Review on the Epidemiology and Public Health Importance of Marburg Hemorrhagic Fever in Africa

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ABSTRACT

Marburg virus disease (MVD), formerly known as Marburg haemorrhagic fever, is a severe, often fatal illness in humans. Rousettus aegyptiacus, fruit bats of the Pteropodidae family, are considered to be natural hosts of Marburg virus. The Marburg virus is transmitted to people from fruit bats and spreads among humans through human-to-human transmission. The Marburg virus causes severe viral haemorrhagic fever in humans. The average MVD case fatality rate is around 50%. Case fatality rates have varied from 24% to 88% in past outbreaks depending on virus strain and case management. Community engagement is key to successfully controlling outbreaks. Good outbreak control relies on applying a package of interventions, namely case management, infection prevention and control practices, surveillance and contact tracing, a good laboratory service, safe burials and social mobilization. Early supportive care with rehydration, symptomatic treatment improves survival. There is as yet no licensed treatment proven to neutralize the virus but a range of blood, immunological and drug therapies are under development. Marburg virus belongs to the genus Marburg virus in the family Filoviridae and causes a severe hemorrhagic fever, known as Marburg hemorrhagic fever (MHF), in both humans and nonhuman primates. Similar to the more widely known Ebola hemorrhagic fever, MHF is characterized by systemic viral replication, immunosuppression and abnormal inflammatory responses. These pathological features of the disease contribute to a number of systemic dysfunctions including hemorrhages, edema, coagulation abnormalities and, ultimately, multiorgan failure and shock, often resulting in death. A detailed understanding of the pathological processes that lead to this devastating disease remains elusive, a fact that contributes to the lack of licensed vaccines or effective therapeutics. This article will review the clinical aspects of MHF and discuss the pathogenesis and possible options for diagnosis, treatment and prevention.

Keywords: Africa, Epidemiology, Marburg Hemorrhagic Fever, Public Health.

Introduction

Marburg hemorrhagic fever (MHF) was first described in 1967 in an outbreak in Germany and the former Yugoslavia that was linked to contact with monkeys imported from Uganda [1]. The causative agent of MHF is Lake Victoria Marburg virus (MARV), a filovirus similar to Ebola virus [2]. Disease onset is sudden, with fever, chills, headache, and myalgia. Approximately 5 days after disease onset, a nonpruritic rash may appear, followed by nausea, vomiting, diarrhea, bone pain, and abdominal pain. Symptoms may become increasingly severe and lead to massive hemorrhaging and multi organ dysfunction [3]. Most deaths occur during the second week of illness [4]. Person-to-person transmission occurs through direct contact with symptomatic patients with MHF, their body fluids, or their remains [4]. The natural reservoir of the virus remains unknown, although bats have been implicated [5, 6].

Since 1967, sporadic cases of MHF [7–12] and 2 large outbreaks have been recorded [3, 13]. The 1998–2000 outbreak occurred in the Durba and Watsa region of the Democratic Republic of the Congo, resulting in 154 cases and 125 deaths (case–fatality rate [CFR], 83%) [14,15]. The 2005 outbreak occurred in Uige, Angola, with 374 putative cases (including 158 laboratory-confirmed cases) and 329 deaths (CFR, 88%) [16]. The low number of recognized infections relatively and the poor quality of their clinical documentation [17] have hampered the assessment of clinical MHF characteristics in humans. Diagnostic tests for MHF include reverse-transcriptase polymerase chain reaction (PCR) assays to identify viral nucleic acids [18]. However, the usefulness of these assays is limited during the first few days of illness because of low concentrations of circulating virus [19, 20] and, at

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times, the nonavailability of on-site testing. Clinical case definitions for MHF determine whether clinicians take a sample for diagnostic testing and influence triage decisions.

Clinical case definitions were developed by the World Health Organization (WHO) during the Durba and Watsa outbreak that were based on the Ebola hemorrhagic fever (EHF) case definition. To fulfil the WHO-recommended definition, which was adapted during the outbreak, a patient must have either (1) an epidemiological link to an individual potentially infected with MARV and at least 3 of the following general symptoms: asthenia, anorexia, myalgia or arthralgia, diarrhea, abdominal pain, nausea, vomiting, headache, dysphagia, dyspnea, conjunctivitis, jaundice, and hiccups; or (2) fever plus at least 3 general symptoms; or (3) fever plus unexplained hemorrhage [21]. A highly sensitive clinical case definition ensures that patients with true MHF are isolated and prevented from transmitting MARV to community members; a highly specific case definition ensures that uninfected patients are not placed at risk of nosocomial infection in the Marburg ward. Until the Uige outbreak, there were limited opportunities to test the validity of individual patient characteristics, symptomology, and contact history as diagnostic criteria of MHF. The Uige outbreak is the largest recorded outbreak of MHF to date. Most cases originated from Uige City, a municipality of ~180,000 inhabitants. The initial investigation, confirmation, and notification of the outbreak are described elsewhere [3, 22–24]. During the outbreak, Uige Provincial Hospital's Marburg ward received patients with MHF compatible symptoms identified by surveillance teams operating in the community, health care workers operating a triage system elsewhere in the hospital, and patient self-referral (Figure 1). On presentation at the hospital, patients with suspected MHF were examined by a clinician and had blood specimens taken for onsite laboratory testing by the National Microbiology Laboratory–Public Health Agency of Canada, who provided results within 4–6 h. A laboratory in Luanda, Angola, operated by the US Centers for Disease Control and Prevention, subsequently confirmed all Marburg-related laboratory results. Patients with positive PCR results were classified as confirmed cases and admitted to the Marburg ward. Patients with negative PCR results who had a blood sample obtained more than 2–3 days after the onset of symptoms were classified as having non-MHF cases and were reexamined for an alternative illness. If a patient with negative PCR results had samples obtained 2–3 days or less after symptom onset, an additional sample was obtained for testing 24–48 h later. Patients with a positive result were admitted to the Marburg ward, and those with a second negative PCR result were classified as not having MHF [19,30].

Marburg virus first identified after some laboratory workers in Marburg, Germany, developed hemorrhagic fever after contacting tissues from African green monkeys.1-3 Although only few outbreaks were reported, 4-7 the high mortality rate once infected, the inability to identify the natural host and poor understanding of transmission make the diagnosis, management and prevention difficult. Like Ebola virus, Marburg virus is considered to have potential to be used as biological weapons in terrorism because of high mortality rates, low virion counts needed for infection, relative stability, infective aerosol nature, and the possibility of person-to-person transmission [31,32].

Two large outbreaks that occurred simultaneously in Marburg and Frankfurt in Germany, and in Belgrade, Serbia, in 1967, led to the initial recognition of the disease. The outbreak was associated with laboratory work using African green monkeys (Cercopithecus aethiops) imported from Uganda. Subsequently, outbreaks and sporadic cases have been reported in Angola, Democratic Republic of the Congo, Kenya, South Africa (in a person with recent travel history to Zimbabwe) and Uganda. In 2008, two independent cases were reported in travelers who had visited a cave inhabited by Rousettus bat colonies in Uganda [33,34].

Since its first identification in 1967, Marburg virus has been notorious in the recent 20 years because of its high mortality rates, and the capacity of dramatic outbreaks. The potential to spread the disease worldwide has become a reality with the expansion of global transportation and international trade. Physicians need to be aware of the potential danger of Marburg hemorrhagic fever, be able to identify the disease, and know how to manage and prevent its transmission. Marburg hemorrhagic fever (Marburg HF) is a rare but severe hemorrhagic fever which affects both humans

and non-human primates. Marburg HF is caused by Marburg virus, a genetically unique zoonotic (or, animal-borne) RNA virus of the filovirus family. The five species of Ebola virus are the only other known members of the filovirus family [34,35].

