names "Ebola virus disease" or Marburg virus disease" are now preferred by the World Health Organization (WHO) and some other groups.

Most species of ebolaviruses and the only known species of marburgvirus occur in Africa. Current evidence suggests that the reservoir hosts are probably bats, while other animals and people are incidental hosts. Humans seem to become infected with marburgviruses mainly in caves or mines harboring bats, while ebolavirus infections are often associated with handling tissues from infected nonhuman primates and other species. Once a virus has entered human populations, it can spread from person to person. Some epidemics have affected hundreds of people, particularly when nosocomial spread occurs from inadequate medical supplies or barrier nursing procedures, or when outbreaks are not recognized for long periods. An outbreak of unprecedented size in West Africa began in December 2013, and was first recognized in March 2014. It has been spread in some densely populated urban regions, and has affected thousands of people to date. Although the mortality rate has varied between outbreaks, some ebolaviruses or marburgviruses have killed up to 90% of those who become infected. Treatment options are limited, and with the exception of experimental treatments, consist of supportive care alone. Epizootics in gorillas and chimpanzees are equally serious, and may threaten the survival of these species in the wild. Other wild mammals including duikers also seem to be killed during outbreaks.

One species, *Reston ebolavirus*, has been reported outside Africa, in the Philippines and China. This virus does not seem to affect humans, although some people may seroconvert. However, it can cause fatal illness in some species of nonhuman primates. 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 after this facility was closed in 1997. In 2008, however, *Reston ebolavirus* was discovered in pigs during an unusually severe outbreak of porcine reproductive and respiratory syndrome (PRRS) in the Philippines. This virus was also found in pigs with PRRS in China. Based on experimental studies, *Reston ebolavirus* alone does not seem to cause any illness in pigs, although its effects during co-infections with other pathogens have not yet been evaluated. Accumulating evidence suggests that ebolaviruses or their relatives may also occur in other locations, although the clinical significance of these viruses for humans and domesticated animals is uncertain.

Etiology

Ebola and Marburg hemorrhagic fevers are caused by members of the genera *Ebolavirus* and *Marburgvirus,* respectively, in the family Filoviridae. The names of these viruses have undergone several taxonomic changes since they were first discovered, including new changes officially accepted in 2013. Currently, the genus *Ebolavirus* contains five recognized viral species: *Zaire ebolavirus*, *Sudan ebolavirus*, *Taï Forest ebolavirus* (formerly *Cote d'Ivoire ebolavirus*), *Reston ebolavirus* and *Bundibugyo ebolavirus*. The common name for the single virus in each of these species is Ebola virus (formerly Zaire ebolavirus), Sudan virus (formerly Sudan ebolavirus), Tai Forest virus (formerly Cote d'Ivoire ebolavirus), Reston virus (formerly Reston ebolavirus) and Bundibugyo virus. *Marburgvirus* contains a single species, *Marburg marburgvirus* (formerly *Lake Victoria marburgvirus*), and two individual viruses, Marburg virus and Ravn virus, within this species.

A third genus, *Cuevavirus*, (species *Lloviu cuevavirus;* Lloviu virus) has been proposed for a filovirus found during an outbreak of viral pneumonia among

Schreiber's bats (*Miniopterus schreibersii*) in Europe. Very little is known about Lloviu virus. To date, it has not been isolated in culture, or found in other species.

[Note: because the distinctions between terms such as 'Ebola virus,' 'ebolaviruses,' '*Zaire ebolavirus*' and the recently used common name 'Zaire ebolavirus' can be confusing, specific viruses are identified by species name rather than common name in this factsheet.]

