



# Bioterrorism potential of haemorrhagic fever viruses – occupational and environmental Implications of filoviruses and arenaviruses

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## Abstract

**Introduction and Objective.** Viral haemorrhagic fevers (VHFs), caused by filoviruses (e.g., Ebola virus, Marburg virus) and arenaviruses (e.g., Lassa virus, Machupo virus), represent a significant bioterrorism threat due to their zoonotic origins, high mortality rates, and severe clinical presentations. This review examines the potential use of VHFs as biological weapons, their zoonotic transmission dynamics, and implications for rural and agricultural health.

**Review Methods.** A comprehensive review was conducted using electronic databases, including PubMed and Scopus, focusing on studies addressing VHFs in the context of bioterrorism and zoonotic disease transmission. Studies published between 2016 – 2024 were included, with search terms such as 'viral haemorrhagic fevers', 'bioterrorism potential', and 'zoonotic transmission'.

**Brief description of the state of knowledge.** VHFs are zoonotic diseases transmitted to humans from animal reservoirs, primarily rodents and bats. Their pathogenicity, coupled with potential for engineered transmission, underscores their bioterrorism risk. Rural and agricultural communities face heightened exposure due to their proximity to these natural reservoirs.

**Summary.** While these viruses are rare and unstable in natural settings, the prospect of their genetic manipulation or combination in order to create novel pathogens introduces new avenues for their potential use in bioterrorism. It is imperative to comprehensively understand their pathogenesis and to establish rigorous control and prevention measures to mitigate their impact on public health and safety. The ongoing vigilance and preparedness efforts are essential to counteract the potential threat posed by these agents in bioterrorism scenarios.

## Key words

bioterrorism, Lassa virus, Ebola virus, viral hemorrhagic fevers, Marburg virus, Machupo virus, CBRN threat

## INTRODUCTION

A current security challenge is the escalating threat of terrorist activities, compounded by the advancement of scientific technologies, which heightens the risk of deploying biological agents for malicious purposes. This phenomenon, known as bioterrorism, involves deliberately using hazardous pathogens – such as viruses, bacteria, fungi, and biological toxins – against humans, animals, and plants. As a result of such an attack, the environment, food, and drinking water become contaminated. The attack can be targeted at a specific group, directed at an individual, or executed on a mass scale [1].

Terrorist attacks, whether perpetrated by extremist groups or individuals, are primarily motivated by political, social, or ideological factors. For a potential terrorist, a key objective is to instill fear among the public, which, when confronted with the threat of an attack, diminishes confidence in the government's ability to ensure security and defend against potential threats. Consequently, this erosion of trust results in a loss of support for the authorities and alters the behaviour of

both society and State officials. Furthermore, State authorities, under pressure from both the populace and terrorists, may be compelled to acquiesce to certain demands. Moreover, the use of biological weapons can lead to mass casualties, resulting in significant chaos within medical services, which may be ill-prepared for a sudden influx of sick and infected individuals during a potential epidemic. Importantly, a bioterrorist attack incurs substantial unexpected costs associated with the treatment of infected individuals, potentially leading to economic deterioration and a decline in residents' earnings. Additionally, such an attack may even result in poverty within segments of the population [2].

The classification system developed by the Centres for Disease Control and Prevention (CDC) is most commonly used to categorize potential biological agents. This system allows for the division of naturally occurring and genetically engineered toxins and microorganisms into three categories based on their potential danger:

Category A – encompasses pathogens known for their extremely high mortality rates, exceptional virulence, and ease of transmission, capable of inducing widespread panic. Examples in this category are *Bacillus anthracis*, haemorrhagic fever viruses, and the smallpox virus.

Category B – includes pathogens characterized by moderate lethality and virulence, and moderate ease of spread, such

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**Table 1.** Characteristics of selected viruses causing haemorrhagic fevers

Family	Virus	Transmission	Incubation period	Mortality	CDC classification	Reservoir/vector of infection	References
Arenaviridae	Lassa	Contact with an infected person or animal, aerosol	2 – 21 days	15% – 20%	A	rodent <i>Mastomys natalensis</i>	[5]
	Machupo	Contact with an infected person or animal, aerosol	3 – 16 days	25%	A	rodent <i>Callomys callosus</i>	[6]
	Guanarito	Contact with rodent excreta	7 – 14 days	20% – 30%	A	rodent <i>Zygodontomys brevicauda</i>	[7]
	Junin	Contact with rodent excreta, inhalation	6 – 14 days	~20%	A	rodent <i>Calomys musculus</i>	[7]
	Sabia	Contact with rodent excreta	7 – 16 days	Unknown (few cases reported)	A	rodents	[7]
Filoviridae	Ebola	Contact with an infected person or animal	2 – 21 days	50% – 90%	A	bat Pteropodidae family	[8]
	Marburg	Contact with an infected person or animal	2 – 21 days	23% – 90%	A	bat <i>Rousettus aegyptiacus</i>	[9]
Flaviviridae	Yellow fever	Mosquito bite	3 – 6 days	20%	C	mosquitoes <i>Aedes</i> , <i>Haemagogus</i>	[10]
	Dengue	Mosquito bite	5 – 7 days	0% – 5%	C	mosquitoes <i>Aedes</i> spp.	[11]
Bunyaviridae	Rift Valley Fever	Mosquito bite, contact with an infected person or animal, aerosol	2 – 6 days	2% – 6%	C	mosquitoes <i>Aedes</i> , <i>Culex</i> , livestock	[12]
	Crimean Congo fever	Tick bite, contact with an infected person or animal, aerosol	3 – 12 days	5% – 75%	A	<i>Hyalomma</i> ticks, livestock	[13]

as *Vibrio cholerae*, *Escherichia coli*, and *Salmonella* spp. Category C – consists of pathogens that are relatively easy to obtain and produce, spread easily, and can be used effectively on large crowds. They possess high pathogenicity and mortality potential. Examples within this category include multidrug-resistant tuberculosis, tick-borne encephalitis virus, and various genetically-engineered pathogens [2].

Biological agents used as weapons share several common characteristics. Firstly, effective pathogens in these scenarios typically exhibit high mortality rates, which can induce panic and lead to increased fatalities. Moreover, they are readily obtainable and producible, often at relatively low cost. Their low molecular weight facilitates easy dissemination and transportation, yet also complicates detection without specialized techniques. Additionally, a significant feature is their prolonged asymptomatic period and the absence of effective treatments, which delay response times of relevant services and prolong the threat’s duration [3].

Due to the challenging geopolitical landscape globally, it is imperative to enhance the understanding of infectious agents that are not endemic to specific regions. In the light of this, the objective of this study was to elucidate the current knowledge regarding infections caused by haemorrhagic fevers (VHFs) viruses, including the latest advancements in their treatment. Particular emphasis is placed on the potential utilization of VHFs in bioterrorism.

The deliberate use of infectious agents, including viral pathogens, in bioterrorism represents a significant global threat. VHFs caused by filoviruses (e.g., Ebola and Marburg viruses) and arenaviruses (e.g., Lassa and Machupo viruses) are of particular concern due to their high mortality rates, severe symptoms, and zoonotic transmission. The ability of these pathogens to cause widespread fear and societal disruption makes them attractive candidates for malicious use. Rural and agricultural communities are at heightened risk due to their proximity to natural reservoirs of VHFs, such as rodents and bats. Understanding the bioterrorism potential of VHFs, along with their zoonotic origins, is essential for developing effective prevention and response strategies in these vulnerable populations [2].