Marburg virus was first recognized in 1967, when outbreaks of hemorrhagic fever occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Belgrade, Yugoslavia (now Serbia). Thirty-one people became ill, initially laboratory workers followed by several medical personnel and family members who had cared for them. Seven deaths were reported. The first people infected had been exposed to imported African green monkeys or their tissues while conducting research. One additional case was diagnosed retrospectively [36,37].

The reservoir host of Marburg virus is the African fruit bat, Rousettus aegyptiacus. Fruit bats infected with Marburg virus do not to show obvious signs of illness. Primates (including humans) can become infected with Marburg virus, and may develop serious disease with high mortality. Further study is needed to determine if other species may also host the virus. This Rousettus bat is a sighted, cave-dwelling bat widely distributed across Africa. Given the fruit bat's wide distribution, more areas are potentially at risk for outbreaks of Marburg HF than previously suspected. The virus is not known to be native to other continents, such as North America [28,39].

Marburg HF typically appears in sporadic outbreaks throughout Africa; laboratory confirmed cases have been reported in Uganda, Zimbabwe, the Democratic Republic of the Congo, Kenya, Angola, and South Africa. Many of the outbreaks started with male mine workers working in bat-infested mines. The virus is then transmitted within their communities through cultural practices, under-protected family care settings, and under-protected health care staff. It is possible that sporadic, isolated cases occur as well, but go unrecognized. Cases of Marburg HF have occurred outside Africa, such as during the 1967 outbreak, but are infrequent. In 2008, a Dutch tourist developed Marburg HF after returning to the Netherlands from Uganda, and subsequently died. Also in 2008, an American traveler developed Marburg HF after returning to the US from Uganda and recovered. Both travelers had visited a well-known cave inhabited by fruit bats in a national park. See the History of Outbreaks table for a chronological list of known cases and outbreaks [28,33].

History and overview (Including Factors Responsible For Emergence/Reemergence)

The first identification of MARV and the associated Marburg hemorrhagic fever (MHF) occurred during an 'outbreak' in Germany and Serbia (former Yugoslavia) in 1967, almost a decade before the discovery of Ebola virus (EBOV) [3]. The source of primary infection during this outbreak was exposure to tissues and blood from African green monkeys imported from Uganda for use in the pharmaceutical industry [3–5]. Although the first outbreak occurred in Europe, since that time almost all MHF cases have been reported from eastern Africa, with the sources of primary infection presumed to be located within 500 miles of Lake Victoria (Figure 1). The exceptions to this are the small cluster of cases in 1975 in Zimbabwe/South Africa [6] and the recent outbreak in Uíge, Angola, in 2004–2005 [1], which is the first MHF outbreak reported from western Africa [1]. While the appearance of MARV in western Africa and Zimbabwe appears initially surprising, ecological niche modeling has demonstrated that these areas are part of a large region with similar ecological conditions to those found in the previously known MARV endemic area [7].

In contrast to Ebola hemorrhagic fever (EHF), for which outbreaks have been reported regularly within the endemic region since its discovery, there have only been three major outbreaks and a few sporadic cases of MARV reported to date (Table 1). Notably, however, one of these outbreaks, in the Durba–Watsa region of DRC, was associated with multiple independent introductions of genetically distinct virus strains from an abandoned gold mine. As a result, infections continued uninterrupted from 1998 to 2000 until flooding of the mine [8]. In total, the number of known MHF cases is approximately 450; however, the observation that this number is almost entirely made up of cases from only two large outbreaks highlights MARV's potential as a serious public health threat. In addition, MARV has the dubious distinction of being the only human pathogenic filovirus to have been imported into western countries. This takes into account not only the original MHF outbreak in Europe but also two recent imported cases into

The Netherlands and USA, respectively [9,10]. These recent importations emphasize not only the necessity for increased awareness when treating returning travellers, but also the necessity of developing effective countermeasures against this pathogen. In addition to these naturally acquired infections, to date, three cases, including one fatal case, as a result of laboratory exposure have been reported in Russia [11–13].

Marburg hemorrhagic fever was first recognized in 1967, when outbreaks occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Belgrade, Serbia. The infected people included laboratory workers handling the tissues of the African green monkeys from Uganda, as well as several hospital staffs and family members caring for them [42,44]. No other case had been recorded thereafter until 1975, when a 20-year-old Australian traveler was admitted to a hospital in Johannesburg, South Africa. He might have been infected in Zimbabwe during his trip, and passed the virus to his traveling companion and a nurse [40,48]. In 1980, a 56-year-old Frenchman became acutely ill after his trip from Western Kenya not far from the Uganda. Marburg hemorrhagic fever was identified, and the patient's attending physician became the second case. Another Marburg infection was recognized in 1987, when a 15-year old Danish boy who had traveled in Kenya, including western Kenya, became ill and died [41,45].

The first large outbreak in Durba, Democratic Republic of the Congo occurred from late 1998 to 2000. 154 people were involved, and 128 were fatal. The majority of victims were young male working in a gold mine [49,50]. After the outbreak subsided, there were still some sporadic cases reported in the region. Recent outbreak happened in October 2004 is believed to have begun in Uige Province, Angola. As of 20 April 2005, the Ministry of Health in Angola has reported 266 victims, of which 244 were fatal, representing the mortality rate more than 90%. This outbreak is the largest and on record for this disease by far [51,56].

