INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD)
© 2026 IJNRD | Volume 11, Issue 2, February 2026 | ISSN: 2456-4184 | IJNRD.ORG

Ebola and Marburg Viruses: Zoonotic Threats and Hemorrhagic Fevers a Review

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Abstract

Ebola and Marburg viruses are highly virulent pathogens belonging to the *Filoviridae* family, responsible for severe hemorrhagic fevers with high mortality rates. These zoonotic viruses primarily originate from fruit bats and can be transmitted to humans through direct contact with infected animals or bodily fluids of infected individuals. Despite their historical significance, the difficulties of managing outbreaks and the lack of effective treatments have limited research into the Ebola and Marburg viruses. Recent advancements in vaccine development and therapeutic interventions show promise for improving outcomes in future outbreaks. Understanding the pathophysiology, transmission dynamics, and immune responses associated with these viruses is crucial for enhancing public health preparedness and response strategies. Continued research efforts are essential to mitigate the risks posed by these zoonotic threats and to develop effective prevention and control measures against future outbreaks of Ebola and Marburg virus diseases.

Keywords: Ebola virus, Marburg virus, Filoviridae, Outbreak, Epidemiology

1. Introduction

Ebola Virus Disease (EVD) and Marburg Virus Disease (MVD) are critical, frequently lethal viral hemorrhagic fevers. Pyrexia, hemorrhagic conditions, and multi-organ dysfunction are characteristics of these illnesses. The etiological agents of EVD are viruses classified under the genus Ebolavirus, whereas MVD is attributed to viruses from the genus Marburgvirus. Both genera belong to the family Filoviridae. EVD was initially recognized in 1976 amid outbreaks in Yambuku, Democratic Republic of the Congo (formerly Zaire), and Nzara, Sudan (Isaäcson et al., 2019). The term "Ebola" comes from the Ebola River, situated near the site of the first outbreak in the Democratic Republic of the Congo. MVD was initially identified in 1967 during epidemics in Marburg and Frankfurt, Germany, and Belgrade, Serbia (formerly Yugoslavia), among laboratory personnel exposed to tissues from infected African green monkeys (*Cercopithecus aethiops*). The initial outbreaks highlighted the viruses' high virulence, ability to spread among humans, and zoonotic nature (Hewson, 2024). This review aims to provide a comprehensive overview of the Ebola and Marburg viruses, emphasizing their transmission from animals to humans and the involvement of specific animal hosts and environmental factors (Mohamadzadeh et al., 2007). The patterns of illness prevalence in human populations encompass geographic distribution, outbreak dynamics, and determinants affecting disease transmission (Mahanty and Bray, 2004). The processes through which these viruses cause disease in humans involve viral entry, replication in host cells, targeting specific organs, and triggering the host immune response (Falasca et al., 2015). The manifestations and clinical consequences of EVD and MVD encompass the progression of illness, the range of symptoms experienced, and the potential clinical outcomes (Bente et al., 2009). The laboratory techniques utilized for detecting Ebola and Marburg virus infections include assessing their sensitivity, specificity, and limitations in diagnostic accuracy. Current strategies for managing EVD and MVD involve providing supportive care, administering investigational medications, and evaluating their effectiveness. Preventive strategies for EVD and MVD include vaccination programs, implementing infection control measures, and promoting public health

initiatives (Rivera and Messaoudi, 2015). Strategies to manage outbreaks of EVD and MVD, encompassing contact tracking, isolation, and community involvement (Rivera and Messaoudi, 2016). The precise mechanisms of viral persistence in reservoir hosts and the factors that trigger spillover events are crucial aspects of zoonotic transmission to be explored. The diverse spectrum of host immunological responses to infection and the factors influencing disease severity are pivotal aspects to consider in understanding the outcomes of viral infections (Swanepoel et al., 2007). The advancement of more efficient and accessible diagnostic instruments, therapies, and immunizations. The enduring ramifications of EVD and MVD infection in survivors. The influence of ecological and societal determinants on the genesis and dissemination of these viruses (Bokelmann et al., 2021). Understanding the entire range of clinical manifestations, including long-term implications and neurological complications, is essential for a thorough assessment of the diseases. These statistics highlight the gravity of these infections and the pressing necessity for effective control strategies. Moreover, both viruses have shown the ability to trigger significant outbreaks, such as the 2014-2016 Ebola epidemics in West Africa, resulting in over 11,000 deaths. The interplay of elevated mortality rates and outbreak potential constitutes a substantial risk to public health (Srivastava et al., 2023). Outbreaks of EVD and MVD can inundate even the most resilient healthcare systems. The convergence of highly infectious patients, the necessity for stringent infection control protocols, and the possibility of a substantial caseload can rapidly deplete resources, including hospital beds, medical staff, and critical supplies (Thomas et al., 1999). The management of these diseases necessitates specialized facilities and educated healthcare professionals, which may be deficient in resource-constrained environments, hence intensifying the situation. The anxiety and stigma linked to certain disorders may result in healthcare avoidance, interrupting standard medical services and potentially causing the healthcare system to deteriorate (Heeney, 2015). The potential for Ebola and Marburg viruses to cross borders poses a significant threat to global health security. The interdependence of the contemporary world, characterized by heightened travel and commerce, facilitates the rapid dissemination of outbreaks from one nation to others. The importation of cases into non-endemic nations, while infrequent, can incite widespread concern and need expensive and intricate public health interventions. The advent of these high-consequence viruses underscores the necessity for vigorous international collaboration, comprehensive surveillance systems, and coordinated initiatives to avoid and manage epidemics. The creation of efficacious vaccinations and therapies is essential for alleviating the worldwide danger presented by these viruses (Hewson, 2024).

2. Filoviridae family

The order Mononegavirales includes the family Filoviridae. This order includes a wide range of viruses that all share a common genomic structure and replication mechanism (Biedenkopf et al., 2024). Mononegavirales encompasses notable virus families, including Paramyxoviridae (e.g., measles, mumps), Rhabdoviridae (e.g., rabies), and Pneumoviridae (e.g., respiratory syncytial virus). The classification adheres to the name criteria established by the International Committee on Taxonomy of Viruses (ICTV) (Feldmann et al., 1993). Enveloped, negative-sense RNA viruses. The name Filoviridae, which comes from the Latin word "filum," meaning thread, refers to the filamentous or thread-like structure that distinguishes filoviruses. They are encapsulated viruses, indicating they have an external lipid membrane acquired from the host cell during the budding process. This envelope is essential for infectivity (Burgueño-Sosa et al., 2020). The genome comprises a singular molecule of linear, non-segmented, negative-sense RNA. "Negative-sense" denotes that the RNA genome is complementary to messenger RNA (mRNA) and requires transcription into mRNA prior to the synthesis of viral proteins. Filoviruses contain a distinctive array of structural proteins crucial for their replication and pathogenicity (Kuhn et al., 2019).

