The Emergence of Marburg Haemorrhagic Fever as a Public Health Threat Transmitted from Wildlife to Human: A Zoonotic Perspective

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ABSTRACT

Marburg virus, a member of the Filoviridae family, is the causative agent of Marburg virus disease (MVD), a severe and often fatal illness in humans. The virus is believed to originate from fruit bats, acting as natural hosts. Human infection results from direct contact with their bodily fluids or contaminated materials. Diagnosis involves detecting viral RNA or antibodies in blood samples, with advanced molecular techniques like PCR being crucial. Prevention strategies encompass strict hygiene practices, particularly in healthcare settings, and the use of personal protective equipment. Control measures involve isolation of infected individuals and contact tracing. Marburg virus, like Ebola, manifests as a viral hemorrhagic fever, impacting vascular integrity and causing multi-organ failure. The zoonotic nature of Marburg virus emphasizes the importance of understanding and monitoring animal reservoirs to prevent spillover events. The pathophysiology involves viral replication in various organs, leading to systemic inflammation and vascular compromise. Developing effective treatments and vaccines remains a critical focus in managing Marburg virus outbreaks, highlighting the interdisciplinary efforts needed to combat emerging infectious diseases. Constant surveillance, international collaboration, and public health awareness are vital components of the global strategy to mitigate the impact of this highly infectious and lethal virus. Addressing Marburg virus (MARV) outbreaks in Africa requires comprehensive research and proactive measures. Despite its origin, the virus's potential to impact the entire continent necessitates continued studies for effective patient management and vaccine development. Trials on non-human primate models are crucial for understanding pathogenesis and drug effects. A robust surveillance system, ecological studies, and sero-epidemiological surveys in endemic regions are vital for outbreak prevention. Collaborative efforts involving public health experts, scientists, and awareness campaigns are essential. Future epidemic preparedness hinges on community education and strategic planning based on thorough research and understanding of MARV's transmission dynamics.

Keywords: Marburg virus, Filoviridae, Outbreaks, Zoonotic, Surveillance

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1. INTRODUCTION

Marburg virus (MARV) is an emerging pathogen of Family Filoviridae containing the deadliest pathogens of public health concern. This family contains only 2 Genera of viruses named Ebola Virus and MARV. Both are known for causing viral hemorrhagic fever in humans, so they are classically characterized as Filoviral Hemorrhagic Fever (FHF) (Hartman et al. 2010) with a 23-90% case fatality rate (Leffel and Reed 2004). According to NIAID (National Institute of Allergy and Infectious Diseases), MARV is characterized as a category A primary infectious agent (Bente et al. 2009). It can easily be disseminated from one person to another and has a major public health impact. It requires an immediate action plan due to the high mortality rate. Moreover, according to WHO and the CDC, it is also considered as a Biosafety level 4 pathogen (Nakayama and Saijo 2013). It is a viral zoonotic disease that can be spread via direct contact with blood, other body fluids, and aerosol droplets. Bats are the reservoir hosts of MARV that can infect both human and non-human primates (NHPs). This disease is getting a major public health importance due to the disruption of the forest ecosystem and increased exposure of humans to wild animals. MARV has been associated with multiple epidemics with high case fatality rates in humans and NHPs since its detection in 1967 (Gonzalez et al. 2015).

Marburg Hemorrhagic Fever (MHF) is clinically characterized by coagulopathy, hemorrhagic fever, and dysfunction of many organs, including the liver, brain, kidney, and spleen (Van Paassen et al. 2012). In addition to its natural occurrence, Ebola and Marburg were used as subjects for biological warfare. The Soviet Biological warfare program initiated in mid-1920 included MARV and other bio-warfare agents (Roffey et al. 2002). Moreover, currently, there is no effective preventive and post-exposure vaccine or treatment available for humans, although significant efforts have been made over a period of last five years to develop protective vaccines. There is increased research interest in this highly fatal filovirus due to its intentional and unintentional introduction of infection outside of central African endemic areas (Paragas and Geisbert 2006).

So, there is a dire need to focus on this lethal virus in research to develop vaccines and antiviral drugs against this deadly virus. Considering the outbreaks of MARV and increasing prevalence, it is necessary to educate the public about this notable disease.

2. ETIOLOGY

MARV is a member of the family *Filoviridae***,** genus *Marburgvirus* and order *Mononegavirales*. The Marburgvirus genus contains two lineages, i.e., Lake Victoria Virus and Ravn Virus (Feldmann et al. 2013). This order of viruses contains notable pathogenic viruses belonging to *Rhabdoviridae*, *Paramyxoviridae* and *Bornaviridae*. The family *Filoviridae* is considered as highly significant because it contains only two viruses, Ebola and Marburg, with great public health concerns. The genus Marburg virus contains only one specie *Marburg Marburgvirus* (Kuhn et al. 2011). In 1967, an outbreak was investigated in Europe using electron microscopic techniques, revealing a filamentous structure resembling Leptospira bacteria or Rhabdoviridae viruses (Fig. 1). After three months, Gerhard and Muller identified MARV based on inclusion bodies and negative staining of infected plasma of patients and Guinea pigs (Slenczka and Klenk 2007).

3. GENOME AND STRUCTURE OF MARBURG VIRUS

The genome of *Marburg marburgvirus* is negative sense single-stranded RNA that is linear and non-segmented. MARV is pleomorphic, including rod shape, circle, U, six digits, or more commonly filamentous (Bharat et al. 2011). The diameter of the virus virion is 80 nm, with great variation in its length. The average length of this virus is 790 nm (Welsch et al. 2010). The virion surface is shielded with glycoprotein spikes of 5-10 nm length, which are placed at a distance of approximately 10 nm (Feldmann et al. 1991). The genome of MARV is 19.1 kb, and it encodes for its seven structural proteins such as nucleoprotein (NP), large protein (L), viral protein-24 (VP-24), VP-40, VP-30, VP-35, glycoprotein (GP), and large protein (L) (Fig. 2). The viral genome is surrounded by enucleocapsid. Nucleocapsid is comprised of 4 structural proteins, namely NP, VP-35, VP-30 and L, that play a significant role in the development of its tubular helical structure (Becker et al. 1998).

These four structural proteins are important for the transcription and replication of the virus. VP-24 interacts with NP and cellular membranes, involved in the release of virion from cell during its lifecycle and pathogenesis. The inner matrix of MARV is made up of VP-40 (Bamberg et al. 2005). The host-derived membrane surrounding the MARV contains spikes that are made up of GP (Bharat et al. 2011). Table 1 shows the viral proteins of MARV with their functions.

