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Marburg virus: an emerging global threat

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Abstract

Marburg virus disease is a rare, but severe illness caused by highly pathogenic Marburg virus, a member of the *Filoviridae* family. The virus was first identified in 1967 in Marburg and Frankfurt, Germany, as well as Belgrade, Serbia. Since then, sporadic outbreaks have been reported in Central and East Africa. The fruit bats of the genus *Rousettus* are the major reservoir for the virus. The largest recorded outbreak occurred in Angola in 2005, with 374 cases and 329 deaths, resulting in a mortality rate of approximately 88%, underscoring this virus's potential for causing a devastating impact. Historically, the Marburg virus has received less attention compared to the Ebola virus. However, the geographical expansion of this virus in new regions such as Guinea, Equatorial Guinea, Ghana, and Tanzania highlights its growing threat. The sporadic outbreaks of this deadly pathogen necessitate continued investment in research, surveillance, and public health preparedness to mitigate the impact of this virus on global health security. This review is intended to provide an overview of our current knowledge of the Marburg virus, which is crucial for the development of Marburg virus countermeasures.

Introduction

Viral pathogens present a significant burden on global health, causing a range of illnesses from mild infections to severe, high-mortality outbreaks. Emerging and re-emerging viruses continually pose new challenges to global health security (1, 2). Marburg virus (MARV) is one of the highly pathogenic viruses that belong to the order *Mononegavirales* and is a member of the *Filoviridae* family (3). It is responsible for severe hemorrhagic fever outbreaks in humans and has emerged as a significant human health threat. MARV was first identified in 1967 during outbreaks in Marburg and Frankfurt, Germany, as well as Belgrade in Yugoslavia (now Serbia) (4). MARV has since been linked to sporadic outbreaks in Africa, posing significant public health challenges due to its high mortality

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rate. MARV is primarily endemic to sub-Saharan Africa, particularly Uganda, Angola, and the Democratic Republic of Congo (DRC), where most outbreaks have occurred. The outbreak in DRC (1998-2000) and in Angola (2004 - 2005) demonstrated a mortality rate of 83% and 90%, respectively (5). MARV is listed as the National Institute of Allergy and Infectious Diseases (NIAID) biodefense pathogen (6).

The virus is maintained in wildlife such as bats, particularly species of the *Rousettus* genus, which serve as reservoir hosts (7). The fruit bats like *Rousettus aegyptiacus* (*Pteropodidae* family) are known to carry MARV (8, 9). Infected bats do not typically exhibit symptoms of Marburg virus disease (MVD). This makes them efficient reservoirs as they can spread the virus to other bats or potentially to other animals, including humans, through their saliva, urine, or feces without showing signs of illness (10). These bats are found in parts of Africa, where MARV outbreaks have occurred, such as Uganda, DRC, and Angola. Human infections typically result from contact with infected bats, or through exposure to body fluids of infected individuals during outbreaks (11).

Viral Genome

MARV is a single-stranded, enveloped, non-segmented, negative-sense RNA virus that belongs to the genus Marburg virus. Its genome size is about 19 kb in length which encodes for seven structural proteins, including nucleoprotein (NP), virion protein 35 (VP35), VP40, VP30, VP24, glycoprotein (GP), and large (L) viral polymerase (12, 13). Each gene has conserved transcriptional start and stop signals and plays important roles in viral replication and pathogenesis. NP binds to viral RNA, forming the nucleocapsid, while VP35 aids in RNA synthesis and immune evasion. VP40 facilitates viral assembly and budding, whereas GP mediates host cell attachment and entry and is a key target for vaccine and therapeutic development. VP30 assists in transcription activation, VP24 regulates viral replication, and L functions as the RNA-dependent RNA polymerase for genome replication and transcription (14). During replication, MARV initially attaches to host cells *via*., GP, enters through endocytosis or membrane fusion, and releases its genomic RNA into the cytoplasm. The polymerase then transcribes mRNA from the negative-sense genome, which is translated into viral proteins by the host cell machinery. The viral genome replication occurs through the production of positive-sense RNA intermediates which acts as a template for generating new viral genomes and mRNA. Viral assembly takes place at the host cell membrane, facilitated by VP40 and GP, leading to budding of mature virions (15, 16).