Species Affected

Reservoir hosts

Bats are thought to be the reservoir hosts for filoviruses, and appear to carry these viruses asymptomatically. Antibodies to ebolaviruses and/or viral RNA have been found in a number of bat species in Africa, with a high seroprevalence in several species of fruit bat. All studies to date have examined bats for *Zaire ebolavirus* or *Reston ebolavirus*, although the other ebolaviruses are probably also maintained in these animals. Outside Africa, antibodies to *Reston ebolavirus* were found in a species of fruit bat (*Rousettus amplexicaudatus*) in the Philippines. The cave-dwelling Egyptian fruit bat (*Rousettus aegyptiacus*) seems to be the primary host for *Marburg marburgvirus*, although evidence of infection has been found in other fruit bats and insectivorous bats. *Marburg marburgvirus* is the only filovirus, to date, that has actually been isolated from the tissues of bats in the wild. Surveillance among wildlife is incomplete, and it is possible that other reservoir or amplifying hosts also exist. In 1998, *Zaire ebolavirus* RNA was found in six mice (*Mus setulosus* and *Praomys* sp) and a shrew (*Sylvisorex ollula*), and these species were proposed as possible reservoir hosts. However, these results have not been confirmed by other groups, and virus isolation was unsuccessful. Domesticated pigs have also been suggested as possible amplifying and/or maintenance hosts for some viruses.

African filoviruses

The African filoviruses (all filoviruses except *Reston ebolavirus*) can cause severe illness in nonhuman primates and some other animals. African ebolaviruses and *Marburg marburgvirus* are typically lethal in experimentally infected nonhuman primates. In Africa, ebolavirus outbreaks have been linked to reports of dead and dying gorillas (*Gorilla gorilla*), chimpanzees (*Pan troglodytes*), mandrills (*Mandrillus* sp.), guenon (*Cercopithecus* sp.) and other nonhuman primates, as well as duikers (a species of forest antelope, *Cephalophus dorsalis*), bush pigs (red river hog, *Potamochoerus porcus*), brush-tailed porcupines (*Atherurus africanus*) and other animals. While there is no formal evidence for a causative role in some species, attempts to isolate ebolaviruses or detect viral RNA were successful in the carcasses of chimpanzees, gorillas and duikers. Antibodies to filoviruses have been reported in nonhuman primates including mandrills, drills (*Mandrillus* sp.),

baboons (*Papio* sp.), colobus monkeys (*Colobus badius*), guenon, chimpanzees and gorillas. .

There have been no reports of illnesses or unusual deaths among domesticated animals during ebolavirus outbreaks in Africa. One study detected antibodies in dogs, but did not find virological evidence of infection at the time the study was conducted. What these antibodies indicate is currently uncertain, as 1) some filoviruses are cross-reactive in serological tests, and 2) the dogs could have either been infected with ebolaviruses or exposed without productive infection. One pet dog exposed to its *Zaire ebolavirus*-infected owner in the U.S. did not become infected. Older serological studies sometimes reported antibodies in guinea pigs, some livestock, and even chickens in Africa, but they used a serological test (IFA) that is no longer considered to be reliable. Viruses were not found during very limited sampling of live cattle, sheep, goats and pigs during outbreaks. Some animal species (e.g., sheep and goats) were described as "completely insensitive" to the effects of the virus when inoculated with large amounts of live ebolaviruses for the production of hyperimmune serum in Russian studies, but whether this indicates asymptomatic infection or complete absence of virus replication seems to be uncertain. Pigs have been infected experimentally with *Zaire ebolavirus* and developed respiratory signs. Various laboratory rodents are used as models for human disease; however, the viruses used have been artificially adapted to replicate at high levels in these animals.

Reston ebolavirus

Other than bats, *Reston ebolavirus* has been found in nature only in nonhuman primates (e.g., cynomolgus macaques, *Macaca fascicularis*), which become ill, and domesticated pigs. Whether *Reston ebolavirus* can be maintained long term in swine populations is not known. In one study, this virus caused severe clinical signs in cynomolgus monkeys, but minimal or no signs in African green monkeys inoculated intraperitoneally with the same virus, despite evidence of viremia in the latter species.

Zoonotic potential

Zaire ebolavirus, Sudan ebolavirus, Bundibugyo ebolavirus and *Tai Forest ebolavirus* can cause severe illness in humans, although *Tai Forest ebolavirus* infections have rarely been documented. *Reston ebolavirus* does not seem to be pathogenic for humans, but people may seroconvert after exposure to infected nonhuman primates or pigs.

Geographic Distribution

Zaire ebolavirus, *Sudan ebolavirus*, *Tai Forest ebolavirus* and *Bundibugyo ebolavirus* are endemic in parts of Africa south of the Sahara desert. Human illnesses caused by these viruses have been reported mainly in central and western Africa, and have typically been associated with rain forests. While outbreaks have been documented in a limited number of countries, serological

surveys, as well as the distribution of bat species known to be infected, suggest that some viruses may be more widespread.