4. EPIDEMIOLOGY AND DISEASE OUTBREAK (EMERGENCE)

In 1967, the first outbreak of MHF was reported in Frankfurt, Marburg (Germany) and Serbia with 31 patients. Out of 31, 25 were primary cases and 6 were secondary cases. All the patients with primary

Table 1: Viral proteins of MARV with their functions (Brauburger et al. 2012; Abir et al. 2022)

Viral Protein	Functions
NP	Formation of nucleocapsid, RNA genome encapsidation, Budding, and Replication and Transcription
VP-35	Formation of nucleocapsid, Cofactor for RNA polymerase, and Interferon antagonist
VP-40	Matrix protein, Budding, and Inhibition of interferon signaling
GP	Virion attachment to target cells, Receptor binding, and Tetherin antagonism for adaptation in host
VP-30	Formation of helical nucleocapsid
VP-24	Budding and Maturation of nucleocapsid, regulation of replication and Cytoprotective genes activation
L	Catalytic domain for RNA dependent RNA polymerase, and Regulation of transcription and replication

infection in Marburg, Frankfurt, and Serbia had direct contact with the cell culture, organs and blood of Green Monkeys *(Cercopithecus aethiops)***.** These monkeys were imported from Lake Victoria Island in Uganda. Identification and characterization of causative agents were done within three months by scientists in Hamburg and Marburg. It was named Marburg because it was first isolated in this city, and the highest number of cases was also reported in this city (Slenczka and Klenk 2007).

In 1975**,** an outbreak was recorded in Johannesburg when an Australian citizen had been hitchhiking and visiting Zimbabwe. He was admitted to the hospital and died after a few days while milder disease appeared in his companion and nurse, and later they recovered. Sero-convalescent studies revealed that the MARV strain was closely related to the virus involved in the 1967 outbreak. Sporadic outbreaks occurred from 1975 to 1985, and most cases were from Eastern Africa except an accidental case reported in a laboratory in Russia (Brauburger et al. 2012).

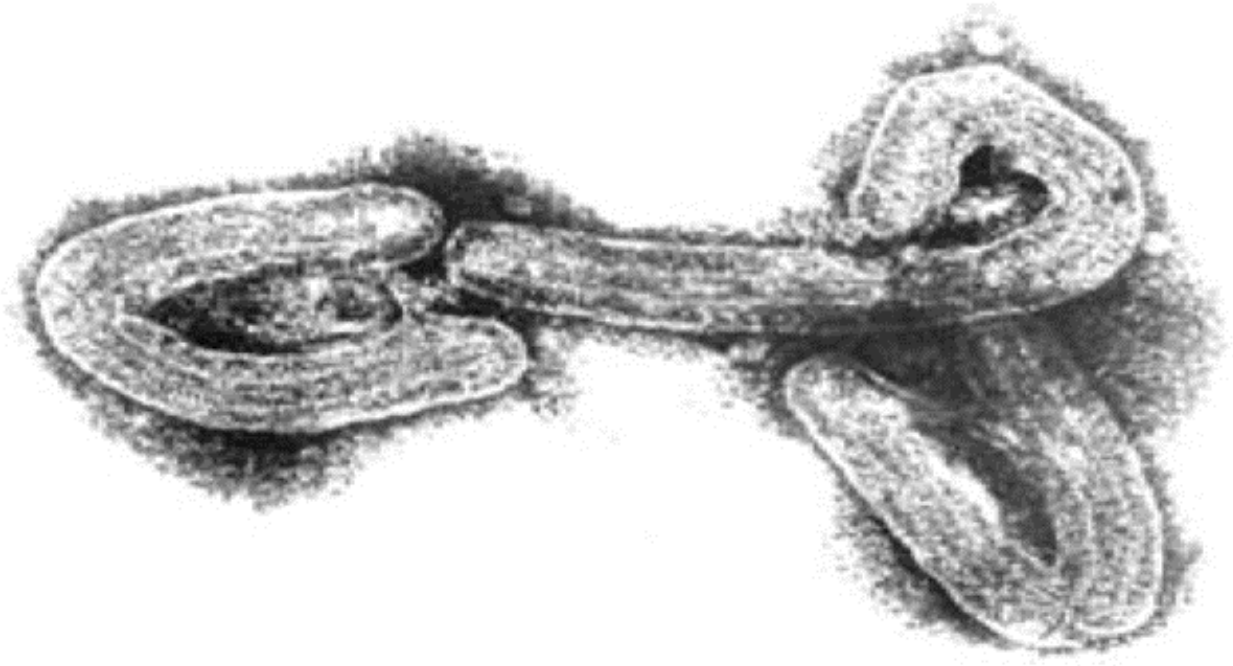

Fig. 1: Electron micrograph of MARV infection By Slenczka and Klenk (2007).

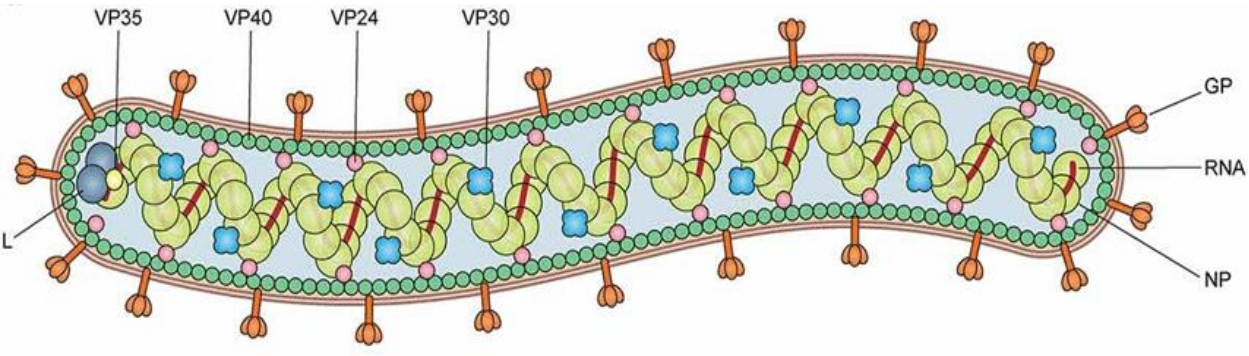

Fig. 2*:* MARV Structure depicting structural proteins*:* Source: https://doi.org/10.1080/21505594.2022.2054760 (Abir et al. 2022).

In 1998-2000, an outbreak occurred in DRC (Democratic Republic of Congo) Durba (Colebunders et al. 2007). In 2004-2005, another outbreak occurred in Angola. Investigations of the Durba outbreak revealed a link between the outbreak and working in a gold mine. In the Durba outbreak, nine different virus variants were identified that were indicative of the exposure of the human population to natural reservoirs in gold mines (Feldmann et al. 2004).

In Kamwenge, a district in Uganda, 4 cases were reported between June and September 2007. The most recent occurrences of MARV infections were in 2008 when two tourists visited Python Cave in Uganda and encountered the virus. One died after returning to the Netherlands, while another developed minor symptoms and recovered. The natural reservoir was frugivorous bats roosting in Africa (Brauburger et al. 2012).

Moreover, Uganda faced another three epidemics from 2012-2017. In 2012, an outbreak occurred in Kabale that affected 15 individuals. In 2014, a health worker was affected and died within a few days in Kampala. The detected MARV strain had similarity with the MARV strain secluded from Egyptian Frugivorous Bats (Nyakarahuka et al. 2017). In the 2017 outbreak, four individuals of the same family were affected in the Kween district of Uganda (Nyakarahuka et al. 2019).

