ERURJ **2024**, *3*, 2, 1090-1110
Review article

The Problematic Diseases of Viral Hemorrhagic Fever: Insights into Ebola, Marburg, and Dengue Fever Viruses

Tharwat R. Elkhamissy[1,] *, Mohammed R. Abdo[1]

[1] Microbiology and Immunology Department, faculty of pharmacy, Egyptian-Russian University, Badr City, Egypt

* Corresponding author: Tharwat R. Elkhamissy, Email: prof.tharwat.elkhamissy@gmail.com

Received 5th October 2023, revised 8th November 2023, Accepted 19th December 2023
DOI: 10.21608/ERURJ.2024.240845.1079

ABSTRACT

Viral Hemorrhagic Fever Diseases are critical health problems worldwide. Several outbreaks of hemorrhagic fever diseases have emerged in the last few years in different countries, particularly in tropical and subtropical regions of Africa, raising concerns in our country, Egypt. The Ministry of Health and Population in Egypt has issued orders and guidelines for the prevention and treatment of Marburg virus infections, as well as for dealing with confirmed and suspected cases of dengue fever. Egypt is on high alert to prevent the entry of Marburg virus infections into the country and to manage and control dengue virus infections. The environmental conditions and non-primate reservoirs of these viruses in areas, including Egypt, can transmit infections to humans, leading to Hemorrhagic fever diseases. The ease of travel and transportation between countries, coupled with a low level of prevention and infection control measures, makes the spread of these infections possible in various locations. In this article, we present selected causative agents of hemorrhagic fever diseases, such as the Ebola virus, Marburg virus, and Dengue fever viruses. We also discuss the properties of these viruses, mode of transmission, clinical and laboratory diagnosis, treatment, infection control, and prevention of these diseases.

Keywords: Ebola virus; Marburg virus; Dengue fever.

1. Introduction

Viral Hemorrhagic Fever (VHFs) can be caused by several different types of viruses. They typically manifest with early symptoms such as fever, headache, weakness, abdominal pain, and other systemic manifestations, including vital organ failure, such as kidney dysfunction, and cannot be clinically diagnosed as a specific disease in the early stages (1). Severe infections can lead to hemorrhaging in different parts of the body and have a high fatality rate if left untreated (2). Various viruses can enter the body through different modes of transmission, either by direct contact with the body or body secretions of the patient or deceased individuals or indirectly. Transmission can also occur through various vectors, such as mosquitoes and fruit bats.

This article will provide a general overview of viral hemorrhagic fevers, focusing on the properties of the viruses, possible modes of transmission, clinical and laboratory diagnostic methods for these diseases, and approaches to prevention and treatment.

1.1. Ebola Hemorrhagic fever

The Ebola virus (EV) belongs to the Filoviridae family, and its name derives from the Latin term 'filum,' which means a thread-like appearance (3). This filamentous virus possesses a distinct helical shape, with its viral genetic material enclosed within a cylindrical capsid featuring a helical structure. The Ebola virus consists of single-stranded, non-segmented RNA with seven genes oriented in the negative sense. In terms of physical dimensions, the Ebola virus measures approximately 80 nm in width and can extend up to a length of 14,000 nm (4).

The virus is classified as a Category A infectious substance according to the regulations set by the Department of Transportation (DOT) (5). There are six identified subtypes of the Ebola virus that cause diseases in both humans and non-human primates, including Ebola (Zaire, Sudan, Tai Forest, Bundibugyo, Bombali, and Reston) (6). Fruit bats are believed to be the natural hosts of the Ebola virus.

The virus's name originates from two simultaneous outbreaks in a village near the Ebola River in Uganda in 1976, where it was initially identified (7). Ebola virus disease (EVD) incidence occurs sporadically in tropical regions of Sub-Saharan Africa. Fatality rates have varied from 25% to 90%, depending on various factors and the response efforts (8). From 1976

to 2013, the World Health Organization (WHO) reported a total of 24 outbreaks comprising 1,716 cases. The most significant outbreak was the West African epidemic, which occurred from December 2013 to January 2016, resulting in 28,638 cases and 11,315 fatalities (9).

The most recent outbreak was reported in January 2023 in Mubende District, western Uganda. This marked the sixth Ebola virus outbreak in Uganda, with five of the six being caused by the Sudan Ebola virus type (10).

- **Transmission:**

Scientists propose that individuals are primarily infected with the Ebola virus through contact with an infected animal, such as a fruit bat or non-human primate. Subsequently, the virus can spread from person to person, potentially affecting a significant population. Transmission occurs through direct contact, specifically through injured skin or mucous membranes in the eyes, mouth, or nose. Furthermore, individuals who are severely ill can transmit the virus via direct contact (11).

The transmission of the Ebola virus can occur through contact with various bodily fluids, including blood, urine, saliva, sweat, vomit, feces, breast milk, tears, and semen. This includes both individuals who are currently ill with Ebola virus disease and those who have passed away from it. Sexual transmission is also possible through oral, vaginal, or anal intercourse (12). It should be noted that the virus can persist in specific bodily fluids, such as semen, even in individuals who have recovered from Ebola virus disease and are no longer experiencing severe symptoms. After recovery, the Ebola virus can remain in the semen for more than three months, potentially leading to infections through sexual intercourse (12). There is no evidence that Ebola can be transmitted by contact with vaginal fluids from an infected woman. It has also been found in the breast milk of women who have recovered from Ebola, although it is unknown when it is safe to breastfeed again after recovery.