Marburg marburgvirus has been found in bats, nonhuman primates and/or humans from eastern Africa to the far western edge of the Congo. The human illness seems to be most prevalent in eastern Africa, although one outbreak was documented in Angola (western Africa). A case reported from South Africa was most likely acquired in Zimbabwe. Imported human cases have been seen sporadically in other areas, including Europe and North America. In recent decades, such cases have mainly been reported among travelers returning from Africa, but a large Marburg hemorrhagic fever outbreak occurred in Germany and Yugoslavia in 1967, among laboratory workers who had been exposed to tissues from imported African green (vervet) monkeys (*Cercopithecus aethiops*).

Reston ebolavirus occurs in the Philippines, and has also been reported in PRRS virus-infected pigs from a 2008 outbreak in China. This or other filoviruses might also exist in other locations. Antibodies to filoviruses have been detected in several species of fruit bats in China and Bangladesh, and 18% of healthy Bornean orangutans (*Pongo pygmaeus*) in rehabilitation facilities were seropositive on Kalimantan Island, Indonesia. Outbreaks among imported, nonhuman primates in the United States and Italy were eradicated.

Transmission

How filoviruses are transmitted between bats, or transmitted from bats to other animals, is still uncertain. Although these viruses can be found in bat tissues and blood, they typically seem to be absent from secretions or excretions such as oral fluids, urine and feces (although virus was found in the feces of one experimentally infected bat), and attempts to inoculate bats by exposing respiratory and oral mucus membranes to virus were unsuccessful. It is possible that virus shedding in secretions and excretions occurs intermittently, at very low levels and/or under certain physiological conditions. There is some evidence that transmission might occur when bats give birth. Seasonal changes in the prevalence of *Marburg marburgvirus* RNA were reported in older juvenile Egyptian fruit bats, with peaks during the twice-yearly birthing seasons. These peaks seem to coincide with a higher risk of human infection. Pregnant fruit bats are also more likely to be seropositive than nonpregnant females. .

Filoviruses emerge periodically in nonhuman primates or people after infection from an outside source. Most *Marburg marburgvirus* infections in humans have been associated with transmission within caves, probably from infected bats, although some people were infected by exposure to nonhuman primate tissues in the laboratory. Some ebolaviruses might also be acquired directly from bats; however, humans often become ill after handling the carcasses of animals found in the forest, especially nonhuman primates and duikers. Blood, secretions and excretions, and tissues from these animals may contain infectious virus. Filoviruses have been reported to survive for some time in blood and tissues at room temperature, and can be transmitted on fomites, particularly those contaminated by blood. Survival is prolonged when viruses are kept at 4°C. In incidental hosts, filoviruses are thought to enter the body mainly through mucous membranes and broken skin. Arthropod-borne transmission is theoretically possible, but most authors suggest it is unlikely.

Once ebolaviruses or marburgviruses have infected humans, they can spread from person to person. Viruses mostly seem to occur in secretions and excretions only after the onset of fever, and the amount of virus increases as the disease becomes more severe. Blood can contain large amounts of virus, contaminating the environment if patients hemorrhage. 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, but *Zaire ebolavirus* was absent from patients' urine during one outbreak. Aerosol and/or respiratory droplet transmission between nonhuman primates is still controversial: it has been implicated in some experimentally infected nonhuman primates, but alternative explanations may be possible, and virus did not seem to spread readily between cages in other studies. While people might theoretically become infected by this route, aerosols do not seem to be important during human outbreaks. Filoviruses disappear from blood and most tissues either during or soon after recovery. They may, however, persist for a time in some "immune privileged" body sites, such as the testes and the anterior chamber of the eye. While persistence within the eye does not seem to lead to virus shedding (virus was found for only 10 days in conjunctival secretions, after clearance from the blood), sexual transmission is a significant risk. *Marburg marburgvirus* has been transmitted sexually, 13 weeks after the onset of disease, and *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 for as long as 16 months. This virus was also recovered from the breast milk of a convalescing patient, 15 days after the onset of disease (after the virus had been cleared from the blood), and transmission to a nursing child may be possible. There is also good evidence for vertical transmission to the fetus, in humans How efficiently filoviruses can spread by casual contact during the early stages of the illness is still uncertain, but the risk is currently thought to be low except during close contact.

