Review

Emerging Threat of Marburg Virus Disease: Epidemiology, Clinical Management, and the One Health Strategy for Prevention and Control

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Emerging Threat of Marburg Virus Disease: Epidemiology, Clinical Management, and the One Health Strategy for Prevention and Control

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Abstract: Objectives: Marburg virus disease (MVD), caused by the Marburg virus, is a severe zoonotic viral hemorrhagic fever with high mortality that threats the Global Health Security. Marburg virus is on the WHO list for the next pandemic-prone pathogens it always emerges in outbreaks. Considering it is current involvement in outbreak in Rwanda, there is an urgent need for up to date information to inform policymaking, resources mobilization, strategic planning and guide the implementation of cost-effective response strategies. **Methods**: Through technical and scientific consultancies with experts and reviewing publicly existed knowledge, we collected and synthesized available information about the disease and summarized it into a brief evidence to inform policymakers, public health leaders, and frontline responders in developing and implementing cost-effective prevention and control measures. **Results**: We have identified the historical outbreaks and geographical distribution of MVD, main clinical signs and diagnostic tools, primary reservoir, transmission dynamics and case management protocol. More importantly, we summarized the best practices for multisectoral One Health strategy for the prevention and control of MVD outbreaks including strict implementation of WASH and infection prevention measures, isolation of infected humans and animals, contact tracking for confirmed cases, and International Health Regulations (IHRs 2005). High risk populations such as frontline responders including healthcare providers and community health worker should be prioritized for the experimental vaccination. **Conclusions**: In lack of licensed treatment or vaccine, cost-effective preparedness and response strategy to MVD should focus on preventive measures including community engagement, reduced contact between humans and reservoirs, supportive care and isolation of patients, and proper waste management.

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1. Introduction

Marburg virus disease (MVD) is a zoonotic viral hemorrhagic fever that is commonly transmitted between humans and other animal hosts mainly fruit bats known as natural reservoirs, and it caused by the Marburg virus (MARV), a close relative of Ebola virus. The disease is characterized by a remarkably high fatality rate up to 90% [1]. The virus was identified for the first during it is involvement two simultaneous outbreaks in Marburg in Germany and Belgrade in Serbia, in 1967 [2]. According to the World Health Organization (WHO), the disease can be acquired from

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direct contact with infected animal and/or human or contaminated products and material [3]. It is classified within the order *Mononegavirales*, the family *Filoviridae*, and the genus *Marburgvirus*. This pathogen poses a significant public health and security threat to human, animal, and environmental health as well as wildlife biodiversity and socioeconomic stability of human populations due to its severity, rapid spread, lack of licensed vaccine or treatment [4]. Therefore, the disease is on the WHO and The Global Alliance for Vaccines and Immunizations (GAVI) lists for pathogens that will very likely causes the next pandemic, and the WHO list of high priority diseases for research and development [5–7].

2. Historical Epidemiology

The ever first recorded cases of MVD were among laboratory workers involved in medical research activities using African green monkeys, which were imported for the production of primary cell cultures [8]. Since its initial discovery, MARV has raised ongoing concerns regarding its potential for high mortality and the challenges associated with its management in outbreak situations. Due to it is natural circulation among animal reservoir that mainly existed in Africa, the disease predominantly affects individuals in Sub-Saharan Africa. To date, there have been a total of 19 reported outbreaks of MARV, primarily occurring in African nations such as Uganda, Ghana, Guinea, Tanzania, Angola, the Democratic Republic of the Congo, Zimbabwe, and most recently, Rwanda (Figure 1). However, outbreaks of MARV have also occurred in Germany, Netherlands, Russia, and Serbia in Europe and in the USA (Figure 1).

