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Re-emergence of Sudan ebolavirus after a decade: new challenge to Ebola control

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Dear Editor,

Outbreaks of African filoviruses often have resulted into high mortality, and of these, the West Africa Ebola outbreak during 2014–2016 accounted for more than 11 000 deaths among around 28 000 cases. Several ebola virus disease (EVD) outbreaks have been documented in East, Central, and Western African countries[1]. Democratic Republic of Congo (DRC) has experienced frequent epidemics of EVD[2]. The genus *Ebolavirus* consists of six enzootic virus species, including *Zaire ebolavirus* (EBOV), *Sudan ebolavirus* (SUDV), *Taï Forest ebolavirus* (TAFV), and *Bundibugyo ebolavirus* (BDBV) that infect human causing deadly hemorrhagic illness, named EVD; *Reston ebolavirus* (RESTV) that causes EVD in nonhuman primates and pigs, but asymptomatic infection in human and *Bombali ebolavirus* (BOMV) that was recently found in the Angolan free-tailed bat (*Mops condyrulus*) and little free-tailed bat (*Chaerephon pumilus*); this virus can infect human cells but has not been shown to be pathogenic[2–4]. EBOV was the causative agent of almost all of the EVD outbreaks during the last decade. Accidental spillover of the EBOV, SUDV, TAFV, and BDBV to humans can lead to EVD outbreaks[2]. The most recent outbreak of EDVD creating an alert has been reported to be caused by SUDV in Uganda during mid of September 2022[5]. Before this, on 21 August 2022, an Ebola outbreak was reported from the DRC, Beni health zone, North Kivu Province, with a fatal case, which was declared to end by 29 September 2022 by the WHO[6,7].

The most extensive outbreak of EVD caused by SUDV [called Sudan virus disease, SVD, as per the International Classification of Disease for filoviruses (ICD-11) released in May 2019 occurred in the year 2000 when 425 cases and 224 deaths (case fatality rate = 52.7%) were recorded[8,9]. The estimated case fatality rates of SVD have varied from 41 to 100% in the past outbreaks[5]. Almost a decade ago (November 2012), SVD occurred in Uganda, when SUDV was last isolated in humans. During that outbre

ak, six confirmed cases were from the relatively close districts of Luwero, Jinja, and Nakasongola. The outbreak was thought to be due to a single chain of human-to-human transmission, as almost identical viral NP gene sequences were detected in three patients' serum samples[10]. Earlier to this, in mid-August, an outbreak of SUDV occurred in Uganda when 11 cases were confirmed and four were dead. The genomes of the isolates recovered during this outbreak were in distant similarity to the isolate causing outbreak later in the same year[10].

On 20 September 2022, an index case of SVD, a 24-year-old male who died within 10 days of symptom onset, was reported from a community in the Madudu subcounty, Mubende district, central Uganda[5]. It was identified at the viral hemorrhagic fever laboratory at the Uganda Virus Research Institute (UVRI) using unbiased next-generation sequencing. The new *Mubende* Sudan ebolavirus genome is most closely related to the Sudan ebolavirus strain that had emerged earlier in 2011. Soon after the Ugandan health authorities declared an outbreak of Ebola illness caused by SUDV. This was the first EVD caused by SUDV in Uganda since 2012. As of 30 September 2022, there has been a total of 35 confirmed cases, 19 probable cases and 25 deaths (seven of these deaths were among confirmed cases) reported from the districts of Mubende, Kyegegwa, and Kassanda[11]. The latest to add to the list of deaths is a 37-year-old Tanzanian medical professional who had tested positive on September 26 and finally succumbed to the illness on the 1st of October. He was among the six healthcare workers who had contracted the disease while providing care to the patients[12]. It is really painful to see healthcare workers still dying from infectious diseases despite the numerous infection control measures that have been initiated after losing hundreds of them during the COVID-19 pandemic. It was thought that several transmission chains might have been missed for the current ongoing SUDV outbreak due to delayed identification of the index case. Some of the patients were initially managed in facilities with suboptimal infection, prevention, and

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control (IPC) practices including inadequate use of personal protective equipment[5].

Direct contact with blood or body fluids from infected people or wild animals (fruit bats, chimpanzees, gorillas, monkeys, forest antelope, or porcupines) and fomites is the only known route of transmission of the Ebola virus. The viral RNA was detected in breast milk, vaginal fluids, and semen of convalescent patients; implying the possibility of sexual transmission of the Ebola virus[13]. The incubation period of EVD can be from 2 to 21 days. People infected with SUDV (and other Ebola viruses) cannot spread the disease until they have symptoms, and they are still infectious as long as the virus is in their blood/body fluids. SVD symptoms can start quickly and include fever, fatigue, muscle pain, headache, and sore throat followed by vomiting, diarrhea, rash, and signs of poor kidney and liver function follow. Some patients might have both internal and external bleeding (e.g. bleeding from the gums, bloody stool)[14].