Epidemiology

The recorded outbreaks of MARV have been infrequent yet significantly impactful due to the disease's severity and high mortality rates. MARV outbreaks have been reported mostly in Central and East Africa (Table 1; 11, 17,18). Countries that have experienced outbreaks include Uganda, DRC, Kenya, Angola, Guinea, South Africa and Tanzania. Outbreaks tend to be smaller in scale compared to Ebola virus outbreaks, but can still have significant public health implications due to the severity of illness and high fatality rate (11, 17, 19).

The first recognized outbreak occurred in 1967 in Marburg and Frankfurt, Germany, as well as in Belgrade, Serbia (formerly Yugoslavia), where laboratory workers handling African green monkeys (*Cercopithecus aethiops*) from Uganda contracted the virus (11). Subsequent outbreaks in 1975 in South Africa, 1980 and 1987 in Kenya, and multiple occurrences in the DRC from 1998 to 2000 underscored the sporadic but constant threat posed by the virus. The largest documented outbreak occurred in Angola in 2005, with 374 reported cases and a mortality rate exceeding 88% (20). This outbreak highlighted significant human-to-human transmission within healthcare settings,

emphasizing the critical need for stringent infection control measures. After this outbreak, no other severe fatal outbreaks were documented other than certain sporadic cases. Recurrent outbreaks in Uganda were reported in 2008-2009, 2012, 2014, and 2017. The first reported outbreak of MVD in Tanzania occurred in 2022, involving a total of eight cases, with five fatalities (11, 17).

Table 1. Recorded Marburg disease outbreaks. The number of reported cases and outbreak location is presented.

Year	Location	Number of cases
1967	Germany, Serbia	31
1975	South Africa	3
1980	Kenya	2
1987	Kenya	1
1998 and 2000	Democratic Republic of Congo	154
2004-2005	Angola	374
2007	Uganda	4
2008	Netherland (ex-Uganda) USA (ex-Uganda)	2
2012	Uganda	18
2014	Uganda	1
2017	Uganda	3
2021	Guinea	1
2022	Ghana	4
2023	Equatorial Guinea, Tanzania	49

Transmission and Symptoms

The available evidence to date suggests that the virus is transmitted to humans *via*, direct or indirect contact with *Rousettus* bats (8). Direct exposure to infected bats or their bodily fluids is a primary route of transmission (21). Subsequent human-to-human transmission occurs through direct contact with the infected person's bodily fluids such as blood, saliva, vomit, urine, feces, respiratory secretions, and semen (11).

MVD manifests with an incubation period ranging from 2-21 days (22), followed by abrupt onset of fever, headache, myalgia, and gastrointestinal symptoms. The illness typically begins with a high fever (> 39°C) accompanied by intense chills, headache, and profound malaise (23). Muscle and joint pain contribute to the discomfort of the affected individuals. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea can quickly lead to dehydration, exacerbating the severity of the disease. Respiratory symptoms may include chest pain, cough, and sore throat. In more severe cases, patients may develop hemorrhagic manifestations, though bleeding is less frequent compared to other viral hemorrhagic fevers. Between 5 to 7 days after infection, many patients experience severe hemorrhagic symptoms (24). Neurological symptoms, such as confusion, agitation, and seizures, may occur in advanced stages. Severe cases progress to multi-organ dysfunction, hemorrhagic manifestations, and shock, with a case fatality rate ranging from 24% to 88% (25). Early detection and isolation of cases are essential to prevent further spread of the virus in affected communities (25).