REVIEW METHODS

The review employed a systematic approach to identify studies relevant to VHFs as bioterrorism agents and zoonotic threats. Literature was retrieved from electronic databases such as PubMed, Scopus, and Web of Science using search terms as ‘viral haemorrhagic fevers’, ‘bioterrorism potential’, ‘zoonotic transmission’, and ‘agricultural health risks’. Inclusion criteria focused on publications discussing bioterrorism, zoonotic reservoirs and public health implications. Exclusion criteria included studies with limited relevance to rural or agricultural settings. A major limitation is the lack of empirical data on VHF stability, weaponization, and outbreak variability.

**Characteristics of viral haemorrhagic fevers.** Haemorrhagic fevers comprise a group of severe systemic diseases induced by RNA viruses from the *Filoviridae*, *Arenaviridae*, *Flaviviridae*, and *Bunyaviridae* families. Despite the classification of these viruses into different families, the clinical presentation of the diseases they cause are similar. Common features of VHFs include a sudden onset and a severe course characterized by fever, pain, and vascular system damage, which manifests as haemorrhagic diathesis and hypotension. VHF viruses are transmitted by vectors such as mosquitoes, ticks, rodents, and bats, as well as through droplets or contact with excretions and secretions from infected individuals (e.g., blood, faeces, urine, sweat, or vomit). The incubation period for viral haemorrhagic fevers ranges from three to 21 days. The prognosis for a patient infected with viral haemorrhagic fever largely depends on the location and intensity of the haemorrhagic diathesis, the occurrence of systemic and organ complications, and any comorbidities [4] (Tab. 1).

**Filoviruses.** The Filoviridae family comprises three distinct genera: Ebolavirus, Marburgvirus, and Cuevavirus. The Ebolavirus genus includes six distinct species, each exhibiting varying levels of virulence and pathogenicity. Among these, Zaire ebolavirus is notable for having the highest mortality

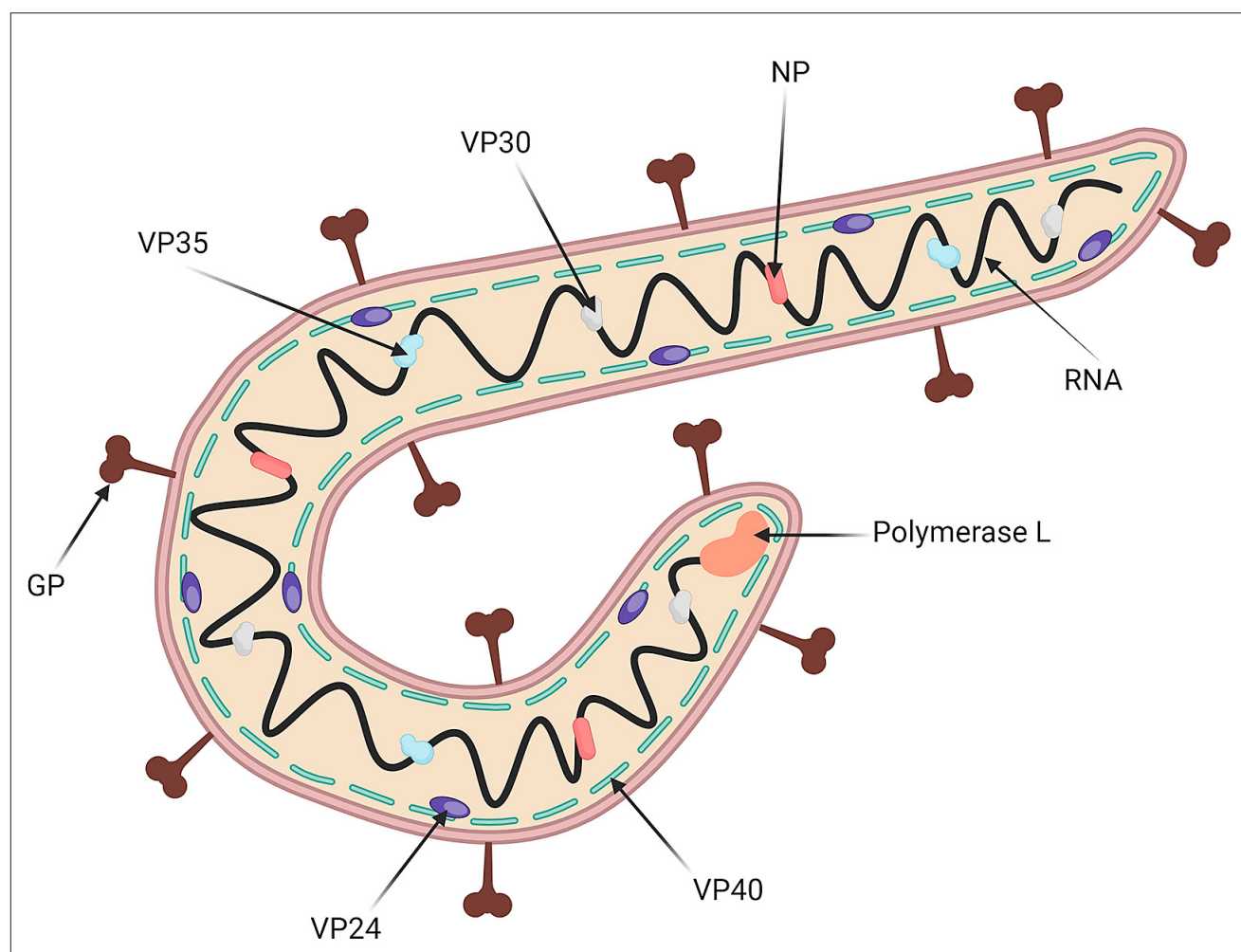
rate – approximately 80%. The Marburgvirus genus consists of a single species, which includes both the Marburg virus and the Ravn virus [14, 15].

Filovirus particles exhibit elongated, thread-like forms that can assume various shapes such as ‘U’, ‘6’, or toroidal (Fig. 1). The diameter of these virions is approximately 80 nm, with the average length of an Ebola virus particle being about 1,000 nm, and that of the Marburg virus about 800 nm. The filovirus genome consists of a single-stranded, negatively polarized RNA, ranging from 15 – 19 kilobases in length, encoding seven genes: nucleoprotein (NP), glycoprotein (GP), virion proteins (VP40, VP35, VP30, VP24), and RNA-dependent RNA polymerase (L). VP35 acts as a co-factor essential for the proper function of polymerase L, while VP40 serves as a matrix protein. The proteins NP, VP30, VP35, and VP24, along with the genomic RNA, form the ribonucleoprotein (RNP), which constitutes a helical nucleocapsid (NC) that protects the viral RNA from degradation by endonucleases and the host immune response [14].

