



Marburg Virus Disease

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ABSTRACT

Marburg virus disease was identified for the first time in 1967 during an epidemic in Marburg and Frankfurt, Germany, after infected monkeys were imported from Uganda. Available and scattered data of Marburg virus disease were collected and summarized in the present report. Marburg virus global data including Pathogenesis, Virus in animals, diagnosis, vaccines transmission and prevention were reviewed. It is a serious and usually fatal disease caused by a virus of the same family as that at the origin of the Ebola virus disease. Because of their extreme pathogenicity and lack of vaccine at present, they are considered a potential biological weapon of category 4. The fatality rate varies from 25% during the first outbreak appeared in a laboratory in 1967 to over 80% between 1998 and 2000 in the Democratic Republic of Congo during the outbreak in Angola in 2005. *Roussettus aegyptiacus* is considered as the natural reservoir of this virus.

Keywords: Marburg virus disease, pathogenicity, *Roussettus aegyptiacus*.

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INTRODUCTION

The Marburg virus (MARV), a single-stranded, negative-sense RNA virus, causes Marburg hemorrhagic fever, a rare human disease. The first case of Marburg hemorrhagic fever was discovered in 1967 in Marburg, Germany, when laboratory personnel were infected while dissecting African green monkeys from Uganda¹. In endemic areas in Africa, MVD is considered a zoonotic illness that is thought to survive in a healthy reservoir host. Humans and nonhuman primates (NHPs) are overflow hosts with a high rate of disease fatality. Almost all of the primary infections associated with natural MVD outbreaks have been attributed to human access into bat-infested caves thus far (e.g., cave visitors, mine workers). As a result, bats have long been suspected of playing a key part in the disease's transmission cycle. The common Egyptian fruit bat (*Roussettus aegyptiacus*) was found to be infected with MARV in 2007, and MARV was isolated from healthy infected *R. aegyptiacus* bats collected in Uganda the same year².

It's a dangerous and typically fatal disease caused by a virus from the same family as the one that causes Ebola. Both the Marburg and Ebola viruses are members of the Filoviridae family (Filovirus). In contrast to the latter, which has five species, phylogenetic analyses show that the Marburg virus only has one species with two different

lineages (MARV and RAVN). Despite the fact that they are caused by distinct viruses, the two diseases are clinically similar. These viruses are among the most dangerous pathogens that may infect humans³.



Figure 1: Marburg virus infection.

History

The virus was discovered in August 1967, when MHF outbreaks in laboratory workers in Germany and Yugoslavia occurred at the same time. The second recorded outbreak of MHF occurred in early February 1975, after two visitors travelling through Zimbabwe reported sleeping in rooms with bats and visiting Chinhoyi caves in the days leading up to developing symptoms. Two patients got MHF after visiting a cave complex with substantial bat populations on Mt Elgon, Kenya, in January 1980 and then again in August 1987. A long-running outbreak occurred between 1998 and 2000 at the Goroubwa mine in Durba village in northeastern DRC, involving many short chains of viral transmission among gold miners and their families⁴.



Pathogenesis

Due to the rural and severe nature of most MVD epidemics in Africa, there are few thorough clinical descriptions, and pathological and analytical data from patients is scarce. The only precise descriptions available come from the original outbreak in Marburg, Germany, a three-patient outbreak in Johannesburg, South Africa, and a few minor isolated cases and outbreaks in Africa. The following are summaries of several cases and outbreaks to give a comprehensive picture of MARV pathogenesis in humans⁵. Similar to many other infectious diseases, cases of MVD begin with flu-like symptoms such as chills, fever, headache, sore throat, myalgia, joint pain, and malaise, 2–21 days after the initial infection. Within 2–5 days of the first symptoms, patients can experience abdominal pain, nausea, vomiting, watery diarrhea, and lethargy. On days 5–7, the intensity of the disease increases, and may include a maculopapular rash spreading from the torso to the limbs, conjunctivitis, sustained fever, and symptoms of hemorrhagic fever, such as mucosal bleeding, petechiae, blood in the stool and vomitus, and bleeding from venipuncture sites. The maculopapular rash begins as

