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Marburg virus disease: A deadly rare virus is coming

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SUMMARY Two cases of the deadly Marburgvirus were reported in Ghana, which might be a new global virus alert following COVID-19 and novel monkeypox. Thus far, there is no vaccine or treatment for Marburg virus disease, which is a disease with a mortality rate as high as that of Ebola. Although now human infections with Marburgvirus occurred mainly in Africa, outbreaks were twice reported in Europe over the past 55 years. A concern is that globalization might promote its global viral transmission, just like what happened with COVID-19. The current study has briefly summarized the etiology, epidemiology, and clinical symptoms of the Marburgvirus as well as vaccine development and experimental treatments in order to prevent and control this virus.

Keywords Marburgvirus (MARV), Marburg virus disease (MVD), emerging infectious disease, public health

On July 17, 2022, the World Health Organization (WHO) declared outbreaks of Marburg virus disease (MVD) in Ghana. The world must be on alert regarding deadly MVD following COVID-19 and the novel monkeypox. The Marburg virus (MARV), a deadly cousin of the Ebola virus, is a member of the Filoviridae family (filovirus), which causes severe viral hemorrhagic fever (VHF) in humans. MARV is one of the most fatal viruses ever known, with a morbidity rate of approximately 50%. During the largest reported MARV outbreak in Angola in 2005, more than 250 people were infected and 90% died (*1*). Facing such a fatal virus, many scientists and clinicians have expressed their concerns about its potential threat to public health. Here, the key characteristics of MVD are highlighted to help prevent and control MVD before it spreads globally.

Pathogenetic characteristics: MARV is an enveloped, single-stranded, negative-sense RNA virus. Morphologically, it resembles silk, with a length ranging from 800 to 14,000 nm. It is most infectious when its length is about 790 nm. MARV consists of seven structural proteins. Although the MARV is almost identical to the Ebola virus in structure, it may induce different antibodies in infectious individuals (*2*). MARV is believed to be the first filovirus discovered by humans (*3*).

Epidemiological characteristics: MVD was first reported in 1967 after outbreaks occurred simultaneously in three cities: Marburg, Frankfurt, and Belgrade (*4*). The source of the outbreak was ultimately traced to a laboratory using African green monkeys imported from Uganda. Henceforward, most human infections were reported in Angola, the Congo, Kenya, South Africa, Uganda and Zimbabwe, along with a laboratory accident in Russia (*5*).

In 2009, scientists successfully isolated MARV from healthy Egyptian fruit bats caught in a Uganda mine, which strongly suggested that the fruit bat is the viral reservoir and natural host of MARV (*6*). MVD outbreaks occurred widely across central Africa, suggesting that MVD is present in chronically infected bats (*7*). In addition, African green monkeys and pigs are susceptible to filoviruses, so they play a role as potential amplifier hosts.

MARV can be transmitted animal-to-human or human-to-human via direct contact with blood, secretions, organs, or bodily fluids of infected people or via surfaces contaminated with these fluids through broken skin or mucous membranes. MARV can persist in the eyes and testes of convalescent patients. It is also found in the placenta, amniotic fluid, and breast milk of pregnant women. Put simply, once the virus is found in the blood, the individual remains infectious. However, there is no evidence that MARV can be transmitted among humans by mosquitoes or other biting arthropods.

Clinical manifestations: The incubation period for MVD commonly ranges from 2 to 21 days (average: 5-6 days), though some studies have extended the maximum period to 26 days (*8*). Three stages of the clinical course can be distinguished. Symptoms of illness start abruptly

Table 1. Progress of vaccine development and experimental treatments for Marburg virus disease