In August 2021**,** one person got infected and died in Guinea, West Africa (WHO 2022). In July 2022, an epidemic of MARV occurred in Ghana, West Africa, where two individuals got infected and died. This epidemic is still under investigation. On February 2023, the Ministry of Health of Equatorial Guinea reported an epidemic with 15 cases confirmed through RT-PCR and 23 probable cases. Moreover, on March 2023, the Ministry of Health of the United Republic of Tanzania reported 8 cases of MHF in northern Tanzania (Deb et al. 2023). The geographical occurences of Marburg virus is highlighted in Fig. 3.

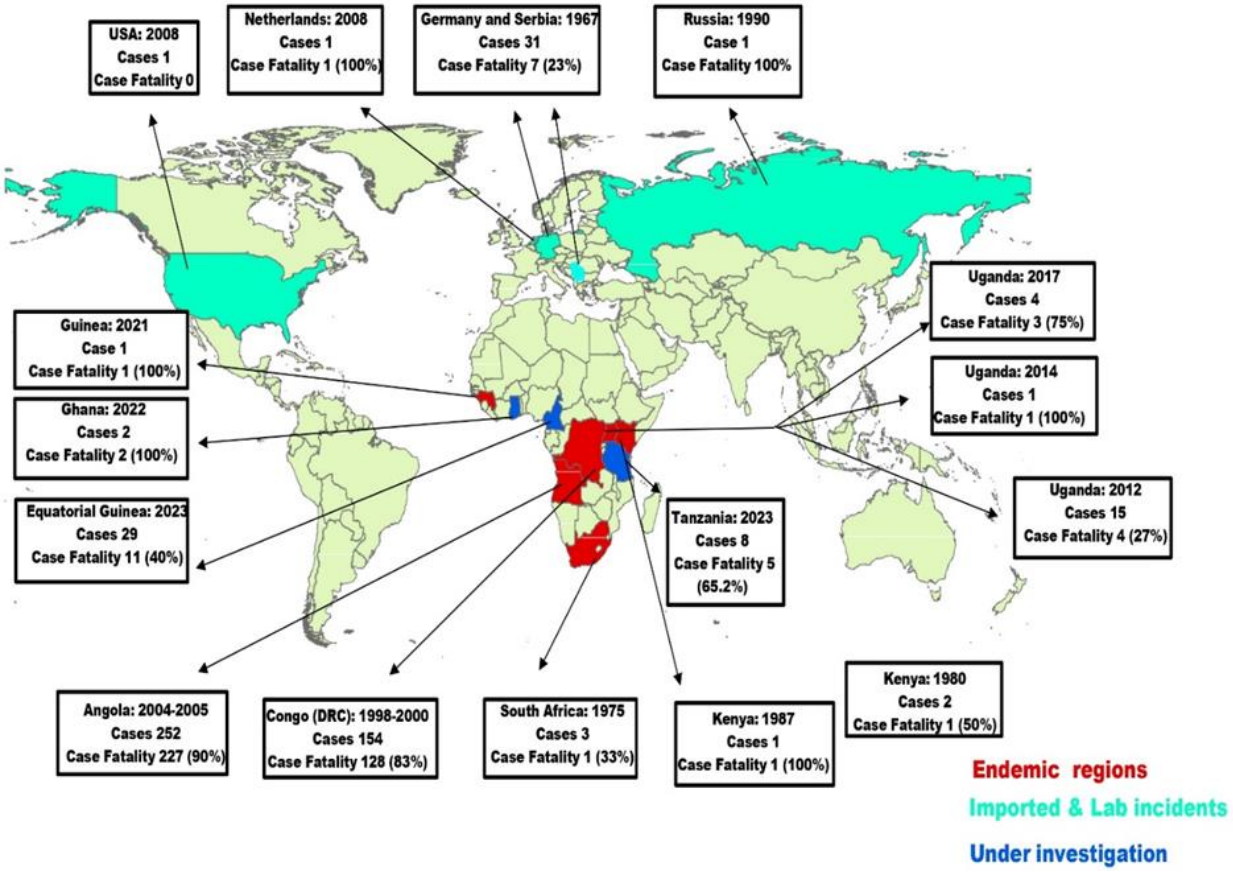

Fig. 3*:* Geographical distribution of MARV Outbreaks (Designed on ArcGIS Desktop 10.5).

So far, 17 outbreaks have been reported around the globe. Due to increased trade and travelling, MARV is considered a major public health concern. On a daily basis, thousands of individuals from African regions come to Guangzhou due to settlement, and similarly, travelling activities happen around the globe. There is a huge risk of MARV importation all over the world. Therefore, there is a need for international cooperation to control MARV (Zhao et al. 2022). Epidemiology and case fatality rate of all MARV outbreaks is enlisted in Table 2.

Table 2: Epidemiology and case fatality rate of all outbreaks related to MARV infection (Zhao et al. 2022; Deb et al. 2023; Kilangisa 2023)

Year	Country	Suspected Origin	Cases	Case Fatality	Notes
2023	Tanzania	Under investigation	8	65.2%	
2023	Equatorial Guinea	Under investigation	29	40%	
2022	Ghana	Under investigation	2	100%	
2021	Guinea	Guinea	1	100%	
2017	Uganda	Uganda	4	75%	
2014	Uganda	Uganda	1	100%	
2012	Uganda	Uganda	15	27%	
2008	Netherlands	Uganda	1	100%	Imported
2008	USA	Uganda	1	0	Imported
2007	Uganda	Uganda	4	75%	
2004-2005	Angola	Angola	252	90%	
1998-2000	Congo (DRC)	Congo	154	83%	
1990	Russia	Russia	1	100%	Laboratory incident
1987	Kenya	Kenya	1	100%	
1980	Kenya	Kenya	2	50%	
1975	South Africa	Zimbabwe	3	33%	Imported
1967	Germany and Serbia	Uganda	31	23%	Imported and Lab leak

5. SOURCES OF MARBURG VIRUS

5.1. RESERVOIR HOST OF MARV

Animals, especially bats are the natural reservoirs of MARV (Swanepoel et al. 2007). Egyptian fruit bat (*Rousettus aegyptiacus*) is the most frequent reservoir host of MARV. Some unidentified Chiroptera and Hipposideros caffer act as minor infection sources (Chakraborty et al. 2022). In 1999, in the DRC, 12 MARV strains were isolated from bats of unclassified species of order Chiroptera (Swanepoel et al. 2007). In 2007, in Uganda, one strain of MARV was isolated from Hipposideros caffer (Towner et al. 2009). *Rousettus aegyptiacus* is the main source of infection from which many MARV strains were isolated, including; 61 from Uganda in 2007-2012, 4 from Gabon in 2005-2009, 11 from Sierra Leone in 2017-2018, 1 from Kenya, two from Zambia in 2018 and 2 from South Africa in 2013-2017 (Abir et al. 2022).

5.2. INTERMEDIATE HOSTS AND AMPLIFIER HOST OF MARV

The main source of virus shedding is saliva, urine, and excrement of the bat. The intermediate hosts, including animals hunted for bush meat and NHPs, are the primary vectors (Abir et al. 2022). The potential amplifier hosts of the zoonotic Marburg Virus Disease (MVD) are Pigs and African green monkeys (Dhama et al. 2022).