small, dark red spots around hair follicles of the trunk and sometimes upper arms, developing into a diffuse rash, and can become a dark erythema that covers the face, neck, chest, and arms. Later stages of the disease can cause neurological symptoms such as confusion, agitation, heightened sensitivity, seizures, and coma, and all patients in the initial outbreak in Marburg, Germany, were described as gloomy, pessimistic, and slightly violent. Increased serum creatinine levels and alanine and aspartate aminotransferase (ALT and AST) levels indicate hepatic and renal impairment. Within a week of the onset of symptoms, disseminated intravascular coagulation (DIC), lymphopenia, and thrombocytopenia occur. Lymphopenia is compensated by neutrophilia in the late stages of the disease. Patients either recover or die as a result of dehydration, internal haemorrhage, organ failure, or a combination of systemic causes helped by a virus-induced immune response that is dysregulated. Patients who survive are less likely to develop severe late-stage symptoms, although they may develop complications such as arthritis, conjunctivitis, myalgia, and psychotic symptoms during and after recovery.

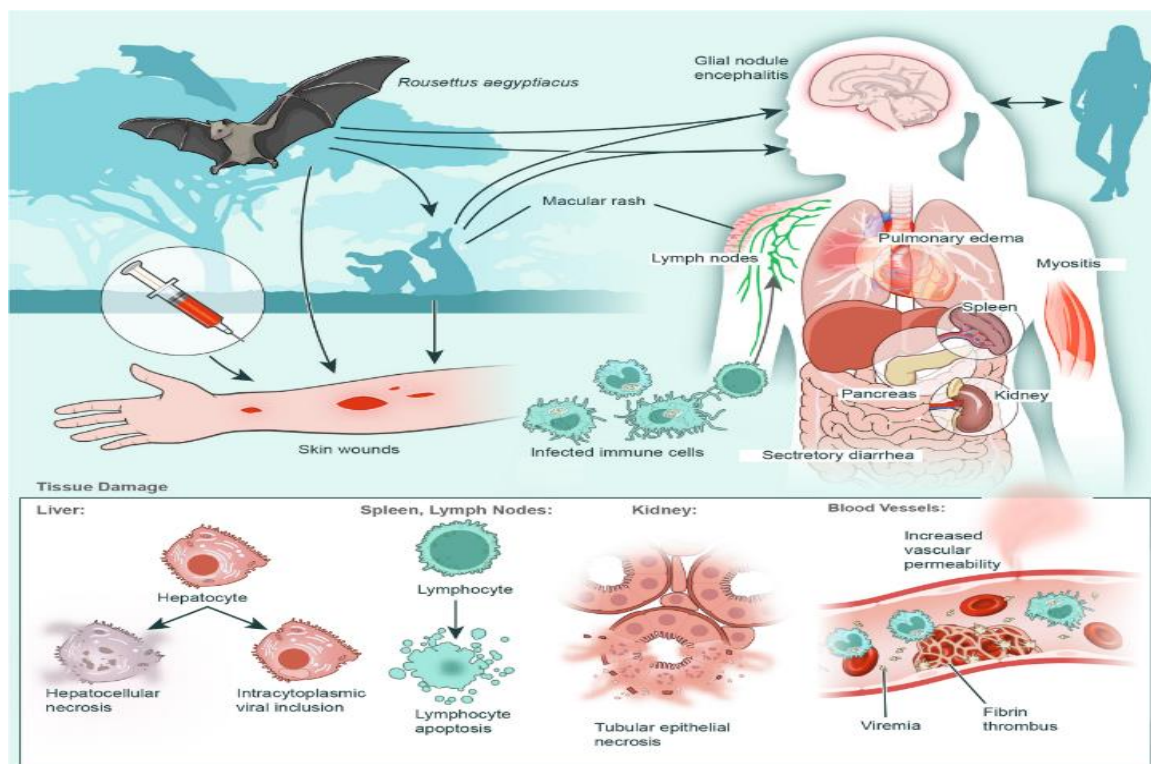


Figure 2: MARV pathogenesis in humans. Transmission and virus spread in the human body are depicted⁵.

