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Review Article

The outbreak of Ebola virus disease in 2022: A spotlight on a re-emerging global health menace

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Abstract

Ebola virus disease (EVD) is a rare but highly contagious and lethal disease that occurs predominantly in African countries, with a case-fatality rate of 30–90%. The causative viral pathogens of EVD are within the genus *Ebolavirus* in the family *Filoviridae*. The primary route of human-to-human transmission is through direct contact with blood, bodily fluids and secretions from infected individuals. Direct contact with virally contaminated objects and sexual transmission have also been reported. Management of EVD is aggressive supportive care with possibly new therapeutic options. On 20 September 2022, an EVD outbreak was declared in Uganda, caused by *Sudan ebolavirus*. As of 7 November 2022, a total of 136 confirmed cases, 53 confirmed deaths have been reported, including 18 cases with seven deaths among healthcare workers. In the Democratic Republic of Congo (DRC), an EVD outbreak was also declared on 22 August 2022 (which ended on 27 September 2022); with only one case, a middle-aged woman. At the time when most countries in the world have been occupied with the coronavirus disease 2019 (COVID-19) pandemic and the recent human monkeypox outbreak, these two outbreaks of EVD have the potential to significantly add to the burden on global health. Authorities need to augment their multi-faceted response, including stringent contact tracing and border control, to avoid the catastrophe of the 2014–2016 EVD epidemic.

Keywords: Ebola virus disease, Congo, Uganda, *Sudan ebolavirus*, *Zaire ebolavirus*

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Introduction

Ebola virus disease (EVD), formerly known as Ebola hemorrhagic fever is one of the rare but highly contagious and lethal diseases that is mainly present in African countries [1,2]. A

Received: November 15, 2022 - Accepted: December 10, 2022 - Published online: December 12, 2022

collective group of a ribonucleic acid (RNA) viruses was identified to be the causative pathogen of EVD, and all of them are within the genus *Ebolavirus* in the family *Filoviridae* [3]. Among the six viral species identified, four are known to cause EVD in humans: Ebola virus (species *Zaire ebolavirus*), Sudan virus (species *Sudan ebolavirus*), Taï Forest virus (species *Taï Forest ebolavirus*, formerly *Côte d'Ivoire ebolavirus*), and Bundibugyo virus (species *Bundibugyo ebolavirus*); of these, the *Zaire ebolavirus* is flagged appears to be the most lethal [6]. The remaining two viruses are Reston virus (species *Reston ebolavirus*), which infects non-human primates, and the recently discovered Bombali virus (species *Bombali ebolavirus*), whose pathogenicity to humans or animals is still not confirmed [2,4].

Since its discovery in the 1970s in the Democratic Republic of Congo (DRC), the Ebola virus has caused many sporadic outbreaks mostly in the African continent [7], with a case-fatality rate in the range of 30–90% [7,8]. Although the origin of the Ebola virus remains undetermined, it is believed that EVD is a zoonotic disease [4,6,9], with fruit bats, among other wild animals, being the possible natural reservoir of the virus [6]. The main route of zoonotic viral transmission (animal-to-human) is through spillover events including direct contact with body fluids, blood, and tissues of infected animals [4]. Additionally, the primary route of human-to-human transmission is through direct contact with blood, bodily fluids and secretions (e.g., saliva, vomit, sweat, breast milk, urine and semen) of infected humans or those who died due to EVD [2,9]. In addition, direct contact with virally contaminated inanimate objects (needles, bedding, or equipments) can transmit the virus to humans [4]. Sexual transmission has been also reported in the literature (e.g., through semen) as the virus remains in the semen with delayed clearance even after full recovery from EVD [4]. This can occur when having oral, vaginal, or anal sex with a male who was sick with EVD, even after recovery [10]. However, EVD spread through food chain transmission is not yet known [11].