The extent of transmission between nonhuman primates during outbreaks in the wild is controversial; however, current evidence suggests that these viruses are not spread efficiently, and nonhuman primates are unlikely to act as maintenance hosts. Virus spread is likely to depend on the extent of interactions between members of the population, as well as the infectivity of body fluids and

carcasses. Most other species (e.g., duikers) have not been examined, but the role of domesticated pigs is under investigation. Young pigs (3-6 months of age) inoculated with either *Zaire ebolavirus* or *Reston ebolavirus* shed these viruses in nasal and oral fluids, and evidence of infection was also found sometimes in blood, rectal swabs and various tissues. Pigs infected with *Zaire ebolavirus* transmitted this virus to pigs in close contact, as well as to cynomolgus macaques housed in the same room but not in direct contact with the pigs. In pigs infected with *Reston ebolavirus*, the virus had disappeared from blood and tissues by one month after infection. Whether sustained transmission of ebolaviruses can occur in swine populations has not yet been determined.

Disinfection

Ebolaviruses and marburgviruses are both reported to be susceptible to sodium hypochlorite, glutaraldehyde, β-propiolactone, 3% acetic acid (pH 2.5), formaldehyde and paraformaldehyde. Recommended dilutions of sodium hypochlorite may vary with the use. Calcium hypochlorite, peracetic acid, methyl alcohol, ether, sodium deoxycholate and some other agents have also been tested against ebolaviruses, and found to be effective. In addition, filoviruses can be inactivated by ultraviolet light, gamma irradiation, heating to 60°C (140°F) for 60 minutes or boiling for 5-20 minutes.

Infections in Animals

Incubation Period

Experimental inoculation of nonhuman primates with filoviruses often results in clinical signs after 3-5 days, although the incubation period was reported to be as long as 16 days in some animals. Pigs developed a fever 4 days after inoculation with *Zaire ebolavirus*.

Clinical Signs

Nonhuman primates are severely affected by filoviruses. Wild chimpanzees and gorillas are often found dead. Clinical signs observed in dying wild animals (of various species) during ebolavirus outbreaks have included 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 uncertain. During the 1989 *Reston ebolavirus* outbreak in Virginia, the clinical signs in cynomolgus monkeys included anorexia, swollen eyelids, increased lacrimation, nasal discharge, coughing and splenomegaly. Fever, subcutaneous hemorrhages, epistaxis and/or bloody diarrhea were less common. These animals were also infected with simian hemorrhagic fever virus; thus, the contributions of each virus to the signs were uncertain. The most common clinical signs at the infected exporting facility were respiratory signs and diarrhea, while hemorrhages occurred but were rare (1% of animals).

However, these signs were reported in both infected and uninfected animals, and some cynomolgus monkeys that died with *Reston ebolavirus* infection had no apparent signs before death.

Nonhuman primates that are experimentally infected with filoviruses may develop fever, anorexia, vomiting, diarrhea, dyspnea, splenomegaly and weight loss. A skin rash is common, although it can be absent in some species, or in animals inoculated by certain routes. 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

Piglets (approximately 5-6 weeks of age) inoculated with *Zaire ebolavirus* developed a fever and respiratory signs, which progressed to dyspnea, anorexia and lethargy, while less severe respiratory signs occurred in slightly younger piglets inoculated with the same virus. Guinea pigs infected with unpassaged filoviruses from primates may have a fever and weight loss, but recover. In this species, severe illness is only seen in animals infected with serially passaged virus adapted to guinea pigs. No clinical signs have been reported in infected wild bats, and experimentally infected bats remain asymptomatic.

Reston ebolavirus does not seem to causes any illness in experimentally inoculated pigs. However, this virus has been detected in pigs with porcine reproductive and respiratory syndrome in both the Philippines and China, and whether it can exacerbate other illnesses or predispose animals to other infections is unknown. The PRRS outbreak in the Philippines and China were unusually severe, but consistent with other outbreaks caused by atypical PRRS viruses. Some of the pigs in the Philippines were also infected with porcine circovirus type 2.

