The Current Pathogenicity and Potential Risk Evaluation of Marburg Virus to Cause Mysterious "Disease X"—An Update on Recent Evidences

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ABSTRACT: The World Health Organization (WHO) defined Disease X as an upcoming disease with the potential to cause a pandemic. Pathogen X is responsible for Disease X. Marburg virus disease (MVD) is one of the diseases from the priority disease list published by WHO. Marburg virus is a filamentous, negative-sense RNA virus that belongs to the same filovirus family as the lethal Ebola virus. Since the first discovery of this virus in 1967, 17 outbreaks occurred sporadically till 2023. *Rousettus aegyptiacus* acts as the natural reservoir of the virus. With an average incubation period of 5 to 10 days, its first target is the mononuclear phagocytic system cells. It is highly contagious and can be easily transmitted from animal to human and human to human via direct contact with blood or body fluid, feces, and semen of the infected host. Although Marburg disease has a high case fatality rate of close to 90%, unfortunately, there is no approved vaccines or treatments are available. The most recent outbreak of Marburg virus in Equatorial Guinea and Tanzania in 2023 caused an alert for global health. However, based on the last global pandemic of COVID-19 and the sudden re-emerging of monkeypox around the world, we can assume that the Marburg virus has the potential to cause a global pandemic. Our modern world depends on globalization, which helps the virus transmission among countries. The Marburg virus can easily be transmitted to humans by fruit bats of the Pteropodidae family. This virus causes severe hemorrhagic disease, and there are no specific vaccines and treatments available to combat it. Therefore, community engagement and early supportive care for patients are keys to successfully controlling MVD.

KEYWORDS: Disease X, Marburg virus, Marburg virus disease, filovirus, viral zoonosis, *Rousettus aegyptiacus*, public health

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Background

Since 2015, the World Health Organization (WHO) has used the term Disease X to describe a disease caused by an unknown pathogen X.[1,2] Disease X from the last pandemic is now known as COVID-19. Devastating outbreaks of the Spanish flu at the very beginning of the 20th century killed up to 100 million individuals globally. Even though COVID-19 seems to be an anomaly, at least 1 new disease emerges annually.[2] Since there may already be an unknown and unidentified entity lurking around, the WHO has selected several highly infectious diseases with the potential to disseminate epidemics with insufficient or no treatment availability.[1,2] Along with Disease X, the priority disease list by WHO includes Middle East respiratory syndrome, severe acute respiratory syndrome, Crimen-Congo hemorrhagic fever, Lassa fever, Rift Valley fever, Marburg virus disease (MVD), Ebola virus disease, Zika, Nipah, and Henipavirus disease.[3] Out of 400 newly discovered infectious disease occurrences since 1940, 54% of them involve bacteria (including rickettsia), whereas the remaining involve viral or prion pathogens (25%), protozoa (11%), fungi (6%), and helminths (3%), being least prevalent. It implies that any infectious entity from bacteria, fungi, parasites, viruses, or prions, could be pathogen X.[1] Majority of pandemics such as SARS, HIV/AIDS, and influenza begin in animals, being caused by viruses, happen to emerge due to changes in the environment, human behavior, or socioeconomic conditions.[4] Moreover, RNA viruses account for 94% of zoonotic viruses that infect people, and their zoonotic transmission frequently happens in environments with a diversity of fauna, insects, and microbes alongside human activity. Human activity has played a significant role in the emergence of zoonotic viruses.

We can speculate that the emergence of a catastrophic Disease X is probably due to the zoonotic spread of virulent RNA virus from a region where a confluence of risk variables and population patterns will lead to persistent transmission between individuals.[1] Although the mechanism by which they originate is becoming increasingly understood, no pandemic has ever been anticipated before its occurrence. Therefore, we need to be ready for more future pandemics.[4] As we know, MVD is one of the diseases on the priority disease list by WHO, and the recent outbreak of this virus threw a threat to national and global health. In this study, we briefly summarized the epidemiology, virology, pathogenesis, and transmission of the Marburg virus, as well as its supportive treatments. Additionally, this study aims to create a picture between unknown Disease X and the Marburg virus, as well as the possibility of any future pandemic by the Marburg virus and its prevention measures.

Methodology of Data Extraction

We performed a comprehensive literature search (Scopus indexed and Web of Science) related to Marburg virus and MVD, like epidemiology, genetic mutation, viral pathogenesis, transmissibility of Marburg virus and extracted the relevant information from appropriate ones. Article published in English were only selected for this review. Updated information on MVD was extracted from the targeted databases.