6. TRANSMISSION OF MARBURG VIRUS

6.1. BAT-TO-BAT TRANSMISSION

In bats, it is hypothesized that biting, sexual interactions, and hematophagous arthropods are the possible routes of MARV transmission (Dhama et al. 2022). A study in the recent past on MARV-inoculated bats

detected the virus shedding in oral, urine and rectal samples of MARV-inoculated bats and in the blood and oral samples of in-contact bats. This study proves the horizontal transmission of MARV (Schuh et al. 2017). The detection of MARV in the intestine, salivary gland, kidneys, bladder, lungs, and tissue of the female reproductive tract of MARV-inoculated bats shows that MARV may spread either by vertical or horizontal route inside the reservoirs (Paweska et al. 2012).

6.2. BAT TO HUMANS & NHPS TRANSMISSION

MARV is mostly transmitted by bats to humans and NHPs through faeces, saliva, and partially consumed MARV-contaminated fruit (Schuh et al. 2017; Amman et al. 2021). The partially chewed MARV-contaminated fruits are frequently dumped on the ground by the reservoir bats during feeding on ripe fruits. These MARV-contaminated fruits can be consumed by susceptible humans or animals (Brainard et al. 2016; Amman et al. 2021). The direct contact with bodily fluids of infected bats and inhalation of MARV-contaminated excreta of bats spread the MARV to humans. The virus is also transmitted through contact with dead or infected animals, such as forest antelopes, monkeys, bats, and chimpanzees (Dhama et al. 2022). The infected intermediate animals may transmit the MARV to humans in the early phase. The MARV-containing bushmeat-hunting animals are common causes of transmission to humans and NHPs (Abir et al. 2022).

6.3. HUMAN-TO-HUMAN TRANSMISSION

MARV transmission occurs directly from human to human through contact via broken skin in various ways. The key factors in the spread of MARV are contaminated surfaces and items, bodily fluids, and nosocomial transmission. Sexual transmission of MARV also occurs due to its presence in the semen of infected males (Kortepeter et al. 2020). Following clinical recovery, the transmission of MARV through infected semen for up to seven weeks has been documented (Kassa 2019). Iatrogenic transmission of MARV has also been reported in humans (Lawrence et al. 2022). Transmission of the MARV occurs via parenteral introduction, mucosal surfaces, and skin damage. Parenteral exposure is the most fatal route of infection, while in an outbreak, the most persistent source of infection is direct contact with infected humans or animals (Fig. 4) (Kassa 2019). The risk of getting a disease is higher in healthcare workers, corpse handlers, spelunkers, and mine workers (Bausch et al. 2003; Mohapatra et al. 2022).

6.4. NHP-TO-NHP AND HUMAN-TO-HUMAN TRANSMISSION

Aerosols are the route of MARV transmission from human to human and NHP-to-NHP (Zhao et al. 2022). During an outbreak, transmission has also occurred through the air, as MARV may remain in the aerosols (Johnston et al. 2015). MARV fomite transmission can play a significant role in spreading the virus from both human to human and NHP-to-NHP (Fig. 4). It can survive at low temperatures for more than three weeks on solid surfaces (glasses and plastics) (Piercy et al. 2010).

7. CLINICAL FINDINGS AND SYMPTOMS

The clinical findings in a MARV-infected patient might change depending on different factors, such as the virulence of the strain, the immune status of the host, and medical maintenance. According to reports, in humans, the incubation period varies from two to twenty-one days, with an average value of five to nine days (Slenczka 1999; Kassa 2019). According to the disease course, MHF can be divided into three separate phases based on disease outcomes: the initial generalization phase, an early organ phase, and the late organ phase or convalescence phase (Kassa 2019). Each phase, along with clinical findings, is elaborated in Fig. 5.

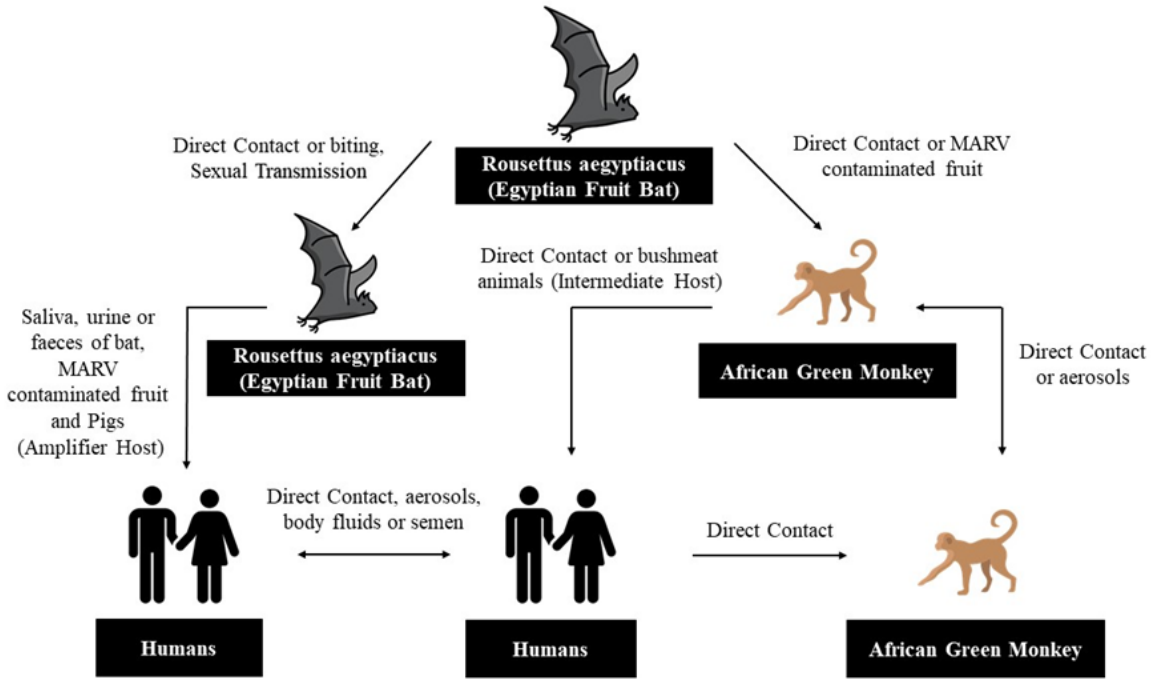

Fig. 4: Transmission of MARV.