Post Mortem Lesions

Hemorrhagic signs (especially petechiae and ecchymoses) may be found in various internal organs, the skin and mucous membranes. The liver, spleen, lymph nodes, adrenal glands and some other organs may be enlarged and/or congested and friable. The liver may be severely reticulated and discolored. Some species have a maculopapular rash. Microscopic lesions include focal to widespread hepatocyte necrosis, necrosis of the zona glomerulosa of the adrenal cortex; signs of lymphoid depletion (with apoptosis and necrosis) in lymphoid tissues including lymph nodes and the white pulp of the spleen, and fibrin deposition or fibrin thrombi in various organs.

The gross lesions in young pigs experimentally infected with *Zaire ebolavirus* were pulmonary consolidation and enlargement of the lung-associated lymph nodes, which were sometimes mildly hemorrhagic. Microscopically, the lung lesions were identified as

bronchointerstitial pneumonia. The right atrium was hemorrhagic in some animals, although the cause of this lesion was uncertain. Mild lung and lymph node lesions were reported in some asymptomatic piglets infected with *Reston ebolavirus,* but it was not certain if they could be attributed to this virus.

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. Ebolaviruses and marburgviruses can be isolated in many cell lines, particularly Vero cells (viruses from pigs may not show cytopathic effect until the 2nd or 3rd passage). Electron microscopy can identify virus particles, which have a distinctive, filamentous pleomorphic, appearance, in tissues. In primates, filoviruses occur in high concentrations in the liver, spleen, lungs, lymph nodes and skin. Liver, spleen, muscle and skin have been taken from wild animal carcasses in good condition for surveillance. 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. In bats, filoviruses or their nucleic acids have been found in tissues such as the liver and spleen, and sometimes in the blood.

Serological tests that may be used to detect antibodies to filoviruses include ELISAs, indirect immunofluorescence (IFA) and immunoblotting, but neutralization tests are unreliable. Cross-reactions can occur, particularly between different species of ebolaviruses. The IFA test is thought to be prone to nonspecific reactions, and is uncommonly used at present.

Treatment

Because most filovirus infections are serious and often fatal in both humans and nonhuman primates, infected animals are usually euthanized.

Control

Disease reporting

Animals that may be infected with ebolaviruses or marburgviruses must be reported immediately, to protect humans who may be exposed and aid in controlling the outbreak.

Prevention

Quarantine of nonhuman primates during importation protects humans and healthy nonhuman primates from exposure to filoviruses. To prevent the exportation of *Reston ebolavirus*, the government of the Philippines has banned wild-caught monkeys from export and established a quarantine period for captive-bred primates. 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 during diagnosis and eradication activities is vital, as humans are severely affected by most filoviruses.

Measures to prevent infection of swine with *Reston ebolavirus* in endemic areas have not yet been established, but normal biosecurity measures should be helpful. Pigs should not be allowed to contact bats or nonhuman primates.

Very little is known at present about the susceptibility of other species. As a precaution, some animals in the U.S. (e.g., pets in the home of an ebolavirus-infected human) may be quarantined and monitored similarly to exposed humans. The disposition of exposed animals may differ in other countries.

Morbidity and Mortality

In Africa, high mortality rates have been reported in some animal populations, including nonhuman primates and duikers, during some human ebolavirus epidemics. Outbreaks in wild animals can 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. Gorilla and duiker numbers fell an estimated 50% in one preserve, while chimpanzee populations decreased by 88% during another outbreak. One study estimated 90-95% mortality (5000 animals) in a population of gorillas. Experimental inoculation of gorillas or chimpanzees is not done, but mortality can be very high in other nonhuman primates inoculated with African filoviruses. Nevertheless, antibodies have also been reported in some wild primates or wild-born captive primate populations, suggesting that some animals can recover or are resistant to disease. (However, reactivity to nonpathogenic filoviruses is difficult to rule out as the cause of these antibodies.)