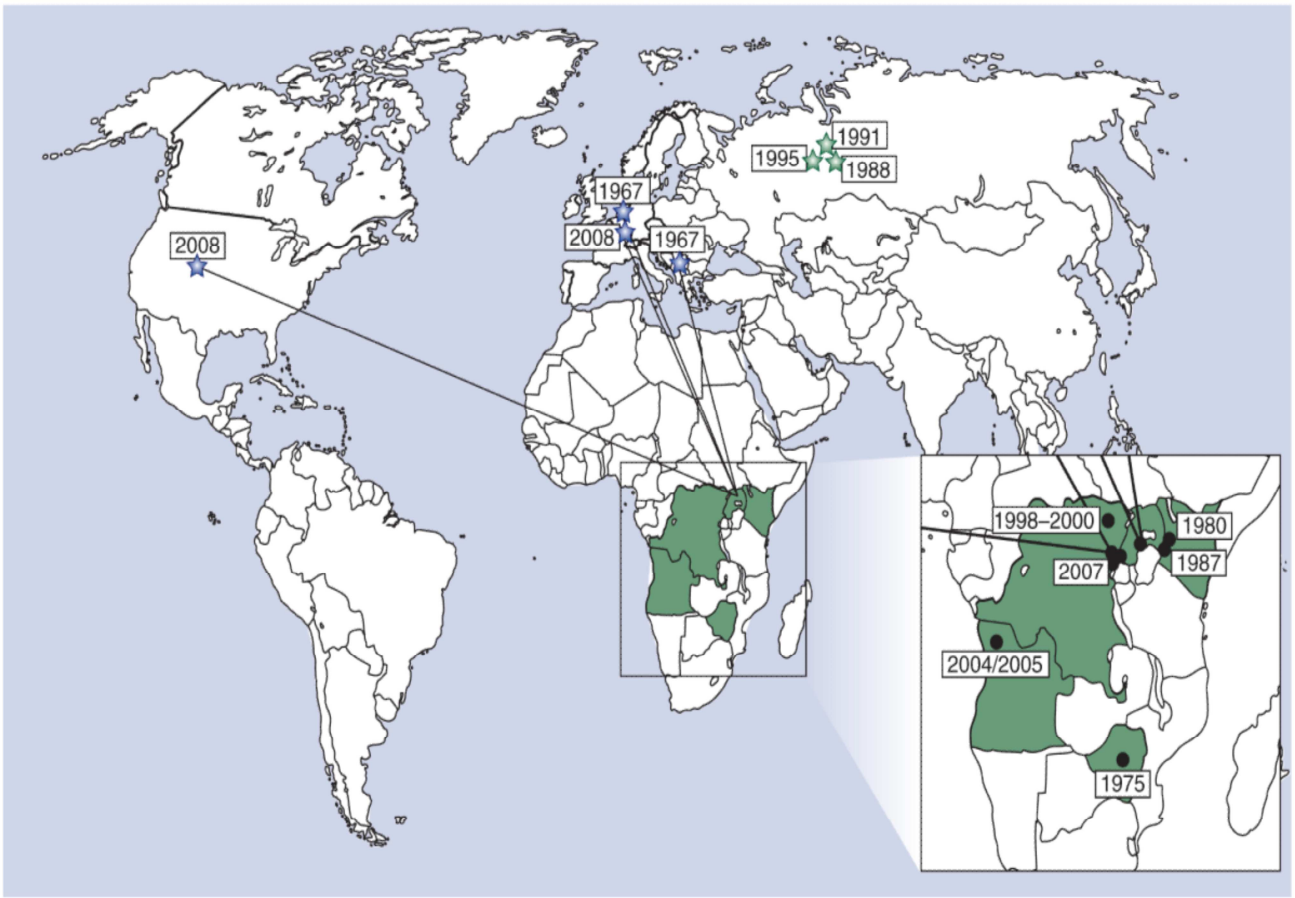


Fig 1. Geographical distribution and epidemiological information regarding known

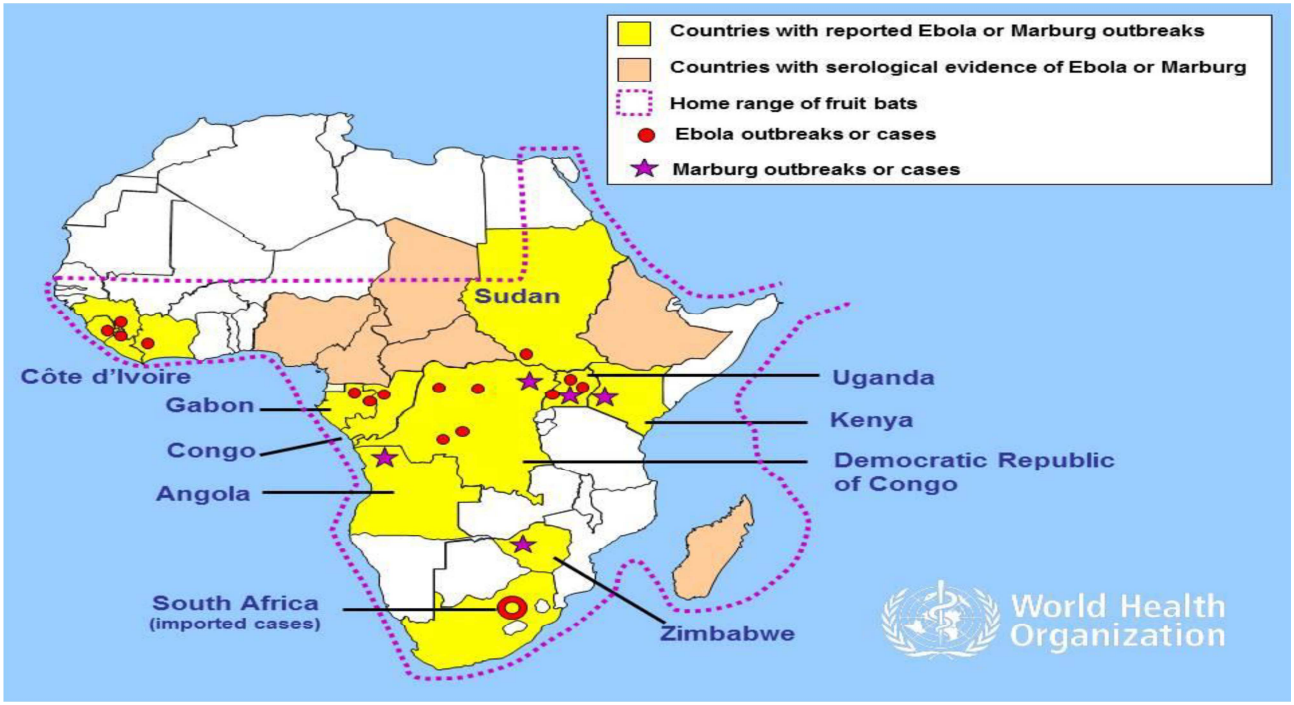


Figure 2. Geographical distribution of Ebola and Marburg outbreaks in Africa (1967-2014)

Known Marburg hemorrhagic fever cases/outbreaks.

Location	Year	Strain(s)	Cases (deaths)	Epidemiology	Ref.
Germany/Serbia	1967	Ratayczak/ Popp	32 (7)	Infection during research using tissues from monkeys imported from Uganda	[3]
Zimbabwe	1975	Ozolin	3 (1)	Unknown origin; index case was infected in Zimbabwe (lethal) with secondary cases in South Africa	[6]
Kenya	1980	Musoke	2 (1)	Unknown origin; lethal index case was infected in western Kenya	[103]
Kenya	1987	Ravn	1 (1)	Unknown origin; expatriate traveling in western Kenya	[31]
Russia	1988	Popp (?)	1 (1)	Laboratory accident	[11]
Russia	1991	Popp	1 (0)	Laboratory accident	[12]
Russia	1995	Popp	1 (0)	Laboratory accident	[13]
Democratic Republic of the Congo	1998–2000	Multiple strains	154 (128)	Infections related to mining; repeated introductions resulting in multiple virus strains; short transmission chains in families	[8]
Angola	2004–2005	Angola	252 (227)	Unknown origin; cases linked to Uíge hospital	[1]
Uganda	2007	ND	4 (1)	Unknown origin; infections related to visits to a mine (Kitaka cave)	[21]
USA	2008	ND	1 (0)	Unknown origin; infection related to visit to a cave in western Uganda; imported infection	[9]
The Netherlands	2008	ND	1 (1)	Unknown origin; infection related to visit to a cave in western Uganda; imported infection	[10]

Marburg hemorrhagic fever cases/outbreaks

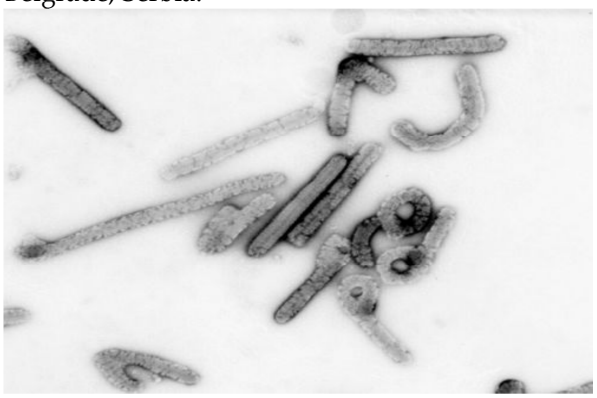
The sites of known Marburg virus outbreaks are indicated as black circles, while the sites of imported outbreaks are marked as blue stars with lines indicating the source location from which the virus was imported. Laboratory accidents are indicated by green stars. The associated outbreak dates are indicated next to the outbreak location [47,52].

