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Overview

Marburg and Ebola Virus Infections in Laboratory Non-human Primates: A Literature Review

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Background and Purpose: **Several non-human primate species are used as laboratory animals for various types of studies. Although importation of monkeys may introduce different diseases, special attention has recently been drawn to Marburg and Ebola viruses. This review presented here discusses the potential risk of these viruses for persons working with non-human primates as laboratory animals by focusing on epidemiology, virology, symptoms, pathogenesis, natural reservoir, transmission, quarantine of non-human primates, therapy, and prevention.**

Conclusion: **A total of 23 Marburg and Ebola virus outbreaks causing viral hemorrhagic fever has been reported among humans and monkeys since the first outbreak in Marburg, Germany in 1967. Most of the 1,100 human cases, with nearly 800 deaths, developed in Africa due mainly to direct and intimate contact with infected patients. Few human cases have developed after contact with non-human primates used for various scientific purposes. However, adequate quarantine should be applied to prevent human infections not only due to Marburg and Ebola viruses, but also to other infective agents. By following proper guidelines, the filovirus infection risk for people working with non-human primates during quarantine exists, but is minimal. There seems to be little risk for filovirus infections after an adequate quarantine period. Therefore, non-human primates can be used as laboratory animals, with little risk of filovirus infections, provided adequate precautions are taken.**

Cynomolgus monkeys (*Macaca fascicularis*), rhesus monkeys (*Macaca mulatta*), and several other non-human primate species are used widely as laboratory animals for various types of studies, including dental studies (1). Although numerous primate centers are breeding monkeys for experimental purposes, animal importation seems necessary in many countries without regional primate centers such as exist in the United States. Consequently, diseases may be introduced into non-human primate laboratory facilities. Several viruses belonging to various viral families may cause diseases, including viral hemorrhagic fever, herpes B infection, and hepatitis B and C in humans and various animal species (2–12). However, special attention has been drawn to Marburg and Ebola viruses during the past decades.

Sporadic Marburg and Ebola virus outbreaks have occurred since 1967 among humans and monkeys (4,13–55). All outbreaks have so far been self-limiting, but of great concern for all healthcare professionals (56, 57). Also, people working with non-human primates as laboratory animals have been seriously concerned due to limited knowledge about the natural reservoir of these viruses, extremely high mortality (22 to 88%), limited knowledge about transmission between individuals, and absence of treatment modalities (4, 17). In addition, recent outbreaks in the Democratic Republic of the Congo (formerly, Zaire) and Gabon, as well as books, magazine articles, movies, and television reports have caused widespread international concern during the past several years.

Recent reviews of filovirus infections have focused on aspects other than the potential infection risk for persons working with non-human primates as laboratory animals (8, 10, 12, 57–66). The present knowledge about the potential risk of Marburg and Ebola viruses by using non-human primates as laboratory animals is therefore assessed in the present review by focusing upon epidemiology, virology, symptoms, pathogenesis, natural reservoir, transmission, quarantine of non-human primates, therapy, and prevention.

Epidemiology

Twenty-three Marburg and Ebola virus outbreaks have been recognized among humans and non-human primates throughout the world during the past 30 years (Table 1). However, most of the 1,100 human cases, with nearly 800 deaths, have developed in Africa.

Marburg virus outbreaks

The first outbreak of hemorrhagic fever caused by Marburg virus was documented at the Behring company in Marburg, Germany in 1967 (13, 14, 17). Further outbreaks took place the same year in Frankfurt, Germany and Belgrade, Yugoslavia (13, 16, 17). All primary infected cases were in direct contact with blood or tissue from recently imported wild-caught African green monkeys (*Cercopithecus aethiops*) from the same central holding station near Entebbe at Lake Victoria, Uganda. Altogether there were 31 infected human cases, with seven deaths reported.

It should be emphasized that the monkeys in Germany were

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Table 1: Recognized outbreaks of Marburg and Ebola virus infections.

Year	Location	Virus type	No. of human cases	Main epidemiology	Human mortality (%)	References
1967	Marburg, Germany	Marburg	23	20 primary cases after direct contact with blood or tissue from African green monkeys imported from Uganda. One secondary infected during sexual intercourse. Two medical staff members secondary infected (needle injury during blood sampling and exposure to patients, respectively)	22	(13–15, 17)
1967	Frankfurt, Germany	Marburg	6	Four primary cases after direct contact with blood or tissue from African green monkeys imported from Uganda. One medical staff member secondary infected by needle injury during blood sampling. One pathology assistant secondary infected during autopsy of patient	33	(13, 16, 17)
1967	Belgrade, Yugoslavia	Marburg	2	One primary case (veterinarian performing autopsy of five African green monkeys imported from Uganda) probably infected through abrasions on unprotected forearms or conjunctivae. One secondary case (wife in contact with husband's blood)	0	(13, 17)
1975	Zimbabwe/ South Africa	Marburg	3	One primary case infected during travelling in Zimbabwe died in Johannesburg, South Africa. No direct contact with non-human primates or other animals. However, indirect contact to non-human primates, bats, and birds was possible. Two secondary infected cases survived (one travelling companion and one nurse exposed to the primary infected case)	33	(18)
1976	Southern Sudan	Ebola/Sudan	284	Initially many cases employed at a factory and their close relatives. 93 acquired the infection in a large hospital (at least a third (72) of the medical staff was infected, 41 died). Apparently not easily transmitted between individuals	53	(4, 20)
1976	Northern Democratic Republic of the Congo	Ebola/Zaire	318	The majority of cases infected after contact with acute cases. 27% probably infected by injections with contaminated syringes and/or needles. 13 out of 17 medical staff members infected, 11 died. Apparently not easily transmitted between individuals	88	(4, 21)
1976	United Kingdom	Ebola/Sudan	1	Investigator pricked finger during laboratory work with guinea pig liver infected by Ebola virus. Survived after treatment with human interferon and convalescent plasma	0	(4, 19, 23)
1977	Tandala, Democratic Republic of the Congo	Ebola/Zaire	1 (4)	One fatal case approximately 325 km from the outbreak in 1976. Three unrelated and unconfirmed cases were suspected	100	(24)