Reston ebolavirus has a case fatality rate greater than 80% in experimentally infected cynomolgus macaques. Infected monkeys at quarantine facilities were euthanized once the outbreaks were recognized, and the cumulative case fatality rate is unknown; however, 82% of the animals with Reston virus antigens in the blood at the infected export facility died. The overall mortality rate was also higher at this facility, compared to similar uninfected facilities in the Philippines. The source of the infection for the monkeys was not found, but imported primates from the Philippines were virus-free after the infected export facility was closed in 1997. However, *Reston ebolavirus* was detected in domesticated pigs in the Philippines in 2008, during an investigation of a PRRS outbreak. Seroprevalence to *Reston ebolavirus* was high (approximately 70%) among pigs on affected farms, but no antibodies were found in pigs from an area unaffected by illness. The illness was reported to be severe in sick pigs infected with both viruses in the Philippines and China, but pigs inoculated experimentally with *Reston ebolavirus* alone remained asymptomatic. In

pigs, *Zaire ebolavirus* infections have currently been described only in experimentally infected animals less than 2 months of age. The illness seems to be more severe in older piglets than one-month-old animals, which all survived in one experiment.

Infections in Humans

Incubation Period

The precise incubation period for filovirus infections is difficult to determine, as the time of exposure is uncertain or not described in most cases. Some estimates indicate a potential range of 2 to 21 days, with symptoms usually appearing in 4 to 10 days. The initial signs occurred after 3 to 13 days in a limited number of cases where the time of exposure was known. Estimates of the mean incubation period during outbreaks have ranged from 6 to 13 days, and sometimes differ even for the same outbreak.

Clinical Signs

Marburg marburgvirus, Zaire ebolavirus, Sudan ebolavirus and *Bundibugyo ebolavirus* appear to cause similar diseases, although the severity of the illness and most prevalent syndromes might differ with the virus. Published information for clinical signs during outbreaks is limited; however, the initial symptoms have been described as nonspecific and flu-like, with a high fever, chills, headache, severe malaise and muscle aches or generalized pain, followed by abdominal pain, nausea, vomiting and diarrhea. A nonpruritic, erythematous, maculopapular rash, which may develop fine scaling, can appear on the face, torso and extremities. Dysphagia, pharyngitis, and conjunctivitis or conjunctival congestion are reported to be common. One clinical summary described a grayish exudate in the pharynx, sometimes with tapioca-like whitish-clear granules on the soft palate. Other mucosal lesions, such as glossitis, gingivitis, and cold-sore like lesions, have been mentioned. Debilitation is often rapid, and generalized pain may be seen. Pregnant women may abort. Common changes in laboratory parameters include leukopenia (at the early stage) and thrombocytopenia, as well as elevated liver enzymes. Some patients are reported to experience a brief remission before deteriorating, while some may recover without developing more severe signs.

After a few days, patients can develop other symptoms including neurological signs, dyspnea, and signs of increased vascular permeability, especially conjunctival injection and edema. Mild to severe bleeding tendencies may also be seen. In mild cases, this can be limited to bruising, bleeding of the gums, epistaxis, petechiae and/or mild oozing from venipuncture sites. While frank hemorrhaging is reported to be uncommon, it can occur, especially from the gastrointestinal tract. Other serious signs include metabolic disturbances, severe dehydration, diffuse coagulopathy, shock and multi-organ failure. Although many patients die, some begin to recover after a week or two. During convalescence, which can be slow, reported complications have included joint pain, uveitis, deafness, orchitis, recurrent hepatitis, transverse myelitis, pericarditis and mental dysfunction (e.g., psychosis). Secondary infections can also occur at this stage, and skin in the area of the rash often sloughs. One recrudescent infection, with encephalopathy, was reported in a patient who had recovered 9 months earlier.

It should be noted that descriptions of the syndromes caused by filoviruses are generally limited to severe cases seen in hospitals, and milder cases might not have been observed. In rare, documented mild cases caused by *Marburg marburgvirus*, nonspecific symptoms and slight signs of purpura were reported in an adult, and fever, diarrhea, vomiting and splenomegaly in an infant. Neither patient was reported to be seriously ill. Evidence for asymptomatic seroconversion has also been documented rarely in ebolavirus and marburgvirus infected patients.