In the initial step of filovirus replication, known as adsorption, the viral glycoprotein GP1 binds to host cell receptors (Fig. 2). Following this, the virus enters the host cell via macropinocytosis, where it is enclosed within an endosome. Within the endosome, cathepsins B and L cleave the viral GP, facilitating its interaction with Niemann-Pick C1 (NPC1) receptors, which are crucial for cholesterol transport

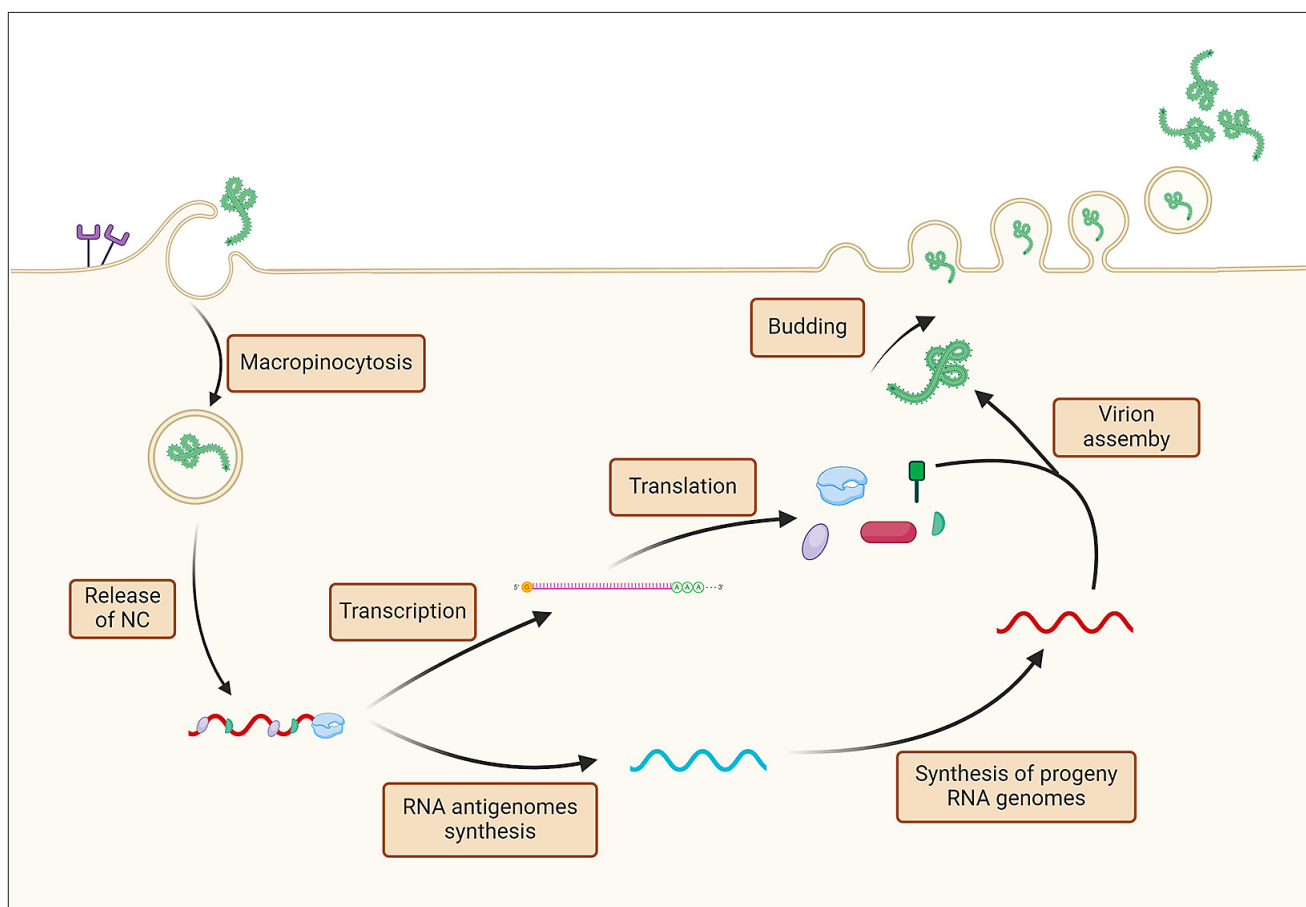
within the cell. This interaction prompts the fusion of the virion envelope with the endosome membrane, resulting in the release of the nucleocapsid into the host cell cytoplasm. The nucleocapsid serves as a template for both replication and transcription. During transcription, viral genes are transcribed into mRNA, which is then utilized to synthesize viral proteins. During replication, RNA antigenomes – intermediate products with positive polarity – are generated and surrounded by nucleocapsid proteins. These antigenomes are subsequently used to synthesize progeny RNA genomes. The newly-formed nucleocapsids are transported to the cell membrane and released through the budding process [15].

**Ebola Virus.** The current understanding recognizes six viruses within the Ebolavirus genus: Bombali ebolavirus, Bundibugyo ebolavirus, Reston ebolavirus, Sudan ebolavirus, Tai Forest ebolavirus, and Zaire ebolavirus (EBOV). Among these species, Zaire ebolavirus is specifically associated with the disease known as Ebola [16, 17]. Ebola virus (EBOV) was first identified in 1976 in the Democratic Republic of the Congo. Since then, more than 20 outbreaks of Ebola have been documented in Sudan, Uganda, and Gabon, as well as the Democratic Republic of Congo [18]. The largest epidemic to date occurred from 2013 – 2016 in West Africa, predominantly affecting Guinea, Sierra Leone, and Liberia. This epidemic spanned both urban and rural areas and



**Figure 1.** Schematic structure of filoviruses. GP – glycoprotein; NP – nucleoprotein; VP40, VP35, VP30, VP24 – virion proteins.

Source created in BioRender. Bijak. M. (2024) <https://BioRender.com/m10f700>



**Figure 2.** Life Cycle of Filoviruses. The cycle begins with viral attachment and entry into the host cell, mediated by glycoproteins and endocytosis. Following fusion in the endosome, the viral RNA is released into the cytoplasm, where it undergoes transcription and replication. New viral proteins and RNA assemble at the plasma membrane, leading to the budding and release of mature virions. The virus then spreads to infect new cells, while employing mechanisms to evade the host immune response.

Source: created in BioRender. Bijak, M. (2024) <https://BioRender.com/f44h879>

resulted in a mortality rate of 62.9%, with over 28,000 confirmed cases, of which more than 11,000 were fatal [8, 19] (Fig. 3).

The incubation period of the Ebola virus ranges from two to 21 days. Initially, the disease presents with flu-like symptoms, including fever with chills, joint and muscle pain, and chest discomfort. Additional early symptoms may include nausea, abdominal pain, loss of appetite, vomiting, and diarrhea. Cough and low blood pressure can also occur [8]. Around five to seven days after onset, a papular rash develops, which progresses to haemorrhagic lesions. Subcutaneous and submucosal haemorrhages, as well as bleeding from the urogenital and gastrointestinal tracts, may also manifest. In severe cases, increased bleeding leads to hypovolaemic shock due to significant fluid loss and subsequent organ failure. Seizures or coma may occur during this acute phase [20]. In severe cases of Ebola virus infection, death typically results from multi-organ failure within seven to 16 days from the initial onset of symptoms [8, 20].