Experiments with grown cells from survivors show that immune cells mount a healthy adaptive response to the viral infection. In addition, IgG responses to MARV NP and GP were found in serum samples from survivors, with two of the patients having high neutralising antibody titers. The neutralising antibody titer decreased over time, starting at 21 months post infection (mpi) and ending at 27 mpi, when it was below detectable limits⁵. Swelling of the heart, brain, spleen, kidneys, and lymph nodes, as well as bleeding of

mucous membranes, soft tissues, and numerous other organs, were found in autopsies of RAVV-infected patients who died. Every tissue tested had some sort of bleeding, and localised necrosis was identified on practically every organ, with the hepatic and lymphatic tissues, as well as the testis and ovaries, being particularly conspicuous. The liver tissue was severely damaged, with significant hepatocellular edema and degeneration. Eosinophils with basophilic cytoplasmic inclusions were detected in sites of

necrosis and tested positive for viral antigen. Hepatocytes and Kupffer cells also exhibited inclusions comparable to those identified in eosinophils, however most Kupffer cells in the tissues examined were unrecognisable. Both the red and white pulps of the spleen had significant necrosis, with lymphoid depletion visible in the white pulp. Fibrin and cellular debris were found in the red pulp⁵. Cellular debris and granular material, as well as a tiny amount of fibrin, had been accumulated in the sinuses. In the germinal centres, there was haemorrhage and severe necrosis. Despite the extreme necrosis, viral antigen was found in the border zone of the red pulp and in macrophages, but not in the germinal centres. A large number of plasma cells and monocytes were found in the lymphatic organs and mucous membranes of the stomach and intestines. A significant reduction in lymphocytes was seen, which is now understood to be the result of bystander apoptosis rather than direct infection. There was tubule necrosis and parenchymal damage, and the kidneys were large, pale, and hemorrhagic. Intestinal and renal macrophages had what seemed to be viral inclusions⁵.

Transmission

Marburg virus transmission can take place through mucosal surfaces, cutaneous breaches or abrasions, and parenteral administration. Direct contact with infected persons or animals is the most prevalent source of infection in outbreak settings, but parenteral exposure, which occurs

often in the nosocomial setting, is the most fatal. The majority of patients during the 1967 outbreak had direct contact with infected African green monkey blood and organs used to make primary cell cultures, or were involved in post-mortem examinations of diseased animals. Secondary dissemination to people who had no interaction with infected animal products, on the other hand, was well established. MARV is transmitted from person to person through direct contact with blood or other secretions/excretions (e.g., saliva, sweat, stool, urine, tears, or breast milk), commonly while caring for infected patients. Furthermore, evidence from the DRC outbreak in 1998–2000 revealed that the handling of bodies during the burial process was a significant risk factor. The 1967 outbreak included the possibility of sexual transmission while the patient was recovering, as evidenced by the presence of virus antigen in the patient's sperm. While the risk of MARV transmission via aerosol is thought to be low in the natural world, the virus is stable in aerosols, and studies on nonhuman primates (NHPs) have shown that MARV is highly infectious and lethal following experimental aerosol exposure, raising concerns that MARV could be used as a bioterrorism agent. Since recent research has strongly shown that some African fruit bat species, particularly *Rousettus aegypticus*, may be a natural reservoir for MARV, transmission via inhalation of contaminated excreta from infected bats could be a key route of introduction into the human population⁶.