Epidemiology of MVD

The MVD is highly contagious and zoonotic in nature, caused by the Marburg virus, a relative of the deadly Ebola virus.[5,6] Marburg virus belongs to the *Filovirus* family and is defined as a category A pathogen by the Centers for Disease Control and Prevention (CDC).[6]

The Marburg virus, which received its name after the city with the largest percentage of infections, first emerged among laboratory personnel in August 1967 after 3 separate incidents of lethal Marburg virus infections took place in Marburg and Frankfurt (Germany), and also included Belgrade and the former Yugoslavia.[7,8] Vervet monkeys (Cercopithecus aethiops) were the source of the infection. The monkeys were brought in from Uganda's Lake Kyoga region for research purposes to collect kidney cells for the culture of poliomyelitis vaccine strains.[8,9] The infection ultimately caused the death of 7 patients out of the 31 people infected by the virus (25 primary cases and 6 secondary cases). The objective of the actual experiment led to the necropsy of the monkeys resulting in the laboratory scientists and workers coming in direct contact with the cell cultures, organs, or blood of these animals that may infect them. However, among medical, paramedical, and family members of the primary patients, secondary infections occurred.[8,10] Following the very first epidemic, there was no further Marburg virus outbreak. However, 8 years later, in February 1975, an Australian man succumbed to a severe hemorrhagic fever in a Johannesburg hospital due to being infected with the virus, eventually a nurse and his traveling partner also contracted the virus.[10] Along this aforementioned case, several outbreaks occurred sporadically since the first discovery of Marburg virus. In 1980, the third outbreak happened in Kenya, following the fourth outbreak in Western Kenya in 1987. In both cases, the root cause of infection was connected to visiting the Kitum cave which was filled with a huge population of bats.[6] Furthermore, Marburg virus infections took place in Russia in 1988, 1990, 1991, and 1995 as a consequence of laboratory error.[11] Marburg virus was neglected and considered to pose a lesser threat to humanity considering its lower case fatality rates than Ebola virus disease until 1998 when a significant number of lethal hemorrhagic cases emerged at 83% fatality rate in the region of Durba, Democratic Republic of the Congo (DRC).[8] Again in 2004 to 2005, for the first time, a second large outbreak was reported in Uige province, Angola. The driving force behind the persistent cases was human-to-human transmission, while the underlying infections of the MVD outbreak in Durba (DRC) were probably linked to working in a gold mine.[8,12] A number of minor Marburg hemorrhagic fever (HF) events were documented in Uganda between 2007 and 2012; 1 case was exported to the United States, and another to the Netherlands as a result of visiting the Python Cave in Uganda.[7,8] There have been 197 new cases of the outbreak in Uganda as of October 2014. Three years later, on October 19, 2017, Eastern Uganda (Kween District) witnessed the first epidemic.[6] The Republic of Guinea in West Africa witnessed its first Marburg virus outbreak in August 2021.[13] Following the next year, in 2022 Marburg virus outbreak took place for the first time in another West African country Ghana (Ashanti region). By June 2022, one adult male and a 14-month-old baby met fatal results.[13,14] As of 29 July 2022, a total of 4 confirmed cases and 3 fatal cases were documented with a case fatality rate of 75%.[14] Equatorial Guinea's Ministry of Health and Social Welfare (MOH) declared a Marburg virus outbreak on February 13, 2023, in the province of Kie Ntem, located in the country's northwest.[15] Following 17 verified cases, 12 fatal cases, and 23 suspected cases, the outbreak eventually prompted the WHO to declare MVD an outbreak in February 2023. However, all the probable cases resulted in death. Despite the fact that Equatorial Guinea first identified MVD patients in Kie Ntem province, the most afflicted area was actually Bata in Litoral province.[14] Unfortunately, Tanzania also witnessed its first MVD outbreak in the same year. On March 21, 2023, the Ministry of Health in Tanzania announced the epidemic in the northwest Kagera region's Bukoba district.[13] Till March 24, 2023, eight confirmed cases and 5 fatal cases were reported. Even though the source of the current MVD outbreaks in Ghana and Equatorial Guinea is unknown, Nabuyongo Island also known as Goziba in Lake Victoria (Tanzania), was connected to the recent outbreak in Tanzania.[14]