There is a hypothesis suggesting that Ebola can be transmitted through large respiratory droplets. However, it is believed that this particular mode of transmission primarily occurs when an individual is in an extremely weakened condition. It can also be transmitted by sharp objects, for example, needles and syringes contaminated with body fluids from infected people to healthy ones.

To date, the spread of the virus by air has not been reported in either natural conditions or laboratories. It also cannot be transmitted through food. Nevertheless, it can be spread through the consumption or processing of bush meat in Africa. There is currently a lack of substantiated evidence indicating that mosquitoes or other insects can transmit the Ebola virus (13).

In conclusion, understanding the modes of transmission and implementing appropriate preventive measures is crucial in controlling the spread of the virus. It is worth noting that individuals infected with Ebola can only transmit the virus once they develop symptoms of the disease (14).

- **Signs and symptoms**

The incubation period of the Ebola virus can vary from 2 to 21 days (15). The onset of symptoms is sudden and characterized by fever, headache, joint and muscle pain, sore throat, and weakness. Subsequently, vomiting, diarrhea, and rash typically occur, accompanied by impaired liver and kidney function. In some cases, bleeding may occur internally or externally, usually starting around 5 to 7 days after the initial symptoms (16). All infected individuals exhibit reduced blood clotting, with reports of bleeding from mucous membranes or needle puncture sites in 40-50 percent of cases (17). This can result in symptoms such as vomiting blood, coughing up blood, or blood in the stool. Bleeding into the whites of the eyes may also occur, although severe bleeding is rare and primarily localized within the gastrointestinal tract. The disease carries a high fatality rate, with 25 to 90 percent of infected individuals succumbing to the illness (18). Death is often attributed to hypotension caused by fluid loss and occurs between 6 to 16 days after symptom onset. Successful recovery from Ebola virus disease depends on effective clinical care and the patient's immune response. Research has shown that survivors of Ebola virus infection possess detectable antibodies in their blood for up to 10 years following recovery. Conversely, patients who do not survive usually do not develop a significant immune response to the virus before death (18).

- **Complications**

Ebola virus infection gives rise to severe complications, such as hemorrhagic fever and multi-system organ failure, which ultimately results in shock and fatality (19). Supportive care is the primary approach for managing the disease. To prevent the spread of infection within healthcare

facilities and subsequent outbreaks, it is crucial to promptly implement isolation precautions for viral hemorrhagic fever. Additionally, proper handling methods must be employed for deceased individuals infected with Ebola, as the virus remains transmissible even after death due to its resilience to moderate temperature variations.

- **Diagnosis**

The early diagnosis of Ebola virus disease (EVD) poses challenges due to its nonspecific symptoms, which include fever, headache, weakness, muscle pain, vomiting, diarrhea, abdominal pain, and unexplained bleeding. These symptoms are commonly observed in patients with other diseases such as malaria and typhoid fever. To determine the possibility of an EVD diagnosis, a combination of suggestive symptoms and potential exposure to the virus within 21 days before symptom onset must be taken into account. Exposure can occur through contact with infected individuals or their bodily fluids, contaminated objects, infected animals, or semen from a recovered patient (20).

Laboratory tests can help confirm the diagnosis of EVD. Non-specific indicators include low platelet count, initial decrease followed by an increase in white blood cell count, elevated liver enzymes, and abnormalities in blood clotting. Filovirions, including the Ebola virus, can be identified by their unique filamentous shape when examined using an electron microscope in cell culture. However, this method cannot distinguish between different filoviruses.

Accurate diagnosis of EVD involves various techniques, including viral isolation, detection of viral RNA or proteins, and identification of antibodies against the virus in the patient's blood. Isolating the virus through cell culture, detecting viral RNA using polymerase chain reaction (PCR), and identifying viral proteins via enzyme-linked immunosorbent assay (ELISA) are effective methods, particularly in the early stages of the disease and for testing human remains. Antibody detection is most reliable in later stages and among individuals who have recovered. IgM antibodies can be detected as early as two days after symptom onset, while IgG antibodies can be detected between 6 to 18 days after symptom onset. During outbreaks, it may not be feasible to isolate the virus using cell culture. In these situations, real-time PCR and ELISA are commonly used in field or mobile hospitals due to their sensitivity and speed. In recent years, mobile testing facilities have been developed, providing test results within 3-5 hours of sample

submission. Additionally, a rapid antigen test was approved in 2015, capable of confirming Ebola in 92% of affected individuals and ruling it out in 85% of non-affected individuals (21).

- **Differential diagnosis**

Early symptoms of EVD may resemble those of other common diseases in Africa, including malaria and dengue fever. They are also similar to symptoms of other viral hemorrhagic fevers, such as Marburg virus disease (22). The comprehensive differential diagnosis encompasses a wide range of infectious diseases, including typhoid fever, shigellosis, rickettsial diseases, cholera, sepsis, borreliosis, entero-hemorrhagic E. coli enteritis, leptospirosis, scrub typhus, plague, Q fever, candidiasis, histoplasmosis, trypanosomiasis, and viral hepatitis, among others (23).

- **Prevention and infection control**

To ensure safety and control the transmission of Ebola Virus Disease (EVD), it is crucial to avoid any contact with blood, bodily fluids, or objects that may have come into contact with infected or deceased individuals. This includes exercising caution around medical equipment, clothing, needles, and bedding that could potentially be contaminated. Additionally, it is important to avoid contact with bats, non-human primates, and raw meat derived from these animals.