1979	Southern Sudan	Ebola/Sudan	34	The first case was employed at the same factory where many cases of the outbreak in 1976 worked. Apparently not easily transmitted between individuals	65	(22, 27)
1980	Kenya	Marburg	2	One primary case infected during travelling in Kenya died. One secondary case (attending doctor) survived	50	(25, 26)
1980	Kenya	Ebola/Zaire	1	A 13-year old girl apparently infected by unknown source. No secondary infected	0	(28)
1987	Kenya	Marburg	1	A 15-year old boy infected after one month stay. No secondary infected	100	(42)
1989/90	Reston, Virginia, USA	Ebola/Reston	0	Numerous simian hemorrhagic fever and Ebola/Reston virus infections and deaths during two outbreaks among cynomolgus monkeys imported from the Philippines. Four animal handlers infected. No symptoms of infection	-	(29–33)
1989	Pennsylvania, USA	Ebola/Reston	0	Deaths among cynomolgus monkeys imported form the Philippines	-	(30)
1990	Alice, USA	Ebola/Reston	0	Numerous simian hemorrhagic fever and Ebola/Reston virus infections and deaths among cynomolgus monkeys imported from the Philippines	-	(33)
1992	Ivory Coast	Ebola/Ivory Coast	0	Eight deaths among wild-living chimpanzees	-	(37, 51)
1992	Siena, Italy	Ebola/Reston	0	Three of 55 cynomolgus monkeys imported from the Philippines died. Remaining monkeys were sacrificed	-	(34)
1994	Gabon	Ebola/Zaire	49	Deaths among humans in different gold-mining camps in the deep rain forest. Originally reported as a yellow fever outbreak	59	(46–48, 52)
1994/95	Ivory Coast	Ebola/Ivory Coast	1	12 deaths among wild-living chimpanzees. One human infected after performing autopsy survived. Gloves, but not masks and gowns, were used	0	(37, 50, 51)
1995	Kikwit, Democratic Republic of the Congo	Ebola/Zaire	315	Many health care workers and wives of infected cases. The first case was a charcoal worker and farmer	81	(35, 36, 38–40, 53, 54)
1996	Texas, USA	Ebola/Reston	0	Four infections among 100 cynomolgus monkeys imported from the Philippines	-	(41, 55)
1996	Mayibout, Gabon	Ebola/Zaire	31	A dead chimpanzee was found in the forest. 20 human cases directly exposed to the monkey. No medical staff members were infected	68	(43, 47, 48, 52)
1996	Booué, Gabon	Ebola/Zaire	60	The first case was a hunter of a logging camp. One infected doctor who went to South Africa for treatment infected a nurse	75	(43–45, 47–49, 52)

used for vaccine production apparently without any quarantine period. Furthermore, blood and tissue from the monkeys were handled without systematic use of protective gloves and masks, because a health risk was not recognized at that time (13). Protective clothing was principally intended for aseptic removal of organs. None of the persons handling and taking care of the monkeys were infected unless they came in direct contact with blood or tissue from the monkeys (13, 14, 17). In addition, persons using protective clothing during handling potentially contaminated material also were not infected.

It has been stated that few originally infected animals were necessary to explain the three episodes (13, 17). Whether hemorrhagic infections developed among the 500 to 600 monkeys before reaching the final destinations is unknown. Illness or mortality was not observed among the monkeys in Germany during the few days between arrival and sacrifice (13, 15). However, unusual high mortality (21 to 46%) was observed in Belgrade among the three groups of imported monkeys during the quarantine period (17).

All African green monkeys died after experimental virus inoculation, documenting the biologic potential of Marburg virus (13, 17, 67). Although monkeys were also received in Japan, Italy, Sweden, Switzerland, and the United States from Uganda during the same period, illness was not observed (13). It has been reported that no unusual diseases were identified among monkey trappers or African green monkeys, neither in their natural environment nor after capture and transportation to Entebbe (17). However, rumors have persistently circulated that commercial interests concealed Marburg virus outbreaks among the African green monkeys in Uganda.

Two subsequent human Marburg virus outbreaks took place in Africa during 1975 and 1980 (18, 25, 26). Only five infected individuals characterized these two outbreaks. The primary case observed in 1975 developed in a person after he had traveled in Zimbabwe, whereas the case in 1980 developed in a person after traveling in Kenya, including the Mount Elgon region near Lake Victoria and consequently close to the trapping places and holding station of the monkeys initiating the outbreak in 1967 (18, 25, 26). The primary infected person of the 1980 outbreak visited caves harboring a large bat population shortly before becoming ill (26). Although extensive studies involving many animal species were performed, the Marburg virus source was not identified (68).

The latest Marburg virus outbreak occurred in 1987 in Kenya (42). A 15-year-old Danish boy was infected after one month's stay in Kenya. He also visited the Kitum Cave in Mount Elgon National Park. He died despite intensive supportive therapy. Marburg virus outbreaks have not been reported since.

Ebola virus outbreaks

Ebola virus was first detected during two almost simultaneous but unrelated human epidemics in southern Sudan and northern Democratic Republic of the Congo in 1976 (4, 20, 21). The virus was named for the small Ebola river in northwestern Democratic Republic of the Congo. More than 600 persons were infected during those two outbreaks.

The outbreak in Sudan was initially characterized by involving many workers at a cotton factory and their relatives (4, 20). The epidemic was later amplified in a large hospital. The transmission between individuals required close contact with acute cases and was mainly associated with nursing of infected patients. Infections were not related to exposure to wild-living animals. However, unrelated cases were observed apparently without any contact with infected patients. There were 284 infected individuals and 151 deaths.

The concomitant outbreak in the Democratic Republic of the Congo involved 318 cases with 280 deaths (4, 21). Consequently, mortality was higher, compared with that for the outbreak in Sudan (4, 20). It is still unknown whether the first identified case was infected by an injection given at a hospital. Although most people acquired the disease after contact with infected patients, the only apparent risk factor for 27% of the cases was receipt of injections at a hospital, probably with contaminated syringes and/or needles. Exposure to domestic or wild-living animals was also not a risk factor during this outbreak.

Both epidemics ended after stopping of injections, use of disinfectants and protective clothing, and isolation of infected cases and potentially contaminated material (4, 20, 21). A link between the two outbreaks was proposed (4, 20, 21). However, it was documented early that they were caused by two related but different viruses (69). A huge number of studies have confirmed this statement.

A solitary human Ebola virus infection was observed the same year in the United Kingdom. An investigator experienced a needle-stick injury through protective rubber gloves during laboratory work with Ebola virus-infected tissue (4, 19, 23). It should be emphasized that bleeding or a puncture wound was not observed. No one was secondarily infected.

From an epidemiologic point of view, significant episodes occurred in 1977 and 1979 in Africa (22, 24, 27). One infected person died in the Democratic Republic of the Congo approximately 325 km west of the original outbreak in 1976 (24). An overt relation to the outbreak in 1976 could not be detected. Three completely unrelated and unconfirmed cases also were reported. Furthermore, two suspected but unconfirmed cases from 1972 were proposed retrospectively. The other outbreak involving 34 persons took place in southern Sudan in 1979 (22, 27). The first identified case worked at the same factory where many cases of the outbreak in 1976 worked. However, previous contact with infected cases could not be identified. Consequently, the source of infection for this outbreak also is unknown. The outbreak was amplified in a hospital, but it ended after the same methods as those used during the previous outbreaks in 1976 were used.