Virology of Marburg Virus

Marburg virus is an enveloped, filamentous, single-stranded, non-segmented, negative-sense RNA virus that belongs to the filovirus family.[16] The Marburg is a single species that consists of 2 viruses Marburg virus and Ravn virus, they exhibit approximately 79% homology whereby the latter first appeared in Kenya in 1987.[17,18] While virions vary in length, Marburg virus particles are typically close to 800 nm in length.[7] The distinct Marburg virus isolates have varying-sized genomes, ranging from 19 111 to 19 114 nts. These genomes contain 7 linearly arranged monocistronic genes to code for 7 proteins that are structural in nature. These 7 viral proteins include nucleoprotein (NP), VP 35 (polymerase cofactor), VP40 (matrix protein), glycoprotein (GP), VP30, VP24, and large protein polymerase (L).[6] The Marburg virus genome is encased in the nucleocapsid complex, which is

composed of the structural viral proteins NP, VP30, VP35, and L. For viral genomes transcription and replication VP35, and the RNA-dependent RNA polymerase L is highly required. Additionally, regular spikes (5-10 nm in length) occur in the host-derived membrane layer of Marburg virus, where the attachment to receptive host cells is facilitated by the trimers of highly glycosylated protein (GP).[8,19] Moreover, it (GP) also contributes significantly to the pathogenesis by influencing immunogenicity and generating neutralizing antibodies.[6] Less genetically distinct Marburg variations include Marburg Angola, Musoke, an unidentified variant from the very first 1967 epidemic (Ci67), and isolates within another variant. Among them, the strain that looks to be the most virulent and causes a faster course of sickness in non-human primates (NHPs) is Marburg Angola, which was isolated from the largest outbreak.[20] The genomic sequence of 2021 Guinean Marburg virus was retrieved up to 99.3%, and phylogenetic studies revealed a relationship between the virus and isolates from the Angolan Marburg virus outbreak that occurred from 2004 to 2005, which are connected to Marburg virus sequences that were retrieved from bats living in Sierra Leone in 2017–2018.[19]

Transmission of Marburg Virus

Corresponding to the coronavirus, Marburg virus is primarily transmitted from animal to human; however, it can travel among humans too.[21] Nearly all of the recorded primary infections of MVD epidemics have been connected to humans visiting bat-infested caves (cave visitors and mine workers). Because of this, it has long been assumed that bats are a crucial factor in the transmission of the disease.[8] According to previous research, a significant number of Marburg virus variants were acquired from *Rousettus aegyptiacus* species, making it a natural reservoir of Marburg virus, alongside *Hipposideros caffer* and several unidentified Chiroptera as secondary sources. A recent study found Marburg virus in mouth, urine, and rectal samples from bats inoculated with Marburg virus, as well as blood and oral samples from in-contact bats. This study has demonstrated the horizontal spread of Marburg virus from contaminated bats to bats in contact.[11] Another study detected Marburg virus in tissue samples of immunized bats' bladder, salivary glands, kidneys, lungs, intestines, and female reproductive system, validating the theory that Marburg virus transmission can occur in reservoirs both horizontally and vertically.[19] Though the precise route of transmission from animals to humans is still unknown, it has been suspected that bat urine, saliva, and feces, together with Marburg virus-contaminated fruits, are the most likely sources of transmission in both humans and NPHs.[11] Similar to that, human-to-human transmission occurs when an individual comes into direct contact with another infected person's body fluid or blood, along with surfaces or objects (cloth or bedding) infected with the same.[22] The probability of Marburg virus transmission via sexual contact had been speculated when the virus was found in the sperm of a previously infected patient in 1968, who later transferred the virus to his wife.[23] In 1975, Marburg virus was found in the aqueous humor of an MVD survivor who had uveitis.[24] Droplet spread to mucosal membranes most likely occurs, even if open airborne transmission has not been verified in human epidemics. Experimental animals have provided evidence of infection through direct aerosol administration to the airways.[20] According to a significant study, Lake Victoria Marburg virus is able to sustain longer in liquids and more than 3 weeks in low temperatures on solid surfaces like plastic and glass. Consequently, Marburg virus transmission through fomite can be a significant factor in the dissemination of the virus, especially amid an outbreak.[11] Besides, proximity to the body of a deceased person during funerals contributes to the transmission of Marburg virus.[21]