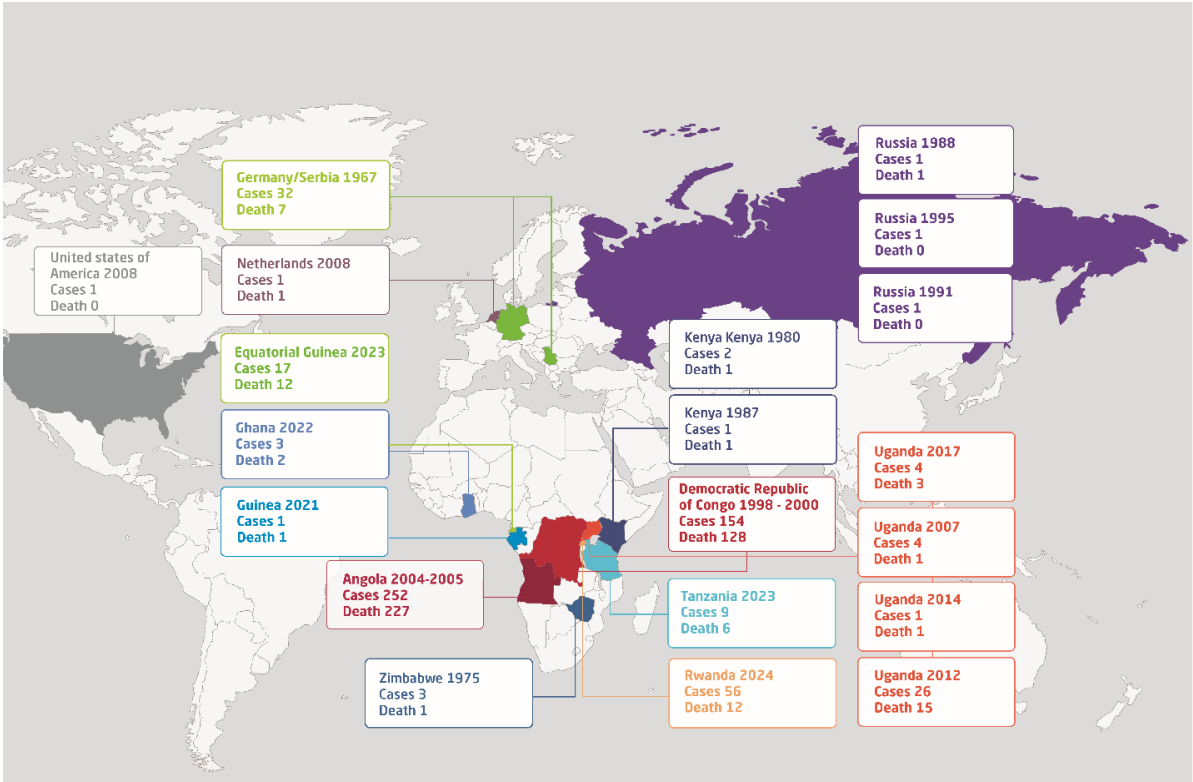

Figure 1. Summary of Marburg Virus outbreaks reported worldwide.

3. Natural Reservoirs and Routes of Transmission

Interestingly, existed evidence shows that all identified and reported outbreak of MARV are involving contact with animal hosts, whether in nature or lab settings. This highlights the zoonotic nature of the virus and indicates a sustainable epizootic transmission that maintains the virus circulation in the environment. Various species of bats have been incriminated to be involved in the virus transmission and some species were identified as natural reservoirs for filoviruses including

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MARV. There is a compelling evidence about the critical role of *Rousettus aegyptiacus*; commonly known as the Egyptian fruit bat, in the ecology and dynamics of MARV [9,10].

In order to investigate the role of the bats as a reservoirs host for MARV, researchers conducted a numerous studies and they succeeded in the isolations of live MARV from *R. aegyptiacus* bats in Uganda, where miners diagnosed with MVD [11,12]. Furthermore, studies involving the direct infection of *R. aegyptiacus* bats with MARV have revealed that infection with MARV in these bats are asymptomatic, therefore, they live normally including traveling between endemic and disease-free areas contributing to the spread of the virus [13,14]. Nevertheless, a mild immune response was noted, along with the detection of the virus in various organs of bat including liver, spleen, blood kidney, salivary gland, intestines, and in the inoculated site of the skin. Viral shedding was identified through oral and rectal swabs [15]. Moreover, despite the presence of viremia and viral shedding, there was no observed transmission to other susceptible *R. aegyptiacus* bats for up to 42 days. Additionally, they demonstrated the shedding of the virus from saliva and excreta of the bats [16]. Therefore, the inhalation of aerosols or contaminated excreta from these bats might be a significant route for introducing the virus into the human population.

4. Transmission Dynamics

MARV transmission occurs through several pathways, primarily involving mucosal surfaces, broken skin, or parenteral routes. In outbreak scenarios, direct contact with infected humans or animals represents the most common source of infection. Notably, parenteral exposure -often occurring in healthcare settings- has proven to be one of the most lethal routes of infection (Figure 2) [17].

During the 1967 outbreak, a significant number of cases resulted from direct contact with the blood and organs of infected monkeys or involvement in post-mortem examinations [18]. However, this was shortly followed by a secondary transmission among individuals with no contact with originally infected animals or their materials, providing the initial evidence of human-to-human transmission of MARV [19].

