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Correspondence

Recent re-emergence of Marburg virus disease in an African country Ghana after Guinea amid the ongoing COVID-19 pandemic: Another global threat? Current knowledge and strategies to tackle this highly deadly disease having feasible pandemic potential

Dear Editor,

Marburg virus (MARV), a highly pathogenic RNA virus belonging to the *Filoviridae* family, the causative agent of Marburg virus disease (MVD), was first identified in Germany and Serbia in 1967 in a laboratory personnel working with African green monkeys (*Cercopithecus aethiops*) imported from Uganda for poliomyelitis vaccine development [1]. Subsequently, MVD cases were reported from the African countries Congo, Angola, Kenya, South Africa and Uganda [2]. Other outbreaks were also reported from Europe and the USA. The MVD outbreak was reported in the West African country Republic of Guinea amid the ongoing COVID-19 pandemic in August 2021 [3,4]. On July 17, 2022, MVD cases were reported from Ghana with deaths of two persons on 27 and 28 June 2022, who presented with symptoms of diarrhoea, fever, nausea, vomiting, and died after hospitalisation in less than 48 hours [2,5,6]. The contacts of these two dead patients were being tracked and monitored, and appropriate disease prevention and control measures were followed to limit further spread of this deadly virus.

MARV is a zoonotic virus. It is contracted from contaminated oral secretions and excreta from fruit bat (*Rousettus aegyptiacus*), the animal reservoir, and contaminated partially eaten fruits consumed by humans or other susceptible animals [7,8]. Further human-to-human transmission occurs through body fluids (blood, saliva or urine), broken skin or mucous membranes with contaminated surfaces and materials (bedding and clothing) from sick patients. Transmission from contaminated injection equipments is another way of virus entry. Workers accessing mines and tourists visiting caves inhabited by such bats are at greater risk of infection.

MARV causes a rare but a lethal and severe hemorrhagic (loss of blood) fever with a very high case-fatality rate (CFR) which ranges from 24% to 88%, making it one of the most deadliest pathogen [9]. MVD exhibits similar manifestations as that of Ebola virus (EBOV) disease and remains a serious threat to human life with its possible pandemic potential [6,10]. Severe headache, high fever, and malaise are followed by abdominal pain, severe watery diarrhoea, nausea and vomiting which progress to multiorgan failure, shock, and finally death in many cases [11,12]. The appearance of a non-itchy rash is also noted in most patients. Severe haemorrhagic manifestations also develop in patients between 5 and 7 days. Orchitis (inflammation of one or both testicles) and involvement of central nervous system are also reported occasionally in the late phase of the disease. Deaths mostly occur between 8 and 9 days after onset of symptoms due to severe blood loss and shock.

The incubation period for MVD varies by large margins and ranges from 2 to 21 days [6], making it very difficult to identify and isolate infected persons, leading to infection spreading. Healthcare workers are frequently infected with this virus while treating confirmed or suspected patients as precautions are not strictly practiced as mentioned by WHO. Marburg virus persists inside eyes and testicles in recovered MVD patients, and in amniotic fluid, placenta, and foetus of women who have been infected during pregnancy. This virus may also persist in breast milk if a woman is infected while breastfeeding. As reported by WHO, pigs are susceptible to filovirus infection, so they should be considered as a potential amplifier host for MVD outbreaks [11]. Association of other domestic animals is yet to be confirmed for precautionary measure, if proven.

It is difficult to distinguish clinically MVD from shigellosis, meningitis, malaria, typhoid fever, and other viral haemorrhagic fevers. The MARV infection is diagnosed with serum neutralization test, antigen-capture detection tests, antibody-capture ELISA, RT-PCR assay, and virus isolation by cell culture [11]. Supportive care such as rehydration and symptomatic treatment may improve survival. More than 50 years have passed but there are no approved vaccines or drugs with proven efficacy to prevent the disease. However, the drugs namely Favipiravir and Remdesivir which were previously used for Ebola disease may also be used under the "compassionate use" clause against MVD in the absence of any other drugs [11]. Therapeutics and antiviral candidates under investigations for filoviruses (EBOV, MARV) comprise of small molecules, antiviral drugs, monoclonal antibodies, cytokines, post-exposure vaccines, host-targeted therapeutics and drugs attempting for pan-filovirus therapeutics [13,14].

The vaccine Mvabea (MVA-BN-Filo) which contains Vaccinia Ankara Bavarian Nordic (MVA) could potentially protect against MARV, however its efficacy is yet to be proven in clinical trials [11]. Various vaccine candidates such as DNA plasmids, adenovirus vectors, virus-like particles (VLP) and vesicular stomatitis virus (VSV) vectors based vaccines are being explored for developing MVD vaccines [15,16]. A VSV-based vaccine which expresses Marburg virus glycoprotein (VSV-MARV) has been developed, and 75% of animals survived when vaccinated 3 days and 100% of animals survived when vaccinated 7 or 14 days prior to lethal MARV challenge [17]. So, VSV-MARV may be a suitable vaccine for emergency use. Monovalent MARV or Sudan virus (SUDV) vaccine candidates have been shown to completely protect *Cynomolgus macaques* from infection with lethal doses of Marburg and Sudan Virus. A combination of SUDV or MARV with the EBOV vaccine may be formulated to yield bivalent vaccines in retaining full efficacy [18]. The recombinant subunit vaccine platform may allow developing an efficacious and safe multivalent vaccine candidate to protect against EBOV, MARV and SUDV [18]. Clinical trials data indicated rVSV-based vaccine (Ervebo) to prevent from EBOV at 97.5–100% levels after 10 days post-immunization. Recently, a highly attenuated rVSV-based Vesiculovax vector (rVSV-N4CT1-MARV-GP) has been reported to protect