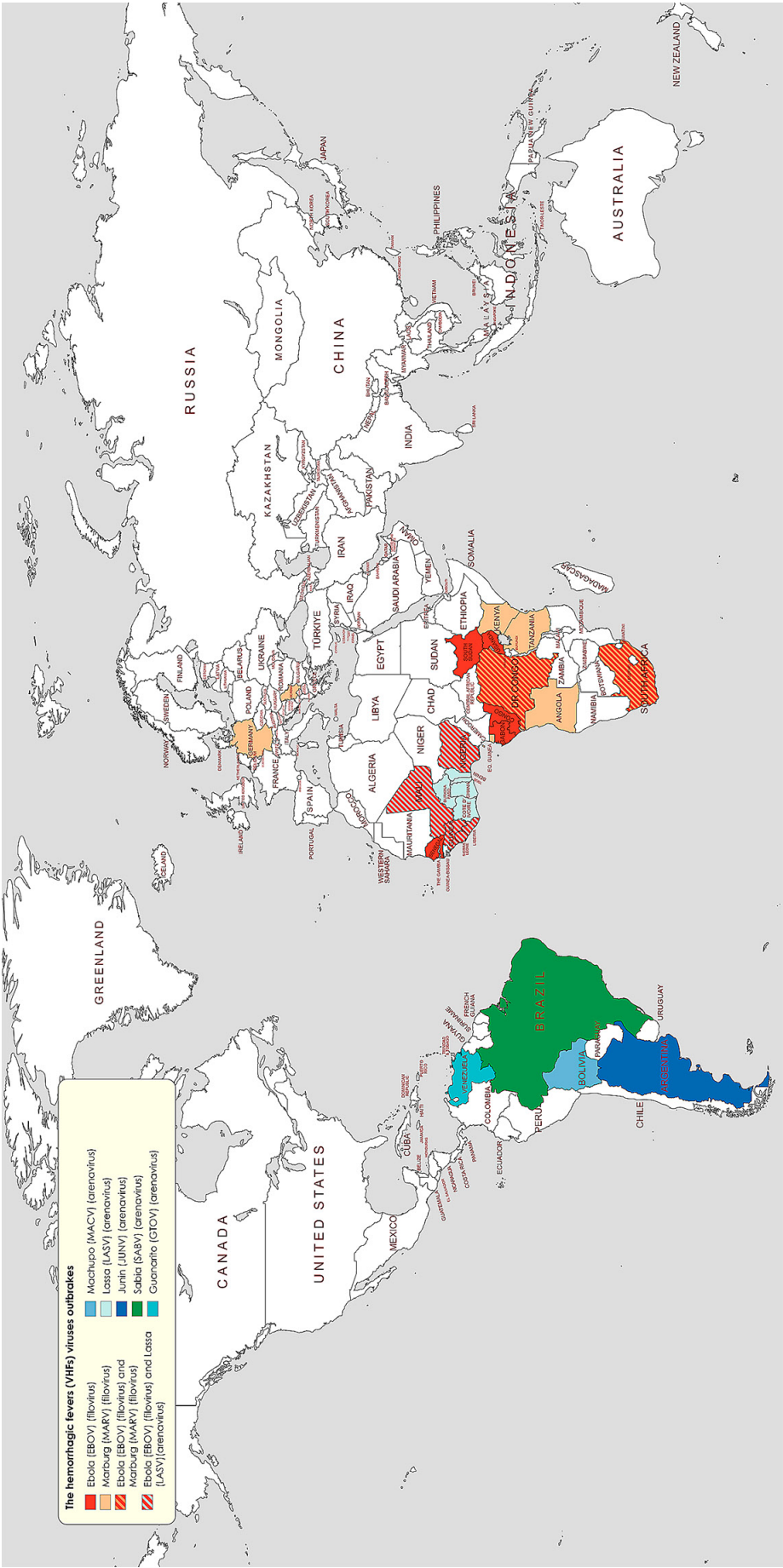
Ebola virus (EBOV) is classified as a zoonotic disease that sporadically infects humans, as well as monkeys and other animals. Bats from the *Pteropodidae* family are currently considered potential natural carriers of EBOV, although this association has not been definitively confirmed. The primary mode of transmission to humans occurs through direct or indirect contact with sick or deceased infected animals [21, 22]. Human-to-human transmission can also occur through contact with blood or other body fluids

of infected individuals. Those who handle the bodies of deceased persons, particularly in healthcare settings, are at high risk, often leading to nosocomial transmission before the threat is identified and proper precautions instituted [23].

Patient care includes symptomatic treatment aimed at maintaining or restoring proper hydration, alleviating discomfort and anxiety, and addressing any concurrent or undiagnosed infections [24]. Currently, experimental therapies involve administering patients with a combination of ZMapp antibodies alongside REGN-EB3, a single MAb114 antibody, or the small-molecule antiviral drug remdesivir [25]. These treatments were employed during the recent Ebola outbreak in the Democratic Republic of the Congo. Results from these therapies demonstrated that the use of MAb114 or REGN-EB3 significantly enhances survival rates, compared to treatment with ZMapp or remdesivir. Additionally, earlier initiation of medical interventions was found to improve patient outcomes, while individuals previously vaccinated against Ebola virus (EBOV) showed more favourable responses to treatment [26].

The development of EBOV vaccines began in the late 20th century. Among the numerous prototypes, only vaccines based on EBOV DNA and adenoviruses underwent initial testing prior to the West Africa epidemic outbreak. The most promising vaccines to emerge from this research are Ervebo (Merck) and Zabdeno (Johnson & Johnson), both approved by the European Medicines Agency and the US Food and Drug Administration [27]. Ervebo employs a





**Figure 3.** Geographical distribution of viral haemorrhagic fever (VHF) outbreaks. The map illustrates historical outbreak locations of Ebola, Marburg, Lassa, Machupo, Guanarito, Junin, and Sabia viruses. Different colours represent regions affected by specific viruses, while overlapping patterns indicate areas with co-occurrence of multiple pathogens.

Source: created with mapchart.net

live viral vector containing the gene encoding the surface glycoprotein of Zaire ebolavirus, while Zabdeno utilizes an adenoviral vector that carries the entire GP gene derived from the Mayinga strain of Zaire ebolavirus. During the epidemic in the Democratic Republic of the Congo, Ervebo was administered and demonstrated 97.5% effectiveness when vaccination occurred more than 10 days before disease onset, and 88.1% effectiveness overall across all EBOV cases, regardless of the timing of vaccination [28].

Epidemiological protocols mandate that upon reporting a suspected Ebola virus (EBOV) infection, the patient is promptly isolated. Simultaneously, contact tracing involves monitoring individuals who have been in close contact with the patient for a period of 21 days. Locations visited by the infected individual are thoroughly disinfected, and burial practices are modified to minimize the risk of transmission [29]. Public education plays a crucial role, aiming to promote early reporting of suspected infections and discourage contact with potentially infected individuals, as well as advocating for safe burial practices [24].

**Marburg virus.** Marburg virus (MARV) is one of two viruses belonging to the genus Marburgvirus. It was first isolated during an epidemic in 1967, which occurred simultaneously in Germany and Serbia. Since then, several outbreaks have been documented, predominantly in East Africa, with occasional cases reported in South Africa [9]. One of the notable outbreaks occurred between 1975 – 2000 in the Democratic Republic of the Congo, where 149 cases were recorded, resulting in 123 deaths. However, the largest Marburg epidemic took place in Angola from 2004 – 2005, with 252 reported cases of infection, of which 227 were fatal (Fig. 3) [30].

The incubation period of the Marburg virus ranges from three to 21 days, with the disease progressing through three distinct stages. The initial phase manifests with influenza-like symptoms, including fever, chills, fatigue, and muscle pain, often accompanied by anorexia, vomiting, and diarrhea. This phase typically lasts up to five days. The second stage, termed the early organ stage, extends up to 13 days. Neurological symptoms emerge, such as aggression, disorientation, irritability, and delirium. Vascular permeability abnormalities may lead to conjunctival injection and periorbital oedema. Additional symptoms include haemorrhages, such as haematomas or petechiae, along with such gastrointestinal manifestations as bloody diarrhea and mucosal bleeding [31]. In the final stage, known as the late organ stage, organ failure, particularly affecting the kidneys, pancreas, and liver, ensues. Patients may experience convulsions, coagulopathy, and severe metabolic disturbances, significantly exacerbating their condition. Death typically occurs between the eighth and 16th day of illness [32].