Known Cases and Outbreaks of Marburg Hemorrhagic Fever, in Chronological Order [Last updated May 5, 2010]

Year(s)	Country	Apparent or Suspected Origin	Reported number of human cases	Reported number (%) of deaths among cases	Situation
1967	Germany and Yugoslavia	Uganda	31	7 (23)	Simultaneous outbreaks occurred in laboratory workers handling African green monkeys imported from Uganda [1a]. In addition to the 31 reported cases, an additional primary case was retrospectively serologically diagnosed [1b].
1975	Johannesburg, South Africa	Zimbabwe	3	1 (33)	A man with a recent travel history to Zimbabwe was admitted to hospital in South Africa. Infection spread from the man to his traveling companion and a nurse at the hospital. The man died, but both women were given vigorous supportive treatment and eventually recovered [2].
1980	Kenya	Kenya	2	1 (50)	Recent travel history included a visit to Kitum Cave in Kenya's Mount Elgon National Park. Despite specialized care in Nairobi, the male patient died. A doctor who attempted resuscitation developed symptoms 9 days later but recovered [3].
1987	Kenya	Kenya	1	1 (100)	A 15-year-old Danish boy was hospitalized with a 3-day history of headache, malaise, fever, and vomiting. Nine days prior to symptom onset, he had visited Kitum Cave in Mount Elgon National Park. Despite aggressive supportive therapy, the patient died on the 11th day of illness. No further cases were detected [4].
1998-2000	Democratic Republic of Congo (DRC)	Durba, DRC	154	128 (83)	Most cases occurred in young male workers at a gold mine in Durba, in the north-eastern part of the country, which proved to be the epicentre of the outbreak. Cases were subsequently detected in the neighboring village of Watsa [5].
2004-2005	Angola	Uige Province, Angola	252	227	Outbreak believed to have begun in Uige Province in October 2004. Most cases detected in other provinces have been linked directly to the outbreak in Uige [6].
2007	Uganda	Lead and gold mine in Kamwenge District, Uganda	2	2 (50)	Small outbreak, with 2 cases in young males working in a mine. To date, there have been no reported cases among health workers [7].
2008	Netherlands ex Uganda	Cave in Maramagambo forest in Uganda, at the southern edge of Queen Elizabeth National Park.	1	1 (100)	A 40-year old Dutch woman with a recent history of travel to Uganda was admitted to a hospital in the Netherlands. Three days prior to hospitalization, the first symptoms (fever, chills) occurred, followed by rapid clinical deterioration. The woman died on the 10th day of the illness. [8] [9]

Cause

Marburg virus (MARV) forms its own genus within the family Filoviridae and, at present, only a single species – Lake Victoria marburg–virus – has been described. Numerous genetically distinct strains of MARV have been isolated from human cases over the years, all of which are closely related to one another, with the exception of the Ravn strain and a closely related but unnamed isolate from the Democratic Republic of the Congo (DRC), which are notably divergent from all other known strains [1,2]. Marburg virus is the causative agent of Marburg virus disease (MVD), a disease with a case fatality ratio of up to 88%. Marburg haemorrhagic fever was initially detected in 1967 after simultaneous outbreaks in Marburg and Frankfurt in Germany; and in Belgrade, Serbia.



Negative stain image of an isolate of Marburg virus, showing filamentous particles as well as the characteristic "Shepherd's Crook." Magnification approximately 100,000 times. Image courtesy of Russell Regnery, Ph.D., DVRD, NCID, CDC.

Marburg and Ebola viruses are both members of the Filoviridae family (filovirus). Though caused by different viruses, the two diseases are clinically similar. Both diseases are rare and have the capacity to cause dramatic outbreaks with high fatality rates [55,54]. Marburg virus can affect both humans and nonhuman primates. It is a unique zoonotic RNA virus of the filoviridae family, which is Latin words for "thread virus"; Ebola viruses are the only other known members of the family by far. The two diseases are almost clinically indistinguishable [54,56]. Both are rare, have high mortality rates, and have the capacity of dramatic outbreaks. Filoviruses have the potential of being used as "Category A" biological weapons, because of the high lethality, ability to be aerosolized, and the ability to induce fear and anxiety. Unfortunately, the outbreaks seemed to alert the health authorities only after the transmission has been aggravated by inadequate disease control [53,58].

Although the native geographic area of Marburg virus is still in question, according to the past records, this endemic area appears to include at least parts of Uganda, Western Kenya, and perhaps Zimbabwe. Like Ebola virus, the actual animal reservoir remains a mystery, and how the animal host transmits Marburg virus to humans is unknown [57,59]. However, victims of Marburg hemorrhagic fever may spread the virus to other people. Spread of the virus between humans often occurred in a hospital, or in close contact. Direct contacts with body fluids, blood of the patients, or other objects contaminated with infectious tissues are all highly suspected as sources of transmission [52,56].

Transmission

Marburg virus transmission can occur through mucosal surfaces and breaks or abrasions of the skin, as well as through parenteral introduction [2]. In outbreak situations, direct contact with infected humans or animals is the most common source of infection, while parenteral exposure, often in the nosocomial setting, is the most lethal route of infection [2]. During the 1967 outbreak, the majority of cases had direct contact with blood and organs of infected African green monkeys used to produce primary cell cultures, or were involved in post–mortem examinations of infected animals [3,14]. However, secondary spread to individuals that did not have contact with infected animal materials was also clearly documented.

Human–to–human transmission of MARV typically occurs via direct contact with blood or other secretions/excretions (e.g., saliva, sweat, stool, urine, tears or breast milk), usually during the care of infected patients [8,15,16]. In addition, data from the 1998–2000 DRC outbreak also indicated that the handling of corpses during burial proceedings was a significant risk factor [17]. The 1967 outbreak included a possible sexual transmission during convalescence, supported by the detection of virus antigen in the patient's semen [18]. While the risk of aerosol transmission of MARV in the natural setting is believed to below, the virus is stable in aerosols, and nonhuman primate (NHP) studies have demonstrated that MARV is highly infectious and lethal following experimental aerosol

exposure [19,20], which raises the concern that MARV may be exploitable as a bioterrorism agent. Since recent studies have strongly suggested that certain African fruit bat species, in particular Roussettus aegypticus, might be a natural reservoir for MARV [21], transmission via inhalation of contaminated excreta from infected bats might be considered as a primary route of introduction into the human population [9,10,21].

It is unknown how Marburg virus first transmits from its animal host to humans; however, for the 2 cases in tourists visiting Uganda in 2008, unprotected contact with infected bat feces or aerosols are the most likely routes of infection. After this initial crossover of virus from host animal to humans, transmission occurs through person-to-person contact [53,60]. This may happen in several ways: direct contact to droplets of body fluids from infected persons, or contact with equipment and other objects contaminated with infectious blood or tissues. In previous outbreaks, persons who have handled infected non-human primates or have come in direct contact with their fluids or cell cultures have become infected. Spread of the virus between humans has occurred in close environments and direct contacts. A common example is through caregivers in the home or in a hospital (nosocomial transmission) [47,59].

Initially, human MVD infection results from prolonged exposure to mines or caves inhabited by Rousettus bat colonies. Marburg spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. Health-care workers have frequently been infected while treating patients with suspected or confirmed MVD [46,55]. This has occurred through close contact with patients when infection control precautions are not strictly practiced [49,61]. Transmission via contaminated injection equipment or through needle-stick injuries is associated with more severe disease, rapid deterioration, and, possibly, a higher fatality rate. Burial ceremonies that involve direct contact with the body of the deceased can also contribute in the transmission of Marburg. People remain infectious as long as their blood contains the virus [58,62].