In order to effectively prevent the spread of infection, practicing proper hand hygiene is paramount. Those responsible for caring for individuals infected with the Ebola virus must wear protective gear, such as masks, gloves, gowns, and goggles. It is essential to isolate the infected person from others and ensure that all equipment, medical waste, patient waste, and surfaces that may come into contact with bodily fluids are thoroughly disinfected.

To eliminate the Ebola virus, heat can be employed by subjecting it to temperatures of 60°C for 30 to 60 minutes or by boiling it for 5 minutes. Surfaces can be disinfected using lipid solvents like alcohol-based products, detergents, sodium hypochlorite (bleach), calcium hypochlorite (bleaching powder), or other suitable disinfectants at appropriate concentrations (24).

When residing in or traveling to an area affected by an Ebola outbreak, it is vital to adopt preventive measures. After returning from such an area, individuals should closely monitor their health for 21 days and promptly seek medical attention if any symptoms of Ebola disease appear.

- **Vaccine:**

An Ebola vaccine is administered through a single-dose injection into a muscle, and it is a live virus vaccine. This vaccine contains a modified strain of the vesicular stomatitis virus engineered to incorporate a gene from the Ebola virus. Currently, there are two approved Ebola vaccines available: a single-dose Ad5-EBOV vaccine in China and a two-dose rVSV/Ad5 vaccine licensed for emergency use in the Russian Federation (25). The FDA approved the rVSV-ZEBOV vaccine, known as ErveboR, on December 19, 2019. This vaccine, administered as a single dose, has been proven to be safe and effective against the Zaire Ebola virus species, which is responsible for the largest and most fatal Ebola outbreaks. On February 26, 2020, the Advisory Committee on Immunization Practices (ACIP) recommended prophylaxis vaccination with rVSV-ZEBOV for adults (26).

- **Treatment**

Regarding treatment, supportive care forms an essential part of handling patients infected with the Ebola virus and exhibiting symptoms. In the treatment of EVD, it is important to administer fluids and electrolytes, maintain oxygen levels and blood pressure, as well as compensate for the lost blood and clotting factors, in addition, control fever with antipyretics. Treatment strategies involve the use of convalescent plasma, monoclonal antibodies, and antiviral drugs such as remdesivir and favipiravir.

Recently, the World Health Organization published treatment guidelines in August 2022 for laboratory-confirmed cases of the Ebola virus. WHO strong recommendations, as of April 20, 2023, advocate for the use of two monoclonal antibody treatments: mAb 114 (An suvimab; Ebanga) and REGN-EB3 (Inmazeb), for all patients (27).

1.2. Marburg Hemorrhagic Fever

Marburg viruses belong to the Filoviridae family, which comprises three genera, including the Ebola virus and the Marburg virus, both known for their high pathogenicity in humans. Marburg

virus is particularly considered extremely dangerous. Marburg hemorrhagic fever (Marburg HF) is a rare but severe illness characterized by hemorrhagic symptoms in humans and non-human primates. The causative agent of Marburg HF is the Marburg virus, a member of the Filoviridae family and the filovirus genus. The first identification of the Marburg virus occurred in 1967 during simultaneous outbreaks of hemorrhagic fever located in Marburg and Frankfurt, Germany, as well as in Serbia. Primarily, laboratory workers were affected, and after that medical personnel and family members who had provided care (28). A total of 31 individuals fell ill, resulting in seven fatalities. The initial cases were linked to exposure to imported African green monkeys or their tissues during research activities. An additional case was retrospectively diagnosed.

In recent outbreaks in February and March 2023, two separate incidents of Marburg virus infection were reported in Equatorial Guinea and Tanzania. In Equatorial Guinea, from February 13 to May 1, 2023, there were 17 laboratory-confirmed cases of Marburg virus disease (MVD) and 23 probable cases. In Tanzania, nine cases were reported in June 2023, with eight of them being laboratory-confirmed and one considered probable (29).

The African fruit bat, Rousettus aegyptiacus, serves as the natural reservoir host for the Marburg virus. Infected fruit bats do not exhibit noticeable signs of illness. Primates, including humans, can become infected with the Marburg virus and may develop severe disease with high mortality rates.

Sporadic outbreaks of the Marburg virus have been documented in countries such as Uganda, Zimbabwe, the Democratic Republic of Congo, Kenya, Angola, and South Africa (28).

- **Transmission**

The Marburg virus can be transmitted to humans through contact with infected bat feces or aerosols, as the virus can be found in the oral secretions, urine, and feces of infected Egyptian rousette bats (30). Transmission between individuals can occur through contact with blood or body fluids, such as urine, saliva, sweat, feces, vomit, breast milk, amniotic fluid, and semen from individuals who are either sick with or have succumbed to Marburg virus disease (30). The virus can also be transmitted through contaminated objects that have come into contact with body fluids from infected individuals, including clothing, bedding, needles, and medical equipment. Furthermore, transmission can occur through the semen of recovered individuals via

oral, vaginal, or anal sexual contact. Similar to the Ebola virus, the virus can persist in the testicles and inside the eye. However, there is no evidence suggesting that Marburg viruses can be spread via sex or contact with vaginal fluids from women who have had Marburg virus disease. The European Centre for Disease Prevention and Control (ECDC) asserts that the Marburg virus is not transmitted through the air (31).

- **Signs and symptoms**

The incubation period for Marburg virus disease ranges from 2 to 21 days, and symptoms typically manifest suddenly, including fever, chills, headache, and myalgia. Around the fifth day after symptom onset, a maculopapular rash, predominantly on the trunk (chest, back, stomach), may appear. Additional symptoms may include nausea, vomiting, chest pain, sore throat, abdominal pain, and diarrhea. Symptoms progressively worsen and can involve jaundice, pancreatitis, severe weight loss, delirium, shock, liver failure, extensive hemorrhaging, and multi-organ dysfunction. The case fatality rate for Marburg virus disease ranges from 23% to 90% (32).