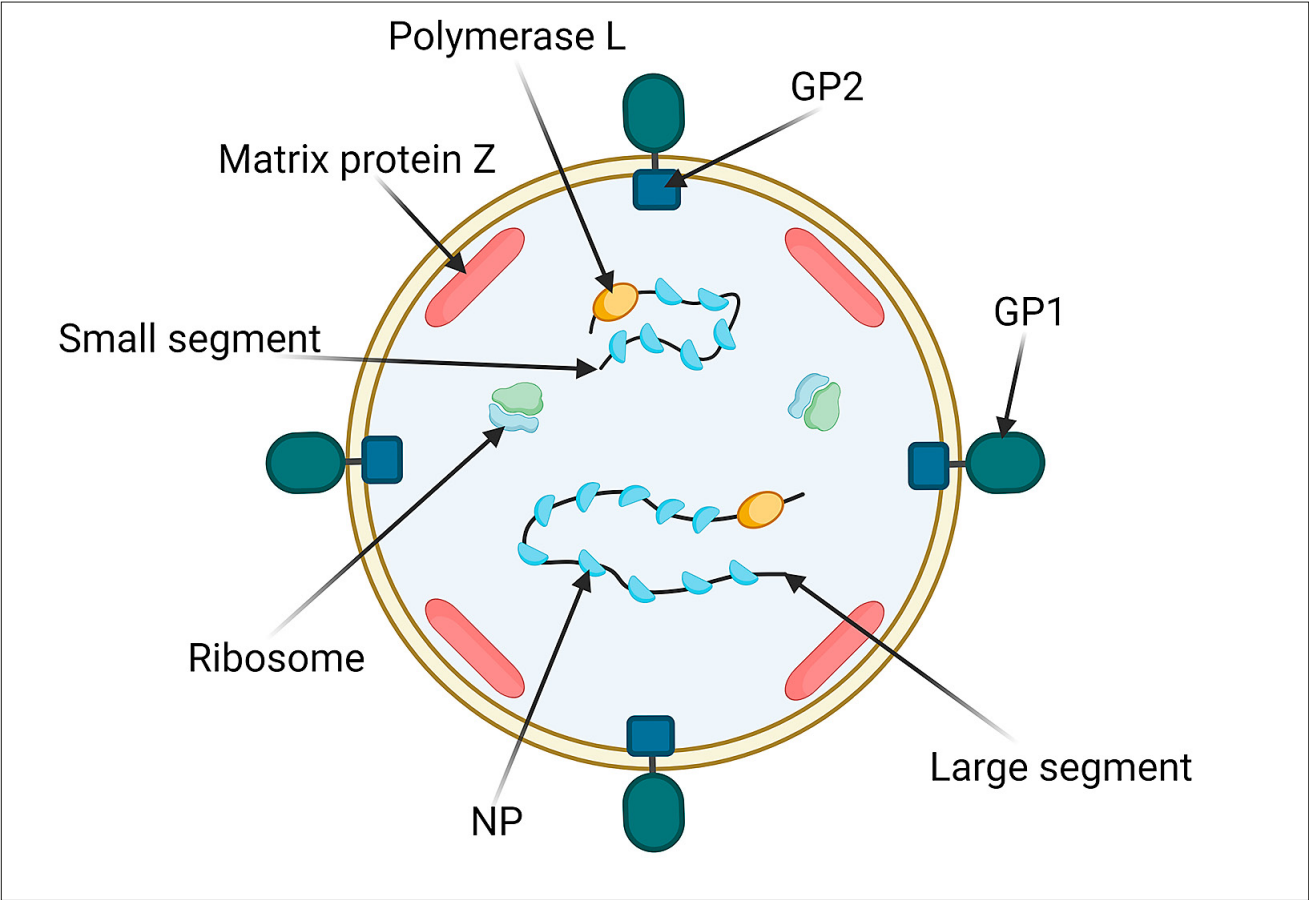
The bat *Rousettus aegyptiacus*, belonging to the *Pteropodidae* family, serves as the primary reservoir for MARV, similar to EBOV [23]. The specific mechanisms of virus transmission to humans and other primates are not completely understood. However, significant attention is focused on potential exposure to biological fluids and consumption of meat from infected animals, as well as the ingestion of contaminated fruit. Transmission among humans can occur through direct contact with bodily fluids. Additionally, there are documented instances of vertical transmission [9].

Currently, no approved specific treatment or vaccine exists for MARV. While experimental immunomodulatory therapies have shown promise in animal models, additional research is necessary to assess their efficacy and safety in humans. Therefore, patients can only receive supportive care, which includes maintaining electrolyte balance and providing symptomatic treatment. Antibiotic therapy may also be necessary due to frequent bacterial superinfections [33]. Preventing transmission of Marburg virus involves breaking the chain of infection by promptly isolating infected individuals and providing appropriate medical care. Implementing stringent safety protocols and educating healthcare personnel can effectively prevent nosocomial infections. Public education plays a crucial role in promoting preventive measures and safe behaviours during potential contact with infected individuals or during burial practices [33].

**Arenaviruses.** The Arenaviridae family comprises two genera of viruses: Mammarenavirus, originating from mammals, and Reptarenavirus, originating from reptiles. Most known arenaviruses are transmitted by rodents, although they vary in their geographical distribution and epidemiological characteristics. The International Committee on Taxonomy of Viruses (ICTV) currently recognizes 33 species of mammarenaviruses, a number expected to rise as new strains are identified. Mammarenaviruses are further categorized into two groups: New World viruses, found in the Americas, and Old World viruses, prevalent in regions of Sub-Saharan Africa and Southeast Asia [34].

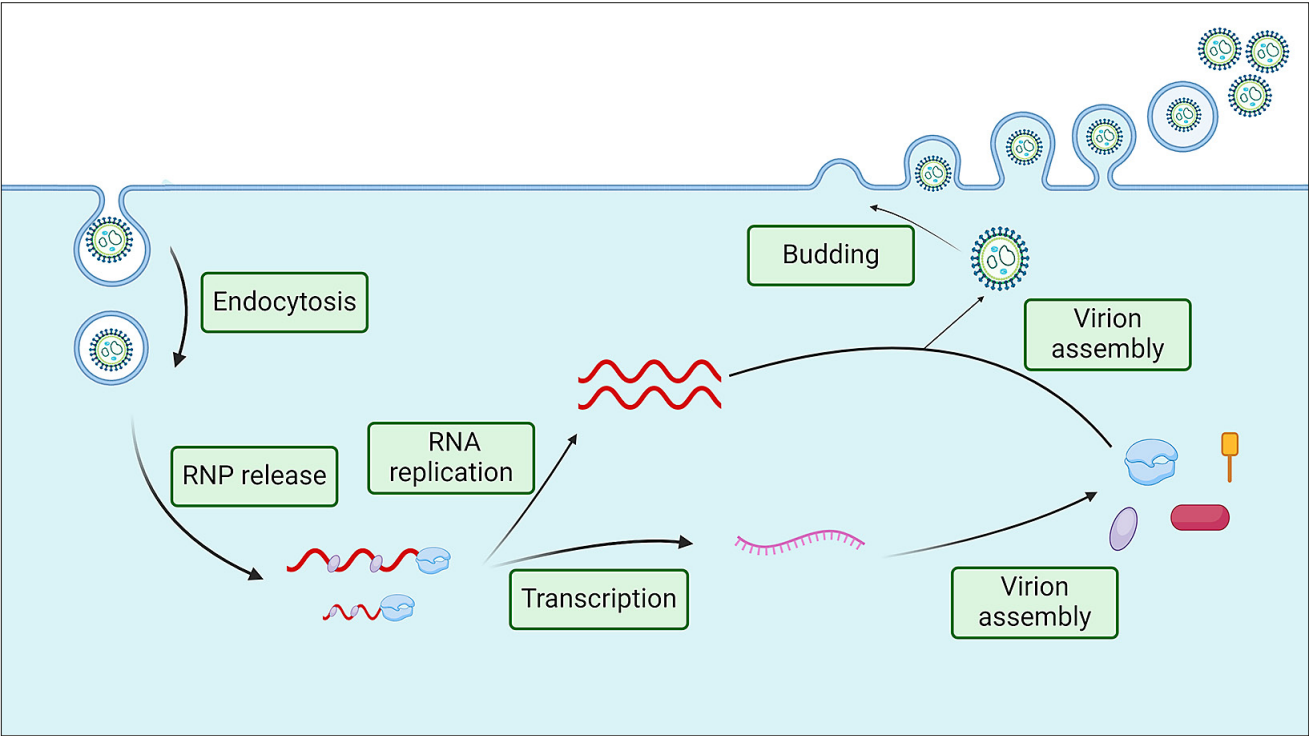
Arenaviruses produce spherical or pleomorphic lipid-enveloped virions, ranging in size from 50 nm – 300 nm. These viruses possess a single-stranded, two-segment negative-sense RNA genome (Fig. 4). The large segment (L) of the arenavirus genome is approximately 7.3 kbp in length and encodes the genes for the viral RNA-dependent RNA polymerase (L) and the matrix protein (Z). The small segment (S) is around 3.5 kbp long and encodes the nucleoprotein (NP) and the envelope glycoprotein precursor (GPC) genes. GPC is proteolytically cleaved into three subunits – GP1, GP2, and SSP, which assemble into homotrimers. The single-stranded RNA, together with the associated NP and RNA polymerase, forms the viral ribonucleoprotein (RNP). Additionally, host ribosomes, present in the virion envelope, impart a granular appearance to the virus under an electron microscope, although their functional significance remains unknown [35].