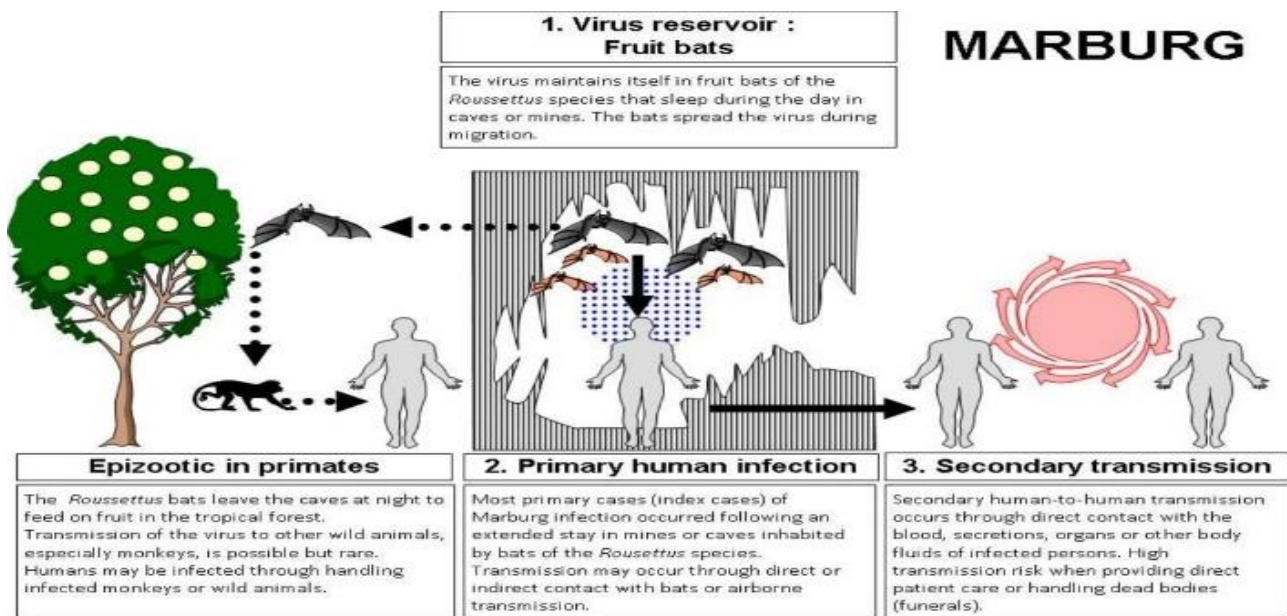


Figure 3: Transmission of Marburg virus disease.

Epidemiology

The genus *Marburgvirus* has one species, *Marburg marburgvirus*, with two viruses, namely MARV and RAVV. Egyptian fruit bats (*Rousettus aegyptiacus*) were recently found to be the most likely natural reservoir host for marburgviruses. Many outbreaks have been associated with entry into working/decommissioned mines or caves in which the bats stay.

The most recent MVD outbreaks occurred in Uganda in 2012. MARV infections in Egyptian fruit bats have been found to have seasonal fluctuations, with biannual peaks that correspond to infections in humans. The 2012 outbreak occurred during one of the peaks of MARV infections in bats. The full length genome sequences from this outbreak showed 99.3% sequence identity to MARV from bats captured in 2008 and 2009 in a nearby cave. In 2007 there were two independent outbreaks in Uganda, occurring in

miners who had close contact with bats. In June 2007, three people were infected and one died, whereas in the later outbreak there was only one case and no mortality. There was 21% sequence variation between the full-length RNA genomes of these viruses, the earlier one being closely

related to historical MARV sequences and the later one more closely related to RAVV, which was first isolated in Kenya in 1987. Both MARV- and RAVV-related sequences were also found in fruit bats (*R. aegyptiacus*) in the same area⁷.

