CD Alert

National Centre for Disease Control,
Directorate General of Health Services, Government of India

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# Marburg Virus Disease

## INTRODUCTION

Marburg virus disease (MVD), formerly known as Marburg hemorrhagic fever, is a rare but severe disease in humans caused by Marburg virus (MARV). Although MVD is uncommon, MARV has the potential to cause epidemics with significant case fatality rates. All recorded MVD outbreaks have originated in Africa. MVD is not an airborne disease and is considered not to be contagious before symptoms appear. Direct contact with the blood and other body fluids of infected people and animals or indirect contact with contaminated surfaces and materials like clothing, bedding and medical equipment is required for MARV transmission. As a result, if proper infection prevention and control and contact precautions are strictly followed, the risk of infection is regarded as minimal. There is no approved vaccine for MVD; however, several candidate MVD vaccines are in clinical trials.

## HISTORICAL BACKGROUND

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). MARV was named after the German city where it was first characterized. 31 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 Ugandan imported African green monkeys or their tissues while conducting research. Over 600 cases have been reported since then in outbreaks in Uganda, Democratic Republic of Congo (DRC), Angola, Equatorial Guinea, and most recently Tanzania.

## EPIDEMIOLOGY

### Burden Worldwide

### Global Situation

**Equatorial Guinea Outbreak:** This year on February 13, 2023, the Government of Equatorial Guinea (GREG) declared a Marburg virus disease (MVD) outbreak, the country's first outbreak of the disease. Cases were reported in several provinces, including Kie-Ntem, Littoral, and Centro Sur. The government declared the outbreak over on May 15, with 16 confirmed cases and 12 deaths. One additional lab-confirmed sample was never linked to a specific patient since the sample was unlabeled. An additional 23 probable cases, all deceased, were also reported during this outbreak. The World Health Organization declared the outbreak over on June 8, 2023, 42 days after the last patient was discharged from treatment.

**Tanzania Outbreak:** On March 21, 2023, Tanzania government officials declared the country's first outbreak of Marburg virus disease. The outbreak was declared over on May 31 with one probable and 8 confirmed cases, with 5 deaths. All cases were reported from the country's northwest Kagera region.

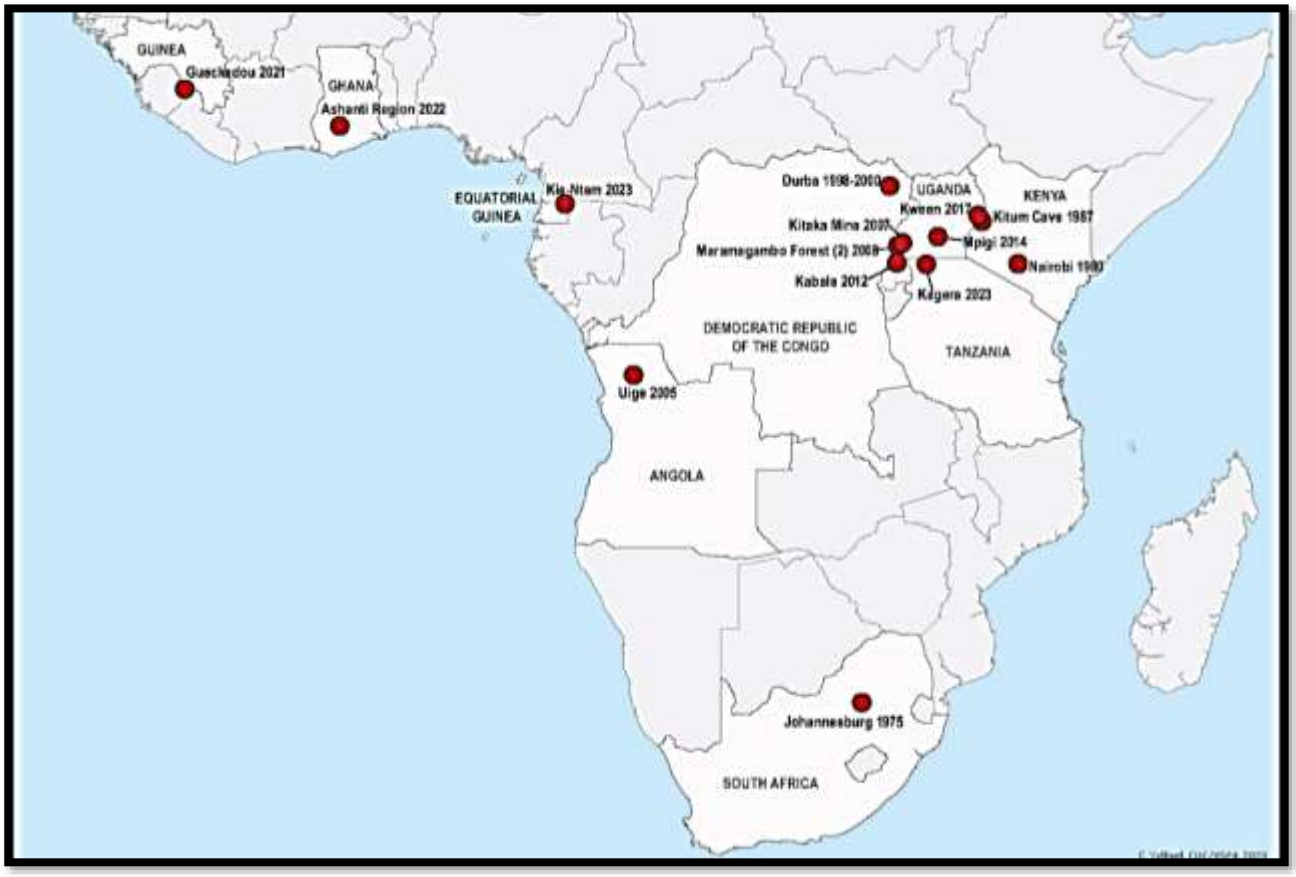
Currently, there is no evidence of a link between the Equatorial Guinea and Tanzania outbreaks. No confirmed cases of MVD related to these outbreaks were reported outside Equatorial Guinea and Tanzania.