- **Diagnosis**

Diagnosing Marburg virus disease can be challenging due to the similarity of clinical manifestations with other infectious diseases or endemic hemorrhagic fever diseases in the area. Laboratory diagnosis may involve antigen-capture enzyme-linked immunosorbent assay (ELISA), molecular diagnosis using PCR, IgM capture using ELISA, and virus isolation (33).

- **Prevention**

Preventing infection with the Marburg virus involves avoiding contact with fruit bats and sick non-human primates. Similar measures used for the Ebola virus and other hemorrhagic fevers can be taken to prevent secondary transmission. This includes implementing nursing techniques to minimize direct physical contact with patients, such as wearing protective gowns, gloves, and masks. Infected individuals should be placed in strict isolation, and needles, equipment, and patient excretions should be properly sterilized or disposed of.

On February 20, 2023, the Egyptian Ministry of Health and Population issued an order that newcomers from Equatorial Guinea and Tanzania must be quarantined before being permitted to

enter the country (34). Egypt has issued guidelines for treating individuals infected with the Marburg virus after the WHO and Equatorial Guinea reported the deaths of 9 people and 16 suspected cases of MVD. The guidelines for MVD include a disease definition and the precautions and preventative measures that must be taken. In addition, they outline the procedures for handling suspected or infected cases (35).

Egypt has also revealed the disinfection and sterilization measures it is adopting to prevent Marburg virus disease after African states announced the virus outbreak. These disinfection measures are carried out using a sodium hypochlorite solution. Egypt is on high alert to prevent the entry of the Marburg virus into the country.

- **Treatment**

Treatment for Marburg virus infection is mainly supportive care that includes rest, hydration, oxygen, and treatment of specific symptoms as they arise. Supportive medications such as acetaminophen may be used to relieve pain and fever. Intravenous and/or oral fluids may be administered to replace lost fluids and stabilize electrolytes. Blood transfusion may also be necessary to replace lost blood and clotting factors. In cases of complicated infections, appropriate antiviral and/or antibiotic therapies may be indicated. Now, Monoclonal antibody therapies are being developed for the treatment of Marburg virus disease. Antiviral therapies used for Ebola, such as Remdesivir and favipiravir, may also be tested for use in Marburg virus disease (36). Supportive hospital therapy should focus on balancing fluids and electrolytes, maintaining oxygen levels and blood pressure, replacing lost blood and clotting factors, and treating any complicating infections.

1.3. Dengue Hemorrhagic Fever

Dengue fever is caused by a positive-stranded RNA virus known as the dengue virus, which is one of the Flaviviridae family and the Flavivirus genus. Other viruses in the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk hemorrhagic fever virus. These viruses are primarily spread by arthropods such as mosquitoes and ticks.

The genome of the dengue virus contains approximately 11,000 nucleotide bases, which encode for 3 different types of protein molecules that make up the virus particle (37). There are 4

antigenically distinct serotypes of the dengue virus (DENV-1, DENV-2, DENV-3, and DENV-4), and a newly discovered fifth type (DENV-5) has also been identified. These serotypes have multiple strains that are found worldwide (38).

Dengue fever is currently one of the fastest-growing mosquito-borne viral infections, with its impact being 30 times greater than it was 50 years ago. In the 1970s, less than 10 countries reported severe dengue epidemics. However, nowadays, dengue is present in over 150 countries, putting approximately 40% of the world's population at risk of infection (39). Once a person has been infected with one strain of the dengue virus, they develop lifelong immunity to only that specific strain. This means that individuals can still be infected with dengue fever up to three more times in their lifetime. Each subsequent infection is more dangerous than the previous one due to a phenomenon called Antibody-Dependent Enhancement. People with chronic diseases like diabetes and asthma are particularly vulnerable to severe dengue.

As of June 8, 2023, there have been 2,162,214 reported cases of dengue fever globally, resulting in 974 deaths (40). Additionally, suspected dengue infections have been reported in Qena governorate, Egypt, during the third week of July 2023. While there have been no deaths, individuals who tested positive for dengue are currently receiving treatment at home. In response to these outbreaks, the Egyptian Health and Population Ministry has issued guidelines for the treatment and control of dengue fever to prevent the further spread of the infection.

There have been previous reports of dengue cases in Safaga and Quser cities on the Red Sea coast, as well as an outbreak in the Assiut Governorate in 2015. Cases of dengue have also been documented in Saudi Arabia and Yemen in recent years, as noted by the World Health Organization.

- **Transmission**

The Dengue virus primarily spreads through the bites of mosquitoes, which are transmitted to individuals through the bites of infected Aedes mosquitoes (Ae. aegypti or Ae. albopictus). These mosquitoes also serve as vectors for the Zika and Chikunya viruses (41). They are widely distributed in tropical and sub-tropical regions across the globe and are found in seven Middle Eastern countries: Egypt, Sudan, Saudi Arabia, Yemen, Somalia, Djibouti, and Pakistan. Humans act as the principal reservoir of the virus, serving as a source for uninfected mosquitoes. Infection can occur with just a single bite from an infected mosquito. Although human-to-human transmission of Dengue is rare, infected individuals can transmit the virus to other mosquitoes.