2.1 The virulence, geographical distribution, and different species of ebolavirus- There are six recognized species of the Ebolavirus genus, each named after the location of its initial discovery. These species display differences in pathogenicity, geographic distribution, and genetic traits (Feldmann et al., 1993). Zaire ebolavirus (EBOV) is the most recognized and highly pathogenic species, accountable for multiple significant outbreaks in Central Africa. Sudan ebolavirus (SUDV) has instigated considerable epidemics, predominantly in East Africa. Bundibugyo ebolavirus (BDBV) was discovered in Uganda and has been linked to outbreaks with

differing mortality rates. Tai Forest ebolavirus (TAFV) was first isolated from a researcher in Côte d'Ivoire and is the least virulent species, with only one documented human case (Biedenkopf et al., 2024). Reston ebolavirus

(RESTV) is distinctive as it predominantly impacts non-human primates and has not demonstrated pathogenicity in humans (Figure 1). It has been discovered in the Philippines and several regions of Asia. The genetic diversity among Ebolavirus species and within each species is considerable. Using comparisons of viral genome sequences for phylogenetic studies has helped scientists figure out how different ebolaviruses evolved and where they came from and how they spread. These investigations are essential for monitoring epidemics, detecting the emergence of novel variations, and formulating focused diagnostic and treatment approaches (Burgueño-Sosa et al., 2020).

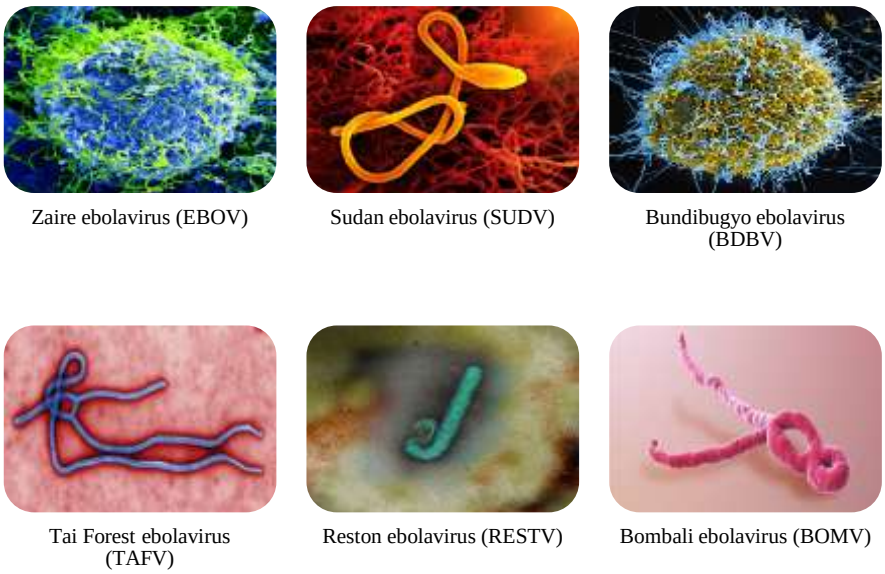

Fig 1. Six recognized species of the Ebolavirus genus

2.1.1 Ebolavirus glycoprotein (GP), nucleoprotein (NP), VP40, VP35, VP24, and L, among others, and their roles in viral replication and pathogenicity - Ebolaviruses possess a filamentous morphology and comprise a sophisticated arrangement of structural proteins.

Glycoprotein (GP) - A surface protein that facilitates receptor binding and cellular entrance. GP is extensively glycosylated and appears in two variants: a soluble form and a membrane-associated form.

Nucleoprotein (NP) - Encapsulates the viral RNA genome, creating the helical nucleocapsid.

VP40 (Matrix protein) - Situated beneath the viral envelope, it is essential for virion assembly and budding.

VP35 and VP24 - are implicated in RNA transcription, replication, and viral assembly. VP35 also functions to inhibit the host immunological response.

L (RNA-dependent RNA polymerase) - The biggest protein, crucial for viral RNA transcription and replication.

These proteins are crucial for the virus's life cycle, facilitating its capacity to infect host cells, multiply, elude the immune response, and induce illness (Biedenkopf et al., 2024).

2.2 A comprehensive examination of Marburgvirus, including its genus, strains, clinical symptoms, and comparisons to Ebolaviruses - The genus Marburgvirus comprises a single acknowledged species belonging to the species Marburg marburgvirus (Figure 2). The Marburg marburgvirus has two different strains -Marburg virus (MARV) and Ravn virus (RAVV) (Gordon et al., 2019). These strains can induce MVD in humans and non-human primates. Although both types are pathogenic, there may be variations in their geographic spread or

virulence noted during outbreaks. Marburgviruses, like ebolaviruses, have genetic diversity (Veronica et al., 2018). Phylogenetic analyses have been performed to examine the evolutionary links between MARV and RAVV, as well as to investigate the origins and dissemination of various outbreaks. Examining viral genome sequences aids in comprehending the genesis of novel variants and in formulating focused diagnostic and treatment approaches (Schmidt et al., 2016).

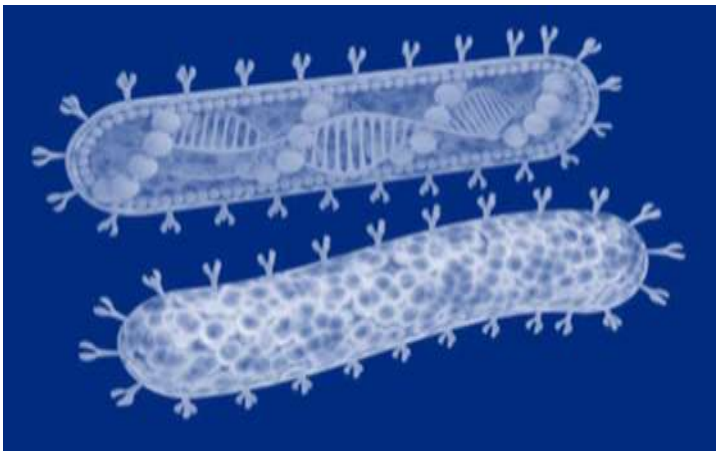

Fig 2. Micrograph of the Marburg viruses

2.2.1 Marburgvirus's glycoprotein (GP), nucleoprotein (NP), VP40, VP35, VP24, and L, among others, and their roles in viral replication and pathogenicity and comparisons to ebolaviruses - Virion architecture is comparable to Ebolavirus. Marburgvirus's possess a comparable filamentous architecture to ebolaviruses (Shifflett et al., 2019). They encompass an identical array of structural proteins, including-

Glycoprotein (GP) - Facilitates receptor binding and cellular entrance.

Nucleoprotein (NP) - Encapsulates the viral RNA.

VP40 (Matrix protein) - Integral to Virion assembly.

VP35 and VP24 are implicated in RNA transcription, replication, and viral assembly.

L (RNA-dependent RNA polymerase) - Crucial for the transcription and replication of viral RNA.