No case has been reported in India so far.

All known cases and outbreaks of Marburg Disease are enlisted in table below:

| Year(s) | Country | Apparent or suspected origin | Reported number of human cases | Reported number (%) of deaths among cases |
|---|---|---|---|---|
| **2023** | Tanzania | Kagera Region | 8 | 5 (62.5) |
| | Equatorial Guinea | Kie-Ntem Province | 16 | 12 (75%) |
| **2022** | Ghana | Ashanti Region | 3 | 2 |
| **2021** | Guinea | Guéckédou | 1 | 1 (100%) |
| **2017** | Uganda | Kween | 4 | 3 (75%) |
| **2014** | Uganda | Kampala | 1* | 1 |
| **2012** | Uganda | Kabale | 15 | 4 (27%) |
| **2008** | Netherlands ex Uganda | Cave in Maramagambo forest in Uganda, at the southern edge of Queen Elizabeth National Park | 1 | 1 (100%) |
| **2008** | USA ex Uganda | Cave in Maramagambo forest in Uganda, at the southern edge of Queen Elizabeth National Park | 1 | 0 (0) |
| **2007** | Uganda | Lead and gold mine in Kamwenge District, Uganda | 4 | 1 (25%) |
| **2004 to 2005** | Angola | Uige Province, Angola | 252 | 227 (90%) |
| **1998 to 2000** | Democratic Republic of Congo (DRC) | Durba, DRC | 154 | 128 (83%) |
| **1990** | Russia | Russia | 1 | 1 (100%) |
| **1987** | Kenya | Kenya | 1 | 1 (100%) |
| **1980** | Kenya | Kenya | 2 | 1 (50%) |
| **1975** | Johannesburg, South Africa | Zimbabwe | 3 | 1 (33%) |
| **1967** | Germany and Yugoslavia | Uganda | 31 | 7 (23%) |

(*Numbers reflect laboratory confirmed cases only) Source: https://www.cdc.gov/vhf/marburg/outbreaks/chronology.html




**Marburg virus disease outbreaks in Africa Source: CDC**

## THE CAUSATIVE AGENT

MVD is caused by the Marburg virus, a genetically unique zoonotic (or animal-borne) RNA virus of the Filoviridae family(filovirus). The six species of Ebola virus are the only other known members of the filovirus family. MARV is classified as a risk group 4 (BSL-4) pathogen and requires high level containment and barrier protection measures for laboratory personnel, as well as for anyone caring for potentially infected patients or deceased bodies.

**Marburg virus**

*Pic courtesy: CDC*

### Source of Infection

The geographical range where MARV has been detected in bats (arid woodlands of Equatorial Africa) is more widespread than recorded human outbreaks and they coincide with the presence of the *Rousettus aegyptiacus* bats. The majority of natural MVD outbreaks have been connected to human entry into bat-infested mines and caves, suggesting that bats play a key role in MARV transmission.