Humans are recognized for facilitating the spread of infection from one country or area to another. Additionally, Dengue can be transmitted through contaminated blood products and organ donations. Recently, vertical transmission from mother to child during pregnancy or at birth has also been documented (41).

- **Signs and symptoms**

A significant proportion, more than 80%, of dengue virus infections may go unnoticed or result in mild symptoms. The onset of symptoms occurs between 3 to 14 days after infection (42). Clinical manifestations of dengue fever include persistent fever above 38°C for more than 2 days, lasting typically for 2 to 7 days, along with symptoms such as headache, pain behind the eyes, prolonged fatigue, and joint pain. Severe muscle pain, commonly referred to as "break bone disease," may also be experienced. A skin rash appears in approximately 50-80% of symptomatic patients, resembling measles with white patches on a background of red skin. This rash may emerge on the first or second day of symptoms or later in the course of the illness (around days 4-7). Some patients may exhibit red spots that do not disappear when pressed, indicating broken capillaries, as well as mild bleeding from the mouth and nose (43).

- **Complications:**

Less than 5% of symptomatic patients may develop complications and severe disease. Dengue hemorrhagic fever develops bleeding from the nose, mouth, and underskin. Complication in Dengue hemorrhagic fever disease leads to cells and blood plasma leaking from blood vessels producing ascites and decreased blood supply to vital organs and dysfunction leading to Dengue shock syndrome (44).

- **Clinical Diagnosis of Dengue fever and Dengue hemorrhagic Fever**

Classic dengue fever, also known as "break-bone fever," presents with a sudden onset of high fever within 3-14 days after being bitten by an infected mosquito. Symptoms include severe headache, pain behind the eyes, muscle and joint pain, hemorrhagic manifestations, rash, and low white blood cell count. Patients may also experience loss of appetite and nausea. Acute symptoms typically persist for approximately one week, but weakness, fatigue, and loss of appetite may continue for several weeks (45).In some cases, dengue fever can progress to a

severe and potentially fatal form called dengue hemorrhagic fever. As the fever begins to subside, usually 3-7 days after symptom onset, patients may exhibit warning signs of severe disease. These signs include severe abdominal pain, persistent vomiting, significant temperature change (from fever to hypothermia), hemorrhagic manifestations, or changes in mental status such as irritability or confusion. Early signs of shock, including restlessness, cold and clammy skin, rapid weak pulse, and narrowing of the pulse pressure, may also be present (45).

Currently, the World Health Organization (WHO) has established four criteria to define dengue hemorrhagic fever. These criteria include fever or a recent history of fever lasting 2-7 days, the presence of any hemorrhage manifestations, thrombocytopenia (low platelet count), and evidence of increased vascular permeability. Mild hemorrhagic manifestations can manifest as a positive tourniquet test, skin hemorrhage, nosebleeds, vaginal bleeding, or microscopic blood in the urine. More severe forms of bleeding may occur, such as vaginal bleeding, vomiting blood, black stools, or even bleeding inside the brain. Moreover, evidence of plasma leakage due to increased vascular permeability is also observed (46).

The WHO is currently undergoing a reassessment of the clinical case definition for both dengue fever and dengue hemorrhagic fever. It is essential to note that the key distinguishing factor between dengue hemorrhagic fever and dengue fever is not the mere presence of haemorrhaging, but rather the plasma leakage resulting from increased vascular permeability.
Dengue Shock Syndrome (DSS) is defined as a case that fulfills the four criteria for dengue hemorrhagic fever and also exhibits evidence of circulatory failure. This failure is characterized by a rapid and weak pulse, narrow pulse pressure, hypotension, restlessness, and cold clammy skin (47).

- **Laboratory diagnosis:**

Elevated liver enzymes, aspartate aminotransferase; alanine aminotransferase; low platelet count, white blood cell, red blood cells, hematocrit, and decrease in haemoglobin (48).
Specific laboratory tests: serological diagnosis is achieved by IgM and Ig G antibodies using ELISA. Specific laboratory tests by isolating the virus in tissue culture; and detection of viral RNA using PCR (49).

- **Prevention and Infection Control**

Protection from mosquito bites is the main point in reducing the dengue fever risks. It can be accomplished by removing stagnant water; covering containers of water to prevent mosquitoes from laying eggs and breeding; spraying pooled water with pesticide; wearing clothes that cover the skin and using mosquito netting in addition to using insect repellant products.

- **Dengue vaccine**

A newly developed vaccine called DengvaxiaTM has received approval and is now commercially available for dengue fever. It is recommended for individuals who have previously contracted dengue. This vaccine can potentially reduce the risk of developing severe dengue, specifically dengue hemorrhagic fever, if they encounter a different strain of the dengue virus in the future (50).

- **Treatment**

The primary approach to treating acute dengue is supportive care, which involves administering fluids orally or intravenously for mild to moderate cases. Fever and pain are typically managed using paracetamol, while non-steroidal anti-inflammatory drugs like ibuprofen and aspirin are avoided due to the potential risk of exacerbating bleeding. In more severe instances involving bleeding, plasma leakage, and significant hypotension, blood transfusions may be necessary (51).

2. Conclusion

Several different types of dangerous viruses cause deadly hemorrhagic fever diseases. Of these viruses are Ebola virus; Marburg virus; and Dengue virus.

The Ebola virus family *Filoviridea* RNA virus can be spread by direct contact with infected African fruit bats (Egyptian bats) or their secretions. The virus can also be spread by contact with blood and body secretions of infected or dead patients from Ebola virus.