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

Diagnostic Tests

Ebola or Marburg hemorrhagic fever can be diagnosed by detecting antigens with an antigen-capture ELISA or immunostaining, and by detecting viral RNA by RT-PCR. Reverse transcription loop–mediated isothermal amplification methods have been described. Virus isolation can also be used (though available in limited locations) and electron microscopy may be helpful. In humans, filoviruses are most reliably detected in the blood (including serum) during the acute-stage of the disease, but they may also be found in oral fluids and in some cases in urine, breast milk, semen, anterior eye fluid and other body fluids, and in many tissues including the skin. Skin biopsies may be collected at post-mortem. Serological assays include ELISA tests, IFA and immunoblotting, but neutralization tests are unreliable. ELISA tests are used most often, while IFA is thought to be prone to nonspecific reactivity. Because the consequences of misdiagnosis (including false positive diagnosis) are severe, multiple techniques are used to confirm the infection whenever possible.

Treatment

Standard treatment currently consists of supportive therapy, including maintenance of blood volume and electrolyte balance, as well as analgesics and standard nursing care.

No specific treatment has been demonstrated yet to be safe and effective in humans; however, experimental drugs, vaccines and monoclonal antibodies to filoviruses have been tested in animals, with varying degrees of success in nonhuman primates. These experimental treatments are diverse, and may be aimed at inhibiting virus replication and/or entry into cells, treating clotting abnormalities or sepsis, or boosting immune responses. Most experimental

treatments have been tested very early in the incubation period, but some were promising when started up to 2 days after exposure, or even after early clinical signs (e.g., mild elevation in temperature) developed. A few drugs have advanced to human phase I clinical trials, which are the initial tests to determine whether agents appear to be safe for human use. When supplies are available, some experimental treatments have been used in humans on a compassionate basis.

Control

Disease reporting

International health regulations require that nations report acute hemorrhagic fever syndromes immediately to WHO, without waiting for the causative agent to be identified. Suspected human cases of Ebola or Marburg hemorrhagic fever should be reported immediately to the nation's public health service, to prevent transmission and aid in case management and diagnosis. In the U.S., cases are reported to public health departments and to CDC's Special Pathogens Branch.

Prevention

In Africa, ebolavirus infections are often linked to exposure to wild animal tissues during butchering. Because the full host range may not be known, all sick and dead wild animals should be avoided (including for use as food). To prevent infection from animals that might be infected but have not yet developed obvious clinical signs, good personal hygiene should be used when handling and preparing meat, and the meat should be thoroughly cooked. Surveillance for deaths and illness in wild animals may provide an early warning to prevent human epidemics, but such deaths have not been seen in all human outbreaks.

Marburg marburgvirus infections have been linked to exposure to caves, mines and cave-dwelling bats, but the means of transmission from bats to humans is still unknown. If contact is unavoidable (e.g., occupational exposure), personal protective equipment and good hygiene should be used. Some caves have been closed to human entry after human cases were recognized.

Human epidemics have been successfully stopped in the past by tracing infected individuals, and isolating patients in facilities with barrier nursing procedures and strict infection control measures. Healthcare workers should use the personal protective equipment currently recommended by experts (e.g., gloves, gowns, masks, eye protection and other equipment) to prevent exposure to blood and body fluids. Burial practices should avoid all contact with the body or fomites. During convalescence, the possibility of exposure during breastfeeding or sexual intercourse should be considered. Ebolaviruses have been found in milk 15 days after the onset of illness (although the maximum period of shedding is unknown), and in the semen of 26% of men after 7-9 months. Sexual abstinence has been recommended for 12 months after recovery, or

until two tests find no viral RNA in semen. Currently, the WHO does not recommend breast-feeding during the acute stage of the illness, and suggests that women also refrain from breast-feeding if they have evidence for virus in the milk after recovery, until viral RNA is no longer demonstrated.

Reston ebolavirus is not known to affect humans. As a precaution, tissues from infected animals should not be eaten or handled. Good hygiene and appropriate personal protective equipment should be used if these animals or their tissues must be handled.

Morbidity and Mortality

Illnesses caused by filoviruses have occurred as isolated cases, small clusters of cases, or large outbreaks which may affect hundreds of people. The 2013-2016 outbreak is unusual in its scale, having affected thousands. Some outbreaks seem to originate with a single person, while multiple transmission events have been reported in others. High risk activities include butchering wild animals and visiting caves and mines. Outbreaks can be propagated by transmission to family members and other close contacts through nosocomial transmission, unsafe self-treatment at home, funeral practices and other routes. Healthcare workers are at high risk, as hospital supplies are limited in some areas where filoviral diseases occur, and barrier nursing practices may be inadequate. Other factors that help propagate the disease include poor availability of healthcare, reluctance to see a medical practitioner, and difficulty in distinguishing some cases from other serious illnesses, particularly in the early stages. As a result, some outbreaks have been identified months after they began. Delayed identification, together with the introduction of the virus into urban areas, and socioeconomic factors (e.g., poverty and healthcare-associated risk factors), are thought to have fueled the current outbreak in West Africa.