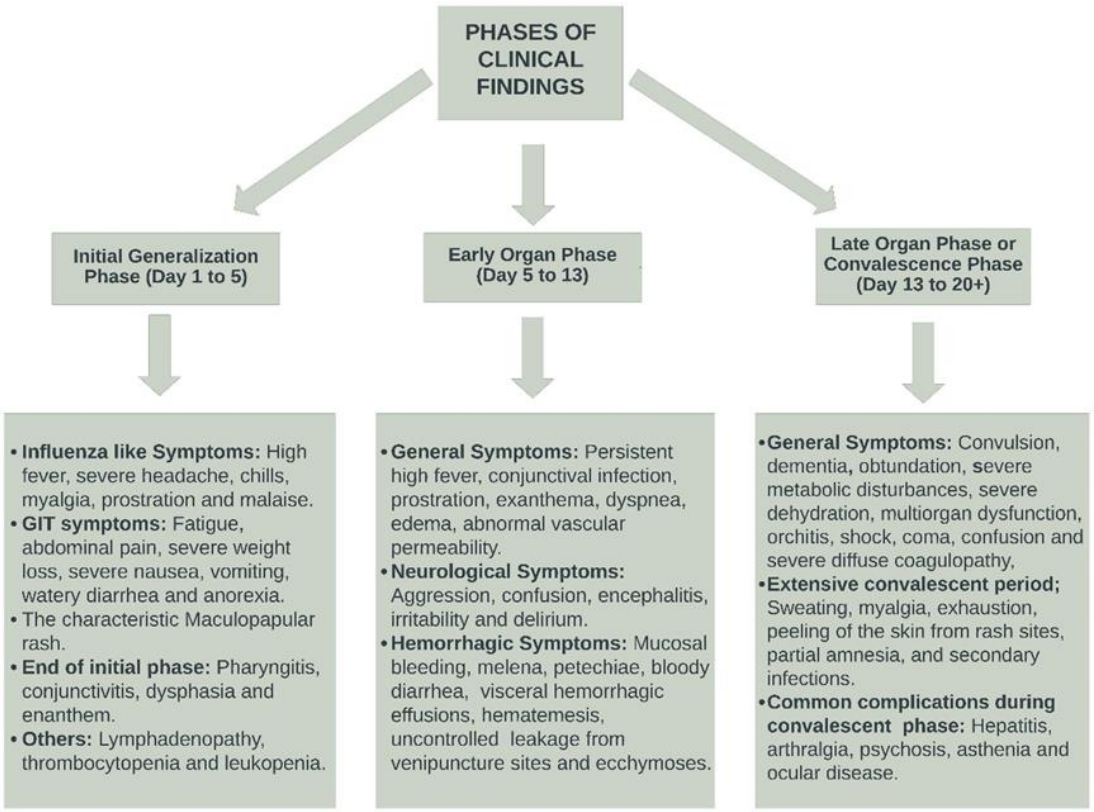

Fig. 5: Clinical findings and symptoms of MARV.

7.1. PHASE 1: INITIAL GENERALIZATION PHASE

The initial generalization phase lasts for five days after the disease onset, followed by rapid debilitation, high fever (~40°C), chills, myalgia, severe headache, pharyngitis, conjunctivitis, enanthem, malaise, anorexia, vomiting, and severe watery diarrhea (Kassa 2019; Abir et al. 2022). Middle to late stage is characterized by an erythematous, non-pruritic, and maculopapular rash on the face, trunk, and extremities. This maculopapular rash is a typical symptom of early MARV infection that can begin focally and then spread from its focal point (Colebunders et al. 2007; Kortepeter et al. 2020).

7.2. PHASE 2: AN EARLY ORGAN PHASE

This phase lasts between five to thirteen days and is characterized by exanthema, dyspnea, prostration, abnormal vascular permeability, and edema (Feldmann et al. 2013; Kassa 2019). Rapidly it develops into a febrile illness that leads to shock and multi-organ dysfunction (specifically pancreas, liver and kidney) (Kuhn 2008; Lawrence et al. 2022). Hemorrhagic manifestations may develop in the later stages, including mucosal bleeding, petechiae, unrestricted leakage from venipuncture sites, melena, dysentery, visceral hemorrhagic effusions, ecchymoses and hematemesis (Kassa 2019). The hemorrhagic manifestations are experienced by only one-third of patients at the peak of MARV infection (Rougeron et al. 2015). Many patients may die within a few days after the onset of this phase (Miraglia 2019). Nervous signs such as encephalitis, disorientation, irritability, and aggressiveness appear at the end of this phase (Mehedi et al. 2011).

7.3. PHASE 3: LATE ORGAN PHASE OR CONVALESCENCE PHASE

This phase lasts from thirteen to 20+ days. This phase has two outcomes; either the infection is fatal, or patients enter the convalescence phase. The late organ phase is characterized by shock, convulsions, agitation, obtundation, dementia, coma, severe metabolic issues, marked dehydration, diffuse coagulopathy, and multi-organ failure. In some reports, orchitis and abortion have also been observed (Borchert et al. 2002, Bausch et al. 2006; Mehedi et al. 2011). Generally, the primary death drivers are multi-organ failure and shock (Abir et al. 2022). Mortality mainly occurs between eight and sixteen days following the onset of signs and symptoms (Kassa 2019).

The convalescent phase is characterized by arthralgia, hepatitis, asthenia, ophthalmic disorders, and psychosis (Hartman et al. 2010). The recovered patients are the carriers of MARV. Sources of this virus in carrier individuals are eyes, testicles, amniotic fluids, placenta, fetus, and breast milk (Mohapatra et al. 2022).

8. PATHOPHYSIOLOGY OF MARBURG VIRUS

A virus typically enters the body through damaged skin or syringe needles and damages many types of cells and organs, leading to MHF (Abir et al. 2022). The binding and entrance of MARV have been linked with numerous attachment factors, such as a GP (glycoprotein) on the surface of the virus. The GP1 (GP surface unit) attaches to cellular receptors and inserts GP2 (an internal fusion loop) into the cell membrane of host cells (Hoffmann et al. 2017). MARV enters the blood or lymph and target the cells of the mononuclear phagocytic system, such as, dendritic cells, kupffer cells, macrophages, and monocytes (Rougeron et al. 2015; Asad et al. 2020). The virus replicates in these cells and disseminates systemically

into other body cells like fibroblasts, hepatocytes, epithelial cells, and endothelial cells (Rougeron et al. 2015). Liver, lymphoid tissues and adrenal glands are the primary targets for MARV at the organ level (Mohamadzadeh et al. 2007). The significant replication of the virus takes place in target organs, including the liver, spleen and secondary lymphoid organs (Geisbert and Jaax 1998).

MARV suppresses innate response and dysregulates lymphocyte costimulation (Messaoudi et al. 2015). The infected macrophages trigger the production of cytokines and chemokines such as tumour necrotic factor alpha (TNF-α), monocyte chemo-attractant protein 1 (MCP-1), macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein-1, interleukin (IL)-1β, IL-1 receptor antagonist, IL-6, IL-8, IL-10, IL-15, IL-16, growth regulated oncogene-α, NO, Chemokine ligand 3 (CCL3), Chemokine ligand 4 (CCL4), C-X-C motif chemokine ligand 10 (CXCL10), and eotaxin (Rougeron et al. 2015). TNF-α causes apoptosis of T lymphocytes and natural killer cells as well as extensive lymphoid depletion in the thymus, lymph nodes and spleen, leading to lymphopenia. This immunosuppression helps MARV to disseminate systemically (Basler and Amarasinghe 2009; Rougeron et al. 2015).