Many outbreaks of Ebola Virus Disease (EVD) resulted in hundreds of infections and deaths have been reported. The case fatality rate of Ebola virus infections ranged from 25% to 90%. Between 1976 and 2013, the WHO reported a total of 24 outbreaks involving 1716 cases. The largest outbreak occurred from 2013 to 2016, in West Africa with 28,638 cases and 11315

deaths. A recent outbreak was reported on September 20, 2022 in Uganda. The Ministry of Health in Uganda declared the end of the Ebola outbreak, on January 2023.

The virus can persist in body secretions like semen and breast milk and transmits infection while the individual appears recovered from the disease.

The early signs and symptoms of Ebola virus disease are confused with other hemorrhagic fever disease and other bacterial diseases. The late stage of the disease can be clinically suspected and confirmed by laboratory testing.

Prevention and infection control of Ebola virus infection includes: avoiding contact with blood and body fluids of patients or dead individuals; avoiding contact with objects contaminated with virus by disinfecting with halogenated detergents; and avoiding contact with fruit bat and its secretions. Ebola vaccine can be used in areas susceptible to frequent epidemics.

Treatment of cases is available by supportive care; maintaining oxygen status and blood pressure. Antiviral agents, remedesvir, and favipiravir can be used for the treatment of patients.

Marburg hemorrhagic fever virus, an RNA virus belonging to the Filoviridea family, causes a disease similar to Ebola virus hemorrhagic fever. This rare yet severe hemorrhagic fever affects both humans and non-human primates. The transmission methods of the Marburg virus are similar to those of the Ebola virus, and the African fruit bat species Rousettus aegyptiacus serves as the reservoir host for the Marburg virus. Recent outbreaks were reported in Guinea and Tanzania in 2023.

The incubation period for the Marburg virus ranges from 2 to 21 days. The onset of symptoms is sudden and includes fever, pain, and a maculopapular rash. As the disease progresses, symptoms worsen and can involve jaundice, pancreatitis, shock, liver failure, extensive hemorrhaging, and multi-organ dysfunction. The case fatality rate for Marburg hemorrhagic fever ranges from 23 to 90%.

Preventing infection entails avoiding contact with fruit bats and implementing measures to prevent person-to-person transmission. On February 20, 2023, the Egyptian Health and Population Ministry issued an order mandating quarantine for individuals arriving from Equatorial Guinea and Tanzania before being allowed entry into the country. The guidelines provided by the Ministry of Health and Development (MDV) encompass a definition of the disease, preventive measures to be taken, and the protocols for managing suspected or confirmed cases.

Treatment of MVD includes supportive care; rest; and maintaining oxygen; blood pressure and hydration status. Monoclonal antibody therapies antiviral therapies remedesvir and favipiravir have been used.

Dengue fever is caused by an RNA virus that belongs to the Flavivirus family. It comprises four distinct serotypes, with a recently discovered fifth serotype. The virus is widespread across more than 150 countries, posing a risk to approximately 40% of the global population. In 2023, there were a total of 2,162,214 reported cases of Dengue fever, resulting in 974 deaths worldwide (52). Notably, during the third week of July 2023, multiple cases of Dengue fever were reported in Qena governorate, Egypt. Consequently, the Egyptian Ministry of Health and Population issued comprehensive guidelines for disease treatment and infection control.

Transmission of Dengue virus occurs exclusively through mosquito bites, primarily by infected Egyptian mosquitoes. Person-to-person transmission of the infection does not occur. Diagnosing the disease based on early clinical symptoms alone is insufficient, necessitating laboratory testing to confirm the infection. Supportive care is the mainstay of treatment for acute Dengue fever, involving the administration of fluids orally or intravenously. To manage fever and pain, paracetamol is the preferred medication, while non-steroidal anti-inflammatory drugs and aspirin should be avoided to minimize the risk of bleeding. In severe cases characterized by bleeding, plasma leakage, and severe hypotension, blood transfusions may be necessary.

The most effective preventive measure against Dengue infection is to protect oneself from mosquito bites. This includes eliminating stagnant water sources, covering water tanks, using mosquito netting, and applying insect repellents. Additionally, a Dengue vaccine is commercially available and is recommended for individuals who have previously contracted Dengue, as it can reduce the risk of severe disease caused by different Dengue virus serotypes in the future.

.

Conflict of Interest

There are no conflicts of interest.

3. References

1. Tariq M, Kim DM. Hemorrhagic fever with renal syndrome: literature review, epidemiology, clinical picture and pathogenesis. Infection & chemotherapy. 2022 Mar;54(1):1.

2. Mariappan V, Pratheesh P, Shanmugam L, Rao SR, Pillai AB. Viral hemorrhagic fever: molecular pathogenesis and current trends of disease management-an update. Current research in virological science. 2021 Jan 1;2:100009.

3. Singh RK, Dhama K, Malik YS, Ramakrishnan MA, Karthik K, Khandia R, Tiwari R, Munjal A, Saminathan M, Sachan S, Desingu PA. Ebola virus–epidemiology, diagnosis, and control: a threat to humans, lessons learnt, and preparedness plans–an update on its 40 year's journey. Veterinary Quarterly. 2017 Jan 1;37(1):98-135.

4. Sudhakar P, Thenmozhi V, Kumar SV, Dhanalakshmi M. A review on emerging and reemerging viral diseases. International Journal of Research in Pharmacy and Pharmaceutical Sciences. 2021 jan 6(1):14-20.

5. World Health Organization. Guidance on regulations for the transport of infectious substances 2019–2020: applicable from 1 January 2019. World Health Organization; 2019.