The structural and functional resemblances between Marburg and Ebola viruses facilitate analogous development and clinical presentations.

3. A thorough analysis of the Marburg and Ebola viruses' replication methods, protein architecture, and genomic organization; highlighting the similarities and contrasts between the two viruses to shed light on their virology

3.1 Genomic structure - Both Ebola and Marburg viruses have a single, continuous strand of negative-sense RNA in their genomes. The organization of the genome is similar, with genes that code for structural proteins arranged in a pattern that hasn't changed over time: 3'-NP-VP35-VP40-GP-VP30-VP24-L-5' (Sanchez et al., 1993). The preservation of this gene order indicates a tight evolutionary link. The genomes of both viruses are comparatively big for RNA viruses, measuring around 19 kb, enabling the encoding of several proteins essential for replication, transcription, and pathogenicity (Sanchez et al., 1992).

3.2 Protein structure - Both viruses exhibit an identical array of structural proteins crucial for their life cycle (Hashiguchi et al., 2015). These include nucleoprotein, which forms the helical nucleocapsid structure that encases the viral RNA. VP35 and VP24 are essential for viral RNA transcription, replication, and assembly (Sanchez et al., 1993). VP35 further aids in suppressing the host's immune response. VP40 (Matrix Protein) is located beneath the viral envelope and is crucial for virion assembly and budding. glycoprotein is a transmembrane protein that enables receptor binding and immunological interactions (Kiley et al., 1988). The glycoprotein is highly glycosylated. L (RNA-dependent RNA polymerase) is the largest protein, essential for viral RNA transcription and replication. Despite the structural and functional similarity of the proteins,

variations in their amino acid sequences may explain differences in virulence and host range (Bharat et al., 2012).

3.3 Replication cycle - The replication cycle of both Ebola and Marburg viruses is analogous. The viruses adhere to host cells through their glycoproteins, thereafter entering via endocytosis (Mühlberger, 2007). The viral RNA undergoes transcription to produce mRNA, which is subsequently translated into viral proteins. The viral genome undergoes replication, and new virions are synthesized and released from the host cell. The replication cycle transpires in the cytoplasm of infected cells (Figure 3) (Shabman et al., 2014).