Finally, a solitary case was suspected in Kenya in 1980 at the base of Mount Elgon (28). Although virus was not identified, antibody titer against Ebola virus in a 13-year-old girl was increased. Secondary infections were not identified. The infection source for this outbreak also is unknown.

All previous Marburg and Ebola virus outbreaks indicated that these virus types were extremely rare African viruses of unknown origin. However, this statement was questioned in 1989-90 when numerous deaths were identified in Reston, Virginia during two outbreaks among cynomolgus monkeys kept in quarantine (29, 32, 33). The wild-caught monkeys were imported from the Philippines. Simian hemorrhagic fever virus and a filovirus closely related to previously known Ebola viruses were isolated from the monkeys. Similar outbreaks were observed in 1989 and 1990 in Alice, USA and Pennsylvania also involving cynomolgus monkeys imported from the Philippines (30, 33). All animals were shipped via Amsterdam, New York, or directly from the Philippines, apparently without any contact

with ill monkeys from Africa (70). Consequently, a new Asian focus was proposed. Subsequent investigations also traced the source of infection back to a single monkey export facility in the Philippines (71). However, the original source of the Asian outbreak remains unknown, but infected wild-living monkeys captured in the Philippines have been proposed as the virus source (32, 59, 71).

Four animal handlers at the quarantine facility in the United States with high level of daily exposure to the animals were infected, documenting that this virus can be transmitted to humans during routine care and management of infected animals (31). Additional seropositive persons with variable amounts of exposure to primates have been reported (72–75). However, none of the infected persons developed clinical signs of infection indicating that this Ebola virus type is less pathogenic for humans than are previously known filovirus types (31, 33, 72–75). Except for one person who cut himself during necropsy of an infected animal, the transmission mode remains unclear. Although a relation between the African and Asian Ebola virus types is undocumented, extensive similarities indicate an intimate evolutionary relation.

Neither Marburg nor Ebola virus infections had been documented in wild-living monkeys until 1992 and 1994–95 when two episodes of increased mortality among a wild-living troop of chimpanzees (*Pan troglodytes*) from the Ivory Coast were reported (37, 50, 51). Classic hemorrhagic signs were observed, and subsequent studies confirmed Ebola virus infection. In 1994, one human infected during necropsy of a freshly dead chimpanzee survived.

The Ebola outbreaks in the United States in 1989–90 among cynomolgus monkeys were not solitary events. Ebola virus infections were again observed in 1992 in Siena, Italy and in 1996, in Texas, also among cynomolgus monkeys imported from the Philippines (34, 41, 55). Human infections were not detected during these two outbreaks. It has been reported that all monkeys were eliminated and cages were extensively disinfected at the facility in the Philippines after the last episodes, but it is still unknown whether the virus persisted or was reintroduced (60). However, recent information indicates that the facility was not totally depopulated until 1997 (76). Although high antibody titers were observed in 1993, viral antigen could not be documented among the monkeys at the Philippine facility (60). However, a recent study in 1996 documented Ebola/Reston among cynomolgus monkeys in an animal facility in the Philippines (76).

A recent huge Ebola virus outbreak occurred in Kikwit, southwestern Democratic Republic of the Congo during 1995 (35, 36, 38–40, 53, 54). In accordance with the epidemic in 1976, high mortality (81%) was observed. Healthcare workers in hospitals and households, as well as persons preparing bodies for burial were at high risk also during this outbreak. Actually, 26% of the infected cases were nurses and students. In addition, 21% were wives of patients.

The latest re-emergence of Ebola virus affecting humans occurred during three completely unrelated outbreaks in northeastern Gabon in 1994 and 1996 (43–49, 52). Those outbreaks were apparently initiated after direct exposure to dead chimpanzees. Further Ebola virus outbreaks have not since been reported.

These epidemiologic studies have documented a limited number of Marburg and Ebola virus outbreaks since 1967, mainly in Africa. Most of the reported cases and deaths occurred during three major outbreaks in Sudan and the Democratic Republic of the Congo. Human infections have been reported after contact with non-human primates, including laboratory non-human primates (Table 2). Approximately 20,000 primates were imported annually into the United States in the early 1990s (77). Consequently, the risk of filovirus infections is small in relation to the huge number of monkeys used for various scientific purposes throughout the entire world. It should also be emphasized that transmission of Marburg and Ebola viruses from laboratory non-human primates to humans have exclusively involved African green monkeys and cynomolgus monkeys. However, there is no reason to assume that other laboratory non-human primate species should not be involved in the future.

Virology

Marburg and Ebola viruses are among the most dangerous virus types classified as "biological class-4 pathogens" (World Health Organization, Risk Group 4). Although virus inactivation can be performed (4, 17, 78–84), identification and studies of these filoviruses are mainly performed in a limited number of biosafety level-4 laboratories. However, recent studies have involved use of pseudotyped viruses, such as vesicular stomatitis virus and retrovirus enabling studies of Marburg and Ebola viruses without the need of these extensive laboratory facilities (85–87).

A huge number of studies have evaluated various biologic and morphologic aspects of filoviruses (4, 12, 17, 58, 61–63). It was demonstrated early that these virus types were unrelated to all previously identified types, including simian hemorrhagic fever virus not affecting humans (4, 15, 17, 67, 78, 88–95). A separate family, called *Filoviridae* was, therefore, proposed in 1982 (96). Linear, undivided, single-stranded, negative-sense, and enveloped RNA viruses are today included in the order *Mononegavirales* with three distinct families, namely *Paramyxoviridae*, *Rhabdoviridae*, and *Filoviridae* (97). The *Filoviridae* constitute a single genus, namely *Filovirus*. This genus includes two types, namely Marburg and Ebola, with a genome approximately 19 kilobases long and consequently larger than similar RNA virus genomes (98-100). Electron microscopic studies have documented a pleomorphic appearance, with long filamentous, branched, "U"-shaped, "6"-shaped, or circular configurations, but without extensive morphologic variations between Marburg and Ebola viruses (17, 78, 79, 88–91, 93, 94, 101–106).

The Marburg virus group seems rather homogeneous and no real subtypes seem to exist (107–109), although recent studies indicate presence of at least two genetic lineages (42, 109). In contrast, Ebola is presently divided into four distinct subtypes, namely Ebola/Sudan, Ebola/Zaire, Ebola/Reston, and Ebola/Ivory Coast (Table 1) (37, 107, 108, 110). Despite major similarities between Marburg and Ebola viruses indicating a common evolutionary origin probably several thousand years ago, a huge number of differences in gene sequence, antigenicity, and structural proteins have been documented (4, 37, 42, 46–48, 69, 98, 99, 102, 106–135). Although some variability has been documented within each subtype, it is mainly low indicating extensive genetic stability over time (52, 69, 100, 107, 108, 115, 136). Consequently, new variants may not emerge in nature as rapidly as do other RNA viruses.