Sexual transmission

Marburg virus transmission via infected semen has been documented up to seven weeks after clinical recovery. More surveillance data and research are needed on the risks of sexual transmission, and particularly on the prevalence of viable and transmissible virus in semen over time. In the interim, and based on present evidence, WHO recommends that:

- All Marburg survivors and their sexual partners should receive counselling to ensure safer sexual practices until their semen has twice tested negative for Marburg virus.
- Survivors should be provided with condoms.
- Male Marburg survivors should be enrolled in semen testing programmes when discharged (starting with counselling) and offered semen testing when mentally and physically ready, within three months of disease onset.
- Marburg survivors and their sexual partners should either:
  - o abstain from all sexual practices, or
  - o observe safer sexual practices through correct and consistent condom use until their semen has twice tested undetected (negative) for Marburg virus.
- Having tested undetected (negative), survivors can safely resume normal sexual practices with minimized risk of Marburg virus transmission.
- Male survivors of Marburg virus disease should practice safer sexual practices and hygiene for 12 months from onset of symptoms or until their semen twice tests undetected (negative) for Marburg virus.
- Until such time as their semen has twice tested undetected (negative) for Marburg, survivors should practice good hand and personal hygiene by immediately and thoroughly washing with soap and water after any physical contact with semen, including after masturbation. During this period used condoms should be handled safely, and safely disposed of, so as to prevent contact with seminal fluids.
- All survivors, their partners and families should be shown respect, dignity and compassion [62,63].

Clinical Disease

The clinical syndromes caused by filoviruses and the associated disease severity may vary depending on several factors such as the medical setting, host susceptibility and genetics and

virulence of the viral strain. However, comprehensive clinical data were obtained during both the first outbreak in 1967 and during the 1998–2000 DRC outbreak, and these form the basis for much of our knowledge about MHF disease progression today [3,8,22,25]. Clinical signs/symptoms during the course of the disease are summarized in Figure 2. Overall, the incubation period in humans ranges from 2 to 21 days, with an average overall incubation period of 5–9 days [3,22]. The disease course largely presents in three distinct phases: a generalization phase, an early organ phase and a late organ or convalescence phase, depending on the outcome of infection [26]. The generalization phase begins with influenza–like symptoms commencing with a high fever (~40°C) accompanied by a severe headache, chills, myalgia and malaise [5,15]. This phase potentially lasts until day 5 after the onset of disease and is accompanied by rapid debilitation. Fatigue, generalized pain and loss of appetite followed by vomiting, nausea, abdominal pain and severe watery diarrhea have all been reported [2]. Conjunctivitis, enanthem, dysphagia and pharyngitis are also common. A rash may also appear on the face, trunk and extremities during the middle–to–late part of the generalization phase and ultimately develops into a maculopapular rash [25].

The disease then progresses into the early organ phase (days 5–13 after onset of disease), which is associated with prostration, dyspnea, exanthema and abnormal vascular permeability including conjunctival injection and edema [2]. This early organ phase represents the beginning of the severe phase of the disease. Patients may continue to sustain a high fever through this phase and into the late organ phase and may also display neurological symptoms including encephalitis, confusion, delirium, irritability and aggression [5,15,16]. During the later part of the early organ phase, patients may start to display clear hemorrhagic manifestations such as petechiae, mucosal bleeding, uncontrolled leakage from venipuncture sites, visceral hemorrhagic effusions, melena, bloody diarrhea, hematemesis and ecchymoses. During this phase, multiple organs are affected including the pancreas, liver and kidneys. The late organ phase is identified as lasting from day 13 until day 20+ in the course of illness. In this phase, the patient's condition develops into a critical state, which can include convulsions, severe metabolic disturbances, diffuse coagulopathy, multiorgan failure and shock. In this stage, severe dehydration reduces circulation, resulting in multiorgan dysfunction and anuria. Patients in the preagonal stage develop neurological symptoms including restlessness, obtundation, confusion, dementia or coma. Spontaneous abortion represents an additional complication in pregnant women [8,16]. Fatalities typically occur between 8–16 days after the onset of symptoms [5,15,16]. Survivors do not normally display the most severe manifestations of disease and may not even reach the late organ phase. During the recovery and convalescent phase, those patients often suffer complications such as myalgia, arthralgia, asthenia, hepatitis, ocular disease and psychosis. Social separation is of particular concern [42,53].

After an incubation period of 5-10 days, symptom onset is sudden and marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea may then appear [56,59]. Symptoms become increasingly severe and can include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, massive hemorrhaging, and multi-organ dysfunction. Because many of the signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases such as malaria or typhoid fever, clinical diagnosis of the disease can be difficult, especially if only a single case is involved. The case-fatality rate for Marburg hemorrhagic fever is between 23-90% [45,67].

The incubation period (interval from infection to onset of symptoms) varies from 2 to 21 days. Illness caused by Marburg virus begins abruptly, with high fever, severe headache and severe malaise. Muscle aches and pains are a common feature. Severe watery diarrhoea, abdominal pain and cramping, nausea and vomiting can begin on the third day. Diarrhoea can persist for a week. The appearance of patients at this phase has been described as showing "ghost-like" drawn features, deep-set eyes, expressionless faces, and extreme lethargy. In the 1967 European outbreak, non-itchy rash was a feature noted in most patients between 2 and 7 days after onset of symptoms [51,64].

Many patients develop severe haemorrhagic manifestations between 5 and 7 days, and fatal cases usually have some form of bleeding, often from multiple areas. Fresh blood in vomitus and faeces is often accompanied by bleeding from the nose, gums, and vagina. Spontaneous bleeding at venepuncture sites (where intravenous access is obtained to give fluids or obtain blood samples) can be particularly troublesome. During the severe phase of illness, patients have sustained high fevers. Involvement of the central nervous system can result in confusion, irritability, and aggression. Orchitis (inflammation of one or both testicles) has been reported occasionally in the late phase of disease (15 days). In fatal cases, death occurs most often between 8 and 9 days after symptom onset, usually preceded by severe blood loss and shock [48,63].

Persistent virus in people recovering from Marburg virus disease

Marburg virus is known to persist in immune-privileged sites in some people who have recovered from Marburg virus disease. These sites include the testicles and the inside of the eye.

- In women who have been infected while pregnant, the virus persists in the placenta, amniotic fluid and fetus.
- In women who have been infected while breastfeeding, the virus may persist in breast milk.

Relapse-symptomatic illness in the absence of re-infection in someone who has recovered from MVD is a rare event, but has been documented. Reasons for this phenomenon are not yet fully understood [50,57].