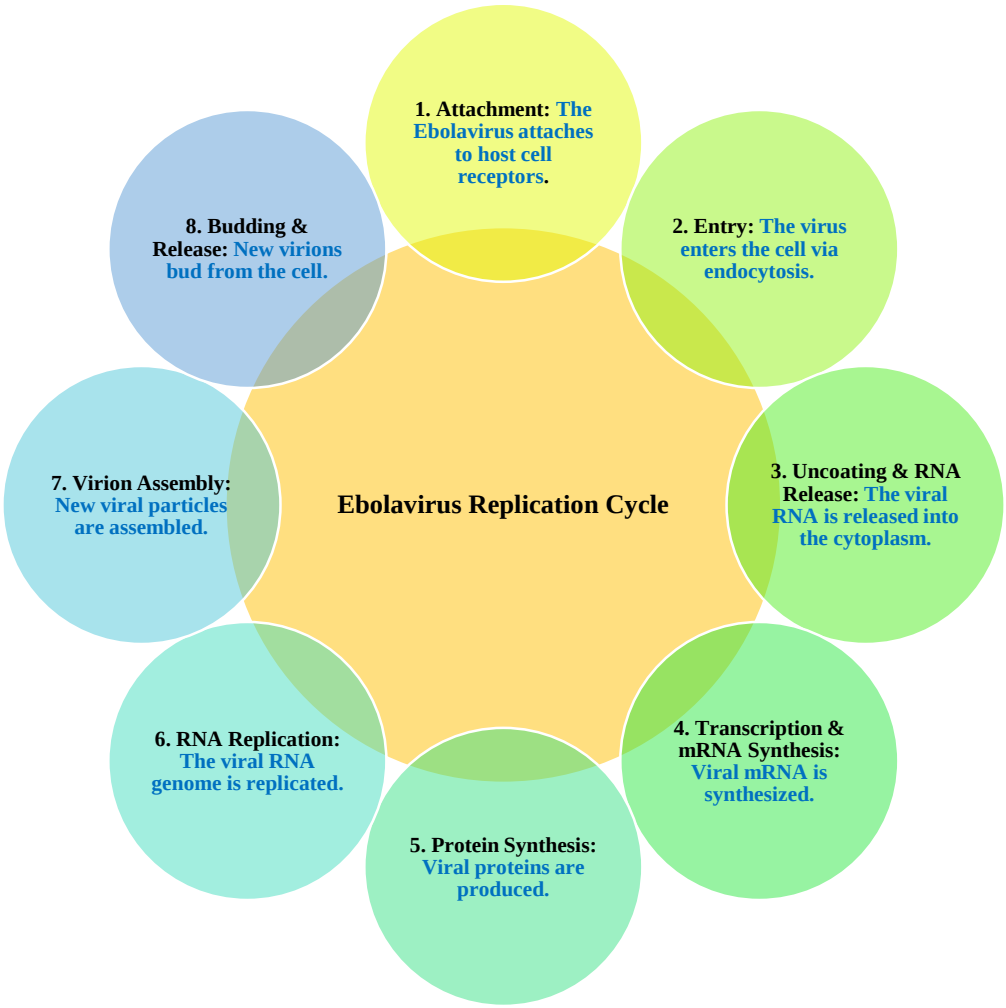

Fig 3. Ebolavirus and Marburgvirus Replication Cycle

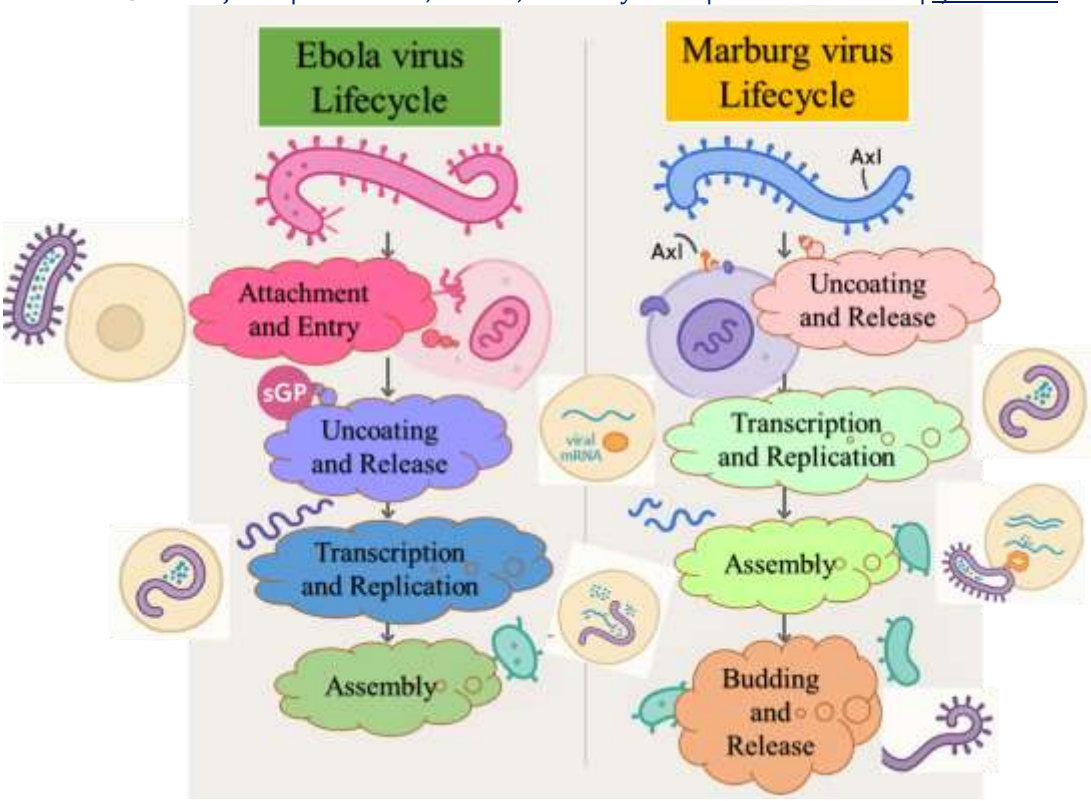

Fig 4. Ebolavirus and Marburgvirus Life Cycle Diagrammatic view

4. Ebola virus and Marburg virus life cycles

4.1 Attachment to host cell- Ebola Virus and Marburg Virus both attach to host cells using glycoproteins (GP) on their surface. They interact with receptors like TIM-1, Axl, and DC-SIGN on human cells. Ebola primarily uses NPC1 (Niemann–Pick C1) and TIM. Marburg also uses NPC1 but may prefer Axl more.

4.2 Entry via macropinocytosis- Both viruses enter the host cell through macropinocytosis, a process where the cell engulfs the virus in a bubble-like vesicle. Once inside, the vesicle (endosome) becomes acidic, triggering changes in the viral glycoprotein.

4.3 Membrane fusion and uncoating- The viral envelope fuses with the endosomal membrane. This fusion is facilitated by NPC1. The viral RNA genome and associated proteins (nucleocapsid) are released into the host cell cytoplasm.

4.4 Transcription of viral mRNA- The L protein (RNA-dependent RNA polymerase) transcribes the negative-sense RNA genome into mRNA. The virus produces its own enzymes and structural proteins using the host's ribosomes. Early proteins include NP, VP35, VP40, GP, VP30, VP24, and L.

4.5 Genome replication- Once enough structural proteins are made, the virus switches to replication mode. It makes full-length copies of its RNA genome (antigenome → genome).

4.6 Assembly- Viral proteins and RNA come together near the inside of the plasma membrane. Proteins like VP40 help drive the assembly of new viral particles.

4.7 Budding and release- The virus pushes out through the plasma membrane, taking part of the host cell membrane with it to form its envelope. Newly formed filamentous virions are released to infect new cells (Figure 4) (Table 1).

Table 1. Key differences between ebola and marburg virus lifecycles

S. No.	Feature	Ebola virus	Marburg virus
1	**Host receptor usage**	More reliance on **NPC1** and **TIM-1**	Broader receptor usage, including **Axl**
2	**Entry mechanism**	Macropinocytosis with GP priming by cathepsins	Similar, but with slightly differing proteolytic sensitivity
3	**Transcription strategy**	Strong gradient favoring structural proteins early	Similar, but gene order and expression may vary slightly
4	**Glycoprotein (GP) expression**	Includes **secreted GP (sGP)** via RNA editing	Lacks extensive RNA editing, **no sGP**
5	**Immune evasion**	Uses sGP to absorb antibodies	Lacks sGP, less decoy effect
6	**Pathogenesis**	More systemic inflammation and vascular damage	Similar but may have slightly different tissue tropism
7	**Virion morphology**	Variable filamentous shape (U-, 6-, or circular)	Similar morphology but may differ in flexibility or size

5. Determinants of virulence and host spectrum - Multiple factors affect the virulence and host range of Ebola and Marburg viruses (Abir et al., 2022). -

5.1 Genetic variations - Genetic changes in viral genome sequences, especially in genes encoding structural proteins such as GP, VP40, and VP35, can influence viral entrance, replication efficacy, and interactions with the host immune system (Rivera and Messaoudi, 2016).

5.2 Protein glycosylation - The degree and configuration of glycoprotein glycosylation can affect receptor affinity, immunological evasion, and virulence (Isaäcson, 2019).

5.3 Immune evasion mechanisms - Both viruses have developed strategies to circumvent the host's immunological response, including the disruption of interferon signaling and the inhibition of T cell activation. Divergences in these processes may lead to variations in virulence (Rivera and Messaoudi, 2015).

5.4 Host factors - Species, age, genetic predisposition, and immune status - significantly influence susceptibility to infection and the severity of disease (Yamaoka and Ebihara, 2021).

5.5 Receptor binding and cell entry - Variations in the interaction between viral glycoproteins and host cell receptors can influence tissue tropism and the capacity to infect diverse cell types and species (Jacob et al., 2020).

5.6 Cytokine dysregulation - The virus's capacity to provoke a "cytokine storm," characterized by excessive production of inflammatory cytokines, may lead to severe illness and shock (Mohamadzadeh et al., 2007).

6. Zoonotic transmission and epidemiology

6.1 Reservoir hosts

Evidence indicates that bats, especially fruit bats, serve as natural reservoirs. Fruit bats of the family Pteropodidae are regarded as the most probable natural reservoirs for both Ebola and Marburg viruses (Swanepoel et al., 2007). The supporting evidence comprises-

6.1.1 Live Marburg virus has been isolated from fruit bats (*Rousettus aegyptiacus*).

6.1.2 Detection of viral RNA and antibodies for Ebola and Marburg viruses in several bat species - Experimental infections indicate that bats may harbor these viruses asymptomatically, implying their capacity to carry and transmit the virus. The capacity of bats to fly and traverse extensive distances underpins their potential contribution to the broad geographic dissemination of these viruses (Swanepoel et al., 2007).

6.1.3 Possible involvement of alternative animals (e.g., primates, rodents) - Bats are the principal suspects; nonetheless, the involvement of other animals in the transmission cycle remains inadequately comprehended. Non-human primates, including monkeys and gorillas, are susceptible to Ebola and Marburg viruses, frequently exhibiting severe illness and elevated mortality rates. Nevertheless, they are regarded as spillover hosts rather than genuine reservoirs, as they do not sustain the virus over an extended period. The function of rodents in the natural maintenance and spread of Ebola and Marburg viruses remains ambiguous despite investigations. Certain investigations have identified viral RNA or antibodies in rats; however, additional research is required to ascertain their relevance in the transmission cycle (Swanepoel et al., 2007).