Gene sequence analyses indicate that Ebola/Reston does not represent a completely different lineage. Consequently, the Asian origin of this type has been questioned (62, 110). The virus may actually have been introduced into Asia from Africa.

Table 2: Documented transmission of Marburg and Ebola viruses from nonhuman primates to humans.

Year	Location	Virus type	Non-human primate species
1967	Marburg, Germany	Marburg	Wild-caught African green monkeys recently imported from Uganda
1967	Frankfurt, Germany	Marburg	Wild-caught African green monkeys recently imported from Uganda
1967	Belgrade, Yugoslavia	Marburg	Wild-caught African green monkeys recently imported from Uganda
1989/90	Reston, Virginia, USA	Ebola/Reston	Wild-caught cynomolgus monkeys recently imported from the Philippines
1994/95	Ivory Coast	Ebola/Ivory Coast	Wild-living chimpanzees
1996	Mayibout, Gabon	Ebola/Zaire	Wild-living chimpanzees

However, filovirus may also have more world-wide distribution than was previously recognized (59).

Symptoms and pathogenesis

Virologic and/or serologic tests are required to confirm filovirus infections. Predominantly, detection of significant antibody titer in serum, virus isolation, viral antigen/RNA detection, and/or inoculation of cell cultures or laboratory animals are used (60, 63, 137).

Various methods can be used to detect IgM or IgG against Marburg and Ebola viruses (60, 63, 137). Complement-fixation tests, indirect immunofluorescence assays, and dot-immunobinding assays were previously used, but mainly enzyme-linked immunosorbent assay (ELISA) as well as Western blot are increasingly used today due to their higher sensitivity and specificity (4, 17, 20–22, 24, 27, 28, 35–39, 46, 52, 55, 68, 71, 75, 76, 119, 129, 135, 138–174).

Definitive evidence of acute filovirus infection is mainly based on virus isolation or viral antigen/RNA detection (171). Various techniques can be used (60, 63, 137). Serum or whole blood frozen on dry ice or in liquid nitrogen vapor is the preferred specimen type (137). Inoculation into cell culture or guinea pigs and/or ELISA, immunofluorescence/immunohistochemistry, and polymerase chain reaction (PCR) have mainly been used (4, 15, 17, 24, 32, 35–39, 41–43, 46, 52, 55, 68, 71, 76, 88, 92, 103, 104, 119, 120, 129, 131, 136, 138, 160, 167, 171, 173, 175–199). In addition, electron microscopy can be used to identify filoviruses, but not for reliable subtyping (4, 17, 19, 25, 26, 32, 34, 37, 41, 42, 78, 79, 88, 91–94, 106, 120, 129, 131, 182, 187, 189, 191, 193–196, 199, 200). Finally, immunoelectron microscopy has been used (42, 118, 120, 129, 201). These techniques can be used directly on tissue or material from humans and animals. However, the described techniques have often been used after inoculation of guinea pigs or various cell cultures with suspected material. By using these methods, virus has been detected mainly in urine, throat secretions, saliva, and serum, and in almost every organ and many cell types, including skin of predominantly humans, monkeys, and guinea pigs. Relevant comparison of these various methods has not been performed. However, ELISA and/or PCR for viral antigen/RNA detection, documented as superior to other methods for various other virus types, should also be preferred for definitive diagnosis of Marburg and Ebola virus infections.

Clinical identification of Marburg and Ebola virus infections, especially in tropical areas, may represent a major diagnostic challenge, because initial symptoms are non-specific and are similar to those of more common infections, including salmonellosis, typhoid fever, yellow fever, viral hepatitis, malaria, Lassa fever, and other hemorrhagic diseases (12). However, the patient's travel history, contact with non-human primates, and symptoms provide important clues for diagnosis, because the manifestations of Marburg and Ebola virus infections usually are rather uniform in humans (Table 3) (4, 14, 16–22, 24–28, 36–38, 42, 43, 45, 46, 50, 52, 54, 84, 202–210). The symptoms may vary from mild disease indistinguishable from other febrile illnesses to severe hemorrhage, but the initial non-specific influenza- or malaria-like symptoms usually develop quickly into the more classic symptoms. It is important to note that hemorrhagic signs are absent in many cases. In addition to these initial symptoms, convalescence of survivors is often prolonged and associated mainly with arthralgia and myalgia as well as hepatic and testicular damage (4, 14, 16, 17, 19–21, 28, 211).

The incubation period in humans usually seems rather short, namely 1 to 2 weeks (4, 13, 14, 16–22, 26, 27, 37, 43, 45, 52, 207, 210). Mortality occurs in 22 to 88% of the infected cases within < 2 weeks (Table 1) (4, 13, 14, 16–18, 20, 21, 27, 35, 36, 38–40, 43, 46, 206). Ebola/Zaire virus infection is associated with the highest mortality, whereas Marburg and Ebola/Sudan virus infections seem associated with lower mortality. However, comparison is compromised by the fact that most Marburg virus cases, unlike most Ebola virus cases, are treated in intensive care facilities of Western standards. Although closely related to Ebola/Zaire, Ebola/Reston probably is of low or no pathogenicity for humans (31, 33, 34, 72–74, 110). The background of the different pathogenicity of Marburg and Ebola viruses is presently unknown. Only one initial study has focused on this aspect (212).

Natural filovirus infections have exclusively been documented in humans and non-human primates. However, various species, including mainly African green monkeys, cynomolgus monkeys, rhesus monkeys, squirrel monkeys (*Saimiri sciureus*), chimpanzees, *Aedes egypti* mosquitoes, guinea pigs, hamsters, and mice, have been infected with Marburg and Ebola viruses (4, 17, 19, 20, 29, 32–34, 37, 41–43, 48, 67, 71, 78, 88, 91, 94, 101, 111, 119, 129, 131, 138, 160, 167, 175, 176, 178–180, 184–189, 191, 193–196, 200, 204, 213–219). Ebola/Zaire virus is also highly virulent for most of these species, whereas Ebola/Sudan and Ebola/Reston viruses seem less virulent, even causing self-limiting infections (4, 24, 33, 71, 94, 101, 111, 119, 129, 131, 160, 180, 184, 189, 191, 192, 217, 220). However, the susceptibility of various monkey species seems different. Ebola/Sudan and Ebola/Reston virus inoculation has documented significantly higher survival rates for African green monkeys, compared with cynomolgus monkeys (119).