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cynomolgus monkeys against MVD [19]. As per human studies, DNA vaccines have shown adverse effects and DNA vaccines provided either low immunogenicity or failure to elicit durable immunity against MARV infection. VSV, adenoviral vectored and VLP vaccines demonstrated favorable survival and immunogenicity parameters. However, further clinical trials are needed to come up with a conclusive MVD vaccine. A multi-epitope vaccine against the structural proteins of MARV by employing the immunoinformatics approach has been designed with promising immunogenicity [20]. A novel chimeric subunit vaccine by adopting the reverse vaccinology approach has been designed against MARV, which requires further explorative studies [21]. Appropriate *in vitro* and *in vivo* investigations as well as adequate clinical trials are highly recommended for acceptance and validation of the different vaccine candidates which are now being explored against MARV.

It is highly essential to design immediate proactive control measures and to develop needful preparedness plans by strengthening surveillance and monitoring activities, and enriching well-facilitated biosafety level 4 (BSL-4) laboratories in different countries, which will be very helpful to prevent Marburg outbreaks. The WHO has also developed the MARV infection prevention and control strategies along with supporting surveillance, laboratory services, contact tracing, case management, and rendering other logistic supports [11]. Making awareness about the risk factors and protective measures among general people will be an effective way to reduce MARV transmission. Healthcare and laboratory workers should be very careful and they need to wear personal protective equipments (PPE), face protection (medical mask and goggles), gloves and a clean, non-sterile long-sleeved gown when dealing the suspected or confirmed patients with MVD. Adequate safety measures including wearing of gloves, masks and other appropriate protective equipments are required to be followed during research and diagnostic activities or when tourists visit caves inhabited by fruit bat colonies. All animal products must be thoroughly cooked before consumption, which may reduce the risk of bat-to-human transmission of this virus. The WHO has suggested to take precautionary measures in pig farms to avoid MARV infection through contact with these fruit bats as pigs may be potential amplifier hosts during outbreaks [11]. Regular hand washing with soap and water is highly recommended, especially after visiting MVD sick relatives in hospitals. As there is a risk of possible sexual transmission, WHO recommends safe sex (semen must tests negative) for male survivors of MVD for 12 months from onset of symptoms [11].

MVD is one neglected infectious disease which can pose significant impact on global public health. Its very high CFR (∼ 90%) and recent outbreaks demand broad and detailed studies on this disease and its causative virus. Though many outbreaks have been reported around the world, large outbreaks are rare for MVD, and clinical investigations have often been inadequate. There are still large gaps in knowledge, and it is highly recommended to fully understand virus/host interactions, and to design evidence-based recommendations regarding prevention and control of MVD outbreaks. Research facilities require upgradation to maximum containment laboratories (BSL-4) to tackle MARV. Being a zoonotic virus, implementation of One Health concept needs to be given due priority. High global efforts of the scientific community, public health professionals, physicians/doctors, veterinarians and policy-makers, along with multidisciplinary collaborative approaches are necessary to prevent and control MARV spread and outbreaks before other regions and countries are affected amid the ongoing COVID-19 pandemic and under the current threats of the rising cases of monkeypox virus in several countries, which has now been declared as a public health emergency of international concern by the WHO. Increasing globalisation, fast international travel and other risk factors may trigger the risk for MARV spread, which needs to be taken care of appropriately. Development of effective vaccines, antiviral drugs and therapeutics, and adopting suitable preventive and control strategies are very crucial for counteracting the challenges of MVD before it could possibly pose any high pandemic threat owing to its very high lethality.

Ethical approval

The authors declare no involvement of animal studies or human participants in the study as it is a compiled letter article.

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RKM, KD: designed the study. RKM: made the first draft. AKS, VK, SC, DC, MA, CC: updated the manuscript. KD: reviewed the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Ranjan K. Mohapatra*
Department of Chemistry, Government College of Engineering, Keonjhar, 758002, Odisha, India

Ashish K. Sarangi
Department of Chemistry, School of Applied Sciences, Centurion University of Technology and Management, Odisha, India

Venkataramana Kandi
Department of Microbiology, Prathima Institute of Medical Sciences, Karimnagar, 505417, Telangana, India

Sandip Chakraborty
Department of Veterinary Microbiology, College of Veterinary Sciences and Animal Husbandry, R.K. Nagar, West Tripura, Tripura, 799008, India

Deepak Chandran
Department of Veterinary Sciences and Animal Husbandry, Amrita School of Agricultural Sciences, Amrita VishwaVidyapeetham University, Coimbatore, 642109, Tamil Nadu, India

Mahmoud Alagawany
Poultry Department, Faculty of Agriculture, Zagazig University, Zagazig, 44511, Egypt

Chiranjib Chakraborty
Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal, India

Kuldeep Dhama**
Division of Pathology, ICAR-Indian Veterinary Research Institute, Bareilly, Uttar Pradesh, 243122, India

* Corresponding author. Department of Chemistry, Government College of Engineering, Keonjhar, 758002, Odisha, India.

** Corresponding author. Division of Pathology, Indian Veterinary Research Institute, Izatnagar, 243122, Bareilly, U.P., India
E-mail address: ranjank_mohapatra@yahoo.com (R.K. Mohapatra).
E-mail address: kdhama@rediffmail.com (K. Dhama).