Clinical diagnosis of SVD can be difficult as the SVD nonspecific symptoms are similar to other diseases like malaria, scrub typhus, leptospirosis, typhoid fever, flu, and meningitis. The gold-standard test for EVD diagnosis is reverse-transcription PCR, performed in BSL-3 laboratories. Point-of-care enzyme-linked immunosorbent assay–based testing for the VP40 matrix protein/glycoprotein (GP) and miniaturized electrochemical EBOV immunosensing have been investigated[15]. Supportive care, like rehydrating with oral or intravenous fluids and treatment of specific symptoms and co-infection can improve the chance of survival[16].

ERVEBO, live-attenuated, vectored vaccine based on a recombinant vesicular stomatitis virus expressing the *Zaire ebolavirus* glycoprotein, is used for the Ebola outbreak in DRC[17]. In the most recent outbreak of *Zaire ebolavirus* in DRC, ring vaccination targeting contacts was effective for outbreak containment[7]. Similar strategy may be applied for SUDV outbreak in Uganda. For SUDV, Zabdeno/Mvabeais vaccine [adenovirus type 26 encoding the *Zaire ebolavirus* (EBOV) and Mayinga variant glycoprotein] has been approved by European Medicines Agency (EMA) under exceptionable circumstance and has completed phase I/II/III trials in USA, Africa, and Europe, but awaits the US Food and Drug Administration (FDA) approval for its use. Two heterologous doses must be delivered: Zabdeno suspension [Ad26.ZEBOV-GP (recombinant); red cap vial] is administered first and Mvabea/SmPC (MVA-BN-Filo; yellow cap vial) is given ~2 months later[18]. This two-dose regimen is not suitable for an outbreak response where immediate protection is necessary[19]. A new vectored vaccine, MVA-VLP-SUDV against SUDV is under animal studies. It has advantage of combining immunogenicity of a live-attenuated vaccine vector (modified Vaccinia Ankara, MVA) with the authentic conformation of virus-like particles (VLPs). In animal studies, a single dose demonstrated protection. This MVA-VLP platform may be useful in emergent situations to contain outbreaks[20].

Advances in developing vaccines and drugs for counteracting EBOV are being made, however since there are no licensed vaccines for general population or direct-acting medicines to prevent or treat SUDV disease, there is a high chance that the disease could have a serious impact on public health[2]. Community deaths and care for patients in private facilities, hospitals, and other community health services with limited protection and IPC measures pose a high risk of many transmission chains. Investigations are going on to find out how big the outbreak is and whether it could spread to other districts as well as to neighboring countries[15].

Case management, surveillance, and contact tracing, along with an optimal laboratory service, implementation of IPC measures in healthcare and community settings, safe and dignified burials, and community engagement and social mobilization are all essential components of effective outbreak control. Prevention and control of epidemics require widespread participation from the public. Human-to-human transmission of Ebola can be reduced by increasing public knowledge of the disease's risk factors and the protective actions that can be taken[13].

With regard to the recent outbreak in Uganda, the risk of disease spread has been deemed to be high due to the following factors: (1) the possibility that the event began 3 weeks before the identification of the index case and several transmission chains have not been tracked; (2) patients presenting at various facilities with suboptimal IPC practices, such as the inadequate use of personal protective equipment when handling patients; (3) the lack of an authorized vaccine; and (4) although Uganda has improved its ability to respond to Ebola outbreaks in recent years and has a local capacity that can be easily mobilized and organized with available resources to mount a robust response, the system could be overwhelmed if the number of cases increases and the outbreak spreads to other subcounties, districts, and regions, as the country responds simultaneously to multiple emergencies, including anthrax, COVID-19, Rift Valley fever, and cholera.

SVD is a life-threatening condition with a high burden of global mortality and chronic sequelae. Poverty, cultural, and religious behaviors are associated with an increased risk for the development of the disease. Survivors exhibit chronic manifestations that resemble autoimmune inflammatory conditions. These clinical features warrant further analysis to clarify the associated immunological mechanisms. Control and prevention of SVD should focus on control of human-to-human transmission. Prophylactic vaccines should be put in the endemic areas to prevent new outbreaks. As the world is grappling with COVID-19 and Monkeypox, the re-emergence of SUDV will burden the already exhausted healthcare services. The serious steps are needed under the umbrella of 'One health' approach so that the spillover events and further outbreaks can be minimized.

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