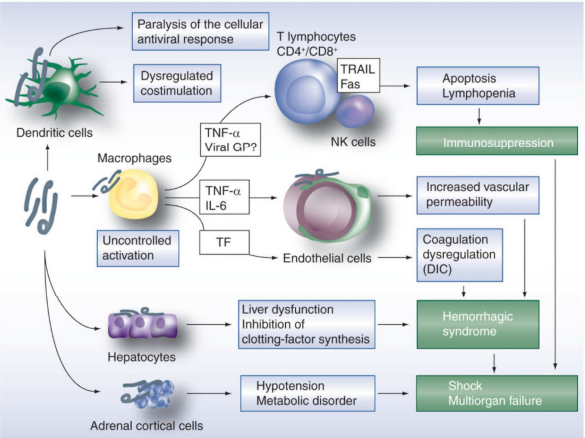


Fig 3. Marburg hemorrhagic fever pathogenesis model

Primary targets cells for Marburg virus infection are macrophages and dendritic cells. In dendritic cells, infection leads to 'paralysis' of the innate response and dysregulation of costimulation of lymphocytes. Macrophage infection leads to the production of proinflammatory mediators such as TNF-α, which may induce bystander apoptosis in lymphocyte populations, thereby contributing to lymphopenia and immunosuppression. Together with IL-6, macrophage-derived TNF-α also induces changes in vascular permeability. In addition, the production of TF by infected macrophages leads to dysregulation of coagulation (e.g., DIC), which is further reinforced by hepatocyte infection, leading to decreased synthesis of liver-derived clotting factors. Infection of adrenal cortical cells results in hypotension and metabolic disorders, which together with immunosuppression and coagulopathy contribute to multiorgan failure and shock.

DIC: Disseminated intravascular coagulation; GP: Glycoprotein; TF: Tissue factor; TRAIL: TNF-related apoptosis-inducing ligand [65,70].

After an incubation period of 3 to 10 days, the onset of Marburg hemorrhagic fever is abrupt with fever, chills, severe frontal headache, and myalgia. Around the fifth day after the onset, maculopapular rashes, most on the trunk (chest, back, stomach), may occur, and followed by nausea, vomiting, diarrhea, abdominal pain, chest pain and sore throat. Rashes may be nonexistent, transient, nonspecific, or petechial. Hemorrhagic symptoms include epistaxis, hemoptysis, hematemesis, or gums bleeding. Symptoms may become increasingly severe, include jaundice, pancreatic inflammation, weight loss, delirium, shock, liver failure, and multi-organ dysfunction. Death often occurs 6 to 9 days after the onset of the symptoms. Recovery from the disease may be prolonged and accompanied by orchititis, hepatitis, transverse myelitis, uvetis or parotitis. Previous large outbreak in the Democratic Republic of Congo from 1998 through 2000, had a mortality rate of 83%. On the other hand, Ebola hemorrhagic fever has shown mortality rates differs from 53% to 88%, according to the different virus strains. The possibility of person-to-person transmission is greatest during the latter stages of illness. Transmission during the incubation period has not been reported, but the patients may become

infectious during the first few days since the onset of fever [52,65].

Diagnosis

Marburg hemorrhagic fever should be considered in patients who had traveled to West Africa in the recent 3 weeks present with acute febrile illness without other apparent source. The diagnosis should also be suspected if patients have had direct contact with body fluids or blood of a person or animal with this disease in either the trip or during the work. The likelihood of acquiring Marburg hemorrhagic fever is extremely low in persons not meeting any of these criteria. Two factors make the rapid recognition of the outbreaks difficult: the extreme rarity and its similarity to other diseases. Many signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases, makes the early diagnosis difficult and early suspicion important. Different diagnosis include dengue hemorrhagic fever, typhoid fever, malaria, leptospirosis, relapsing fever, meningococcemia, relapsing fever, rickettsial infections, viral hepatitis, the acute form of African trypanosomiasis, and other arboviral infections [45,68].

The laboratory assessment of suspected patients should include a complete blood cell counts with differential, hepatic function testing, urinalysis, chemistries, blood cultures, and urine cultures. Leukopenia and thrombocytopenia may increase the likelihood of viral hemorrhagic fever, but these results are not specific. Blood cultures may help to diagnose bacterial infection, and peripheral blood smear may help to rule out malaria. Polymerase chain reaction (PCR), virus isolation, antigen-capture enzyme-linked immunosorbent assay (ELISA) testing and IgM-capture ELISA can be used to confirm the diagnosis within a few days after the onset of symptoms, but these examinations are not available worldwide. Confirmation of the disease is often made long after the emergency department visit [68,69].

The control of MHF outbreaks relies on a combination of case identification, contact tracing and patient isolation, supported with laboratory diagnostics. Clinical diagnosis of MHF is difficult in the early phase of an outbreak because of the similarities in the clinical symptoms with many tropical infectious diseases, in particular malaria, rickettsial infections and typhoid fever [66]. This often results in a critical delay in implementing infection control procedures and the initiation of patient management. Individual cases outside the epidemic area need more extensive diagnostic evaluation and careful consideration of the patient's travel history to confirm MHF [47,51].

Laboratory diagnostics consist of virological, serological and molecular methods. The most suitable and reliable specimen for diagnostics is blood (whole blood and serum) but other specimens such as saliva (oral swab) and urine (less reliable), as well as breast milk, can serve as alternative specimen sources if blood is not available [67,68]. First–line diagnostics for MHF rely primarily on the detection of viral genome by reverse transcription PCR (RT–PCR) methods or viral antigen by ELISA technology [66]. Detection of the host immune response is achieved mainly using antibody detection ELISA. Virus isolation and electron microscopy serve as confirmatory options with the restriction that they can only be performed at certain specialized locations having the necessary facilities. To date, conventional RT–PCR, quantitative real–time RT–PCR and reverse transcription loop–mediated isothermal amplification methods have been developed for the detection of MARV RNA in clinical specimens [1,68–71]. These techniques are high throughput and rapid. They also display high sensitivity and specificity and are widely applied primary choices for MARV diagnosis. In addition, the chaotropic agent guanidinium isothiocyanate, a major component of most commercial RNA extraction buffers, has been proven to render the diagnostic samples noninfectious, allowing safe handling of clinical material.

Furthermore, pan–MARV or pan–filovirus RT–PCR assays that amplify all known MARV strains or even all known filovirus species using consensus PCR primer sets have been developed for rapid diagnostic screening [72]. These broadly cross–specific primer sets will potentially provide an increased ability to detect a wide array of filoviruses, which would aid not only in patient identification and early outbreak control, but also in epidemiological and epizoological investigations. Currently, RT–PCR and quantitative real–time RT–PCR are utilized as the standard for molecular diagnosis in the field. In the future, however, the reverse transcription loop–mediated isothermal amplification method

may replace these assays owing to its simplicity and lower costs [70].

The main alternative and confirmatory assay for acute MHF diagnostics is the antigen detection ELISAs. These assays use either hyperimmune serum or virus protein–specific (e.g., nucleoprotein) antibodies to capture MARV antigen [66,73]. Direct IgM and IgG ELISAs, as well as IgM–capture ELISAs, are commonly used for the detection of virus–specific antibodies. MARV–specific IgM antibodies can appear as early as 2 days postonset of symptoms and disappear from 30 to 168 days after infection, while IgG antibodies can persist for many years (Figure 2). Accordingly, IgM–capture ELISAs are more frequently used for the diagnosis of acute illness, while IgG ELISAs are primarily used to identify individuals who have recovered from MHF infection or for conducting epidemio logical (serosurveys) and epizoological studies [60]. The more recently developed ELISAs use recombinantly expressed viral proteins rather than infected cell lysates as antigens for the detection of virus–specific antibodies [74–76].

In addition to these highly specific tests for MARV diagnostics, broad clinical syndrome–based technologies have been developed on the basis of multiplex PCR and pan–microbial oligonucleotide array technologies [77]. These assays; however, have yet to be implemented into common diagnostic settings. It can be difficult to clinically distinguish MVD from other infectious diseases such as malaria, typhoid fever, shigellosis, meningitis and other viral haemorrhagic fevers. Confirmation that symptoms are caused by Marburg virus infection are made using the following diagnostic methods:

- antibody-capture enzyme-linked immunosorbent assay (ELISA)
- antigen-capture detection tests
- serum neutralization test
- reverse transcriptase polymerase chain reaction (RT-PCR) assay
- electron microscopy
- virus isolation by cell culture.