The manifestations of Marburg and Ebola virus infections in non-human primates are rather similar to those in humans (Table 3) (4, 17, 33, 34, 37, 41, 42, 51, 55, 71, 91, 94, 111, 119, 120, 129, 131, 138, 176, 179, 180, 184, 186–189, 191, 192, 198, 200, 215, 217, 219, 221). The initial symptoms characterized by anorexia, cough, and decreased activity and vocalization quickly develop into death. Except for failure of clot formation after blood sample collection, the hemorrhagic diathesis may not always be as manifested as that in humans. The incubation period usually is 2 to 14 days (4, 17, 33, 42, 91, 94, 111, 119, 129, 131, 138, 176, 179, 180, 184, 187–189, 191, 192, 217, 219, 221). The manifestations are frequently, as in humans, non-specific and similar to those of other infectious diseases. In addition, Marburg and Ebola virus infections have several pathologic features in common with other severe hemorrhagic diseases, in-

Table 3: Main symptoms of Marburg and Ebola virus infections in humans and nonhuman primates.

Sudden onset of illness
Myalgia, arthralgia, headache, chest pain, abdominal pain, and malaise
Cough and dry/sore throat
Anorexia, nausea, and vomiting
High fever and loss of body weight
Diarrhea and melena
Conjunctivitis and other ocular symptoms
Petechiae of skin and oral mucosa and maculopapular skin rash followed by desquamation
Edema and discoloration of scrotum and labia major
Lymphadenopathy and splenomegaly
Pneumonia
Mental disturbances
Hemorrhage from multiple sites and organs (Hemorrhagic diathesis)
Focal necrosis/degeneration without inflammatory reactions affecting vessels and many organs (mainly liver, lymphatic organs including the spleen, lung, kidney, testis, and ovary)
Immunosuppresion, leucocytopenia, thrombocytopenia, and atypical morphology of peripheral blood cells
Disseminated intravascular coagulation and changed vascular permeability including endothelial damage
Virus presence in blood and organs

cluding simian hemorrhagic fever (33, 222). However, the virulence of simian hemorrhagic fever seems high for cynomolgus and rhesus monkeys, compared with filovirus infections affecting African green monkeys and cynomolgus monkeys. Mortality is usually 100% within a few days from the onset of clinical signs of infection. Although Ebola and Marburg virus infections clinically cannot be differentiated from simian hemorrhagic fever, the histopathologic findings considered specific for Ebola and Marburg virus infections include hepatocellular necrosis, necrosis of the zona glomerulosa of the adrenal cortex, and interstitial pneumonia (33). However, definitive diagnosis should be based on the previously described methods for virus identification.

Several studies have focused on the pathophysiology of Marburg and Ebola virus infections (12). Although some aspects have been clarified, the background of hemorrhagic diathesis and sudden collapse is, at present, inadequately understood. However, multiple factors seem involved. Endothelial cell damage/dysfunction, platelet dysfunction, thrombocytophenia, impairment of the mononuclear phagocyte system cells, disseminated intravascular coagulation, and reduction of several coagulation factors have been documented (4, 14, 17, 50, 131, 184, 187, 193, 194, 196, 200, 219, 221). However, the direct background is still unknown. Viral infection of endothelial cells and/or release of tumour necrosis factor alpha (TNF-α) from virus-infected monocytes/macrophages have been suggested as important factors of endothelial destruction, increased endothelial permeability, and immunosuppression (105, 223, 224). Also a novel identification of fibroblastic reticular cells in lymph nodes being target cells of Ebola virus may play an important role by amplifying the infection and affecting the immune response (131). Recently, it has been claimed that hemorrhage is caused by a viral selenoprotein inducing selenium depletion (225). However, all these observations warrant further investigations.

Recent studies have focused on the secreted as well as the transmembrane glycoprotein of filoviruses. Release of a structural glycoprotein from filovirus-infected cells is presently considered important for the immunopathology of the disease (87, 109, 110, 126, 134, 226, 227). The high homology with an immunosuppressive domain of the envelope glycoproteins of various oncogenic retroviruses may explain the immunodeficiency of filovirus infections (126, 226). Furthermore, it has been proposed that the inflammatory response is diminished by the secreted glycoprotein, which binds to neutrophils and thereby inhibits neutrophil activation (87). The transmembrane glycoprotein may also be important for infection and destruction of endothelial cells, thereby inducing hemorrhage (87). However, these important studies necessitate further research before conclusion of filovirus pathophysiology can be made.

Virus reservoir

Development of effective preventive strategies necessitates knowledge about the natural reservoir of filoviruses. It has been possible during most outbreaks to identify the first infected human case or a group of infected monkeys (4, 13, 14, 16–18, 20–22, 26, 27, 33, 35–40, 42–46). However, the source of their infection is still an enigma (228). The origin and natural habitant of Marburg and Ebola viruses remain a mystery despite extensive research, including capturing and analysis of a huge number of wild-living monkeys, rodents, birds, and insects as well as various domestic animals (4, 17, 20, 21, 68, 146, 155, 173, 229, 230).

Extensive human serologic studies performed predominantly in Africa are rather inconclusive, probably due to questionable sensitivity and specificity of the used methods for detecting filovirus-specific antibodies (4, 17, 20–22, 24, 26, 27,68, 139, 141, 144, 145, 147–149, 151–157, 162–164, 166, 170, 231, 232). Antibodies against Marburg and Ebola viruses have been identified in most of these studies, but with variable frequency. However, concomitant clinical or epidemiologic evidence of filovirus infections has not usually been observed in these studies. In addition, presence of antibodies seems not exclusively restricted to outbreak areas, but is more widespread. Although sporadic cases may be found (170), it is still unknown why Marburg and Ebola virus infections are not seen despite apparent presence of antibodies against these viruses. Presence of unidentified strains has been proposed (12, 59, 152, 168). Subclinical infections cannot with certainty be ignored. However, it has been stated that only antibody surveys using ELISA should be used to evaluate filovirus epidemiology due to more specific antibody detection (12, 60, 172). This new development has been used during the recent outbreaks (52, 76, 168, 174). By use of these methods, antibodies against filoviruses have also been documented in Germany and the United States indicating that filoviruses may be present in more world-wide distribution (73, 159, 162).

Although guinea pigs, mosquitoes, and ticks have been proposed as natural hosts, bats have most seriously been proposed and examined (4, 17, 20, 26, 229, 230, 233–235). Bats can actually be experimentally infected with Ebola/Zaire virus and virus replication may occur (234). Although Marburg virus is able to multiply in *Aedes egypti* mosquitoes (17), Ebola/Reston seems unable to multiply in three other mosquito species or in soft ticks (235). These studies are rather inconclusive, but vector transmission cannot presently be excluded.

One patient infected while traveling in Zimbabwe was strung or bitten by an unknown insect six days before onset of illness while sitting at the roadside (18, 68). However, a relation between this event and the later Marburg virus infection has never been documented.

It has recently been suggested that filoviruses may be plant viruses. However, inoculation of various plants with Ebola/Zaire was unable to induce infection (234). Plants therefore, presently seem not to be obvious filovirus reservoir candidates.