6. Pourrut X, Kumulungui B, Wittmann T, Moussavou G, Délicat A, Yaba P, Nkoghe D, Gonzalez JP, Leroy EM. The natural history of Ebola virus in Africa. Microbes and infection. 2005 Jun 1;7(7-8):1005-14.

7. Nicastri E, Kobinger G, Vairo F, Montaldo C, Mboera LE, Ansunama R, Zumla A, Ippolito G. Ebola virus disease: epidemiology, clinical features, management, and prevention. Infectious Disease Clinics. 2019 Dec 1;33(4):953-76.

8. Omoleke SA, Mohammed I, Saidu Y. Ebola viral disease in West Africa: a threat to global health, economy and political stability. Journal of Public Health in Africa. 2016 Aug 8;7(1).

9. Hemashree S, Rubini KR, Lohala S, Nithya S. Ebola Virus-A Review. Research Journal of Pharmacy and Technology. 2016;9(5):617-20.

10. Chavez S, Koyfman A, Gottlieb M, Brady WJ, Carius BM, Liang SY, Long B. Ebola virus disease: A review for the emergency medicine clinician. The American Journal of Emergency Medicine. 2023 Apr 29.

11. Hambese H, Hadush T, Tilahun A, Teshale A, Getachew A. Ebola virus disease in Domestic and wild animals: A review. Journal of Pharmacy and alternative medicine. 2016;10:54.

12. Chughtai AA, Barnes M, Macintyre CR. Persistence of Ebola virus in various body fluids during convalescence: evidence and implications for disease transmission and control. Epidemiology & Infection. 2016 Jun;144(8):1652-60.

13. Rewar S, Mirdha D. Transmission of Ebola virus disease: an overview. Annals of global health. 2014 Nov 1;80(6):444-51.

14. Wilken JA, Pordell P, Goode B, Jarteh R, Miller Z, Saygar BG, Maximore L, Borbor WM, Carmue M, Walker GW, Yeiah A. Knowledge, attitudes, and practices among members of households actively monitored or quarantined to prevent transmission of Ebola Virus Disease—Margibi County, Liberia: February-March 2015. Prehospital and disaster medicine. 2017 Dec;32(6):673-8.

15. Fletcher TE, Fowler RA, Beeching NJ. Understanding organ dysfunction in Ebola virus disease. Intensive care medicine. 2014 Dec;40:1936-9.

16. Mustafa M, Yusof IM, Kassim M, Jeffree MS, Illzam EM, Sharifa AM. Ebola Virus Disease, Management, and Prevention. IOSR J Dent Med Sci. 2016;15:142-8.

17. Dhama K, Malik YS, Malik SV, Singh RK. Ebola from emergence to epidemic: the virus and the disease, global preparedness and perspectives. The Journal of Infection in Developing Countries. 2015 May 18;9(05):441-55.

18. Corti D, Misasi J, Mulangu S, Stanley DA, Kanekiyo M, Wollen S, Ploquin A, Doria-Rose NA, Staupe RP, Bailey M, Shi W. Protective monotherapy against lethal Ebola virus infection by a potently neutralizing antibody. Science. 2016 Mar 18;351(6279):1339-42.

19. Hunter N, Rathish B. Marburg Fever. [Updated 2023 Feb 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK578176/.

20. Moghadam SR, Omidi N, Bayrami S, Moghadam SJ, SeyedAlinaghi S. Ebola viral disease: a review literature. Asian Pacific Journal of Tropical Biomedicine. 2015 Apr 1;5(4):260-7.

21. Martin P, Laupland KB, Frost EH, Valiquette L. Laboratory diagnosis of Ebola virus disease. Intensive care medicine. 2015 May;41:895-8.

22. Bettini A, Lapa D, Garbuglia AR. Diagnostics of Ebola virus. Frontiers in Public Health. 2023 Feb 23;11:1123024.

23. Paquet D, Jung L, Trawinski H, Wendt S, Lübbert C. Fever in the returning traveler. Deutsches Ärzteblatt International. 2022 Jun;119(22-23):400.

24. Haddock E, Feldmann F, Feldmann H. Effective chemical inactivation of Ebola virus. Emerging infectious diseases. 2016 Jul;22(7):1292.

25. Finch CL, Martinez C, Leffel E, Skiadopoulos MH, Hacker A, Mwesigwa B, Maïga D, Mugisa I, Munkwase G, Rustomjee R. Vaccine licensure in the absence of human efficacy data. Vaccines. 2022 Feb 26;10(3):368.

26. mondiale de la Santé O, World Health Organization. Global Advisory Committee on Vaccine Safety, 5–6 June 2019–Comité consultatif mondial pour la sécurité des vaccins, 5-6 juin 2019. Weekly Epidemiological Record= Relevé épidémiologique hebdomadaire. 2019 Jul 12;94(28):309-16.

27. Torreele E, Boum Y, Adjaho I, Alé FG, Issoufou SH, Harczi G, Okonta C, Olliaro P. Breakthrough treatments for Ebola virus disease, but no access—what went wrong, and how can we do better?. The Lancet Infectious Diseases. 2023 Jan 19.

28. Wellington J, Nur A, Nicholas A, Uwishema O, Chaito H, Awosiku O, Al Tarawneh YJ, Sharafeddine JA, Onyeaka CV, Onyeaka H. Marburg virus outbreak in Ghana: An impending crisis. Annals of Medicine and Surgery. 2022 Sep 1;81:104377.