Samples collected from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions. All biological specimens should be packaged using the triple packaging system when transported nationally and internationally.

One health approach in control and prevention (including treatment prevention and vaccines)

Since there is no specific therapy for MARV available, treatment currently involves palliative management of symptoms, including pain management and supportive care measures, such as maintenance of blood volume and electrolyte balance [5,78]. While it remains unclear to what extent this kind of supportive therapy improves patient outcome, it must be noted that patients treated in countries with the infrastructure to provide a high standard of intensive care have much lower case–fatality rates than those reported during the recent outbreaks in Angola and DRC. Over the years, different, mainly unspecific, treatment approaches have been applied in MHF patients. In addition, several experimental approaches have also been evaluated in animal models. Table 2 summarizes and discusses the outcomes of those attempts. During the 1967 MARV outbreak, patients were treated with various antibiotics, antipyretics and clotting factor concentrates [3,79], mainly to reduce fever, prevent and treat secondary infections and counteract coagulation disorders, respectively. This approach still forms a part of any intensive care regime today. In addition, convalescent serum transfer was applied in a few secondary cases during the 1967 outbreak [26,80] and extracorporeal hemosorbent and hemodialysis therapy was applied in a Russian case resulting from laboratory exposure [12]. Despite positive outcomes in these cases, the actual value of these treatment approaches is questionable owing to the low number of cases. In addition, those treated by passive transfer of convalescent plasma were secondary cases, which are generally less severe regardless of treatment.

Experimental approaches evaluated in the various animal models for MHF have mostly targeted either the virus or host responses. Ribavirin, a broad–spectrum synthetic guanosine analog, with virustatic activity against a number of DNA and RNA viruses [81], and IFN have demonstrated no beneficial effect on MARV infection [82,83]. The value of passive antibody therapy using either convalescent serum or monoclonal antibodies has been revisited over the years. While the initial success in the 1967 outbreak was questionable [22], IgG purified from horse serum has shown efficacy in the guinea pig model [84] and, more recently,

researchers have demonstrated efficacy of NHP–derived convalescent serum in a passive–transfer experiment using the NHP model [85]. Monoclonal antibodies targeting glycoprotein or VP40 have also shown efficacy in the guinea pig model [86,87]. Among the most promising approaches currently being investigated is the use of phosphorodiamidate morpholino oligomers inhibiting viral protein expression, which has also shown efficacy in the NHP model [88]. The other promising approach is postexposure treatment with a recombinant vesicular stomatitis virus (VSV)–based vaccine expressing MARV glycoprotein [34,89,90]. This approach has demonstrated efficacy in NHPs when administered once up to 48 h postinfection. While the mechanism of this vaccine in post exposure treatment remains unknown, it is most likely related to viral interference and/or the induction a strong innate immune response.

Some therapeutic success has also been reported by targeting deleterious host responses; however, most of these approaches have not yet been evaluated in NHP models. Neutralizing antibodies against TNF–α have demonstrated efficacy in the guinea pig model only when administered 3 days post-infection [91,92], but not if administered earlier in infection, perhaps indicating that TNF–α plays a beneficial role for the early host immune response. Guinea pigs were also protected by treatment with Desferal® (Novartis), an IL–1 and TNF–α antagonist [82], and partially protected by treatment with an IL–1 receptor antagonist [93]. More recently, moderate effects have been achieved in NHPs using treatment with the TF/factor VIIa inhibitor rNAPc2. The effect was reduced compared with previous promising data in the EBOV NHP model [24], and may suggest a less prominent involvement of the TF pathway in MARV pathogenesis. However, since challenge in this study was performed with the seemingly more virulent Angola strain, the outcome may also be more promising with other MARV strains.

Early attempts at vaccine development against MARV used formalin–inactivated virus and demon strated partial protection in both the guinea pig and NHP models [94]. However, given the inherent safety concerns with this approach, efforts to further develop this platform have ceased. DNA vaccination approaches based on plasmids expressing MARV glycoprotein and/or nucleoprotein require multiple vaccinations to achieve protection from lethal outcome, but not disease development, suggesting that this approach alone is also not ideal [95,96]. More recently, many of the attempts to develop a vaccine have focused on the use of various live attenuated (e.g., VSV) and replication defective (e.g., Venezuelan equine encephalomyelitis and adenovirus, mainly adenovirus serotype 5) vectors, with significant successes in the NHP model (summarized in [97]. Those vaccination approaches that have been shown to be protective in NHPs are summarized in Table 3. At present, the most promising approaches are the recombinant Ad5– and VSV–based vectors expressing the Musoke strain glycoprotein. Both of these platforms have shown protective/cross–protective efficacy after a single immunization in the NHP model against challenge with all known MARV strains, even the genetically divergent Ravn strain and the more virulent Angola strain [33,98–100]. Equally promising is vaccination based on the use of virus–like particles (VLPs), which physically resemble authentic MARV particles but are only composed of glycoprotein, nucleoprotein and VP40, and thus nonreplicating and noninfectious. VLP vaccination works best in combination with an adjuvant and showed protective efficacy in NHPs against challenge with a range of MARV strains [101]. Each of these approaches has advantages and disadvantages. The VSV vectors are attenuated but replication competent, thus their safety remains the major concern. The Ad5 vectors are replication incompetent but pre–existing immunity in the human population is expected to reduce their efficacy, and while the VLP platform is seemingly the safest approach, large–scale production and multiple administrations remain issues [97].

Treatment for Marburg hemorrhagic fever is primarily supportive, including airway protection with ventilator support when necessary, adequate fluid supply, maintenance of electrolytes balance, and vasopressors for the hypotension. If the coagulopathy was developed, transfusion of fresh-frozen plasma and other blood products may be needed to replace the coagulating factors and platelets. Most patients need to be admitted to the intensive care unit for continuous monitoring and management. Ribavirin, which has been seemed effective in the treatment of Lassa fever, does not have good in-vitro activity for Marburg virus [53,59].

Supportive care (rehydration with oral or intravenous fluids) and treatment of specific symptoms, improves survival. There is as yet no proven treatment available for MVD. However, a range of potential treatments including blood products, immune therapies and drug therapies are currently being evaluated [60,85].

Preventive measures against Marburg virus infection are not well defined, as transmission from wildlife to humans remains an area of ongoing research. However, avoiding fruit bats, and sick non-human primates in central Africa, is one way to protect against infection. Measures for prevention of secondary, or person-to-person, transmission are similar to those used for other hemorrhagic fevers. If a patient is either suspected or confirmed to have Marburg hemorrhagic fever, barrier nursing techniques should be used to prevent direct physical contact with the patient. These precautions include wearing of protective gowns, gloves, and masks; placing the infected individual in strict isolation; and sterilization or proper disposal of needles, equipment, and patient excretions. In conjunction with the World Health Organization, CDC has developed practical, hospital-based guidelines, titled: Infection Control for Viral Haemorrhagic Fevers in the African Health Care Setting. The manual can help health-care facilities recognize cases and prevent further hospital-based disease transmission using locally available materials and few financial resources [62,75,103].

Marburg hemorrhagic fever is a very rare human disease. However, when it occurs, it has the potential to spread to other people, especially health care staff and family members who care for the patient. Therefore, increasing awareness in communities and among health-care providers of the clinical symptoms of patients with Marburg hemorrhagic fever is critical. Better awareness can lead to earlier and stronger precautions against the spread of Marburg virus in both family members and health-care providers. Improving the use of diagnostic tools is another priority. With modern means of transportation that give access even to remote areas, it is possible to obtain rapid testing of samples in disease control centers equipped with Biosafety Level 4 laboratories in order to confirm or rule out Marburg virus infection [78,81, 102].