It has previously been discussed whether monkeys could be the primary virus reservoir (17, 32, 59, 60, 71, 233). Serologic studies involving various monkey species are inconclusive, although most studies have documented presence of antibodies against filoviruses, but with variable frequency (17, 138, 140, 145, 158–162, 165, 216). However, high frequency of false-positive results cannot be excluded (17, 60, 63, 140, 162, 165). Weak antibody titers also have been identified among three of 79 monkey trappers in Uganda, indicating presence of infections among these people in Africa (17). However, simultaneous evidence of filovirus infection was not observed. Furthermore, neither Marburg nor Ebola virus have, in general, ever been isolated from monkey trappers or wild-trapped monkeys (4, 17).

Filovirus infections are rather pathogenic for monkeys. Extensive infection of wild-living monkeys is not likely, because illness is usually not observed. Consequently, non-human primates seem also not to be primary virus reservoir. However, it is well known that the pathogenicity of several viruses (e.g., herpes B) is different among humans and various animal species. Similar characteristics may also be valid for Marburg and Ebola viruses. Filovirus infections may be characterized by mild clinical signs in some monkey species and by high mortality in others. Furthermore, a mechanism of long-term infection of monkeys, with reactivation similar to several other virus infections, has been proposed (59).

Thousands of monkeys were handled before 1967 without evidence of filoviruses. However, filoviruses are probably not new pathogens, but have existed for millions of years and only emerged due to environmental changes (11). These environmental changes may be related to several factors, including the expanding agriculture and human population, thus perturbing previously stable ecosystems (11). Furthermore, the increasing human population may support development of modified viruses (60).

Although only wild-living and wild-trapped monkeys have been the source of human filovirus infections (Table 2) (13, 14, 16, 17, 29, 30, 32–34, 37, 71), it cannot be ignored that non-human primates born in captivity also may introduce filoviruses in the future.

Virus transmission

Although the transmission mode is not fully understood, human infections develop mainly after contact with blood and body fluids, as do other blood-borne viral infections including hepatitis B and C viruses and human immunodeficiency virus (HIV) (4, 13, 14, 16–18, 20–22, 26, 27, 35–40, 43, 45, 53, 174, 236). Direct and intimate contact with infected individuals and animals, traveling in Africa, and injections by use of contaminated syringes and/or needles seem to predominate (Table 1). Nursing of patients and preparation of infected bodies for burial seem to increase the infection risk (4, 18, 20–22, 26, 27, 35, 36, 38–40, 45, 236). In contrast, normal social interactions are characterized by low risk (4, 20, 21, 24, 26, 236).

Although their transmission may occur more easily than that of HIV in hospital settings, Marburg and Ebola viruses seem not highly contagious and uncontrolled person-to-person transmission is, therefore, considered unlikely (4, 13, 14, 16, 17, 20–22, 24, 27, 236). According to epidemiologic studies, persons infected but asymptomatic seem not infectious for others (49, 237). Consequently, recovery seems not to be associated with virus carriage. However, it should be emphasized that Marburg virus has been isolated from infected monkeys appearing healthy for several days before clinical signs appear (138, 179). Furthermore, Marburg and Ebola viruses may persist in seminal fluid for several months, and indirect evidence of cases infected after sexual intercourse have been reported (14, 15, 17, 26, 211).

The previously described larger outbreaks in Africa have mainly been characterized by a single case apparently disseminating the infection to family members and/or medical staff (4, 20–22, 27, 35, 36, 38–40). In addition, transmission by contaminated syringes and/or needles was evident. Transmission has previously been interrupted successfully after closure of hospitals/health centers, avoidance of traditional burying rituals, isolation of infected patients, and use of uncontaminated syringes, needles, and instruments as well as protective clothes, gloves, and masks (4, 18, 20–22, 24, 26, 27, 53, 54, 238, 239).

Due to the low frequency of secondary infected cases, airborne transmission involving humans is considered a possibility only in rare instances from persons with advanced stages of disease (4, 20–22, 27, 236, 237). However, infection via large droplets presently cannot be excluded and extreme care should be taken with blood, tissue, and fluids from infected individuals and animals (4, 20, 21, 84, 236, 237).

Few studies have evaluated possible portals of virus entry, although some infections due to needle accidents have been reported (4, 14, 16, 17, 19, 53, 207). An initial study using guinea pigs documented virus transmission through skin lesions, but not through intact skin (213). In contrast, virus transmission through mucosa seems possible. It was also documented early that Marburg virus administration into the mouth and nose of African green monkeys was able to induce infection (17, 179). In addition, rhesus monkeys have recently been experimentally infected by oral and conjunctival exposure to Ebola/Zaire virus (191).

Although it is presently uncertain whether airborne virus transmission plays any appreciable role in humans, these aspects have been studied in primates. It was documented early that Marburg virus could be transmitted among monkeys in adjacent cages due to direct contact (17); in contrast, monkeys without direct contact with experimentally infected monkeys were not infected. However, monkeys have been infected despite absence of direct contact, probably due to aerosol generated at urination (138, 179). It has also been claimed after evaluation of the facilities in the Philippines, that the type of holding cage is important for transmission among monkeys (71). The use of gang- type cages seems to be a major risk factor, compared with captivity in single cages, probably due to close physical contact between the monkeys in gang-type cages (71, 76).

During the outbreaks in the United States in 1989–90 and 1996, virus transmission also occurred between monkeys despite no direct contact between them (33, 55). Also, recent studies have documented transmission of Ebola/Zaire virus to rhesus monkeys from experimentally inoculated monkeys despite no direct contact and a distance of 3 m between monkeys (188). The airborne transmission route was supported by virus presence in the lungs of infected animals (120, 188). Pulmonary, nasopharyngeal, oral, or conjunctival exposure to airborne virus-containing droplets was considered the most likely mode of infection (188). Recent experimental studies using rhesus monkeys and guinea pigs exposed to inhalation of aerosol containing Ebola/Zaire and Marburg viruses, respectively, also documented that aerosol containing virus is able to infect these species (189, 194).

Quarantine of non-human primates

Non-human primates generally represent a greater risk for zoonoses than do other laboratory animal species. The main background of quarantine is to protect people working with laboratory non-human primates from zoonoses and to protect established colonies of non-human primates from introduction of not only Marburg and Ebola viruses, but also other infectious diseases. Consequently, the presently recommended guidelines for transportation, transit, and quarantine of non-human primates have been established not only for protection against Marburg and Ebola virus infections, but also against other potentially infectious diseases (Table 4) (3, 7, 8, 13, 17, 30, 55, 240–242). However, primate importation was reduced substantially or banned world-wide for a longer period after the US Ebola outbreaks in 1989–90 among cynomolgus monkeys (243). In addition, previously recommended quarantine and management guidelines were revised.