6.1.4 Mechanisms of viral persistence in reservoir populations- The processes via which Ebola and Marburg viruses are sustained in reservoir populations are intricate and not fully understood (Rivera and Messaoudi, 2016). Numerous hypotheses have been suggested, including- Bats may harbor the virus for prolonged durations without exhibiting clinical symptoms, presumably due to chronic infection in specific tissues or organs. The virus may be intermittently excreted in bat saliva, urine, or feces, facilitating transmission to other bats or mammals. The virus can be passed from mother to offspring in bats, aiding its continued presence in the population over generations (Jayaprakash et al., 2023). The investigation of co-infection in bats with various virus strains and subsequent recombination, which may result in the creation of novel variations, is ongoing. Transmission to Humans Modes of exposure include contact with tissues or fluids from infected animals (e.g., during hunting, slaughtering, or handling).

6.1.5 Transmission to humans - The principal mode of transmission of Ebola and Marburg viruses to humans is thought to occur via direct contact with the tissues or fluids of infected animals (Swanepoel et al., 2007). This may transpire throughout a range of activities, including- Capturing or ensnaring wild fauna (e.g., bats, primates, duikers), Butchering or processing contaminated carcasses and Managing uncooked meat or other animal-derived goods.

6.1.6 The significance of bush meat eating - The intake of bush meat poses a considerable danger for the transmission of Ebola and Marburg viruses. In numerous regions of Africa, bush meat serves as a significant source of protein and revenue. Nonetheless, if the animals are infected with the Ebola or Marburg virus, the handling and consumption of their meat may result in human illness. The risk is further elevated if the meat is inadequately cooked, as this may fail to inactivate the virus (Onyekuru et al., 2020; Tumelty et al., 2023).

6.1.7 Spillover occurrences and determinants of emergence - The transfer of Ebola and Marburg viruses from animal reservoirs to humans is referred to as a "spillover" occurrence (Lee-Cruz et al., 2021). Multiple variables may contribute to these spillover events, including heightened human-animal interaction. Deforestation, agricultural development, and many human activities might enhance interactions between humans and animal reservoirs, hence elevating the probability of transmission. Alterations in climate, precipitation patterns, and other ecological factors might influence the distribution and behavior of animal reservoirs, thus heightening the risk of spillover. The hunting of reservoir species and the bush meat trade can enable the transfer of viruses to humans (Agusi et al., 2022). Genetic alterations in the virus may enhance its capacity to infect humans or result in more severe illness. Transmission of Ebola and Marburg viruses between humans primarily happens through direct contact with the blood or body fluids of infected persons. The fluids encompass the following: • Blood • Urine • Feces • Vomit • Saliva • Semen (the virus may remain in semen for several months post-recovery). Indirect transmission may also transpire via contact with things affected by the virus (fomites). This encompasses infected needles, syringes, medical apparatus, garments, and surfaces (Chang et al., 2023).

6.1.8 Transmission risk during medical operations and interment practices - Specific circumstances present an elevated danger of human-to-human transfer. Healthcare professionals face a significant risk of infection if they fail to comply with stringent infection control protocols. Invasive treatments, including injections and surgeries, elevate the risk of exposure to contaminated bodily fluids. Conventional burial

customs that entail direct interaction with the departed, including cleansing and physical contact with the body, may facilitate transfer (Thomas et al., 1999).

7. Epidemiology of EVD and MVD

7.1 Geographic distribution: Endemic areas in Africa

Ebola and Marburg virus illnesses predominantly occur in sub-Saharan Africa. Ebola virus disease predominantly occurs in Central and West Africa, although Marburg virus sickness has been documented in other regions of Africa, including Central, East, and Southern Africa. Outbreaks of Ebola and Marburg viruses are irregular, exhibiting diverse frequencies, magnitudes, and durations. Outbreaks may vary from a handful of cases to several hundred or even thousands, as evidenced by the 2014-2016 West Africa Ebola pandemic (Lawrence et al., 2022). The duration of outbreaks may vary, ranging from several weeks to several months. Factors influencing the dynamics of Ebola and Marburg virus outbreaks include environmental changes, human behavior, and healthcare infrastructure. Environmental alterations - Deforestation, climate change, and various ecological factors can modify the distribution and behavior of animal reservoirs, hence influencing the risk of spillover to humans (Cuomo-Dannenburg et al., 2024). Cultural practices, including hunting, bush meat intake, and traditional burial rituals, can elevate the risk of transmission. Deficient healthcare systems, insufficiently trained people, and inadequate infection control protocols might exacerbate the transmission of the virus within healthcare environments, intensifying epidemics. Elevated population density and enhanced human mobility may facilitate the transmission of the virus (Stephens et al., 2022).

7.2 Case fatality rates: variability across outbreaks and species/strains- The case fatality rates (CFRs) for Ebola and Marburg virus diseases are elevated but exhibit significant variability. For Ebola virus disease, CFRs have fluctuated between 24% and 90%, contingent upon the species and the particular outbreak, with Zaire Ebolavirus typically linked to the highest CFR. In the case of Marburg virus disease, CFRs have ranged from 23% to 90% in previous outbreaks. Factors such as healthcare quality, treatment timeliness, and the age and overall health of the infected individuals can also affect CFRs (Izudi and Bajunirwe, 2024).

8. Pathogenesis and immunology

8.1 Pathogenesis of EVD - EVD is a grave and frequently lethal condition in humans. The pathophysiology is intricate and entails a sequence of events resulting in immunological dysregulation, vascular impairment, and multi-organ failure (Jacob et al., 2020).

8.2 Viral entry and replication in host cells - The Ebola virus (EBOV) infiltrates host cells via a multi-faceted mechanism. It binds to cell surface receptors, such as C-type lectins, T-cell immunoglobulin and mucin domain-containing protein 1 (TIM-1), among others. Subsequent to attachment, the virus is absorbed through macropinocytosis. Inside the endosome, the viral glycoprotein is broken by host proteases, facilitating the fusion of the viral membrane with the endosomal membrane. The viral RNA genome is subsequently released into the cytoplasm, where viral replication and protein synthesis take place (Sakurai, 2015).

8.3 Target organs and tissues - EBOV targets a variety of cells, including - Macrophages, dendritic cells, and monocytes are key targets, resulting in their malfunction and contributing to immunological dysregulation. Hepatocytes are infected, leading to hepatic damage and compromised coagulation. Infection of splenic cells impairs immunological function and leads to lymphopenia. Infection of endothelial cells that line blood arteries results in vascular dysfunction and heightened permeability. The extensive proliferation of these cells contributes to the systemic aspect of the disease (Falasca et al., 2015).