The primary target cells for mammarenaviruses are those within the phagocytic system, particularly dendritic cells and macrophages. The arenavirus life cycle commences with the viral entry into the host cell (Fig. 5). Specifically, the GP1 subunit of the viral envelope glycoprotein attaches to membrane receptors on the host cell, triggering endocytosis. In New World arenaviruses, this binding occurs at the transferrin receptor (TfR1), whereas the Old World arenaviruses utilize the  $\alpha$ -dystroglycan ( $\alpha$ DG) receptor. Subsequent to endocytosis, the acidic environment within the endosome induces a conformational change in the GP2 subunit of the envelope glycoprotein, facilitating the fusion of the viral envelope with the endosomal membrane. This fusion event releases the ribonucleoprotein complex (RNP) into the cytoplasm, where the viral polymerase L initiates the transcription of viral genomic RNA into messenger RNA (mRNA). The host cell ribosomes then translate this



**Figure 4.** Life Cycle of Arenaviruses. The cycle begins with viral attachment to host cell receptors, followed by entry through endocytosis. Inside the endosome, viral fusion releases the ribonucleoprotein complex into the cytoplasm, where viral RNA is transcribed and translated. Genome replication occurs, leading to the assembly of new virions at the host cell membrane. The virions bud off and are released to infect new cells. Arenaviruses also employ immune evasion strategies, including suppression of interferon responses.

Source: created in BioRender. Bijak, M. (2024) <https://BioRender.com/y54b126>



**Figure 5.** Schematic structure of arenaviruses. GP1 – glycoprotein 1; GP2 – glycoprotein 2; NP – nucleoprotein.

Source: created in BioRender. Bijak, M. (2024) <https://BioRender.com/c23n607>



mRNA into viral polypeptides. Concurrently, polymerase L replicates the viral genome [36].

**Lassa virus (LASV).** A member of the genus *Mammarenavirus* and classified under the Old World viruses, first identified in Nigeria in 1969. Predominantly affecting West Africa, it is estimated that there are between 300,000 – 500,000 infections annually in this region. Specifically, in Nigeria, 246 confirmed cases of LASV infection were reported in 2017. By the end of 2020, this number had escalated to 1,181 confirmed cases, of which 224 resulted in fatalities [5] (Fig. 3).

The incubation period for LASV ranges from seven to 21 days. Approximately 80% of infected individuals experience a mild or asymptomatic form of the disease, while the remaining 20% develop acute symptoms. Early manifestations include fever, general weakness, and malaise. Within two to four days, patients may experience myalgia, arthralgia, lumbago, and abdominal pain, in addition to retrosternal pain, headaches, and dizziness. These symptoms are frequently accompanied by hypotension, diarrhea, vomiting, and cough [37]. As the disease advances, patients may develop pharyngitis or conjunctivitis, mucosal haemorrhaging, pleural or pericardial effusions, and facial or neck edema. In severe cases, the disease can progress to acute respiratory failure, shock, or varying degrees of encephalopathy approximately seven days post-onset. Terminal stages may present with disorientation, rapidly progressing to seizures, tremors, coma, and abnormal posturing. Furthermore, about 30% of survivors experience unilateral or bilateral hearing loss [38].

The primary reservoir of LASV is the rodent *Mastomys natalensis*, a member of the Muridae family. Transmission from rodents to humans occurs through direct contact with contaminated rodent feces or saliva, exposure of mucous membranes or compromised skin to the virus, or consumption of infected rodent meat. Human-to-human transmission can occur through direct contact with blood, urine, or other bodily secretions and excretions from individuals with an acute Lassa virus infection. Additionally, nosocomial infections can arise from the use of contaminated medical equipment [39].

Research into potential drugs or vaccines against Lassa virus is currently conducted primarily in animal models and has not yet been approved for human use. Tested substances such as ribavirin, a guanosine analogue, favipiravir, an RNA-dependent RNA polymerase (RdRp) inhibitor, and monoclonal antibody therapies have shown effectiveness in animal studies [40, 41]. However, further clinical trials are required to evaluate their safety and efficacy in humans. Currently, patients with Lassa virus infection receive mainly supportive care, which includes fluid administration, electrolyte monitoring, and, if necessary, supplemental oxygen therapy and dialysis [5].

Preventing Lassa virus transmission involves measures such as controlling rodent populations and minimizing contact with them. Public education on safe rodent handling practices and the use of appropriate personal protective equipment is crucial. In healthcare settings, strict adherence to infection control protocols is essential to prevent nosocomial transmission of the virus. Establishing and rigorously implementing these procedures can effectively curb further spread of Lassa virus [42].

**Machupo Virus (MACV).** An etiological agent of Bolivian haemorrhagic fever belonging to the genus *Mammarenavirus*, classified as a New World virus. The virus was first identified in Bolivia in 1959, with its formal description published in 1964. During the initial epidemic from 1959 – 1962, 470 cases of infection were documented. The subsequent epidemic, spanning 1962 – 1964, saw over 1,000 reported cases, including 180 fatalities. In 2008, more than 200 probable infections were reported, marking the highest incidence since 2000 [43].

The incubation period of MACV ranges from three to 21 days. The disease manifests in three distinct phases: prodromal, haemorrhagic, and convalescent [6]. During the prodromal phase, patients typically experience non-specific symptoms, such as fever, malaise, headaches, joint and muscle pain, dehydration, and anorexia. After approximately three days, more severe symptoms emerge, including nausea, vomiting, diarrhea, abdominal pain, skin hypersensitivity, and initial signs of circulatory system impairment, such as petechiae, bleeding gums, and conjunctival hyperaemia. Around 30% of patients progress to the haemorrhagic phase, characterized by subconjunctival haemorrhages, gingival and nasal bleeding, and widespread petechiae. Additionally, manifestations may include haematemesis, haematuria, pulmonary oedema, and neurological symptoms, such as tremors, convulsions, muscle spasms, and coma. Fatal outcomes typically occur seven to 12 days after the onset of symptom, predominantly due to severe internal bleeding, pulmonary oedema, or hypovolemic shock [6].

The reservoir host for MACV is the rodent *Callomys callosus*. Transmission to humans typically occurs through direct contact of compromised skin or mucous membranes with infected rodent faeces, or through consumption of food contaminated with such material. Current scientific understanding suggests that human-to-human transmission of MACV is unlikely [44].