As indicated in Table 4, use of protective clothing, including mucous membrane protection while handling monkeys and potentially contaminated material, is essential to decrease the risk for not only Marburg and Ebola viruses, but also for other infective agents as previously mentioned, including herpes B virus (30, 240). Personal protective equipment commonly involves proper-fitting face mask, disposable latex or vinyl gloves, safety glasses with side shields, gown or laboratory coat, long-sleeved shirts, and non-slip steel-toed shoes/boots (30, 240). In addition, stainless-steel or kevlar meshed gloves may also be useful for special procedures to prevent deep punctures and lacerations. In addition, face shields should be worn when performing procedures with high aerosol potential.

The present recommendations were evaluated during the filovirus outbreak in Texas in 1996, and current knowledge about filovirus infections and other viral diseases indicates that the infection risk for people working with non-human primates during quarantine is present, but minimal when these guidelines are followed (Table 4) (55). In addition, use of an adequate quarantine period guarantees high recognition of filovirus infections before the end of the period. Consequently, there seems to be little risk of filovirus infections for persons working with non-human primates as laboratory animals after a quarantine period.

Although a 31-day quarantine period has been recommended by the Centers for Disease Control and Prevention (CDC) (30), a 60- to 90-day quarantine period has more recently been recommended (240). The CDC recommendations are based on studies involving African green monkeys and cynomolgus monkeys. Consequently, a modified quarantine duration may be relevant for other non-human primate species or other Marburg and Ebola virus subtypes. In addition, immunosuppression due to stress of shipment as well as concurrent presence of other viral infections, such as simian retrovirus, may alter disease development. Therefore, it is presently not possible to recommend a fixed quarantine duration relevant for all situations. The quarantine duration should be based in each case on careful analysis of potential risk factors. However, there is no reason to assume that primates surviving Marburg and Ebola virus infection should be able to carry virus after recovery.

The outbreak in 1996 among cynomolgus monkeys documented the fact that testing of blood samples from animals immediately at arrival was unable to detect a symptomatic Ebola virus-infected animal (55). Consequently, routine collection of blood samples on arrival are presently not advocated (Table 4) (55). It has also been discussed whether presence of antibodies against Marburg and Ebola viruses should be acceptable in primates used as laboratory animals. Health monitoring on the basis of routine antibody screening in breeding colonies has been used for other species (244). It is presently unknown whether stamping out seropositive animals will be sufficient for filovirus eradication from an infected colony. Monitoring of antibody titers against filoviruses seems, therefore, of questionable value in preventing introduction and spreading of disease (33). Antibody titers have been detected as previously described in healthy primates (172). In addition, filoviruses can only be isolated within 20 days after onset of infection from surviving monkeys (160, 241). Furthermore, virus has never been identified concomitant with high antibody titers (160). Consequently, healthy monkeys with low-titer antibodies against filoviruses should be regarded as uninfected, if no illness is observed after an adequate quarantine period (160, 241). Furthermore, antibody evaluation for filoviruses should predominantly be performed in cases of severe illness or death in recently imported or otherwise suspected animals (241).

Various initiatives have been taken when a filovirus infection developed among non-human primates (10, 33, 55) (Table 5). All rooms with infected animals or the entire facility were previously depopulated when filovirus presence was confirmed (17, 33, 55, 59). The rooms and adjoining corridors were sprayed with 5% sodium hypochlorite then were cleaned the following day with conventional disinfectant and detergent solutions.

Table 4: Guidelines for transportation, transit, and quarantine of non-human primates.

1.	Crates with primates should be separated from all other animals and cargo at all time
2.	Risk for scratches or wounds should be minimized/eliminated during handling of crates with animals by using adequate crates, elbow-length reinforced leather gloves, sturdy waterproof shoes/boots, long-sleeved shirts, and trousers of sufficient thickness to resist tears
3.	Adequate information to all persons at risk about the potential risks of handling primates
4.	A minimum of 31 days' quarantine after arrival
5.	Prohibition of drinking, eating, and smoking while handling monkeys and potentially contaminated material
6.	Access to secure quarantine facilities should be restricted to a minimum of essential, authorized, trained, and informed persons
7.	Use of protective clothing, gloves, and surgical masks while handling monkeys and potentially contaminated material
8.	Potentially contaminated material and clothing should be incinerated and/or disinfected on site before removal from the facility
9.	Use of separate non-glass water bottles. Reusable items should be decontaminated between each use
10.	Use of uncontaminated needles, syringes, and surgical instruments to avoid disease transmission between animals
11.	Non-quarantined monkeys and other animals should not be placed in or permitted access to areas with quarantined animals. Different lots of primates should not be mixed while in quarantine
12.	Direct handling of primates should be minimized. Procedures that may cause bites or scratches should be avoided. All animal handling should whenever possible involve anesthesia or tranquillization. Squeeze-back cages are preferred
13.	Use of records to document health status and injections of each monkey. Relevant authorities should be informed about serious illness or death in recently imported monkeys. Adequate veterinary control at frontier and during the quarantine period is mandatory. The cause of monkey death should always be identified, if possible
14.	Routine serum samples from primates upon arrival and test for filovirus antibodies is normally not required. If illness or death occur during quarantine, blood samples from all animals must be taken to test for filovirus infections. If any of the monkeys demonstrate significant filovirus antibody response, a supplementary quarantine period must be followed
15.	Serious febrile illness of persons having direct contact with monkeys in transit or quarantine should promptly be notified to physician and relevant authorities

Furthermore, sealing of the entire facility and paraformaldehyde fumigation followed by use of conventional disinfectants/detergents also have been recommended. It was previously discussed as unknown whether a filovirus outbreak among non-human primates can be eliminated using a test-and-sacrifice approach, not mass depopulation (33). It would probably be an effective approach due to the slow rate of disease spreading.

Guidelines for persons that have been exposed to infected animals, blood, or tissue have been established (29, 30, 55, 84, 237). If accidental exposure to potentially infected material occurs, use of soap and disinfectant solution has been recommended before notifying health authorities (84, 237). Mucous membranes (e.g., conjunctiva) should be irrigated with copious amounts of water or eyewash solution (237). During the outbreaks at various primate quarantine facilities in 1989–90 and 1996, all exposed persons were placed under surveillance for 3 weeks after their last known exposure (29, 30, 55). In addition, all were tested for antibodies against Ebola virus (30, 55). All potentially exposed individuals should be questioned, counseled, and placed in appropriate risk categories on the basis of level of exposure (33, 84). Periodically collected blood samples and daily recording of body temperature should be obtained from individuals in the high-risk group, whereas those in the lower risk groups should notify health authorities if unusual symptoms are experienced (33, 84). However, it should be emphasized that, although general guidelines for a filovirus outbreak among laboratory non-human primates can be outlined, management of an outbreak should always be performed in close cooperation with relevant national and international authorities.