29. Cuomo-Dannenburg G, McCain K, McCabe R, Unwin HJ, Doohan P, Nash RK, Hicks JT, Charniga K, Geismar C, Lambert B, Nikitin D. Marburg Virus Disease outbreaks, mathematical models, and disease parameters: a Systematic Review. medRxiv. 2023:2023-07.

30. Amman BR, Schuh AJ, Albariño CG, Towner JS. Marburg virus persistence on fruit as a plausible route of bat to primate filovirus transmission. Viruses. 2021 Nov 30;13(12):2394.

31. Suliman A. What to know about the deadly Marburg virus as new outbreak emerges. The Washington Post. 2023 Feb 15:NA-.

32. Onyeaghala CA, Omoha AR. The Threat of Marburg Virus Disease in West Africa: Implications for Public Health Control in Nigeria. Nigerian Health Journal. 2022;22(3):336-8.

33. Grolla A, Lucht A, Dick D, Strong JE, Feldmann H. Laboratory diagnosis of Ebola and Marburg hemorrhagic fever. BULLETIN-SOCIETE DE PATHOLOGIE EXOTIQUE. 2005 Sep 1;98(3):205.

34. Independent E. Egypt on high alert to prevent entry of Marburg virus into country [Internet]. Egypt Independent. 2023 [cited 2023 Sep 15]. Available from:

https://www.egyptindependent.com/egypt-on-high-alert-to-prevent-entry-of-marburg-virus-into-country/

35. Eneh SC, Okonji OC, Chiburoma AG, Francisca Ogochukwu O, Tuwleh L, Gideon I, Okonji EF, Bushabu FN, Mgbere O. Marburg virus disease amid COVID-19 in West Africa: an emerging and re-emerging zoonotic epidemic threat, future implications and way forward. Therapeutic Advances in Infectious Disease. 2023 Apr;10:20499361231168520.

36. Zhao F, He Y, Lu H. Marburg virus disease: a deadly rare virus is coming. BioScience Trends. 2022 Aug 31;16(4):312-6.

37. Shanmugapriya E, Ravichandiran V, Aanandhi MV. Molecular docking studies on naturally occurring selected flavones against protease enzyme of Dengue virus. Research Journal of Pharmacy and Technology. 2016;9(7):929-32.

38. Roy SK, Bhattacharjee S. Dengue virus: epidemiology, biology, and disease aetiology. Canadian journal of microbiology. 2021;67(10):687-702.

39. Suchithra BS. Study to Assess the Knowledge of People About Dengue Fever in Selected Rural Area of Mangalore. Indian Journal of Public Health Research & Development. 2020 Jun 25;11(6):993-6.

40. Dengue virus disease cases, June 2022-May 2023 [Internet]. www.ecdc.europa.eu. 20s23. Available from: https://www.ecdc.europa.eu/en/publications-data/dengue-virus-disease-cases-june-2022-may-2023

41. Ferreira-de-Lima VH, Lima-Camara TN. Natural vertical transmission of dengue virus in Aedes aegypti and Aedes albopictus: a systematic review. Parasites & vectors. 2018 Dec;11:1-8.

42. Jain M. Dengue: Emerging Health Problem. INROADS-An International Journal of Jaipur National University. 2012;1(1):17-8.

43. Chaudhary PK, Bhalla VK. Assessment of cases of dengue fever by clinical and laboratory findings. Journal of Advanced Medical and Dental Sciences Research. 2017 Aug 1;5(8):24.

44. Mohsina FP, Faheem IP, Mohammad M, Tabassum S, Tarkash S, Shah I, Patil A. Prevalence, Pathogenesis and Identification of Clinical Risk Factors Associated with Dengue Virus (DENV). Indo Global Journal of Pharmaceutical Sciences. 2022 Jun 30;12:189-96.

45. Muller DA, Depelsenaire AC, Young PR. Clinical and laboratory diagnosis of dengue virus infection. The Journal of infectious diseases. 2017 Mar 1;215(suppl_2):S89-95.

46. Srikiatkhachorn A, Gibbons RV, Green S, Libraty DH, Thomas SJ, Endy TP, Vaughn DW, Nisalak A, Ennis FA, Rothman AL, Nimmannitaya S. Dengue hemorrhagic fever: the sensitivity and specificity of the world health organization definition for identification of severe cases of dengue in Thailand, 1994–2005. Clinical infectious diseases. 2010 Apr 15;50(8):1135-43.

47. Rigau-Pérez JG. Clinical manifestations of dengue hemorrhagic fever in Puerto Rico, 1990-1991. Revista Panamericana de Salud Publica. 1997;1:381-8.

48. Arshad I, Malik FA, Hussain A, Shah SA. Dengue fever: Clinico-pathologic correlations and their association with poor outcome. The Professional Medical Journal. 2011 Mar 10;18(01):57-63.

49. De Paula SO, Fonseca BA. Dengue: a review of the laboratory tests a clinician must know to achieve a correct diagnosis. Brazilian Journal of Infectious Diseases. 2004;8:390-8.

50. Kasi SG. 33 Adult Vaccination. IAP Q & A on Vaccines & Vaccinology. 2021 Mar 30:306.

51. Madanayake PM, Jayawardena AE, Wijekoon SL, Perera N, Wanigasuriya JK. Fluid requirement in adult dengue haemorrhagic fever patients during the critical phase of the illness: an observational study. BMC Infectious Diseases. 2021 Dec;21:1-9.

52. Megawati EL, Aldila D. A stability and optimal control analysis on a dengue transmission model with mosquito repellent. Commun. Math. Biol. Neurosci.. 2023 Sep 18;2023:Article-ID.