Location	Year	Strain(s)	Cases (deaths)	Epidemiology
Germany/Serbia	1967	Ratayczak/Popp	32 (7)	Infection during research using tissues from monkeys imported from Uganda
Zimbabwe	1975	Ozolin	3 (1)	Unknown origin; index case was infected in Zimbabwe (lethal) with secondary cases in South Africa
Kenya	1980	Musoke	2 (1)	Unknown origin; lethal index case was infected in western Kenya
Kenya	1987	Ravn	1 (1)	Unknown origin; expatriate traveling in western Kenya
Russia	1988	Popp (?)	1 (1)	Laboratory accident
Russia	1991	Popp	1 (0)	Laboratory accident
Russia	1995	Popp	1 (0)	Laboratory accident
Democratic Republic of the Congo	1998–2000	Multiple strains	154 (128)	Infections related to mining; repeated introductions resulting in multiple virus strains; short transmission chains in families
Angola	2004–2005	Angola	252 (227)	Unknown origin; cases linked to Uíge hospital
Uganda	2007	ND	4 (1)	Unknown origin; infections related to visits to a mine (Kitaka cave)
USA	2008	ND	1 (0)	Unknown origin; infection related to visit to a cave in western Uganda; imported infection
The Netherlands	2008	ND	1 (1)	Unknown origin; infection related to visit to a cave in western Uganda; imported infection

ND: Not determined.

Figure 4: Known Outbreaks of Marburg hemorrhagic fever.



Figure 5: A women with Marburg virus disease has a rash.

Incubation Period

The incubation period is estimated to be 3–21 days (typically 5– 10 days), likely related to infectious dose and route. The original Marburg outbreak described a range of 5– 9 days among patients with well-defined exposure dates. A 2011 review noted a range of 3–13 days for filoviral (Zaire Ebolavirus and Marburgvirus) infection based on definitive exposure dates (such as a known laboratory accident). A study focused on Marburg calculated an incubation period of 2–26 days⁸.

What research is ongoing about Marburg virus infections?

Research about these viruses is ongoing. Sarepta Therapeutics has been developing the RNA interfering drug termed AVI-7288. This drug is targeted against the nucleocapsid protein of the virus, and the company has reported infection protection in monkeys ranging from 83%-100% when given four days after the monkeys were

infected with Ebola. This drug is undergoing a phase 1 safety trial that began in May 2014. Another company, Tekmira Pharmaceuticals from British Columbia, has a lipid nanoparticle that interferes with the RNA replication of this virus. It too has shown protection against Marburg virus infection in monkeys. This drug is termed TKM-Marburg (also termed NP-718m-LNP)⁹.

Signs and Symptoms

Signs and symptoms typically begin abruptly within five to 10 days of infection with Ebola virus or Marburg virus. Early signs and symptoms include:

- Fever
- Severe headache
- Joint and muscle aches
- Chills
- Weakness

Over time, symptoms become increasingly severe and may include:

- Nausea and vomiting
- Diarrhea (may be bloody)
- Red eyes
- Raised rash
- Chest pain and cough
- Sore throat

- Stomach pain
- Severe weight loss
- Bruising
- Bleeding, usually from the eyes, and when close to death, possible bleeding from the ears, nose and rectum
- Internal bleeding¹⁰.

Diagnosis

Marburg virus disease (MVD) can be difficult to diagnose clinically. Many of the symptoms of MVD are similar to those of other infectious diseases (such as malaria, typhoid fever, or dengue fever) or viral hemorrhagic fevers that are endemic in the area (such as Lassa fever or Ebola). This is especially true if there is only one case. If a person displays early symptoms of MVD and has been exposed to the Marburg virus, they should be isolated and public health officials should be contacted. The patient's samples can then be taken and examined to confirm infection. Within a few days of symptom onset, antigen-capture enzyme-linked immunosorbent assay (ELISA) testing, polymerase chain reaction (PCR), and IgM-capture ELISA can be performed to confirm a case of MVD. Virus isolation is also possible, but only in a high-containment facility using acceptable laboratory practices¹¹.

- **ELISA testing:** Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing looks for antibodies or antigens in the blood, which are signs that someone has been exposed to the virus.
- **Reverse transcription polymerase chain reaction (PCR):** This test looks for the virus' genetic material, specifically RNA, in order to detect the virus in a blood sample¹².