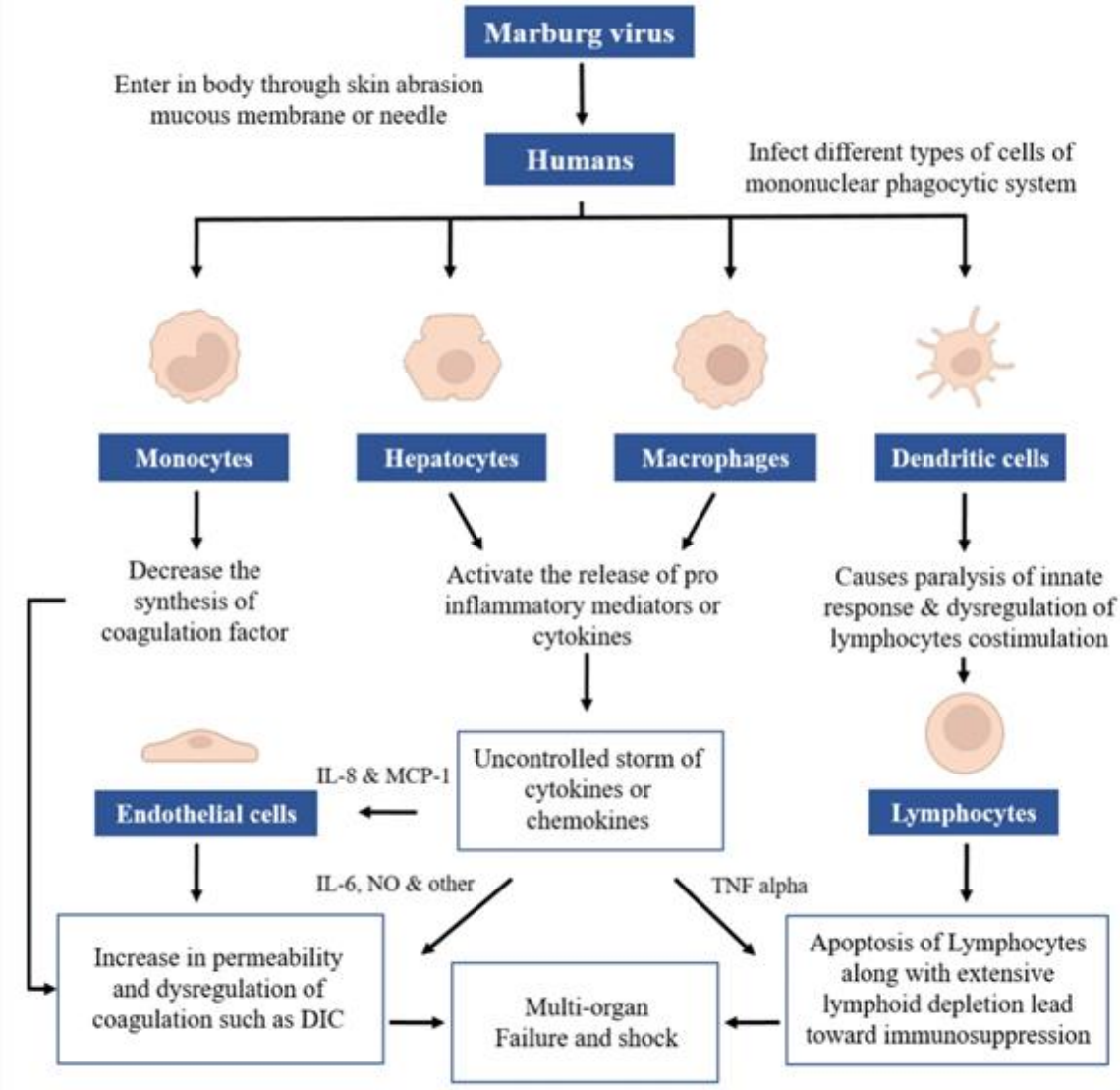

Fig. 6*:* Pathophysiology of MARV infection at cellular level in humans.

MCP-1 and IL-8 cause tissue damage that leads to the expression of adhesion molecules on endothelial cells. This expression of adhesion molecules allows the neutrophils and monocytes to damage sites (Gerszten et al. 1999). TNF-α, together with IL-6, NO, and other vasoactive substances, increases the permeability of the endothelial blood vessels lining. These vasoactive substances also cause coagulopathies, such as disseminated intravascular coagulation (DIC) and reduce the synthesis of clotting factors due to impaired hepatocytes (Adegboro and Adeola 2011; Rougeron et al. 2015). Dissemination of MARV in the adrenal cortical cells causes hypotension and metabolic disturbances. These hemodynamic disturbances, immunosuppression, and coagulopathy lead to shock and multi-organ failure (Kassa 2019). Fig. 6 indicates the pathophysiology of MARV at a cellular level in humans.