8.4 Cytokine storm and immune dysregulation - EBOV infection triggers a significant release of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). The "cytokine storm" triggers pyrexia, inflammation, and increased vascular permeability. Simultaneously, EBOV undermines the host's antiviral immune response by obstructing interferon (IFN) signaling. The disruption of antigen presentation, the induction of lymphocyte apoptosis, and the interaction between an exaggerated pro-inflammatory response and a weakened antiviral response result in considerable immunological dysregulation (Younan et al., 2017).

8.5 Vascular dysfunction and hemorrhagic manifestations - EBOV infection of endothelial cells compromises the vascular endothelium, resulting in heightened vascular permeability. This leads to the extravasation of fluids from blood arteries into adjacent tissues, resulting in edema and hypovolemia. Impaired coagulation, possibly resulting from liver damage and depletion of clotting factors, contributes to hemorrhagic symptoms, which may not always be evident. The glycoprotein of the Ebola virus also contributes to vascular dysfunction (Moni et al., 2022).

8.6 Mechanisms of shock and multi-organ failure - The synergistic consequences of hypovolemia, cytokine storm, and organ injury may result in distributive and hypovolemic shock. Multi-organ failure, encompassing the liver, kidneys, and lungs, is a prevalent consequence of severe Ebola Virus Disease (EVD). The ultimate outcome is a systemic inflammatory response syndrome (SIRS) that advances to multiple organ dysfunction syndrome (MODS). The substantial viral load and the resultant damage to the immunological and circulatory systems are the primary reasons leading to the elevated death rate. MVD, induced by the MARV, exhibits numerous similarities with EVD as both viruses are classified under the Filoviridae family. Nonetheless, significant disparities exist in their etiology (Kozlov and Grillari, 2022).

9. Pathogenesis of MVD

9.1 Similarities and differences in pathogenesis compared to EVD

9.1.1 Similarities - Both MARV and EBOV affect analogous cell groups, such as macrophages, dendritic cells, and endothelial cells. This results in analogous disease processes. Both viruses provoke a "cytokine storm," resulting in systemic inflammation and disruption of the immunological response. Both viruses impair endothelial cells, causing heightened vascular permeability, which results in hemorrhagic symptoms and shock. Both conditions may advance to multi-organ failure owing to the systemic characteristics of the infections. Both viruses commence with analogous first symptoms, including fever and myalgia (Yamaoka et al., 2024).

9.1.2 Differences - Although both diseases exhibit hemorrhagic fever, their severity and specific signs may differ. Variations exist in the specific proteins expressed by each virus and in the manner these proteins interact with host cells. This leads to variations in the specific processes of disease. Variations in mortality rates are evident during outbreaks (Nyakarahuka et al., 2016).

9.2 Potential for more severe neurological involvement - Observations suggests that MVD may exhibit more severe neurological symptoms under specific conditions than EVD. This may manifest as bewilderment, agitation, and aggression. This may stem from the virus's ability to penetrate the blood-brain barrier in specific patients. Additional inquiry is necessary to thoroughly understand the extent and mechanisms of neurological involvement in MVD (Yu et al., 2022).

9.2.1 Key pathogenic mechanisms - Similar to EBOV, MARV infiltrates host cells, multiplies, and initiates a series of inflammatory reactions. The virus assaults immunological cells, resulting in dysfunction and compromised antiviral responses. Vascular injury and coagulation disorders lead to hemorrhagic symptoms. The elevated viral load and the damage inflicted on the immunological and circulatory systems are the primary factors leading to the high death rate. Research on filoviruses is continuing, and our comprehension of their pathophysiology is continually advancing (Mohamadzadeh et al., 2007).

10. Host immune response

10.1 Innate immune responses

10.1.1 Interferons (IFNs) - These are essential antiviral cytokines. During a conventional viral infection, infected cells secrete IFNs that activate antiviral mechanisms in adjacent cells, therefore restricting viral dissemination. Filoviruses have developed strategies to obstruct interferon synthesis and signaling, so impeding this essential first defense response (Mertowska et al., 2023).

10.1.2 Natural killer (NK) cells - NK cells constitute a component of the innate immune system and has the capability to eliminate virus-infected cells. Although NK cells are activated during filovirus infection, the virus's capacity to inhibit IFN signaling may constrain their efficacy (Mertowska et al., 2023).

10.2 Adaptive immune responses

10.2.1 Antibody production - B cells generate antibodies that neutralize the virus and facilitate viral clearance. Antibody responses are detected in survivors of EVD and MVD, and these antibodies may confer protection against future infections. Nonetheless, the first cytokine storm and the disturbance of the immune system may impede the synthesis of effective antibodies (Olejnik et al., 2017).

10.2.2 T cell responses - T cells, comprising CD4+ helper T cells and CD8+ cytotoxic T cells, are essential in regulating viral infections. CD8+ T cells immediately eliminate infected cells, whereas CD4+ T cells facilitate the coordination of the immune response. Filoviruses can trigger lymphocyte apoptosis, diminishing the quantity of functional T cells and thereby impairing the adaptive immune response (Olejnik et al., 2017).

11. Role of immune evasion mechanisms employed by the viruses - Filoviruses has developed intricate strategies to circumvent the host's immune system. Viral proteins, including VP24 and VP35, obstruct interferon signaling pathways, hindering the formation of an antiviral state. Viruses can obstruct the processing and presentation of viral antigens, impeding T cell activation. Filoviruses can trigger lymphocyte apoptosis, resulting in a reduction of immune cells available to combat the infection. The manipulation of the "cytokine storm" occurs as the virus induces a cytokine storm while simultaneously impairing the immune system's functionality, rendering the immune response ineffective in eliminating the infection. The viral glycoprotein may function as a decoy, so impeding the activation of immune cells (Olejnik et al., 2017).

12. Factors influencing disease severity and outcome - Several factors can influence the severity of EVD and MVD - Elevated viral loads are typically correlated with increased disease severity. Variations in immune response genes can affect susceptibility and illness outcomes. Younger persons and those possessing robust immune systems may experience more favorable outcomes. Prompt and comprehensive supportive care, encompassing fluid replenishment and complication management, can markedly enhance survival rates. Various strains of Ebola and Marburg may demonstrate varying degrees of pathogenicity (Cnops et al., 2016).

13. Clinical manifestations and diagnosis

13.1 Clinical features of EVD

The incubation time for EVD generally spans from 2 to 21 days, with a mean duration of 8 to 10 days. This diversity complicates early diagnosis. The initial symptoms of EVD typically manifest suddenly and include - MVD is a severe fever, weariness, and discomfort, with symptoms including cephalalgia, myalgia, and pharyngitis. As the condition progresses, patients may experience severe vomiting, diarrhea, abdominal discomfort, and maculopapular rash. Hemorrhagic symptoms may include petechiae, ecchymoses, and mucosal hemorrhage. In severe cases, EVD can lead to shock, multi-organ failure, and DIC. Survivors may experience an extended convalescence period with symptoms like exhaustion, myalgia, arthritis, ocular complications, and psychological disorders. Long-term consequences may manifest months' post-recovery. The Ebola virus can remain in certain fluids, such as semen, for extended periods, posing a transmission risk. MVD shares similarities and differences with EVD, but it has distinct clinical characteristics (Khalafallah et al., 2017) (Table 2).