Human-to-human transmission of MARV typically occurs via direct contact with bodily fluids, including blood, saliva, sweat, stool, urine, tears, semen and breast milk, particularly during the care of infected patients [19–21]. Additionally, in the 1998-2000 outbreak in the Democratic Republic of the Congo (DRC), handling corpses during traditional burial practices was identified as a leading factor for infection with MARV [22]. Furthermore, evidence from the 1967 outbreak suggested possible sexual transmission during the convalescence phase, as virus antigens were detected in the semen of an infected patient [19].

Experimental study among group of non-human primate; *Cynomolgus macaques* also known as Crab-eating macaque, has established a compiling evidence of aerosol transmission of MARV in confined space [23]. This piece of evidence is of high concern, because it indicate the risk of nosocomial outbreaks of MARV in healthcare facilities, which threats the live and health of healthcare providers, community health workers, patients, co-patients, visitors, and supportive staff in these facilities. Particularly that, aerosolized particles can remain suspended in the air for extended period of time leading to a rapidly growing transmission rate of the disease.

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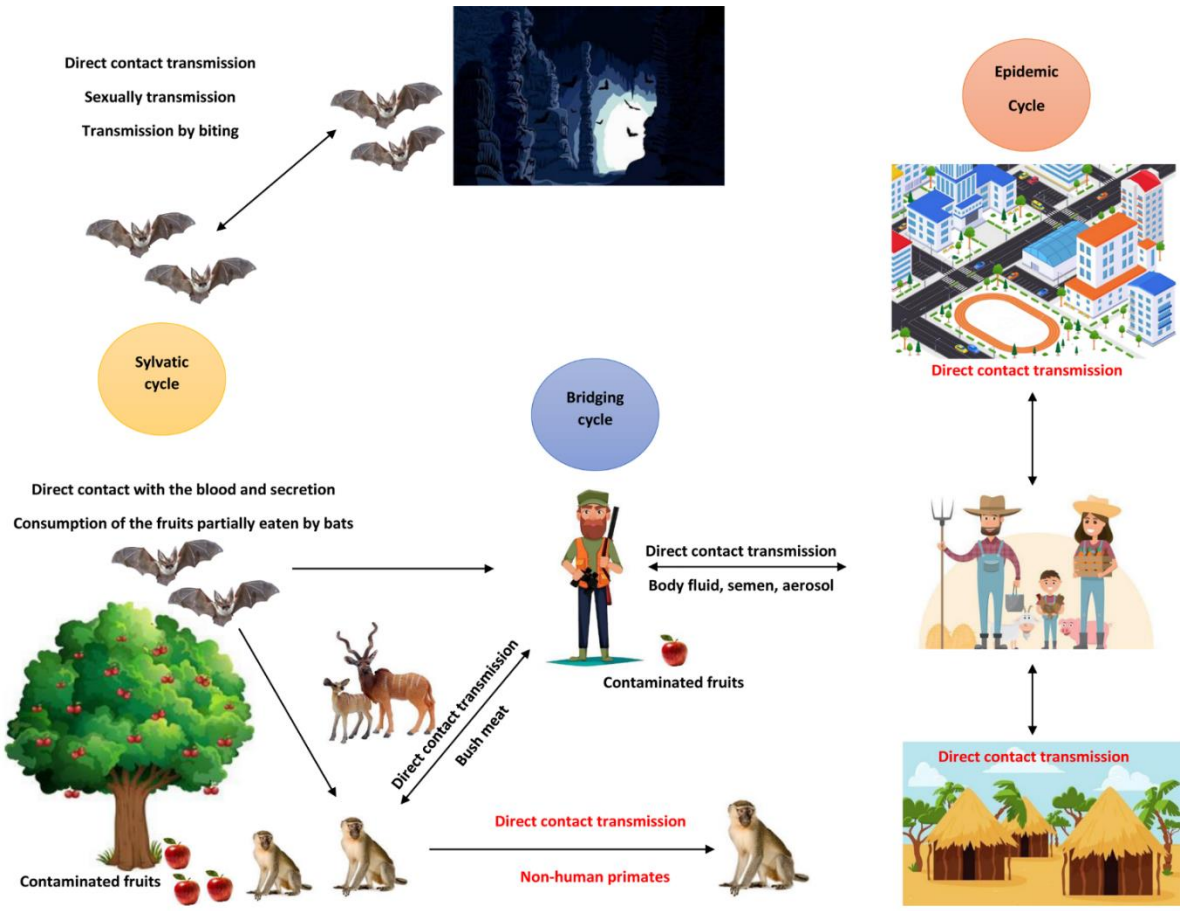

Figure 2. Illustration of the various transmission cycles of Marburg virus (MARV) in different ecological settings.