Next steps: While research efforts have led to significant advances in recent years, particularly with respect to our understanding of MARV ecology and the development of treatment and vaccination options, much remains to be done. In particular, there are surprisingly few data regarding MARV pathogenesis in either humans or animal models, with the limited studies indicating differences between MARV and EBOV biology and pathogenesis. In addition, the occurrence of larger outbreaks in recent years suggests that MARV should be considered a much greater public health threat in the future than it is currently [102]. This highlights the need for the development of quick and reliable diagnostic methods that can be applied both in laboratory and field settings, more careful clinical investigations during future MHF outbreaks in order to better understand pathogenesis in humans and intensified efforts to develop new therapies and vaccines, as well as pushing current promising products through the regulatory licensing process [55,66,104].

Prognosis

Recent outbreaks have shown that MARV is capable of causing much more serious outbreaks than once thought. These large outbreaks not only had unprecedentedly high case–fatality rates but also demonstrated that MARV affects a much larger geographical region than was previously appreciated. This, together with two recently imported MHF cases into Europe and the USA, emphasizes the potential role of MARV as a serious public health threat, not just in Africa, and makes clear the need to better understand the pathogenesis of MARV and develop therapeutic and/or prophylactic interventions [40,54]. At present, much of our current appreciation of MARV pathogenesis is based on early case reports together with comparisons to EBOV. However, research in this area has begun to identify an increasing number of differences between EBOV and MARV in terms of their pathogenesis, both at the clinical and molecular levels. This highlights the need for more research into MARV infection and MHF specifically, as well as a need for greater appreciation of MHF as a distinct clinical entity. Certainly, our ability to manage future MHF outbreaks as well as imported cases or laboratory–acquired infections would be vastly enhanced by the availability of vaccines and therapeutic options. While this area of research has seen tremendous progress in recent years, these efforts must be maintained

and targeted towards product development and licensure [67,79,105].

Recommendations for people at high risk

People who have close contact with African fruit bats, humans patients, or non-human primates infected with Marburg virus are at risk. Historically, the people at highest risk include family members and hospital staff who care for patients infected with Marburg virus and have not used proper barrier nursing techniques. Particular occupations, such as veterinarians and laboratory or quarantine facility workers who handle non-human primates from Africa, may also be at increased risk of exposure to Marburg virus. Exposure risk can be higher for travelers visiting endemic regions in Africa, including Uganda and other parts of central Africa, and have contact with fruit bats, or enter caves or mines inhabited by fruit bats [61,71,106].

Marburg virus in animals

Rousettus aegyptiacus bats are considered natural hosts for Marburg virus. There is no apparent disease in the fruit bats. As a result, the geographic distribution of Marburg virus may overlap with the range of Rousettus bats. African green monkeys (Cercopithecus aethiops) imported from Uganda were the source of infection for humans during the first Marburg outbreak. Experimental inoculations in pigs with different Ebola viruses have been reported and show that pigs are susceptible to filovirus infection and shed the virus. Therefore pigs should be considered as a potential amplifier host during MHF outbreaks. Although no other domestic animals have yet been confirmed as having an association with filovirus outbreaks, as a precautionary measure they should be considered as potential amplifier hosts until proven otherwise. Precautionary measures are needed in pig farms in Africa to avoid pigs becoming infected through contact with fruit bats. Such infection could potentially amplify the virus and cause or contribute to MHF outbreaks [69,78,107].

Controlling infection in healthcare settings

Healthcare workers should always take standard precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe and dignified burial practices [40,50].

Healthcare workers caring for patients with suspected or confirmed Marburg virus should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with MVD, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures) [52,58].

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Marburg infection should be handled by trained staff and processed in suitably equipped laboratories [45,56].

Since its first identification in 1967, Marburg virus has been notorious in the recent 20 years because of its high mortality rates, and the capacity of dramatic outbreaks. The potential to spread the disease worldwide has become a reality with the expansion of global transportation and international trade. Physicians need to be aware of the potential danger of Marburg hemorrhagic fever, be able to identify the disease, and know how to manage and prevent its transmission [90,98]. Owing to the limited knowledge of the disease and the absence of a vaccine, effective prevention against transmission from the original hosts has not yet been established. Preventions of secondary transmission are therefore the most important prophylaxis by far. Rapid identification the disease and isolation of patients is the first step to prevent the outbreak. Patients in the hospital should be placed in negative-pressure isolation rooms to minimize the possibility of in-hospital spread and the need for transfer if the condition deteriorates. When caring patient with suspected or confirmed Marburg hemorrhagic fever, barrier nursing techniques should be used to prevent direct physical contact. These precautions include wearing of protective masks, gloves, and gowns, and proper disposal of patient excretions, needles, and equipments [89,91,107].

Since people who have close contact with patients are at risk, they should undergo daily medical surveillance by an appropriate infection control agency. These include the healthcare workers in the hospital. Isolation measures should be started immediately in any febrile

patient who has traveled to the endemic area of Marburg hemorrhagic fever within 10 days before fever onset, has contacted with blood or other body fluids from a infected person or animal, or worked in a laboratory handling the specimens of Marburg hemorrhagic fever [88,99].

Recommendations for people not at high risk

Marburg hemorrhagic fever is an uncommon infectious disease. However, its outbreak is a disaster for the affected people and involved area. Better awareness and prevention can keep the disease from spreading. Improved diagnostic tools, more detailed pathophysiology, the specific treatment and even a vaccine are other urgent issues. Human-to-human Ebola and Marburg transmission occurs through blood, body fluids, and contaminated objects. Strict compliance with biosafety guidelines is required to prevent epidemic spread and reduce the number of victims [92,101].

Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe and dignified burials, and social mobilization. Community engagement is key to successfully controlling outbreaks. Raising awareness of risk factors for Marburg infection and protective measures that individuals can take is an effective way to reduce human transmission [79,85].

Risk reduction messaging should focus on several factors:

• Reducing the risk of bat-to-human transmission arising from prolonged exposure to mines or caves inhabited by fruit bat colonies. During work or research activities or tourist visits in mines or caves inhabited by fruit bat colonies, people should wear gloves and other appropriate protective clothing (including masks). During outbreaks all animal products (blood and meat) should be thoroughly cooked before consumption [84,92].

• Reducing the risk of human-to-human transmission in the community arising from direct or close contact with infected patients, particularly with their body fluids. Close physical contact with Marburg patients should be avoided. Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home. Regular hand washing should be performed after visiting sick relatives in hospital, as well as after taking care of ill patients at home [70,86].

• Communities affected by Marburg should make efforts to ensure that the population is well informed, both about the nature of the disease itself and about necessary outbreak containment measures [87,97].

• Outbreak containment measures include prompt and safe burial of the dead, identifying people who may have been in contact with someone infected with Marburg and monitoring their health for 21 days, separating the healthy from the sick to prevent further spread, and maintaining good hygiene and a clean environment need to be observed [82,83].

• Reducing the risk of possible sexual transmission. Based on further analysis of ongoing research, WHO recommends that male survivors of Marburg virus disease practice safe sex and hygiene for 12 months from onset of symptoms or until their semen twice tests negative for Marburg virus. Contact with body fluids should be avoided and washing with soap and water is recommended. WHO does not recommend isolation of male or female convalescent patients whose blood has been tested negative for Marburg virus [63,73,108].

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