13.2 Clinical features of MVD

13.2.1 Similarities and differences in clinical presentation compared to EVD

13.2.1.1 Similarities - MVD, similar to EVD, commences with an abrupt onset of elevated fever, intense headache, and myalgia. Both disorders advance to gastrointestinal manifestations, encompassing severe watery diarrhea, nausea, vomiting, and abdominal pain. Hemorrhagic symptoms, including gingival, nasal, and other orifice bleeding, may present in both conditions. Both illnesses may result in serious complications such as shock and multi-organ failure.

13.2.1.2 Differences - Although both disorders feature hemorrhagic fever, the severity may differ. Neurological symptoms may be more prominent in MVD than in EVD. This constitutes a significant distinction. Hiccups have been identified as a symptom associated with Marburg Virus Disease.

13.2.2 Higher proportion of neurological symptoms - A greater occurrence of neurological symptoms, such as confusion, irritability, and aggression, may be observed in MVD. Some cases have documented seizures and cerebral edema. Clinical management may be complicated by the increased neurological involvement that distinguishes MVD from EVD (Velásquez et al., 2015).

13.2.3 Key clinical aspects - From two days to twenty-one days is the typical incubation period for MVD, the same as for EVD. Diagnosis might be difficult in the early stages because the symptoms are not always specific. The sickness advances swiftly, and within a few days, you'll start to feel really sick. Although they are not always present, hemorrhagic signs have the potential to be extremely dangerous and even fatal (Sah et al., 2022). Early diagnosis and supportive care are critical for improving patient outcomes in MVD, a severe and frequently fatal illness (Table 2).

13.3 Diagnostic methods

13.3.1 Laboratory diagnosis

13.3.1.1 Reverse transcription-polymerase chain reaction (RT-PCR) - In order to detect viral RNA, this is considered the gold standard. RT-PCR enables precise and rapid diagnosis due to its extreme sensitivity and specificity. Even at the earliest stages of infection, it can identify the virus.

13.3.1.2 Enzyme-linked immunosorbent assay (ELISA) - ELISA has the ability to identify host-produced antibodies as well as viral antigens (proteins). When symptoms are first appearing, antigen-capture ELISA can be helpful. When the condition has progressed or if an infection has already occurred, ELISA can confirm the diagnosis.

13.3.1.3 Virus isolation and cell culture - Viruses are cultured in cell cultures for this purpose. It calls for dedicated lab space and takes a long time. Biosafety level 4 (BSL-4) laboratories are required to conduct this technique because of the significant risk of infection.

13.3.1.4 Electron microscopy - The virus particles can be seen by electron microscopy. Its complexity and the requirement for specialist equipment make it less often employed. Can verify the existence of filoviruses.

13.3.1.5 Rapid diagnostic tests - In order to get findings faster, rapid antigen detection techniques were developed. In the event of an epidemic, when immediate answers are critical, these tests are invaluable. Although helpful, their sensitivity could be inferior to that of RT-PCR.

13.3.1.6 Differential diagnosis - It is of the utmost importance to differentiate EVD/MVD from other hemorrhagic fever causes. Lassa fever, yellow fever, dengue hemorrhagic fever, malaria, typhoid fever, and other viral hemorrhagic fevers are among the other diseases that can cause comparable symptoms. A correct diagnosis requires extensive laboratory testing in addition to a comprehensive clinical evaluation. Important details to consider include the patient's travel history, particularly any contacts with potentially infected individuals and endemic areas (Kadanali and Karagoz, 2015).

Table 2: Key features of ebola and marburg viruses

S. No.	Feature	Ebolavirus	Marburgvirus
1	**Genus**	*Ebolavirus*	*Marburgvirus*
2	**Species**	*Zaire ebolavirus* (EBOV)*Sudan ebolavirus* (SUDV)*Bundibugyo ebolavirus* (BDBV)*Tai Forest ebolavirus* (TAFV)*Reston ebolavirus* (RESTV) *Bombali ebolavirus* (BOMV)	*Marburg marburgvirus*

3	**Strains/Subspecies**	N/A	Marburg virus (MARV)Ravn virus (RAVV)
4	**Reservoir Host(s)**	Fruit bats (likely)	Fruit bats (likely)
5	**Transmission Routes**	Zoonotic (contact with infected animals), human-to-human (direct contact with bodily fluids, contaminated materials)	Zoonotic, human-to-human (similar to Ebola)
6	**Incubation Period**	2-21 days	3-21 days
7	**Key Symptoms**	Fever, fatigue, myalgia, headache, sore throat, vomiting, diarrhea, rash, hemorrhage	Similar to Ebola, but neurological symptoms may be more prominent
8	**Case Fatality Rate**	25-90% (species-dependent and outbreak-specific)	24-88% (outbreak-specific)
9	**Diagnosis**	RT-PCR, ELISA, virus isolation	RT-PCR, ELISA, virus isolation
10	**Treatment**	Supportive care, monoclonal antibodies (for EBOV), experimental antivirals	Supportive care, experimental therapies
11	**Prevention**	Vaccination (for EBOV), infection control, community education	Infection control, community education

13. **Treatment and prevention**

13.1 Treatment of EVD - Supportive care is crucial in managing EVD, addressing symptoms and complications. Fluid and electrolyte management is essential for severe vomiting and diarrhea, as dehydration and electrolyte imbalances can occur. Blood transfusions may be necessary for severe bleeding, and patients with multi-organ failure may require intensive care, including mechanical ventilation and dialysis (Leligdowicz et al., 2016).

13.1.1 Management of secondary bacterial infections - specific therapies

13.1.1.1 Monoclonal antibody (m Abs) - The treatment of EVD is now advised based on the considerable efficacy of mAb114 (Ansuvimab) and REGN-EB3 (Inmazeb) in clinical trials. These monoclonal antibodies neutralize the Ebola virus and block cell infection by focusing on the virus's glycoprotein. When given early on in the disease's progression, they significantly improve survival rates (Moekotte et al., 2016).

13.1.1.2 Antiviral drugs - There has been limited investigation into the efficacy of Remdesivir as a therapy for EVD. Presently, it is not recommended as a main course of treatment (Pardo et al., 2020; Mirza et al., 2019).

13.1.1.3 Convalescent plasma therapy - Some outbreaks have made use of convalescent plasma, which contains antibodies from individuals who have recovered from EVD. Its effectiveness varies and is inferior to that of monoclonal antibody therapies, despite the fact that it has demonstrated some promise. One constraint is the plasma's availability (Garraud, 2017).

13.2 Treatment of MVD - Supportive care is crucial for managing MVD, including fluid and electrolyte replacement to combat dehydration, maintaining oxygenation and blood pressure to address shock and respiratory distress, managing bleeding complications through blood transfusions and clotting factor replacement, and treating secondary infections due to compromised immune systems (Alla et al., 2023).