Similar to most haemorrhagic fevers, there is currently no approved specific treatment for Bolivian haemorrhagic fever. Experimental therapies involving ribavirin or monoclonal antibodies are under investigation and require further study to establish their efficacy [45]. In certain cases, a vaccine targeting the related Junin virus, specifically Candid 1, may be considered due to cross-reactivity [46]. Historically, during the epidemic in the 1960s, convalescent plasma from immunized individuals was administered to infected patients. However, this practice is not currently utilized due to limited availability of recovered donors and the absence of a structured plasma collection and storage programme. Preventing Marburg virus (MARV) transmission involves isolating infected patients using stringent procedures to prevent further spread. Additionally, efforts are focused on controlling rodent populations and advising against consuming raw food and untreated water that may be contaminated with animal faeces [6].

*Machupo virus* is not the only New World arenavirus that could serve as a potential bioterrorism agent. This group also includes Guanarito, Junin, and Sabia viruses, all classified as Risk Group 4 pathogens by the World Health Organization (WHO). Notably, these viruses have been the subject of comparatively limited scientific research.

*Guanarito virus (GTOV)* is the etiological agent of Venezuelan haemorrhagic fever, an endemic disease in western Venezuela. The primary reservoir of GTOV is the



short-tailed cane mouse (*Zygodontomys brevicauda*), with an endemic region spanning approximately 9,000 km<sup>2</sup>. Between 1989 – 2006, 618 cases of infection were documented in Portuguesa state, with a case fatality rate of 23.1%. Although epidemiological data were scarce after 2006, 36 cases were confirmed in 2021 in the states of Barinas and Portuguesa. The primary at-risk population comprised agricultural workers, particularly males, with zoonotic transmission occurring primarily through direct or indirect contact with infected rodents. There is also evidence suggesting the possibility of human-to-human transmission [7].

*Junin virus (JUNV)* is the causative agent of Argentine haemorrhagic fever (AHF), first isolated in the 1950s among agricultural workers in the Pampa region. The principal reservoir of JUNV is the rodent *Calomys musculus*, which facilitates both horizontal and vertical transmission. The endemic region extends over approximately 150,000 km<sup>2</sup>, placing an estimated five million individuals at risk. The incidence of AHF has declined substantially since the 1980s due to the widespread administration of the Candid 1 vaccine, which has demonstrated 95.5% efficacy. However, the discontinuation of vaccination programmes raises concerns regarding the potential resurgence of the disease. An alternative therapeutic approach under consideration is the administration of monoclonal antibodies [7].

*Sabia virus (SABV)*, the etiological agent of Brazilian haemorrhagic fever, was first identified in 1990 in São Paulo. To date, only a limited number of cases have been confirmed, primarily among agricultural and laboratory workers, with some fatalities reported. Transmission of SABV is known to occur via aerosol, posing an occupational hazard. In 2019, SABV was detected postmortem in two individuals presenting with clinical symptoms resembling yellow fever. The natural reservoir of the virus remains unidentified, although rodents are suspected [7].

**The potential of utilizing haemorrhagic fever viruses as biological warfare agents.** Haemorrhagic fever viruses are associated with significant pathogenicity, high mortality rates, and severe haemorrhagic symptoms, posing serious risks within the agricultural, forestry, and food industries, as well as other rural settings. These viruses are a particular concern in the context of zoonoses and immunotoxic diseases, making them a pressing issue for occupational health in high-risk environments [47].

The molecular and cellular biology of HFVs contributes to their potential as bioterror agents. These viruses exhibit robust replication strategies, enabling rapid host cell entry, immune evasion, and extensive systemic effects. Filoviruses and arenaviruses primarily target endothelial cells, dendritic cells, and macrophages, leading to dysregulated immune responses, increased vascular permeability, and widespread haemorrhaging. These viruses manipulate host immune signalling pathways, such as the suppression of interferon responses, allowing them to evade early immune detection and enhancing their pathogenicity and spread [48].

Additionally, HFVs exhibit prolonged incubation periods (ranging from several days to three weeks), providing an added tactical advantage as infected individuals may unknowingly transmit the virus, amplifying the scale of outbreaks. Recent studies have suggested that viral stability under engineered conditions could be enhanced, facilitating airborne or surface-based transmission. This characteristic could be

exploited in controlled environments for bioterrorism purposes, further increasing the risks associated with these pathogens [49].

Despite their high pathogenic potential, HFVs face limitations in weaponization due to their environmental sensitivity and typical transmission routes. The primary modes of transmission generally limit large-scale dispersal without sophisticated bio-weapon delivery methods. HFVs degrade rapidly under environmental conditions, such as UV light exposure, temperature fluctuations, and varying humidity, making aerosolization and prolonged stability outside a host challenging [4].

However, advancements in viral engineering and aerosol technology are raising concerns about the potential stability and dispersal of HFVs in controlled settings. Aerosolized HFVs with particle sizes between 0.5 – 10 µm can penetrate alveolar spaces in the lungs, potentially enhancing infectivity when delivered under precise conditions [49]. Additionally, the application of nanotechnology and microencapsulation may theoretically stabilize these viruses against environmental degradation, although practical applications remain largely speculative. The complexities of viral weaponization are compounded by significant bio-security risks, including self-infection and containment failures, posing high risks to handlers.

Considerable progress has been made in the early detection and rapid response to HFV outbreaks, which is essential for countering bio-terrorism threats. Technologies such as real-time reverse transcription PCR (RT-PCR), immunological assays (e.g., ELISA), and next-generation sequencing enable high-sensitivity detection of HFVs, even at low viral loads [50]. Portable diagnostic devices and bio-sensors facilitate rapid, point-of-care testing, which is crucial in outbreak scenarios. Advanced imaging techniques, such as electron microscopy paired with immunohistochemical approaches, further assist in diagnosing HFVs and assessing viral morphology under controlled laboratory conditions [4].

Epidemiological modelling, supported by artificial intelligence (AI), is becoming indispensable for simulating potential HFV outbreak scenarios and evaluating transmission dynamics in the context of bioterrorism. Real-time data integration allows for efficient resource allocation and containment strategies. Surveillance networks, such as the World Health Organization's (WHO) Global Outbreak Alert and Response Network (GOARN), play a pivotal role in early outbreak identification and international communication, facilitating prompt responses to limit secondary transmission [51].

**Occupational consequences of VHF.** VHF pose significant occupational and environmental risks due to their high transmissibility and severe clinical outcomes. These pathogens present a substantial threat to various professionals, including healthcare workers, laboratory personnel, veterinarians, first responders, and field researchers. Effective risk mitigation strategies are critical for protecting individuals in high-risk occupations and preventing further transmission. Healthcare professionals are among the most vulnerable to VHF outbreaks due to their direct patient interactions. Exposure to infectious bodily fluids, coupled with inadequate personal protective equipment (PPE), significantly increases the risk of transmission. Previous outbreaks, such as those caused by the Ebola virus, have demonstrated high infection

rates among medical personnel, resulting in workforce depletion, psychological distress, and increased mortality. Furthermore, the fear of contracting the disease may discourage professionals from providing care, exacerbating healthcare system challenges. European guidelines, such as those from the European Centre for Disease Prevention and Control (ECDC), recommend standardized PPE protocols, routine training, and enhanced hospital preparedness measures to mitigate these risks [52]. Individuals working in research and diagnostic laboratories handling VHF are at high risk of accidental exposure through aerosols, needle-stick injuries, and breaches in biosafety protocols. Bio-safety Level-4 (BSL-4) containment is required for safe handling, but lapses can lead to outbreaks within laboratory settings. Strict adherence to bio-safety measures, regular training, and stringent decontamination protocols are crucial for mitigating occupational hazards in research and diagnostic settings. The WHO and ECDC have established strict guidelines for handling haemorrhagic fever viruses, including routine inspections of high-containment facilities and emergency decontamination protocols [53–55].