However, the virus maintenance and transmission within bat populations remains unknown.

In addition, it is not clear how MARV transmission from bat reservoir to humans occurs.

**African fruit bats (Rousettus aegyptiacus) roosting inside a cave in Uganda**

*Picture courtesy: CDC*

### Natural host

The reservoir host of Marburg virus is the African fruit bat, *Rousettus aegyptiacus*. Fruit bats infected with Marburg virus do not show obvious signs of illness. Primates (including people) 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.

**Incubation period:** The incubation period (interval from infection to onset of symptoms) varies from 2 to 21 days.

**Infectious Period:** Marburg virus is known to persist in immune-privileged sites in some people who have recovered from Marburg virus disease. Viral persistence has been demonstrated in anterior chamber of eye and semen despite an apparently normal immune system. Marburg virus transmission via infected semen has been documented up to seven weeks after clinical recovery.

In women who have been infected while pregnant, the virus persists in the placenta, amniotic fluid and foetus.

- 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.

## ROUTES OF TRANSMISSION

After this initial crossover of virus from host animal to people, transmission occurs mainly through person-to-person by intimate contact. The virus spreads through contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth) with:

- Blood or body fluids (urine, saliva, sweat, faeces, vomit, breast milk, amniotic fluid, and semen) of a person who is sick with or died from Marburg virus disease, or
- Objects contaminated with body fluids from a person who is sick with or has died from Marburg virus disease (such as clothes, bedding, needles, and medical equipment).
- Semen from a man who recovered from MVD (through oral, vaginal, or anal sex). Data on Marburg virus is limited; however, it is known to persist in the testicles and inside of the eye, like ebolaviruses. Since Marburg virus and ebolaviruses are both in the same virus family (*Filoviridae*) it can be assumed that persistence of the Marburg virus in other immune privileged sites (placenta, central nervous system) may be similar. There is no evidence that Marburg virus can spread through sex or other contact with vaginal fluids from a woman who has had MVD.

Spread of the virus between people has occurred in close environments and among direct contacts. A common example is through caregivers in the home or in a hospital via contaminated syringes/ needles etc (nosocomial transmission).

In previous outbreaks, people who have handled infected nonhuman primates or have come in direct contact with their body fluids have become infected with Marburg virus. Laboratory exposures can also occur when lab staff handle live Marburg virus.

**Case Fatality Rate (CFR):** 23-90%

**Risk assessment**

People may be at risk of exposure to Marburg virus if they have close contact with:

- African fruit bats (Rousettus aegyptiacus – the reservoir host of Marburg virus), or their urine and/or excretions;
- People sick with Marburg virus disease; or
- Non-human primates infected with Marburg virus

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 infection prevention and control measures. Certain 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 those travelers visiting endemic regions in Africa who have contact with fruit bats (Rousettus aegyptiacus) or enter caves/mines inhabited by these bats.

## CASE DEFINITION

- **Suspected (clinical) case:**
  Any person living or dead who has or had an acute onset of
  1. Fever

     **AND**

  2. One or more of the following signs/symptoms:
     - severe headache
     - muscle pain
     - erythematous maculopapular rash
     - vomiting
     - bloody diarrhoea
     - abdominal pain
     - bleeding from gums
     - bleeding from other body orifices

     **AND**

     Epidemiologic Linkage

One or more of the following exposures **within the 3 weeks before onset of symptoms:**

- Contact with blood or other body fluids of a patient with MVD
- Residence in—or travel to—an area with active transmission of MVD
- Work in a laboratory that handles MVD specimens
- Work in a laboratory that handles bats, rodents, or primates from an area with active transmission of MVD
- Sexual exposure to semen from a confirmed acute or clinically recovered case of MVD

**Laboratory confirmed case:**

A suspect case with laboratory confirmation (positive IgM antibody, positive PCR or viral isolation) as per laboratory criteria.
In certain scenarios, a case can be considered as lab confirmed even in absence of epidemiological linkage like (contract/travel or lab) if confirmatory test are positive.