Treatment

There is no specific treatment for Marburg virus disease. Supportive hospital therapy should be utilized, which includes balancing the patient's fluids and electrolytes, maintaining oxygen status and blood pressure, replacing lost blood and clotting factors, and treatment for any complicating infections. Experimental treatments are validated in non-human primate models but have never been tried in humans¹³.

Potential treatment or prophylaxis countermeasures

Pre-exposure prophylaxis No Marburg vaccines are approved in the U.S. or worldwide. There is no cross protection between Ebola and Marburg virus vaccines, although several constructs tested in cynomolgus macaques have demonstrated protection against both Marburg and Ravn viruses (Table 1). Three candidate Marburg vaccines (cAd3, MVA-BN-Filo and MARV DNA) are in Phase I clinical trials and one (MVA-BN-Filo) is scheduled for a Phase 2/3 clinical trial. Multiple Marburg candidate platforms (rVSV, VLP, Adenovirus, DNA) have demonstrated protection in NHPs⁸.

Adenovirus vectored vaccines

For EBOV, several adenovirus-based vaccines have been explored, but there have been few investigations for MARV. The most popular vector for glycoprotein (GP) vaccinations is recombinant adenovirus serotype 5 (rAd5). A single dose of rAd5 vaccination expressing MARV-Angola GP was given to macaques in one research. Four weeks later, they were challenged with homologous MARV, and none of them developed clinical disease. In four macaques given three doses of MARV-Angola GP DNA prior to vaccination in a prime-boost method, a comparable reaction was seen.

Table 1: Vaccines

Vaccine	Manufacturer or source/ contact	Description	NHP studies	Human use (INDs, case reports, phase 1 or 2)	Phase 3/RCTs
cAd3		Chimpanzee adenovirus serotype 3 vector, encoding wild type (WT) glycoprotein (GP) from Marburg virus	No data for this construct for Marburg. Protection with other constructs: Ad26 alone (75%) better than Ad35 with Ebola. Ad26 plus Ad35 boost 100%. cAd3 prime followed by MVA boost was protective against Ebola	Phase 1 clinical trial with Marburg construct active, not yet recruiting (NCT03475056)	
MVA-BNFilo	Janssen Pharmaceuticals, Titusville, NJ (of Johnson and Johnson)	Modified vaccinia Ankara vector, encoding glycoproteins from Ebola, Sudan, and Marburg viruses, and Tai Forest virus nucleoprotein	No data for this construct for Marburg. An Ebola vaccine demonstrated protection out to 10 months in Ebola-infected NHPs using a cAd3 prime followed by MVA boost 8 weeks later	Phase 1 trial for MVA-BN-filo in prime-boost with Ad26.ZEBOV. Better immune response after Ad26.ZEBOV primary. Sustained Ebola GP immunity after either primary followed by alternate boost. Response to Marburg antigens not measured.	



MARV DNA plasmid vaccine		Marburg DNA plasmid expressing GP from Marburg Angola	Study using a DNA prime/boost vaccine demonstrated protection, but all animals developed signs/symptoms	90% antibody response in Phase 1 trial, 10 people; 1 discontinued for non-lifethreatening side effects; 4th dose at 12 wks improved.	Phase 2/3 trials planned. Use of construct against Ebola planned in response to DRC Ebola outbreak 2019.
Rvsvmarvgp		Recombinant vesiculo stomatitis virus vector for Marburg GP	Several tried with good immune response. Sustained IgG response and protection against clinical illness: protected 20–30 min (5/5), 24 h (4/6) and 48 h (2/6) post challenge.	No human trials, although a similar Ebola vaccine has now been used in three different Ebola virus outbreaks in Africa is now licensed.	