Outbreaks of Ebola hemorrhagic fever are reported periodically in Africa. The number of reported outbreaks has increased, 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. This disease was initially recognized in 1967, during an outbreak in laboratory workers exposed to infected primate tissues. Only 6 cases were described during the following 3 decades, 3 cases in travelers to Africa and three in their contacts. In 1998, however, this virus caused an epidemic affecting 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 viral strains were isolated during the epidemic, suggesting that the 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

outbreak was reported in Angola, where *Marburg marburgvirus* was not thought to exist. Unlike the previous outbreak, it seems to have originated with a single person, and was propagated by person-to-person transmission. Several additional cases have been reported since that time, in miners or travelers who visited caves.

Case fatality rates are usually high for African filoviruses, and the prognosis is poor in patients who become severely ill. *Zaire ebolavirus* is thought to be the most pathogenic virus, with case fatality rates from outbreaks in Africa ranging from 44% to 88%. *Sudan ebolavirus* appears to somewhat be less virulent, with a case fatality rate estimated to be 41-65%, (or 26-54%, depending on the cases included). However, higher mortality rates have been reported in small numbers of *Sudan ebolavirus*-infected individuals who were not treated. The reported case fatality rate was 36% in the initial outbreak caused by *Bundibugyo ebolavirus.* It varies widely in Marburg hemorrhagic fever, from 22-23% during the 1967 laboratory-associated outbreak in Europe, to 83% (56% in laboratory-confirmed cases) during the outbreak in DRC, and 88% in Angola. It is not known whether higher mortality rates are associated with more virulent filoviruses (or strains of these viruses), higher doses of virus, concurrent malnutrition and disease, or the availability and quality of healthcare. Only a limited number of cases have been treated in Western countries with advanced healthcare facilities.

The incidence of mild or asymptomatic infections is still uncertain. Asymptomatic infections have been documented in rare cases, and the possibility of such infections is also suggested by reports of antibodies and cell-mediated immune responses to filoviruses in people who have no history of Ebola or Marburg hemorrhagic disease. Seroprevalence rates tend to be higher in groups that have more contact with wild animals or live in rural forest ecosystems. However, illnesses without hemorrhages might have been misdiagnosed as other diseases such as malaria, which can also be severe. Cross-reactivity with other viruses may also be a problem in serological tests. In particular, there may be undiscovered filoviruses in Africa (and other locations) that are less pathogenic or nonpathogenic for humans.

Seroconversion to *Reston virus* does not seem to be common. In the Philippines, seroprevalence rates ranged between 1% and 4% (overall 2%) in people who had been exposed to either nonhuman primates or infected pigs. All of the primate-exposed positive samples came from people associated with the single export facility known to have housed infected animals.

Internet Resources

American Veterinary Medical Association (AVMA). Ebola and animals
https://www.avma.org/KB/Resources/Reference/Pages/Ebola-virus.aspx

Centers for Disease Control and Prevention (CDC). Ebola Hemorrhagic Fever
http://www.cdc.gov/vhf/ebola/

CDC. Marburg Hemorrhagic Fever
http://www.cdc.gov/vhf/marburg/

Public Health Agency of Canada. Pathogen Safety Data Sheets
http://www.phac-aspc.gc.ca/lab-bio/res/psds-ftss/index-eng.php

Wisconsin Primate Research Center. Primate Info Net.
http://pin.primate.wisc.edu/

World Organization for Animal Health. Ebola fact sheet
http://www.oie.int/fileadmin/Home/fr/Media_Center/docs/pdf/Ebola_fact_sheet_EN_Final.pdf

World Health Organization (WHO). Ebola virus disease
http://www.who.int/csr/disease/ebola/en/

WHO. Marburg virus disease
http://www.who.int/csr/disease/marburg/en/

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*Link defunct as of 2014