Diagnosis and Treatment

Given the potential for rapid disease progression and severe outcomes associated with MARV infection, early diagnosis is critical for initiating appropriate patient management and implementing infection control measures. The diagnosis of MVD requires laboratory testing due to the similarity of its early symptoms to those of other infectious

diseases, such as malaria, typhoid, and other viral hemorrhagic fevers (26). MARV infection diagnosis relies on detecting viral RNA in blood or tissues using reverse transcription polymerase chain reaction (RT-PCR; 27). Serological tests, including enzyme-linked immunosorbent assays (ELISA), detect antibodies against MARV antigens, serum neutralization test, and virus isolation by cell culture (28-30). The samples should be tested in maximum biological containment conditions. The rapid diagnostic tests are essential for early disease identification and outbreak control in resource-limited settings.

There are no specific antiviral therapies or vaccines approved presently for MARV, leaving supportive care as the primary treatment option. Fluid and electrolyte replacement, symptomatic relief, and intensive care support may improve the condition significantly (31). Advances in supportive care have improved the survival outcomes of the affected individuals. The development of effective vaccines and treatment options is highly essential to control the virus (11).

Prevention and Control Strategies

The prevention of MARV outbreaks relies on proactive measures at various levels, from individual protective behaviors to national and international public health interventions. The virus has the potential to spread globally due to international travel and trade, necessitating robust surveillance and response capabilities to detect and contain outbreaks promptly. As the world is slowly recovering from the COVID-19 pandemic, there are now concerning reports indicating the increasing cases of monkeypox and SARS-CoV-2 variants across multiple countries (32, 33). The international community must remain vigilant regarding MARV, a highly contagious and lethal pathogen. If this virus spreads globally, it will have a devastating impact on the human population. Hence, effective preparedness response efforts and community engagement are crucial to mitigate the public health impact of MARV outbreaks. This includes strengthening the surveillance systems to detect early signs of outbreaks, enhancing laboratory capacity for rapid diagnosis, establishing emergency response plans, training healthcare workers in prevention, and control measures, and accelerating research into vaccines and treatments. Public awareness campaigns and community engagement are also essential to promote understanding of the virus, encourage timely healthcare-seeking behavior, and foster cooperation with outbreak response activities (34).

It is important to follow stringent infection control practices in healthcare settings, including the use of personal protective equipment (PPE), hand hygiene, and isolation protocols for confirmed/susceptible cases. The collected samples in testing laboratories should be managed by trained personnel and processed carefully in well-equipped laboratories. Additionally, ensuring proper use, disinfection, and appropriate disposal of instruments and equipment used in patient care are essential components of comprehensive infection control measures (11). Several studies are ongoing to develop vaccines against MARV. Ongoing vaccine studies and trials for MARV utilize various platforms to induce protective immune responses (35). Vaccines targeting MARV glycoprotein are in development, showing promise in preclinical studies and phase 1 clinical trials (36). The recombinant vesicular stomatitis virus (rVSV), adenovirus vector vaccines, DNA vaccines, virus-like particle (VLP) vaccines, mRNA vaccines, and protein subunit vaccines are also being explored for their potential to protect against MARV (36-44). Continued research and clinical trials are essential to advance the promising vaccine candidates toward licensure and deployment to protect at-risk populations.

Conclusion

Emerging infectious diseases significantly impact public health and the global economy. MARV represents a significant public health concern due to its high mortality rate, potential for global spread, limited treatment

options, and impact on vulnerable healthcare systems and communities. Due to the increase in the incidence of MARV infections, there is an immediate need to develop effective diagnostic tools, therapeutics, and vaccines for improving outcomes and reducing the burden of MVD in endemic regions. Considering the intensity of past outbreaks, MARV has the potential to cause severe outbreaks, if not properly controlled. The epidemiologists have identified MARV as a significant threat to global public health. Therefore, increased research and focus on this virus are imperative for mitigating potential future outbreaks. Hence, a concerted global effort is needed to strengthen surveillance, enhance healthcare infrastructure, and promote interdisciplinary collaboration to effectively combat this deadly pathogen.

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Ethical approval

Not applicable.

Conflicts of Interest

The author declares no conflict of interest.

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