DNA Vaccines

DNA vaccines against filoviruses have shown poor immunogenicity in clinical studies despite having favourable safety profiles in NHP trials, being easy to make, and having the ability to generate humoral and cellular protection. In cynomolgus macaques, DNA vaccines containing MARV-Musoke GP and MARV-Angola GP elicited an IgG response and provided protection against homologous challenge. All developed clinical disease, implying that the IgG response alone was insufficient to suppress infection. DNA-based vaccines, such as an adenovirus vector, have been employed with higher success as part of a prime-boost strategy. Phase 1 clinical testing of a Marburg DNA plasmid vaccine (VRCMARDNA025-00-VP) expressing MARV Angola DNA has been completed. Ten persons were given the vaccination (0, 4, and 8 weeks) and 90% of them developed antibody responses; seven people were given a fourth dose at 12 weeks, which helped to increase waning antibody titers. Trials for Nophase2/3 are presently underway⁸.

Testing in Humans

In 2016, a phase 1 safety study was completed, however the results have yet to be released.

T-705 Favipiravir (Toyama Chemical Co., Ltd)

In Japan, favipiravir, a synthetic guanidine nucleoside analogue with broad-spectrum action against various RNA virus families, has been approved for influenza treatment. Early research revealing efficacy against the Ebola virus in mice models sparked curiosity in potential application during the West African outbreak. Although it appeared to have efficacy in patients with lower viremia levels (Ct value 20), the results of a large-scale experiment (JIKI) in Guinea were unclear. Instead of using present controls, this study used historical control. presented a study from Guinea that showed a trend toward improved survival in the treated sample, but not a substantial survival benefit.

Remdesivir (Gilead Sciences)

Remdesivir is a prodrug of an adenosine analogue that has anti-Marburg action in vitro. It has been used to treat EVD in NHPs, and it has recently been shown to be effective in treating Marburg-infected cynomolgus macaques 4–5 days after exposure with once daily dosages of 5 mg or 10 mg for 12 days (two doses, 50% and 83 percent survival, respectively). A nurse who had recovered from EVD was given Remdesivir, but 9 months later got meningoencephalitis. After 14 days of treatment, which included high-dose steroids, Ebola was undetectable in blood at a lower concentration than in CSF. Remdesivir was also administered to a premature baby born to a pregnant lady who had been infected with Ebola. The infant was also given leukocytes and ZMapp, and he tolerated the medication well enough to be released from the hospital⁸.

Prevention

With no real effective treatment options, the most effective way to protect yourself from Marburg virus disease is to prevent it altogether. No vaccine is currently available to prevent Marburg, though one is in the early stages of development. Instead, methods to prevent Marburg virus center on barrier nursing techniques (like personal protective equipment used to prevent Ebola), as well as avoiding animals that might be carrying the virus.

Use Barrier Nursing Techniques

When someone has a virus like Marburg or Ebola, healthcare providers and caregivers should use barrier nursing measures to protect themselves.

- Wearing personal protective equipment (PPE) such as gowns, gloves, and masks before coming into contact with someone who has or may have Marburg virus disease
- Using single-use medical equipment, such as needles, wherever possible, and thoroughly disinfecting multi-use medical equipment (such as bedsheets)

These precautions extend beyond healthcare settings. Just like nurses should take precautions when changing soiled



sheets or clothing when caring for someone with Marburg virus disease in a hospital setting, so should family members or friends caring for the individual in the home. Likewise, loved ones of someone who died from Marburg virus disease should be careful when touching their loved one's body, including during funerals or other cultural traditions used to honor the deceased.

Avoid Potential Animal Hosts

Exactly how the Marburg virus jumps from animals to humans isn't well understood among public health and medical officials. As a result, researchers are still figuring out the best ways for humans to avoid getting the virus from an animal. However, given what we know already, certain animal groups should be avoided. These include:

- African fruit bats, including being in spaces like caves or mines where the bats live
- Non-human primates that show signs of infection
- Domestic pigs, especially in the event of an outbreak or if the animals are exposed to other animal hosts like African fruit bats¹².

CONCLUSION

In the future, the results of this research should allow better delineation geographical areas potentially concerned by the presence of the Marburg virus. The identification of the natural reservoir of this virus should also foster the development health measures and prevention campaigns to the population to reduce the apparition and emergence of potential outbreaks of hemorrhagic fever.

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