To prevent infections, potentially contaminated items and instruments should be adequately handled before reuse. Filoviruses are sensitive to many ordinary disinfectants. Therefore, inactivation can easily be performed. Marburg virus is quite stable at room temperature (79), but an initial study indicated Marburg virus destruction by heat at 60°C for 20 minutes (17). However, other studies have advocated heating at 60°C for 60 minutes to completely destroy infectivity (79, 83). In addition, primary soaking of nondisposable materials in 2 to 5% sodium hypochlorite has been recommended (4). The instruments should then be boiled for 20 minutes or autoclaved for 15 minutes before washing and sterilization (4). Ultraviolet light, gamma irradiation, formalin, β-propiolactone followed by acetone, quaternary amines, phenolic disinfectants, sodium hypochlorite, and lipid solvents (sodium deoxycholate, chloroform, or ether) are also able to inactivate filoviruses (17, 78–82, 84, 245). In addition, various soaps and detergents seem useful when used liberally (84).

Treatment and prevention

The challenge of managing patients with viral hemorrhagic fever is to provide the highest quality of care without risk of disease transmission. Isolation of patients in special facilities and protection of medical staff members working with infected patients by using so-called strict barrier nursing regimens, including routine use of protective eye wear, gowns, masks, shoe covers, and gloves, is essential (4, 10, 17, 20–22, 26, 27, 53, 84, 237–239, 246).

Although a virus-specific treatment has not been developed until now (8–10, 63, 247), intensive supportive care should be provided (4, 8, 14, 16–18, 20, 50, 53, 84, 237). Maintenance of adequate blood volume and electrolyte balance as well as management of cerebral edema, renal failure, coagulation disorders, and secondary infections may actually, in many instances, be lifesaving. Heparin/fibrinogen, interferon, and human convalescent plasma have been used, but the effect has never been documented (4, 16–19, 21, 206, 248). Various antiviral drugs have been used for the treatment of various types of viral hemorrhagic fever (9, 247). However, only one study has documented cure of Ebola virus-infected mice by use of antiviral drug therapy (249).

Table 5: Mandatory initiatives when a filovirus infection occurs among non-human primates.

1. Dead animals should be placed in sealed plastic bags. The exterior of the bag should be sprayed with a 5% sodium hypochlorite solution and placed in a second plastic bag, which also is sealed and sprayed before transportation to necropsy in biosafety level 4 facilities
2. Animal shipment out of the facility should be suspended
3. Recent recipients of primates should be alerted
4. All persons in the animal facility should be fitted with full-face respirators, gloves, and protective suits. All procedures other than once daily feeding, observing, and cleaning should be suspended. All medical treatments should be suspended
5. In an attempt to minimize the potential for animal-to-animal spread, the waste collection troughs should be sprayed with a 5% sodium hypochlorite solution

Passive immunization of guinea pigs by administration of serum from immunized or convalescent animals seems possible (167, 169, 248). However, the effect in cynomolgus monkeys was limited to delayed onset of viremia and clinical signs of infection (169, 192). Similar disappointing results were obtained after recombinant α_2-interferon treatment (169). Whole blood transfusion from convalescent patients seems not to significantly increase survival rate (210, 250). Four persons suspected of being accidentially infected with Ebola virus were reported to be successfully treated with anti-Ebola virus immunoglobulin from Ebola virus-infected goats and recombinant human α_2-interferon (248). However, all treatment modalities for human filovirus infections need further investigation, using controlled trials. Use of recombinant human monoclonal antibodies may be a future possibility (251).

Although an obvious role of vaccine does not exist today, vaccine development may be of special value in the future, not only for African medical staff members, but also for persons working with non-human primates predominantly in quarantine and/or with potentially filovirus-infected material. Initial studies have documented protection of guinea pigs from a lethal Marburg or Ebola/Zaire virus dose after vaccination with inactivated virus (167, 252). Also, results of a preliminary study documented that mice survived a lethal dose of Ebola/Zaire virus, if they previously had been inoculated with a non-lethal dose (195, 253). However, these results can not be confirmed in non-human primates (17, 254).

To eliminate infection risk during vaccine production as well as the risk of incomplete inactivation, use of recombinant vaccines should be preferred. Recent initial studies using guinea pigs and mice have documented at least partial protection against Marburg and Ebola/Zaire viruses (167, 255–257). These study results should be confirmed in non-human primates. However, development of vaccines may be complicated by the fact that predictable cross-protection of the various filovirus subtypes has not been documented in various experimental animal models (111, 119).

Conclusions

The aforementioned summarized literature warrants the following main conclusions:

1. A total of 23 Marburg and Ebola virus outbreaks causing viral hemorrhagic fever have been reported among humans and non-human primates since the first outbreak in 1967. Most of the 1,100 human cases with nearly 800 deaths developed in Africa. Most infections developed after direct and intimate contact with infected patients. Furthermore, nosocomial transmission was a major factor sustaining the outbreaks. All outbreaks have so far been self-limiting, and there is no reason to assume that the last filovirus outbreak has occurred.
2. Marburg and Ebola viruses are extremely dangerous types. Although subtypes of Marburg virus do not exist, Ebola virus is classified into four distinct subtypes, namely Ebola/Sudan, Ebola/Zaire, Ebola/Reston, and Ebola/Ivory Coast. Significant biologic differences have been documented among these types.
3. The manifestations of Marburg and Ebola virus infections are rather similar in humans and non-human primates. The symptoms vary from slight non-specific symptoms to the more classic manifestations characterized by severe hemorrhage. The pathophysiology of filovirus infections is poorly understood.
4. Despite extensive investigations, the natural reservoir of Marburg and Ebola viruses as well as the trigger of virus re-emergence are still unknown. However, it is generally accepted that monkeys are not the natural reservoir of these viruses.
5. Although aerosol transmission seems possible in non-human primates, this transmission route has never been documented in humans.
6. Great concern has recently arisen about the risk of filovirus outbreaks among non-human primates used as laboratory animals. Human infections have been documented, but the number is small in relation to the number of monkeys used.
7. Adequate quarantine and handling procedures of non-human primates are mandatory to prevent not only human filovirus infections, but also other infectious diseases. By following internationally accepted guidelines, the filovirus infection risk for people working with non-human primates during quarantine is present, but minimal. There seems to be little risk after an adequate quarantine period. Consequently, non-human primates can be used as laboratory animals with little risk for filovirus infections provided adequate precautions are taken.
8. Proven prophylactic or therapeutic measures to combat filovirus infections do not yet exist despite recent extensive research. However, supportive intensive care may be lifesaving. Vaccine development has, until now, been disappointing.

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