Therapy	Description	Animal studies	Clinical trials	*Ref.*
Vaccine				
MVA-BN-Filo	Modified vaccinia Ankara vector encoding GPs from Ebola virus, Sudan virus, Marburg virus, and Tai Forest virus nucleoproteins.	No data.	Phase 1 indicated sustained Ebola GP immunity 8 months post-vaccination. No results related to MARV were published.	(*10*)
rVSV-MARV-GP	Recombinant vesicular stomatitis virus vector expressing the MARV glycoprotein (GP).	100% survivability in study animals (macaques) 14 months post-vaccination.		(*9*)
cAd3-MARV	Chimpanzee adenovirus type-3 vector encoding the GP from MARV.	No data for cAd3-MARV.	Phase 1 trial: 80-90% produced a Marburg-specific antibody response.	*NCT03475056*
CAdVax-panFilo	The complex adenovirus (CAdVax) encoding GPs from EBOV, SUDV and MARV, and EBOV and MARV-Musoke nucleoproteins.	Antibodies were produced against all five filoviruses and no macaques developed clinical illness.		(*14*)
DNA plasmid vaccine	A Marburg DNA plasmid expressing MARV Angola DNA.	A DNA prime/boost vaccine in macaques provided protection, but all animals developed clinical illness.	Phase 1 trial: 90% had antibody responses in 10 people.	(*15,16*) *NCT00605514*
Antivirals				
Galidesivir (BCX4430)	Synthetic nucleoside analogue that inhibits viral RNA polymerase.	17/18 macaques survived with treatment 1, 24, and 48 h post-infection.	Phase 1 trial: results not published.	(*17*)
Remdesivir (GS-5734)	Mono-phosphoramidate prodrug of an adenosine analog with broad antiviral activity. Inhibits MARV *in vitro*.	Protected 50% and 83% of MARV-infected macaques from lethal disease when initiated up to 4-5 days post-infection with MVD.		(*18*)
Favipiravir (T-705)	Synthetic guanidine nucleoside analogue with broad-spectrum antiviral activity against multiple RNA viruses.	5/6 macaques survived when administered IV on the day of the challenge, but not with oral doses.		(*19,20*)
AVI-7288/7287 or AVI-6003	Positively charged antisense phosphorodiamidate morpholino oligomers AVI-7287 and AVI-7288 target the VP24 and NP genes, respectively.	AVI-7288:83-100% of infected monkeys survived when treatment was initiated 1, 24, 48, or 96 h post-infection.	AVI-6003: no significant safety signals in two RCTs with 70 subjects.	(*21-23*)
NP-718m-LNP	Lipid nanoparticle small-interfering RNA targets MARV nucleoprotein.	All 16 macaques survived with treatment 30 to 45 min, 24, 48, or 72-h post infection.		(*24*)
Antibody				
Polyclonal IgG	Concentrated IgG derived from previously vaccinated NHP survivors from Marburg challenge.	3/3 macaques survived with treatment at D2/D2/D8 post infection.		(*17*)
MR 191N (mAb)	Made in Nicotiana tobacco plants binds the receptor of MARV GP.	9/10 macaques survived with treatment at D5/D8 post infection.	Used following a U.S. lab exposure, but details have not been published.	(*25-27*)
MR186-YTE (mAb)	Made in CHOK1-AF cells binds the receptor of MARV GP.	4/4 and 0/5 macaques survived with treatment at D5 or D6 post infection.		(*11*)

Table 2. Chronology of major Marburg virus disease outbreaks

Year	Country	Suspected origin	Cases	Deaths (mortality rate)	Notes
2022	Ghana	Under investigation	2	2 (100%)	
2021	Guinea	Guinea	1	1 (100%)	
2017	Uganda	Uganda	4	3 (75%)	
2014	Uganda	Uganda	1	1 (100%)	
2012	Uganda	Uganda	15	4 (27%)	
2008	Netherlands	Uganda	1	1 (100%)	Imported
2008	USA	Uganda	1	0 (0)	Imported
2007	Uganda	Uganda	4	1 (25%)	
2004-2005	Angola	Angola	252	227 (90%)	
1998-2000	Democratic Republic of the Congo (DRC)	DRC	154	128 (83%)	
1990	Russia	Russia	1	1 (100%)	Laboratory accident
1987	Kenya	Kenya	1	1 (100%)	
1980	Kenya	Kenya	2	1 (50%)	
1975	South Africa	Zimbabwe	3	1 (33%)	Imported
1967	Germany and Yugoslavia	Uganda	31	7 (23%)	Imported & lab leak

Table adapted from the WHO Marburg Virus Disease Factsheet (August 7, 2021).

with a high fever, and severe myalgia and headaches are also reported in the early stage, often followed by vomiting, diarrhea, and abdominal pain on the third day. Watery diarrhea may last for a week, along with severe exhaustion and lethargy. A severe hemorrhagic rash may develop between 5 and 7 days. Patients who die commonly have fresh blood in their vomit and feces and they may also have bleeding from the nose, gums, or vagina. Patients who die commonly do so from shock and multi-organ failure 8-9 days after infection.

