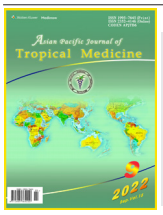

Perspective

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Recurrent Marburg virus disease outbreaks from 1967 to 2022: A perspective on challenges imposed and future implications

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Ongoing COVID-19 pandemic and rapid increase in monkeypox cases across the globe have led to growing realization among the masses that early containment of infectious diseases may prevent their emergence as global havoc. Recently, four cases of Marburg virus disease have been identified in Ghana, a country in West Africa. Marburg virus is one of the causes of deadly viral hemorrhagic fever in humans with a significantly high mortality rate. The management of affected individuals merely relies on supportive care, as no treatments or vaccines have been globally approved yet. Although most of the cases were reported from African countries, the current era of globalization poses a very high probability of its spread across the world.

The global burden of infectious disease epidemics is evident from history, leading to over 25% of fatalities among 60 million deaths reported every year[1]. The recently reported outbreak of Marburg virus disease in Ghana, 2022 can be detrimental for already fragile local healthcare systems as well as a potential hazard for public health globally. Marburg virus is listed among one of the fatal viral hemorrhagic fever etiologies. Until effective therapeutic approaches other than symptomatic relief measures and vaccination are finalized, the need to ensure development and implementation of proper public healthcare strategies is growing concern.

A significant public health concern for more than five decades, the Filovirus disease outbreak was first reported in 1967. The Marburg virus and the Ebola virus, largely reported in the literature as the etiological agent for deadly human viral hemorrhagic fever since 1967, belongs to the family Filoviridae[2]. The history of Marburg virus disease dates back to 1967, with over 14 outbreaks and 471 confirmed cases reported over fifty-four years. Most of the cases were reported in the East and South African countries. Moreover, the cases identified in non-African countries were attributable to laboratory contamination, travelers and animals imported from the endemic regions. Of all these outbreaks, the largest was reported in Angola (2004-2005) with a drastic mortality rate of 90%. Overall, the average case mortality rate ranged from 24% to 88%, determined in large part by the early diagnostic and management strategies employed[3]. Amidst the global burden to mitigate the fatal COVID-19 pandemic, Ghana, a country in West Africa, alarmingly registered its first four Marburg virus disease (MVD) cases in July 2022. Although the two index cases were unrelated, the other two cases identified, as of August 2022, belonged to the same household as one of the index cases. Initial investigations showed that the index cases had no contact with any sick person or animal, dead animal, and had not attended any social events within three weeks of symptoms' onset. Sequencing of the virus is being conducted at regional facilities. Despite the rapidly employed supportive treatment, three of the four confirmed cases succumbed to the deadly illness[4].

Wild animals could serve as important reservoir for emerging and re-remerging human infectious diseases[5]. Although the host reservoir for MVD has not been conclusively documented, *Rousettus aegyptiacus* (Egyptian fruit bats) is likely to be the primary reservoirs as indicated by epidemiological evidence. Human-to-human transmission is mediated by infected fomites, body fluids, and breastmilk. After an incubation period of 2 to 21 days, MVD demonstrates rapid onset of initial generalized symptoms including high-grade fever, joint/muscle pain and headache followed by abdominal pain associated with diarrhea, vomiting, and nausea on the third day lasting for a week. As the disease advances, hemorrhagic signs, such as petechiae, hematemesis, melena, bleeding from the vagina, gums, or runny nose, as well as venipuncture sites are detected. Multi-organ failure and shock in the late-organ phase lead to death after 8-9 days. Among the post-convalescent complications, psychosis, asthenia, hepatitis, arthralgia, and ocular disturbances are rampant. As evidenced by experiments during the Kenyan outbreak in 1987, Marburg virus (MARV) majorly infects dendritic cells and macrophages, which secrete pro-inflammatory cytokines, causing lymphocyte apoptosis and immune suppression. Dissemination leads to widespread MARV replication and systemic inflammation, the sequelae being hypotension, fever, increased vascular permeability

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and coagulopathy. The diagnosis of MARV requires antigen-capture enzyme-linked immunosorbent assay (ELISA), viral isolation, or real-time polymerase chain reaction (RT-PCR) laboratory tests. In the absence of an absolute cure of MVD because of inadequate study data available, symptomatic treatment approaches are employed like pain-reducing palliatives, antibiotics, cardiac glycosides, steroids, and fluid resuscitation to maintain hydration and electrolyte balance[2].

In contrast to the previous outbreaks, the primary source of infection in the current outbreak has not been identified yet. This has raised a matter of concern as to whether the virus has inhabited a previously unknown reservoir, or a mutant viral strain has emerged. This could significantly overwhelm the already weakened local healthcare system due to COVID-19 and various recurring epidemics[6]. Moreover, in Africa, the high frequency of public traveling across the poorly regulated inter-country borders and lack of sufficient resources available for mass screening can potentially add to the disease burden and surge in unidentified cases. Getting over the viral transmission is popping up as the utmost need in order to avoid this viral emergence as a pandemic.

Detailed investigations need to be carried out to identify all the missing links in the chain of transmission in order to develop appropriate strategies. Meanwhile, educating people in the wide context of involved transmission routes, rapid screening techniques including RT-PCR and Taqman based multiplex PCR testing on large scale can help reduce the spread among masses[7]. Simultaneously, designing a prompt public healthcare and socio-economic policy in the West African countries where the outbreak has been reported[8] along with setting air- and seaports' screening protocols with proper isolation setups for passengers returning from affected areas, may help in early diagnosis and reduce spread thereby.

Keeping in view the high basic reproductive number, transmission rates and fatality percentages of Marburg virus, relentless efforts to prepare targeted vaccination against Marburg virus are going on, subject to its unavailability as of yet. Recently, animal trials with a DNA prototype vaccine have been successful as evidenced by serum antibody production and increased antibody titers against the Marburg specific glycoproteins. Moreover, new drugs like remdesivir in macaque models, 4-aminomethyl benzamide, and cholesterol conjugated fusion inhibitors have demonstrated significant efficacies against MARV[2]. However, large scale trials on humans and final approval of these treatments will need more time to achieve targeted availability for the general public.

In conclusion, although MARV is most prevalent among African countries, the current outbreak trend owing to the detrimental and high infectivity rates poses a potential epidemic threat over other countries. Limited availability of data pertaining to the MARV reservoir, mode of spread, pathogenicity, treatment, and management including vaccines and antiviral therapies necessitates further research studies to prevent and mitigate recurrent MVD outbreaks effectively in Africa and beyond.

Conflict of interest statement

All authors declared that there are no conflicts of interest.

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Authors' contributions

YM contributed to conception, drafting, critical review and approval of final version. FR contributed to conception, write-up and approval of final version. AZ contributed to drafting and approval of final version. The manuscript has been read and approved by all the authors.

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