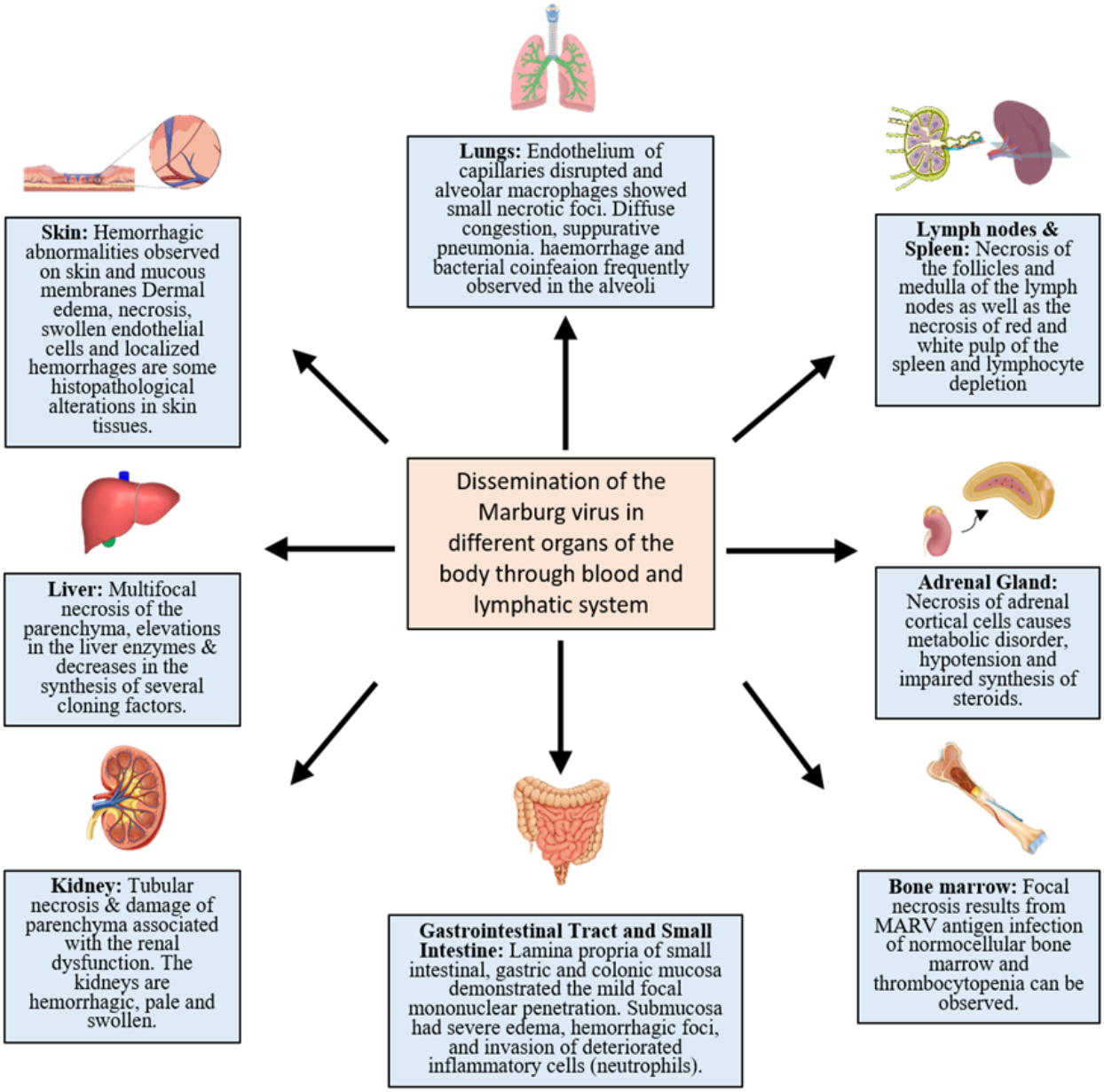

Fig. 7*:* Pathological changes caused by MARV in humans.

9. PATHOLOGICAL CHANGES IN MARV INFECTION

In hepatocytes, necrosis of the parenchyma of the liver causes significant damage to the reticuloendothelial system and coagulation abnormalities. Proteinuria is frequently seen in MHF patients who show renal dysfunction caused by tubular necrosis and damage to parenchyma (Asad et al. 2020). Microscopically, the affected kidneys are hemorrhagic, pale, and swollen, indicating grave damage to the parenchyma (Shifflett and Marzi 2019). The adverse changes occur in the lymphoid tissues, such as necrosis of the medulla and follicles of the lymph nodes, along with necrosis of the red and white pulp of the spleen (Mariappan et al. 2021). Fig. 7 below shows pathological changes caused by MARV in humans. The endothelium of capillaries of alveoli was frequently disrupted, and alveolar macrophages showed small necrotic foci or micro-necrosis and fibrin (Geisbert and Jaax 1998). Diffuse congestion, suppurative pneumonia, hemorrhages, and bacterial coinfection were frequently observed in the lung alveoli (Abir et al. 2022). It is still unclear exactly how MHF causes morphological alteration of the bone marrow. Focal necrosis results from MARV antigen infection of normocellular bone marrow (Zapata et al. 2014). Dermal oedema, necrosis, swollen endothelial cells, and localized haemorrhages are limited histopathological alterations in skin tissues. The cutaneous effects develop during recovery and appear between the second and seventh day following the onset of symptoms (Nkoghe et al. 2012). In the GIT, lamina propria of small intestinal, colonic, and gastric mucosa demonstrated mild focal mononuclear penetration. The submucosa has severe oedema, many haemorrhage foci, and an invasion of deteriorated inflammatory cells (Abir et al. 2022).

10. DIAGNOSIS OF MARV

As MVD has low prevalence, few conditions make a person suspected of MHF. The person must have contacted the bodily fluids of the African natives or recently visited people or animals. Mostly the transmission of virus occurs when the person is a health worker that contacts infected patients or visits outbreak areas. Typhoid fever, rickettsial infections, and malaria have semiological similarities to MHF, so clinical identification is challenging in the early stages of an outbreak (Grolla et al. 2005). Diagnosis of MHF includes molecular, serological, and virological techniques. Blood and serum are the best and most reliable specimens for diagnostic purposes, other specimens, like breast milk, saliva, and urine (uncertain), can be used (Kassa 2019). Blood tests help to rule out the differential of MHF.

Confirmatory diagnostic tests for MARV include a Reverse transcriptase polymerase chain reaction assay (RT-PCR), serum neutralization test, Electron microscopy, Enzyme-linked immunosorbent assay (ELISA) and virus isolation by cell culture (Chakraborty et al. 2022). Contact tracing and case identification are the only approaches to control the disease outbreak, as all above mentioned diagnostic facilities are not available worldwide. IgG ELISAs are mainly used to identify people who recovered from MHF as IgG lasts for several years, whereas IgM-capture ELISA is more typically employed for the diagnosis of acute sickness as IgM are MARV-specific antibodies and emerge two days post-infection (Kassa 2019). Antibody ELISA is used to detect the host immune response. Virus isolation and electron microscopy are limited to specific specialized locations with the required facilities. Conventional RT-PCR, quantitative real-time RT-PCR, and Reverse transcription loop-mediated isothermal amplification have been developed to detect MARV RNA in clinical specimens (Towner et al. 2006).

11. MANAGEMENTAL APPROACHES FOR MARV

A common treatment strategy is using remedies for pain management because of the absence of documented treatment. Supportive treatment often includes; maintenance of blood volume and

electrolytes (Jeffs 2006). Treatments or vaccines with clinical validation to prevent or treat MVD are currently absent, though some reliable techniques can be adopted to control outbreaks and cases (Islam et al. 2023). The supportive therapy used in the past is enlisted in Table 3.

Table 3: Supportive therapy used in the past

Year	Area	Supportive treatment	Reference
1967	-	Cardiac glycosides, Serum, Fluid infusion, Antipyretics, Steroids and Electrolytes.	(Todorovitch et al. 1971)
1980	Kenya	Antimalarial drugs.	(Smith et al. 1982)
1990	Russia	Extracorporeal hemosorbents.	(Nikiforov et al. 1994)
2004-2005	Angolan	Antimalarial drugs, Heparin, Antibiotics, Analgesics, Antiemetics, sedatives, Cimetidine, Oral rehydration and IV fluids.	(Ndayimirije and Kindhauser 2005; Jeffs 2006; Roddy et al. 2007)
2008	Uganda	Blood transfusion, Malaria prophylaxis, Antiemetics and Antibiotics.	(Leggiadro 2010)
2008	Netherland	Hemofiltration, Plasma, IV fluids, Hypertonic saline.	(Clark et al. 2012)

12. CURRENT SUPPORTIVE THERAPY

Remdesivir exhibited clinical effectiveness when administered once daily for 12 days at a dose rate of 5 mg/kg or as a 10 mg/kg initial dose followed by a 5 mg/kg after four days of inoculation (Porter et al. 2020). Phosphorodiamidate positive-charged morpholino oligomers (PMOs), Small virus-like proteins and interfering RNAs are under study as a treatment for advanced diseases since they have been shown to prolong disease survival in animal models (Lawrence et al. 2022).