Pathogenesis of MVD

The mortality rates of MVD vary based on the severity of the epidemics and virus variants, however, the overall case mortality rate is closer to 50%.[19] Nevertheless, Angola and the Democratic Republic of the Congo experienced the worst outbreaks, with corresponding mortality rates of 90% and 83%.[25] In various experimental animal models and human patients, cells of the mononuclear phagocyte system, such as macrophages, and dendritic cells, and macrophages, have been demonstrated to be early targets of Marburg virus, whereas endothelial cells tend to be late targets of Marburg virus infection (Figure 1). Furthermore, endothelial cells and primary human monocyte-derived dendritic cells facilitate Marburg virus replication.[8] Based on the rate at which the disease progresses, MVD can be categorized into 3 separate phases during its incubation period, which can range from 3 to 21 days (usually 5-10 days). The first phase is known as the generalization phase, and the progress is continued by the second early organ phase, which is followed by the late organ phase (convalescence phase).[8,11] The initial phase commences with flu-like symptoms including chills, an elevated body temperature (usually between 39°C and 40°C, or 102°F and 104°F), sore throat, joint pain, muscular aches, headache, and lastly malaise after 2 to 21 days of initial infection. The condition becomes noticeably more severe on days 5 to 7 when a maculopapular rash that extends from the body to the limbs develops along with conjunctivitis. Additional symptoms that also intensify at this time include leukopenia, lymphadenopathy, and thrombocytopenia.[26] The second phase usually lasts 5 to13 days following the initial occurrence of symptoms and is accompanied by a persistently high fever and other nonspecific signs.[19] Patients with neurologic symptoms have also reported experiencing encephalitis, aggression, irritability, psychosis, and disorientation. Among the patients, 75% of them show hemorrhagic symptoms, along with hematemesis, bloody diarrhea, petechiae, melena, visceral hemorrhagic effusions, ecchymoses, mucosal