Considerations regarding diagnosis: An appropriate clinical diagnosis of MVD may be difficult because its signs and symptoms are quite analogous to those of other infectious diseases, such as malaria, typhoid fever, meningitis, and the other viral hemorrhagic fevers. Diagnosis can be confirmed using the following diagnostic approaches: *i)* an antibody-capture enzyme-linked immunosorbent assay (ELISA); *ii)* an antigen-capture ELISA test; *iii)* a serum neutralization test; *iv)* a reverse transcription-polymerase chain reaction (RT-PCR) assay; *v)* electron microscopy; or *vi)* virus isolation by cell culture. Laboratory staff must implement stringent protective measures because MARV is classified as a Risk Group 4 pathogen (RG-4).

Treatment and prevention: Thus far, there is no approved vaccine or antiviral treatment for MVD. However, supportive care including balancing fluid and electrolyte levels, maintaining oxygen levels and blood pressure, and replacing lost blood and clotting factors might be helpful.

Several potential MARV vaccines are under investigation. For example, a recombinant vesicular stomatitis virus (VSV)-based vaccine expressing the MARV glycoprotein (VSV-MARV) rapidly protected hosts from MVD in animal models (*9*). Another vaccine candidate, MVA-BN-Filo, containing both Marburg and Ebola virus antigens was also reported to potentially protect against both hemorrhagic viruses (*10*). A phase 3 trial is currently underway, and it seems to trigger good immunity against the Ebola virus, but it has not yet been tested against MARV.

Besides prophylactic vaccines, researchers are now attempting to develop effective postexposure therapies for MVD, including MARV-specific monoclonal antibodies (mAbs) and small-molecule antivirals. Researchers combined a monoclonal antibody (MR186-YTE) and an antiviral (remdesivir) against MVD in a non-human primate model (*11*). Data indicated that this particular combination was highly effective in eliminating the virus. The progress of vaccine development and experimental treatments for MVD are summarized in Table 1.

Public health measures: Emerging infectious diseases, and particularly those caused by bat-borne viruses (*e.g.*, Coronaviruses and the Ebola virus), markedly affect public health and the global economy. Like the Ebola virus, MARV is a highly contagious and deadly virus. Once an MVD outbreak is out of hand, it will expand rapidly and cause severe social and health problems. Key protective measures should be immediately taken to prevent this situation.

The main goal of controlling an MVD outbreak is to interrupt direct human-to-human transmission. The control strategy is analogous to that for other infectious disorders, including early identification and rapid isolation of cases, timely tracing, close monitoring of people at risk, proper personal protection, and safe burial. In addition, avoiding the handling and eating of bush meat is also critical to avoiding any potential infection from animals. The spread of MARV outside Africa is primarily due to international travel (*12,13*). Rapid diagnostics are therefore indispensable to identify the infected before they can carry the virus to other countries.

In conclusion, there have been 15 MARV outbreaks reported around the world thus far (Table 2). Because of its potent infectivity and high fatality rate, MARV is a major public health concern in Africa. Nowadays, however, its impact might be global because of frequent migration and travel. Due to the rapid growth of trade

with African countries, Guangzhou, the biggest city in South China, has become the largest African settlement in Asia. Thousands of people from Africa enter this city every day, and the same thing happens in many parts of the world as well. There is a risk of imported MARV in every country. Hence, international cooperation seems to be crucial to preventing and controlling MARV. Scientists should continue study MARV in the field of vaccine and antiviral medicine to stop this deadly illness as quickly as possible.

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