Cholesterol-conjugated fusion inhibitors have activity against MARV (Pessi et al. 2019). 4-(aminomethyl) benzamide is an effective entrance inhibitor of MARV infection (Gaisina et al. 2020). Galidesivir, favipiravir and aloperine have shown efficacy against MARV infection, and more recently, an inhibitor chemical called FC-10696 has been found to prevent MARV from egressing (Abir et al. 2022). *Nigella Sativa* (Black seeds) is a supportive therapy with antiviral, anti-inflammatory, and antioxidant properties.

Black seed's antiviral activities lower the viral burden of the MARV-infected patient (Maideen 2023). Monoclonal antibody (MR186-YTE) alone can provide 100% protection, and when combined with Remdesivir five days after infection, can provide 80% protection in NHP (Cross et al. 2021). Thus, additional research regarding combination therapy or monoclonal antibodies and their application in humans could be another potential aspect of managing MVD. Table 4 shows complete supportive treatment and vaccination.

13. VACCINATION STRATEGIES

Rodent and NHPs models were used in different research to investigate the effectiveness of MARV vaccines. Some vaccinations have so far undergone human usage trials (Dulin et al. 2021). The Chimpanzee adenovirus serotype three vector vaccine, encoded with glycoprotein from MARV, is in phase 1 of the clinical study (Trovato et al. 2020). BN-Filo vaccine, encoded by the glycoprotein from MARV, Ebola and Sudan, is in phase 2/3 trials after completing the phase 1 trial (Roozendaal et al. 2020).

DNA plasmid vaccine includes GP from MARV Angola, and MARV Sudan completed phase 1 clinical trial (Abir et al. 2022). Trivalent vaccines in a single vial have recently been developed, and tests on mice and NHPs models revealed strong antibody levels. This vaccine may simplify administering and distributing immunizations in remote and underdeveloped locations (Preston et al. 2021). A recombinant vesicular stomatitis virus-based vaccine that indicates glycoproteins of MARV has demonstrated encouraging outcomes if administered 48 hours after exposure (Asad et al. 2020). VSV-based vector and Recombinant

AD5 (showing Musoke glycoproteins) usage is currently the best approach toward MARV (Mehedi et al. 2011). Experimental methods are still used on both human and animal models to check the effectiveness of treatment and vaccines (Table 4).

Table 4: Evaluation of MARV treatment and vaccination in the NHP model (Abir et al. 2022)

Sr. No	Animal model	MARV strain	Compound used	Dose	1st dose after infection	Dose number	Rate of survival
			Antibody treatment				
01	Rhesus macaque	Angola	MR191-N	50mg/kg	4th &	2	100%
					5th day	2	80%
02	Rhesus macaque	Ci67	Purified immunoglobin- E	100mg/kg	15-30 minutes	3	100%
			Antiviral drugs treatment				
01	Cynomolgus macaque	Musoke	BCX4430 (Galidesivir)	15mg/kg	1st & 2nd day	28	100%
						26	100%
02	Cynomolgus macaque	Angola	GS-5734 (Remdesivir)	10mg/kg loading dose then 5mg/kg	5th day (5mg/kg)	12	83%
						12	50%
03	Rhesus macaque	Ravn	siRNA NP	0.5mg/kg	3rd &	7	100%
					6th day	7	100%
			Pre-exposure vaccine				
01	Cynomolgus macaque	Musoke, Angola, Ravn	rVSV-MARV	2x10^7 PFU	-	1	100%
02	Cynomolgus macaque	Angola	DNA MARV GP	4mg	-	4	100%
03	Cynomolgus macaque	Musoke, Ci67, Ravn	VLPs+QS-21 adjuvant	1mg VLps +0.1ml QS-21	-	3	100%
04	Rhesus macaque	Popp	Inactivated MARV	7µg	-	2	50%
			Post-exposure vaccine				
01	Rhesus macaque	Musoke	rVSV-MARV	10^7 PFU	20-30 minutes	1	100%
02	Rhesus macaque	Musoke	rVSV-MARV	2x10^7 PFU	1st &	1	83%
					2nd day	1	33%

14. PREVENTION AND CONTROL OF MARV

Effective controlling of MARV is difficult because no proper treatment and vaccine (licensed) is available. So the control of MARV is done by breaking its secondary transmission cycle. Persons who have contacted the index case should check their temperature twice daily for three weeks since contact and report it to the public health officer, and if fever develops should be quarantined (Timen et al. 2009). Due to the danger of sexual transmission, WHO advises safe sex for male survivors of MHF for 12 months after the development of symptoms until their semen results negative for MVD twice (Mohapatra et al. 2022).

The first approach is to reduce the likelihood of bat-to-human transfer brought on by extended exposure to mines or caves where fruit bat colonies are found, and people should wear gloves and other suitable protective clothes when working, conducting research, or visiting mines or caves. The second approach is to limit the possibility of transmission from one human to another, occurring due to direct contact or contact with fluids of the body of infected patients (Kassa 2019).

To investigate MARV infection, samples from humans and animals should be manipulated by qualified experts and managed in biosafety level 4 laboratories, which are fully furnished with maximum

containment facilities (Sah et al. 2022). All animal products, like raw and undercooked meat, must be thoroughly cooked before being consumed by humans (Dhama et al. 2022).

Proper burial of the deceased, identifying the infected persons, and isolating infected persons from healthy ones help control and prevent the disease. Using proper personal protective equipment like gloves, masks and washing your hands after taking care of sick patients help control and prevent the disease. WHO suggests that when in close contact (1-meter distance), the caretaker of the patient should use a mask, long-sleeved gown, and gloves ("Marburg Virus Disease." *World Health Organization*, 7 Aug. 2021, www.who.int/news-room/fact-sheets/detail/marburg-virus-disease. Accessed 05 July 2023). The staff should have a separate room to change clothes, and a separate container should be used to collect and burn all patient waste (Bauer et al. 2019). The corpse of a patient should be covered in a coffin that has been bleach-sprayed before being buried (Bauer et al. 2019).

15. FUTURE PERSPECTIVE

Although MARV originates in Africa, its outbreaks with high CFR and complex transmission cycles indicate that it can affect the whole continent. More studies focused on MARV are still essential to deliver clear direction for managing patients and the progress of vaccine development. To design a proper management course, it is crucial to conduct more trials on NHP models to understand the complex pathogenesis and the effect of different drugs. A proper surveillance system approach should be adopted for outbreak prevention and management. The ecology of MARV and the transmission cycle should be properly studied to control disease outbreaks. Taking measures like Seroepidemiological surveys of the MARV endemic locations and international travellers is beneficial. It will assist in developing a region-specific plan to halt the spread of the MARV disease in future. Proactive planning, collaborative activities involving public health experts, scientists, biologists, legislators and awareness campaigns can create effective measures to combat MVD. The public health sector should educate the community for future epidemic preparation.

16. CONCLUSION

In conclusion, the main focus is on the future perspectives after exploring various managemental approaches to find a research gap so that a proper study should be conducted to limit the chances of MVD from becoming an epidemic. Many past and recent studies regarding this virus are summarized its complex pathogenesis and comprehensive transmission cycle to devise a plan and strategies for control and prevention. Mapping systems and data regarding endemic areas and outbreaks also help to plan a strategy for international travel and bans.

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