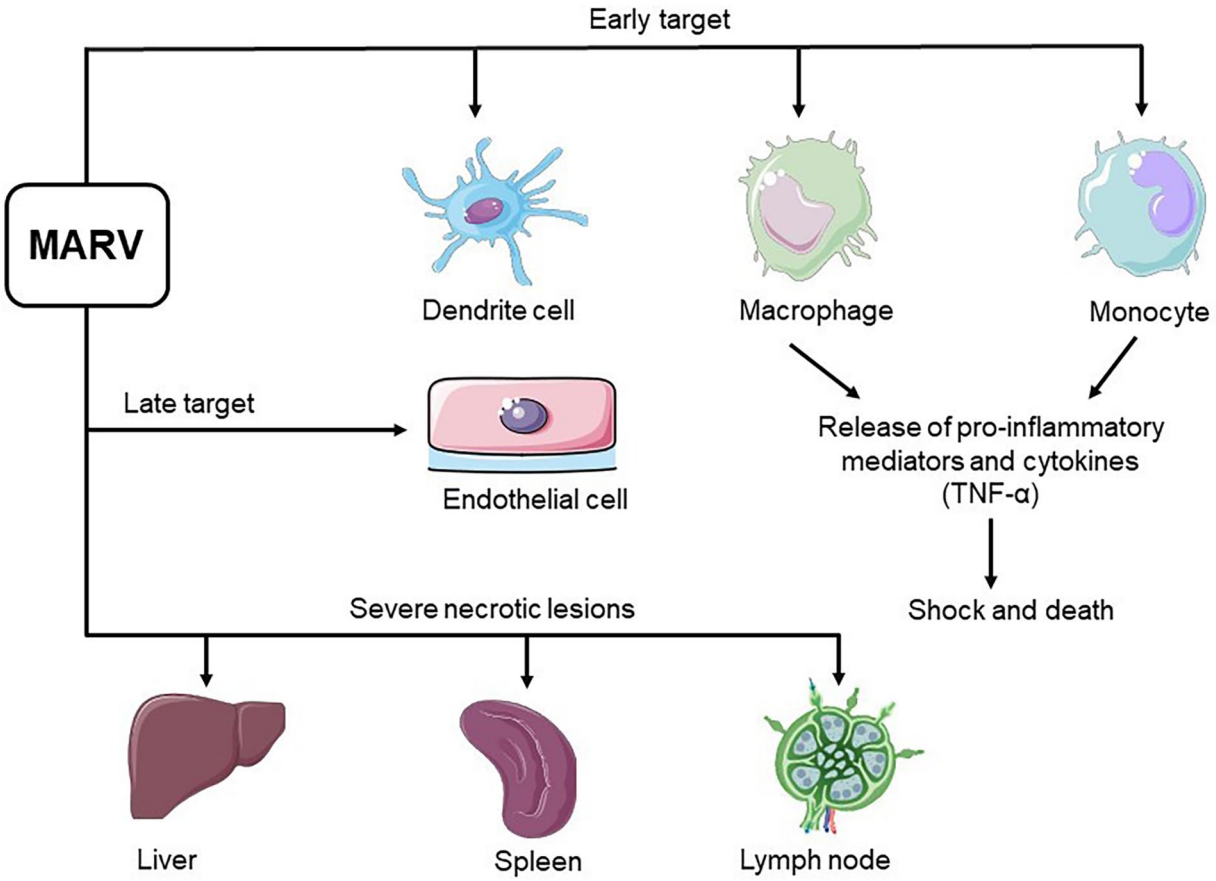

Figure 1. Target cell and cellular damages due to the Marburg virus disease.

bleeding, and uncontrollable leaking from venipuncture sites. When Marburg virus infection reaches its late stages, there are 2 main outcomes: either the patient goes into a long-term recovery phase or meets a fatal outcome. Death usually happens 8 to16 days after the appearance of first symptoms. Shock and damage to multiple organs are most likely to be the primary reasons for death.[19]

Public Health Burden and Implications of MVD in Africa

Several microbial diseases with zoonotic origins, including COVID-19 and mpox, have emerged and been reintroduced in recent years. According to reports, the prevalence of these diseases is rising, particularly in Africa.[14] We know nearly all MVD epidemics have arisen in Africa.[27] We saw immense damage due to the limited outbreaks of MARV.[26] The MVD outbreak in Guinea during the COVID-19 pandemic exacerbated the country's already precarious healthcare system with many epidemics.[21] It is difficult to prevent and control epidemic diseases in endemic regions.[8] Furthermore, it renders economically poorer nations more susceptible to these epidemics, which may result in insufficient control and containment of the virulent spread and even extend the outbreak.[26] An MVD outbreak can spread rapidly and cause societal and medical issues if it grows out of reach.[16] Unlike the Ebola virus, the MARV has received less attention until now. It is now gaining global attention as several countries (Guinea, Equatorial Guinea, Tanzania, and Ghana) have recently detected the virus for the first time. Although the required diagnostic tests are accessible, many countries don't have the facilities, staff, and funding. In African healthcare settings, there is a greater awareness of viral hemorrhage fever, and outbreak control has progressed remarkably. The WHO and health organizations like Médecins Sans Frontières appear to be assisting national and regional organizations in controlling epidemics lately.[17] The African nations have made zoonotic diseases a top priority for public health, aiming to close the gap by working together across divisions that address the health of people, animals, and the environment in the context of the "One Health" approach. Establishing a budget planning and carrying out the cross-sector activities proved challenging even with the backing of "One Health" in Ghana.[14] Apart from its effects on mortality as well as morbidity, MVD also has an economic impact on the country, causes social and emotional anguish to affected household members, and lowers household production, besides additional consequences.[13]

Therapeutic and Prevention Measures

Although Marburg virus vaccine development began shortly after the virus was discovered, till now there are currently no

Marburg virus vaccines or treatments approved by regulatory agencies.[28] Adenovirus, DNA, MVA-BN-Filo, and cAd3 are 3 Marburg candidate vaccines that are undergoing Phase I clinical studies, while MVA-BN-Filo is slated for a Phase 2 or 3 clinical study. Several Marburg prospective platforms, including VLP, DNA, rVSV, and Adenovirus have shown efficacy in NHPs.[20] According to a comprehensive literature evaluation, antiviral medications like Favipiravir, Remdesivir, and Galidesivir have shown promising results, ranging from 83% to 100% when administered according to a prescribed dosage regimen.[29] In addition to other medications, combination therapy utilizing monoclonal antibodies (mAbs) and antivirals has demonstrated positive outcomes for numerous viruses, such as Marburg virus and Ebola virus family, and lately SARS-CoV-2. Findings indicate that effective (80%) protection is obtained when Remdesivir, a small-molecule antiviral, is combined with a human mAb (MR186-YTE), thus expanding the treatment window.[30] Numerous drugs that are effective against Marburg are being developed, including immunotherapeutics, lipid-encapsulated small interfering RNAs, phosphorodiamidate morpholino oligomers (PMOs), small molecule inhibitors, antiviral nucleoside analogs, and interferons.[20] Currently, supportive care approaches are the only kind of treatment available to patients with MVD.[6] Outbreak management methods depend on safe burial practices, contact tracking and monitoring, early detection of cases and isolation, and social awareness regarding transmission risk factors.[31] According to the CDC's biosafety measures for Marburg virus HF, the patient must be in an isolation room with low-air pressure, and any other person entering the room must put on disposable gowns, gloves, and FFP2 masks to decrease the risk of infection. Disposal material from the patient's room should be handled separately and non-disposal material should be cleaned and disinfected with bleach[18]