5. Clinical Presentations

Marburg virus disease is characterized with an extended incubation period that ranging between two and 21 days [24]. This highly depends on factors such as the infectious dose and route of infection. More importantly, during this incubation period individuals are not infectious and the transmission occurs after the onset of the disease [4,25]. The clinical course of MVD infection is generally divided into three phases (Table 1).

Table 1. Summarizes phases of Marburg virus infection including the duration, characteristics, and symptoms.

Phase	Duration	Characteristics	Symptoms
Generalized Phase	Days 1 to 4	Abrupt onset of nonspecific symptoms	High fever (39–40°C), severe headache, chills, myalgia, prostration, malaise

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Early Phase	Days 5 to 13	50–75% of patients experience gastrointestinal symptoms	Anorexia, abdominal discomfort, severe nausea, vomiting, diarrhea; maculopapular rash; symptoms of hemorrhagic fever (petechiae, mucosal and gastrointestinal bleeding, hemorrhage from venipuncture sites)
Convalescence Phase	After Day 13	Survivors may skip the most severe symptoms and may not progress to this phase	Neurological symptoms may present (disorientation, agitation, seizures, coma); recovery symptoms

The first phase, known as the generalized phase, lasts from days one to four and is characterized by an abrupt onset with nonspecific, flu-like symptoms, including high fever (typically between 39–40°C), severe headache, chills, myalgia, prostration, and malaise [17].

The second phase, the early phase, spans from 5 to 13 days, during which 50–75% of patients experience gastrointestinal symptoms, such as anorexia, abdominal discomfort, severe nausea, vomiting, and diarrhea, within the first two to five days. The intensity of the disease often escalates between day five and seven, presenting with a maculopapular rash and symptoms of hemorrhagic fever, including petechiae, mucosal and gastrointestinal bleeding, as well as hemorrhage from venipuncture sites [17].

The final phase, convalescence phase, begins after day 13, during which survivors may skip the most severe symptoms and may not reach the late organ phase altogether. Neurological symptoms like disorientation, agitation, seizures, and coma may manifest in the later stages of the disease [26]. Moreover, in some cases infection with the virus can lead to complications even during the recovery period that can include joint pain, uveitis, orchitis, and pericarditis, with recovery often being slow. Furthermore, throughout the course of MVD, disseminated intravascular coagulation (DIC), lymphopenia, and thrombocytopenia are typically emerging within a week from the onset of symptoms. Patients ultimately, either recover with appropriate supportive care or end up with fatal outcomes, such as dehydration, internal bleeding, and multi-organ failure, usually occurring eight to sixteen days after symptoms begin.

6. Diagnosis

MVD diagnosis employs various laboratory-based techniques that adapt to the disease's stages for effective management. In the early stage, detection of viral antigens in the bloodstream is crucial, utilizing methods such as virus isolation via cell culture, antigen capture enzyme-linked immunosorbent assay (ELISA) with monoclonal antibodies produced to the recombinant nucleoprotein including MAb2A7 and MAb2H6, and immunohistochemical analysis of tissue samples to identify MARV antigens [27,28]. As the disease progresses, serological assays become essential for detecting IgM and IgG antibodies, employing indirect immunofluorescence assays and IgM/IgG capture ELISA to assess infection history and immune response.

Molecular diagnostics, including reverse transcription polymerase chain reaction (RT-PCR), nested RT-PCR, and real-time quantitative RT-PCR (qRT-PCR), which can be done from blood samples as well as buccal swab, offer sensitive and specific detection of viral RNA, aiding diagnosis in both early and late stages [29].

In addition to above mentioned specific tests, complementary diagnostic evaluations are essential for physicians to suspect arboviral infections, including Marburg Virus Disease (MVD). A

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Complete Blood Count (CBC) often reveals hallmark laboratory findings such as thrombocytopenia (reduced platelet count) and leukopenia (decreased white blood cell count), both of which are critical indicators of viral infection and the body's immune response. Moreover, MVD patients frequently exhibit elevated liver enzyme levels, particularly aspartate aminotransferase (AST) and alanine aminotransferase (ALT), which signal hepatic involvement and can provide valuable insight into liver function, aiding in clinical management decisions. Additionally, the presence of proteins in urine samples can indicate renal dysfunction associated with MVD, making urinalysis an important component of a comprehensive patient evaluation. Collectively, these diagnostic tools enhance the clinician's ability to assess disease severity and tailor interventions effectively.

7. Case Management

Currently, there are no specific antiviral treatments that is approved and licensed for MVD, so medical management primarily involves supportive care. This includes rehydration, managing symptoms, and maintaining electrolyte balance.