Many VHF, including filoviruses and arenaviruses, are zoonotic, originating from animal reservoirs before spilling-over into human populations. Veterinarians, wildlife researchers, and animal handlers working in endemic regions face significant exposure risks when interacting with infected rodents (Arenaviruses) or bats and primates (Filoviruses) [53]. Fieldwork in high-risk environments necessitates enhanced protective measures, surveillance programmes, and rapid response capabilities to prevent zoonotic transmission. In Europe, initiatives such as the One Health approach promote close collaboration between veterinary and human health sectors to monitor zoonotic diseases.

Emergency responders, including paramedics and burial teams, face substantial risks when handling infectious cases. Direct contact with contaminated cadavers, bodily fluids, and surfaces can result in secondary infections. Protocols for safe handling, disinfection, and dignified yet safe burials are critical to reducing occupational risks for this group. The implementation of specialized training programmes for first responders, such as those promoted by the European Commission, is crucial for improving outbreak preparedness [54, 56].

VHF are maintained in specific ecological niches, with natural reservoirs including bats, rodents, and non-human primates. Human activities, such as deforestation, agricultural expansion and urbanization, have intensified human-wildlife interactions, facilitating viral spillover events. A thorough understanding of environmental dynamics and pro-active habitat conservation efforts are essential for reducing the risk of future outbreaks.

Medical waste generated from VHF treatment, including contaminated PPE, needles, and biological fluids, poses a significant environmental hazard. Inadequate disposal methods can contribute to secondary infections among sanitation workers and surrounding communities. The implementation of rigorous biohazard waste management protocols, including incineration and autoclaving, is crucial in preventing environmental contamination and pathogen persistence. European guidelines emphasize the importance of controlled incineration and regulatory compliance to mitigate these risks. The European Union's Horizon 2020 programme supports research into climate-driven changes

in infectious disease epidemiology, including haemorrhagic fever viruses [13].

Climate change has the potential to alter the epidemiology of VHF by influencing vector and reservoir distributions. Rising temperatures, shifts in precipitation patterns, and habitat fragmentation may affect viral transmission cycles, leading to expanded endemic areas. Pro-active environmental surveillance, combined with predictive modelling, can aid in early outbreak detection and prevention [56].

To address the occupational and environmental risks associated with VHF, a multifaceted approach is necessary. Healthcare and laboratory workers must receive extensive training and have consistent access to adequate PPE to minimize infection risks. Research facilities handling VHF should adhere to the highest bio-safety standards to prevent accidental exposure and potential outbreaks. Monitoring wildlife reservoirs and human populations in endemic regions can facilitate early detection and containment of potential spillover events. The proper disposal and decontamination of medical waste should be mandated to reduce environmental contamination [51]. Increasing awareness among at-risk populations can improve early detection efforts and reduce occupational exposure risks. Filoviruses and arenaviruses pose severe occupational and environmental hazards, necessitating comprehensive preventive strategies. By addressing occupational safety concerns, reinforcing environmental management practices, and implementing proactive surveillance measures, the risks associated with these lethal pathogens can be significantly mitigated. A coordinated global response is crucial to safeguarding both human health and ecological stability, ensuring preparedness for future outbreaks.

**Mitigating the threat of VHF in Europe.** VHF, while historically endemic to Africa and parts of South America, are increasingly posing a threat to Europe due to globalization, climate change, and intensified human-animal interactions. The agricultural, forestry, rural, and food industry sectors are particularly susceptible, necessitating comprehensive prevention, surveillance, and response strategies. A key pillar in combating VHF is the establishment of robust surveillance systems. The integration of the One Health framework, which encompasses human, animal, and environmental health, is imperative for early detection and intervention [57]. In Europe, real-time wildlife and livestock monitoring can facilitate the early identification of viral spillover events. Advanced diagnostic technologies, including PCR assays and next-generation sequencing, should be deployed to detect potential outbreaks before they escalate. Additionally, enhancing Europe-wide data-sharing platforms and fostering collaboration between veterinary and human health agencies will enable a coordinated and timely response [58].

The agricultural and food-processing sectors must implement stringent bio-security measures to prevent viral transmission. Farms should adopt rigorous sanitation protocols, including equipment disinfection, restricted personnel access, and controlled interactions between domesticated and wild animals. In forestry and rural regions, minimizing human contact with wildlife reservoirs, such as bats and rodents known to harbour VHF, is crucial. Training programmes should educate farmers and forestry workers about protective measures, such as the appropriate use of PPE and safe handling practices for potentially infected animals [54].

Educational initiatives are vital in empowering rural communities and industry workers with knowledge about VHF. Awareness campaigns should target high-risk populations, promoting best practices in hygiene, food handling, and early symptom recognition. Online platforms and local workshops can serve as effective means of disseminating information. Furthermore, training emergency response teams in rural and agricultural regions ensures rapid containment of potential outbreaks [55].

Given the zoonotic nature of VHFs, food production and processing facilities must implement stringent safety protocols. Proper food storage, handling, and cooking methods are essential in reducing the risk of viral transmission through contaminated animal products. Reinforcing supply chain security through traceability systems will facilitate the identification of contamination risks. Regulatory agencies must collaborate with industry stakeholders to enforce compliance with these safety measures [59].

Investments in vaccine research and antiviral therapeutics are critical for bolstering Europe's defences against VHFs. While vaccines exist for certain haemorrhagic fever viruses, further research is required to develop broad-spectrum prophylactic and therapeutic solutions. Governments should support clinical trials and ensure the availability of emergency medical stockpiles, including diagnostic kits, PPE, and antiviral medications. Additionally, the establishment of well-equipped treatment centres in rural areas will enhance Europe's capacity for rapid medical response [54].

Given the trans-boundary nature of VHF threats, international cooperation and coordinated policies are essential. ECDC should work alongside global health organizations to develop standardized outbreak management protocols. Cross-border contingency plans must be established to ensure swift and coordinated action in the event of VHF emergence [60]. Furthermore, European legislative frameworks should align with WHO recommendations to create a unified response strategy. The growing risk of VHFs in European agriculture, forestry, rural communities, and the food industry, necessitates a pro-active, multidisciplinary approach. Strengthening surveillance, bio-security, public awareness, food safety, medical preparedness, and policy coordination are fundamental to mitigating these threats. By integrating contemporary scientific recommendations and fostering global collaboration, Europe can enhance its resilience against potential outbreaks, safeguarding both public health and economic stability [54, 55].

## CONCLUSIONS

The threat of bio-terrorism has increased with advancements in bio-engineering and synthetic biology, enabling the creation of modified pathogens with enhanced pathogenicity and stability. Haemorrhagic fever viruses (HFVs), particularly from the Filoviridae and Arenaviridae families, pose significant risks due to their high mortality, severe clinical symptoms, and prolonged incubation periods. Although HFVs are currently rare and environmentally unstable, their potential for genetic manipulation raises concerns. Advances in aerosolization and microencapsulation could enhance their stability and facilitate controlled dispersal. To address this threat, strong international bio-security frameworks,

pathogen surveillance, and investment in diagnostic and containment technologies are essential. Continued research into HFV pathogenesis, immune evasion, and antiviral strategies, along with cross-disciplinary collaboration, is critical for preparing for and mitigating bioterrorism risks.

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