Possibility of MVD to Cause Global Pandemic

MVD is categorized by the WHO as a neglected tropical illness because it receives less funding, awareness, and study than other viral diseases.[14] Computational modeling indicates that 105 million individuals in Africa and Madagascar might succumb to Marburg virus.[32] Since the majority of MVD outbreaks over the past 50 years have occurred in Africa, Marburg virus has become a serious public health concern there. But we can't neglect the fact that the Marburg virus outbreak has been reported twice in Europe.[17] Equatorial Guinea was the origin of the most current outbreak, and soon after it reached Tanzania. Marburg virus can cause a severe hemorrhagic fever. It can affect multiple organ systems. The mortality rate is very high (average 50%) in the severe form of MVD. The virus can spread via direct person-to-person contact. At present, no vaccine is available against the Marburg virus. Therefore, like COVID-19 or MPVX, Marburg virus has the potential to cause multi-nation outbreaks.[33]

Recommendations Based on the Present Assessment

Marburg virus outbreak in Ghana and Guinea amidst COVID-19 posed an extra burden on the African continent. The recent Marburg virus outbreak in Equatorial Guinea and Tanzania is enough to bell a global alarm. One efficient method of reducing the transmission of viruses is to include the community and educate the general population about the risk factors. Given the increased risk, miners and visitors to the caverns where fruit bats reside should take appropriate safety precautions. To lessen the chance of zoonotic (bat-to-human) transfer, bush meat should be cooked properly before eating. As we know the virus transmission can be transferred during sexual intercourse, so male survivors should follow the recommendation given by WHO for safe sex.[14]

The ongoing emergence and reemergence of infectious illnesses throughout the African continent, the one-health approach should be put into practice to curb the dissemination of zoonotic infectious diseases.[15] Transportation outside of Africa is the main cause of the dissemination of Marburg virus. Therefore, quick diagnostics are essential to identifying the afflicted before they can spread the virus to other nations. During the outbreak, the primary objective to control the situation is to stop direct transmission between humans. Similar to other infectious diseases, early detection and quick isolation of cases, prompt tracing, vigilant supervision of individuals at risk, appropriate personal protection, and secure burial are all part of the control approach.[34] Based on the previous outbreak history, we can assume there is a high chance of infection among health workers who treat patients. To decrease this risk, health workers also should follow the guidelines and wear masks, gloves, and personal protective equipment. Countries should advise their citizens about living or traveling guidelines to a region where Marburg viruses are potentially present. The World Bank, the WHO, the International Monetary Fund (IMF), and others may provide technical and financial assistance in accumulating the required resources because the affected countries may lack the means to combat the illness. All research organizations should take Marburg virus seriously and produce effective vaccines and treatments to reduce the risk of global threats.

Conclusion

The last COVID-19 pandemic proves that we are still helpless before lethal pathogens even though we are in an advanced era. Marburg virus outbreaks with up to 90% fatality rate in recent years make it a potential candidate for future pandemics. By its past epidemiology records, researchers can predict that Marburg virus can spread from 1 region to another region because of the highly contagious efficacy of Marburg virus and the lack of approved vaccines. A small outbreak can turn into an epidemic and finally into a pandemic. So, it should work as a wake-up call for the Government and health organizations to reduce the gap that burdens the public health of Africa. To

reduce the risk to public health, researchers should work to a large extent to produce an effective vaccine and other possible treatments. Sufficient medical countermeasures should be sent to the critical region. Every outbreak that happens around us is a given opportunity to educate the public about the disease and pathogen. Along with treatments, international cooperation is necessary in mitigating the Marburg virus global threat.

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Author Contributions

Rahima Akter Mitu: Conceptualization; data curation; writing-original draft. **Md. Rabiul Islam**: Conceptualization; supervision; visualization; writing-review and editing. The author(s)read and approved the final manuscript.

Data Availability Statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

Transparency Statement

The lead author Rahima Akter Mitu affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

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