Experimental treatments, such as monoclonal antibodies (e.g., REGN3470-3471-3479) [30]. In addition to monoclonal antibodies, researchers tried some antiviral in animal models including Galidesivir (BCX4430) which is an antiviral agent that functions by terminating RNA chains and inhibiting the activity of viral RNA polymerase. Study conducted on six *cynomolgus macaques* infected with MARV demonstrated its efficacy, resulting in increased survival rates, reduced levels of viremia [31,32]. However, it is important to note that data from human trials regarding Galidesivir's effectiveness have not yet been published.

Another antiviral therapy included, Favipiravir (T-705), a broad-spectrum antiviral, was previously utilized during the Ebola virus disease outbreak in West Africa. In the context MVD, promising outcomes were observed when intravenous Favipiravir was administered to six *cynomolgus macaques* infected with MARV, with five of the animals surviving the disease [33]. Furthermore, remdesivir (GS-5734) has shown effectiveness against both Ebola and MVD in non-human primate studies [34].

8. Integrated Multisectoral One Health Strategy for Prevention and Control of MVD

Due the zoonotic nature of MDV, cost-effective prevention and control measures should target the main hosts and reservoirs. Particularly that MVD is a pandemic-prone disease with high mortality and socioeconomic impacts that imposes serious threat on the Global Health Security, therefore, affected countries and countries at risk should invest on strengthening pandemic preparedness, prevention, and response (PPPR) [35,36]. To enhance the cost-effectiveness of such PPPR framework, it needs to be implemented through an integrated multisectoral transdisciplinary One Health strategy that includes integrated collaborative surveillance supported with genomics analysis [37–40]. This should take account of strengthening the diagnostic capacity for the early detection among humans, animals, and the environment, isolating confirmed cases, and tracking the contact of confirmed infections to identify all the suspected cases and monitor their health for three weeks. Additional public health interventions include community engagement by health education to raising awareness as well as improving hygiene and sanitation [41]. Other major interventions are strengthening the implementation of the International Health Regulations (IHRs 2005) [41].

Infection prevention and control measures are vital. This should be strictly implemented in public facilities including healthcare units, restaurants, Airports, and public toilets. It also essential to enforce the use of proper personal protective equipment (PPE) for healthcare provider and community health workers, strict adherence to hygiene protocols, safe burial practices to prevent post-mortem transmission, and firm waste management for medical and personal waste that came in direct and/or indirect contact with confirmed and suspected cases [42]. Furthermore, collaboration with international health organizations can enhance response capabilities, ensuring resources and expertise are mobilized to address and contain outbreaks effectively. Therefore, live communication and immediate public sharing of information is a key for effective community and stakeholders engagement [43]. During outbreak, health authorities should considering administrating the

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experimental vaccine of MARV for at high risk populations mainly including frontline responders such as healthcare providers and community health workers [44,45]. However, this should be done under close monitoring and observation in the immediate availability and accessibility to a supportive care whenever it is needed.

Moreover, additional One Health interventions include reducing the contact between humans and bats, pigs, and non-human primates particularly those show signs of illness. Careful attention should be given to endangered species such as the mountain gorilla as they are susceptible for fatal infection with MARV. Therefore, it important to improve the living environment including the housing for humans and domestic animals to avoid the manifestation with bats [46]. Also, avoid the consumption of food contaminated came in contact with bats or their feces, animal products must be cocked thoroughly, and consider vaccinating the mountain gorilla [46]. Recovered males should avoid non-protected sex until their semen was tested and confirmed to be virus-free [47].

9. Conclusions

Marburg virus remains a major threat to the Global Health Security due to its potential for high mortality, devastating health, socioeconomic, and political impacts, and it challenges the health systems to manage it is outbreaks. Evident by historical outbreaks and recent emergences, mainly in Africa, countries at risk need to invest in strengthening the Global Health Security and the pandemic preparedness, prevention, and response (PPPR) framework through the implementation of an integrated multisectoral and transdisciplinary One Health strategy. Such investment should include improving the diagnostic capacity for the early detection, integrated collaborative surveillance system that monitor the health metrics and dynamics of zoonotic diseases in humans, animals, and the environment. Cost-effective healthcare and public health interventions including response protocols to health emergencies, risk communication, health education, and community and stakeholders engagement are essential for health emergencies response and containment. Strict implementation of the International Health Regulations (IHRs 2005), effective infection prevention and control, and adequate hygiene and sanitation are cost-effective measures for prevention and control of MARV outbreaks. Considering the global lack of safe, effective, and affordable licensed vaccine and treatment for the disease, per the WHO recommendation, stakeholders of human and animal health should invest and collaborate on research and development of vaccines and treatment to cost-effectively prevent and response to future pandemics.

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