**Definition of Marburg case contacts:**

Any person having been exposed to a confirmed case of Marburg within last 21 days, in at least one of the following ways:

- slept in the same household with a case
- direct physical contact with the case (alive or dead) during the illness
- direct physical contact with the (dead) case at the funeral –
- touched his/her blood or body fluids during the illness
- touched his/her clothes or linens
- been breastfed by the patient (baby)
- exposed to biological material in a laboratory

## SURVEILLANCE STRATEGIES

- As cases have not been reported from India, so the surveillance strategies should be more focused at the point of entry in the country (PoE).
- Adequate measures shall be instituted at Points of Entry (PoEs) to make operating airlines and travelers aware of the signs & symptoms of MVD for self-reporting.
- Any person coming from MVD affected areas or having come in contact with suspected or confirmed MVD and develops symptoms within 21 days should immediately report to the designated health care facility.
- The isolation of infected patients combined with appropriate infection prevention and control measures is one of the important public health surveillance activities.
- Contact tracing shall be carried out by IDSP and all identified contacts shall be quarantined as per the protocol.

## CLINICAL FEATURES

After an incubation period of 2-21 days, symptom onset is sudden and marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a nonpruritic, maculopapular centripetal rash, most prominent on the trunk (chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea may appear. Diarrhea 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. 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.
Many patients develop severe hemorrhagic 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 venipuncture 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.

## DIAGNOSIS

Clinical diagnosis of Marburg virus disease (MVD) can be difficult. Many of the signs and symptoms of MVD are like other infectious diseases such as malaria, dengue, typhoid fever or shigellosis, meningitis or viral hemorrhagic fevers that may be endemic in the area (such as Lassa fever or Ebola virus disease).
If a person has early symptoms of MVD and a possible exposure to Marburg virus, the patient should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection.
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 facilities. All biological specimens should be packaged using the triple packaging system when transported nationally and internationally.

## TREATMENT

Currently there are no antiviral treatments approved for MVD. Since, there is no specific treatment for Marburg virus disease, supportive hospital therapy should be utilized, which includes balancing the patient's fluids and electrolytes, maintaining oxygen status and blood pressure, replacing lost blood and clotting factors, and treatment for any complicating infections. There are monoclonal antibodies (mAbs) and drug therapies under development to combat MARV.
Prognosis is generally poor. If a patient survives, recovery may be prompt and complete, or protracted with sequelae, such as orchitis, hepatitis, uveitis, parotitis, desquamation, or alopecia.

## PREVENTIVE MEASURES

Good outbreak control relies on using a range 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.

**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.

**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.

- **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.

- **Outbreak containment measures** include prompt, safe and dignified burial of the deceased, 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 providing care to confirmed patient and maintaining good hygiene and a clean environment need to be observed.

- **Reducing the risk of possible sexual transmission.** Based on further analysis of ongoing research, WHO recommends that male survivors of Marburg virus disease practice safer 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.

**Controlling infection in healthcare settings**

Healthcare workers should always take standard and contact 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.

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).

Standard operating protocols for infection control and BMW management practices should be implemented at every level of healthcare facility and monitored regularly. Well-equipped isolation wards (adequate infection control practices in place) for patients with symptoms suggestive of highly infectious/contagious diseases are essential to reduce the risk of the spread of nosocomial infection in hospital settings.

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 high-maximum containment equipped laboratories.

Biosafety recommendations for laboratories conducting diagnostic testing for EVD/ MVD with appropriate biosafety BSL3/BSL4 facilities www.paho.org/hq/dmdocuments/2014/2014-cha-procedures-inactivation-ebola.pdf

- Virus isolation or any protocol with viable virus should be done only in a maximum containment BSL4 laboratory. Ensure safe and secure handling and storage of the virus isolates and other specimens from accidental or deliberate release.
- The inactivation of specimens, depending on the detection protocol used, should be performed under BSL3 conditions.
- For non-inactivated samples, RT PCR and enzyme-linked immunosorbent assay (ELISA) testing can be performed at a BSL3 laboratory.
- If samples have been inactivated (i.e. cell lysis) RT PCR and ELISA testing can be performed at a BSL2 laboratory.

**Vaccines**: Currently there are no vaccines approved for MVD.

## CONCLUSION

- Marburg virus disease (MVD), formerly known as Marburg haemorrhagic fever, is a rare but severe, often fatal illness in humans.
- The Marburg virus is transmitted to people from fruit bats and spreads among humans through human-to-human transmission.
- The virus causes severe viral haemorrhagic fever in humans.
- The average case fatality rate is around 50%. Case fatality rates have varied from 23% to 90% in past outbreaks depending on virus strain and case management.
- Currently there are no vaccines or antiviral treatments approved for MVD
- Early supportive care with rehydration, and symptomatic treatment improves survival.
- There is an urgent need for accelerated research and development for the Marburg virus as there is, yet no licensed treatment proven to neutralize the virus, but a range of blood products, immune therapies and drug therapies are currently under development.
- Community engagement is key to successfully controlling outbreaks.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