13.2.1 Experimental therapies and potential use of EVD treatments - Currently, there are no approved antiviral therapies for MVD, but research is ongoing to identify potential treatments. Similar to EVD, there is interest in exploring EVD treatments for MVD. Monoclonal antibodies, preclinical data, convalescent plasma,

and antiviral medications are being investigated. However, research on treatments has been slower due to less frequent outbreaks. Experimental therapies would need clinical trials to determine safety and efficacy (Hayden et al., 2017).

13.3 Prevention and control measures

13.3.1 Infection prevention and control (IPC) in healthcare settings

Healthcare workers are at high risk of infection, so proper use of Personal Protective Equipment (PPE) is crucial. Proper donning and doffing procedures are also essential. Hand hygiene is vital, with frequent hand washing using soap and water or alcohol-based sanitizer. Safe injection practices, sterile equipment, and proper disinfection of surfaces and medical equipment are also essential (Shaver and Unit, 2022).

13.4 Outbreak control - The text emphasizes the importance of early detection and rapid response to contain outbreaks of EVD/MVD. It emphasizes the need for contact tracing and surveillance to identify and monitor individuals who have had contact with infected persons. Strict isolation of suspected or confirmed cases is crucial to prevent further transmission, and safe and dignified burial practices are essential. Community and family involvement in these practices is also crucial. The text emphasizes the need for active surveillance and proper equipment for isolation (Muvunyi et al., 2024).

13.5 Vaccination - Ebola vaccines, such as rVSV-ZEBOV and Ad26.ZEBOV/MVA-BN-Filo, have proven effective in preventing EVD. Ring vaccination, where contacts and contacts of contacts are vaccinated, is a successful strategy. Research is ongoing to develop effective Marburg vaccines due to the similarity of the viruses. Raising awareness about EVD/MVD transmission, symptoms, and prevention is crucial for building trust and cooperation with control measures. Addressing misinformation and rumors is also important. Investing in public health infrastructure, including laboratory capacity, surveillance systems, and healthcare worker training, is essential for long-term prevention and control (Shaver and Unit, 2022).

14. Research gaps and future directions

14.1 Key research areas - Understanding reservoir ecology and virus maintenance in bats is crucial for preventing future outbreaks. Research into the factors triggering spillover events from bats to humans is essential for preventing future outbreaks. Studying the viral load in bats and its changes over time is also important. Developing more effective and broadly protective vaccines against Ebola and Marburg virus strains is a priority. Research into broadly neutralizing antibodies and their potential for vaccine development is ongoing. Identifying novel therapeutic targets and antiviral drugs is essential, such as host cell factors involved in viral replication. High-throughput screening and drug repurposing efforts are needed to identify effective antiviral compounds. Advanced diagnostic tools for rapid and point-of-care testing are essential for early diagnosis and outbreak control. Research into new diagnostic technologies, such as microfluidic devices and biosensors, is ongoing. Tests that differentiate between EVD and MVD and other hemorrhagic fevers are crucial. Studies on long-term sequelae and post-EVD/MVD syndrome are also necessary for improving patient care. Mathematical modeling to predict outbreak dynamics and inform control strategies is essential, incorporating environmental factors and modeling the effects of interventions like vaccination campaigns or quarantine procedures (Wolfe et al., 2020; Monath, 1999).

14.2 Future directions - The One Health Approach emphasizes the interconnectedness of human, animal, and environmental health, focusing on collaboration across disciplines to understand and address factors contributing to filovirus emergence and transmission. This includes surveillance of filoviruses in animal reservoirs, monitoring environmental factors, and working with communities to reduce human-animal contact. Global collaboration and data sharing are crucial for rapid response and research, with robust data-sharing platforms fostering collaboration among researchers, public health agencies, and international organizations. Strengthening healthcare systems in endemic regions is essential, with investments in infrastructure, training, and improved access to diagnostic and treatment resources. Building local capacity for outbreak response is crucial for effective control. Proactive planning and preparedness are essential for mitigating future outbreaks, including developing contingency plans, stockpiling essential supplies, conducting simulation exercises, monitoring for novel filoviruses, and creating adaptable response protocols. Ethical considerations in research and outbreak response include obtaining informed consent, ensuring equitable access to treatment and care,

addressing social and cultural factors, maintaining transparency and accountability, and providing ethical guidelines for the use of experimental treatments (Wolfe et al., 2020; Monath, 1999).

15. Conclusion- Viruses belonging to the Filoviridae family, such as Ebola and Marburg, are extremely dangerous because they produce hemorrhagic fevers that can be fatal. We now know that these viruses cause cytokine storms, vascular dysfunction, and multi-organ failure as a result of intricate interactions with the host immune system. Patient outcomes have been enhanced by advancements in diagnostics and therapies, including the introduction of monoclonal antibodies for EVD. There is still a lot to learn about these viruses, though, due to their complexity and the challenges associated with studying them. The fact that these viruses can spread from person to person and that bats are thought to be repositories for them emphasizes how important it is for animals and humans to interact for diseases to originate. When it comes to public health, hemorrhagic fevers are a major concern, especially in areas where medical resources are scarce. These viruses are cause for grave concern due to their high fatality rates and the possibility of fast transmission. The development of better diagnostic tools, vaccines, and antiviral treatments, as well as a deeper knowledge of filovirus biology, all depend on ongoing study. Information sharing, coordinated response to outbreaks and capacity building in endemic locations can only be achieved through global collaboration. In order to detect, contain, and manage epidemics early, it is crucial to strengthen public health systems. This includes monitoring, laboratory capacity, and healthcare worker training. To avoid similar spillovers in the future, we need a "One Health" strategy that considers the well-being of all living things. It is imperative that all research and response endeavors prioritize ethical considerations. We must be fully prepared for future epidemics and for the possible introduction of new filoviruses.

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17. Keywords-

Bundibugyo ebolavirus (BDBV)

Case fatality rates (CFRs)

Ebola virus (EBOV)

Ebola Virus Disease (EVD)

Glycoprotein (GP)

Infection Prevention and Control (IPC)

Interferon (IFN)

Interferons (IFNs)

Interleukin-1β (IL-1β)

Interleukin-6 (IL-6)

International Committee on Taxonomy of Viruses (ICTV)

Marburg virus (MARV)

Marburg Virus Disease (MVD)

Matrix protein (VP40)

Multiple organ dysfunction syndrome (MODS)

Natural Killer (NK)

Nucleoprotein (NP)

Ravn virus (RAVV)

Reston ebolavirus (RESTV)

Sudan ebolavirus (SUDV)

Tai Forest ebolavirus (TAFV)

T-cell immunoglobulin and mucin domain-containing protein 1 (TIM-1)

Tumor necrosis factor-alpha (TNF-α)

Zaire ebolavirus (EBOV)