The incubation period for EVD ranges from two to 21 days [6,8,9]. EVD symptoms start with a prodromal phase (non-specific flu-like symptoms) that is characterized by general malaise, high fever, joint pain, headache, sore throat, anorexia, nausea, vomiting and diarrhea [1]. Later, more severe symptoms arise from multi-organ involvement, including gastrointestinal, neurological, vascular, cutaneous and respiratory symptoms [12]. Additional symptoms include internal/external bleeding, bruising and hiccups in the later stages [4,12]. Post-infection sequelae of EVD include rheumatological (arthralgia and periarticular tendinitis), ocular (uveitis, conjunctivitis, photophobia, hyper-lacrimation, and loss of visual acuity), neurological (encephalopathy and seizures), auditory (tinnitus and hearing loss), and dermatological (pruritus, skin desquamation and alopecia) [10]. It is important to stress that infected individuals are not considered to be infectious until they have become symptomatic [4,7,8]. Pregnant women, children, and the elderly have poorer outcomes compared to others [1]. Healthcare workers (HCWs) are considered one of the high-risk groups to contract EVD, especially in the context of limited resources and insufficient supply of personal protective equipment (PPE).

The diagnosis of EVD is made by the classic clinical presentation, particularly during a declared outbreak, and confirmed by various laboratory techniques, including antibody-capture enzyme-linked immunosorbent assay (ELISA), serum neutralization test, antigen-capture detection tests, reverse transcriptase polymerase chain reaction (RT-PCR) [7,13], in addition to multiplex PCR and micro-array-based assay [9].

Management of EVD begins with strict isolation of victims, followed by aggressive supportive care including hydration, anti-pyrectics, analgesics, anti-emetics, and antidiarrheals; new therapeutic options include the recently FDA-approved Inmazeb® (three monoclonal antibodies: atoltivimab, maftivimab, and odesivimab-ebgn) or Ebanga® (single monoclonal antibody: mAb114) [4,12]. Of note, the two FDA-approved monoclonal antibodies have only been evaluated in clinical trials against the species *Zaire ebolavirus*. However, none of the above FDA-approved Ebola medications is registered in any African country [14]. Additionally, advanced critical care of patients with EVD that comprises both aggressive symptomatic and organ-supporting care has been shown to be feasible and promising in terms of improving survival rate among patients [15]. Nevertheless, unsatisfactory clinical outcomes are expected to

occur in patients without the use of effective antiviral medications against Ebola virus [15]. Acute organ failure (renal or hepatic), and high viral load were found to be associated with high likelihood of fatal clinical outcomes [16]. Moreover, advanced supportive care was reported to be an essential step in managing patients with EVD considering the high mortality rate that characterizes EVD despite the treatment options available. The advanced critical care might be of a significant challenge especially in poor-resources contexts.

Previous EVD outbreaks in the period 2014–2021

The Ebola virus has caused many outbreaks in various African countries, especially in the DRC where the disease is considered endemic [17]. In 2014, 66 cases and 49 deaths were attributed to the EVD outbreak in the DRC. In 2014–2016 many other countries in west Africa suffered from EVD outbreak which the World Health Organization (WHO) declared as a Public Health Emergency of International Concern (PHEIC) in August 2014 [18]. During this outbreak, EVD spread from Guinea, Liberia, and Sierra Leone, to Italy, Spain, the United States (US), and the United Kingdom (UK). During this epidemic more than 28,000 EVD cases were identified, with a death toll surpassing 11,000 deaths [18]. In 2017, a small-scale EVD outbreak occurred in the DRC with a total of eight cases and four deaths [4]. In 2018, another small-scale EVD outbreak occurred in the DRC with 38 laboratory-confirmed cases and 33 fatalities [4]. In 2020, an EVD outbreak occurred in the DRC with a total of 130 cases and 55 deaths [4]. In 2021, a total of 23 cases and 12 deaths were attributed to EVD outbreaks that occurred on two occasions in the DRC [4]. In the same year, Guinea reported 23 EVD cases and 12 deaths [7]. **Table 1** presents more detailed information about the recent EVD outbreaks in the period 2014–2021 [4,7,18].

Table 1. Characteristics of Ebola virus disease (EVD) outbreaks in the period 2014–2021

Date of outbreak declaration	Date of outbreak ended	Country	Total Cases	Deaths	Species
8 October 2021	16 December 2021	DRC	11	6	*Zaire ebolavirus*
7 February 2021	3 May 2021	DRC	12	6	*Zaire ebolavirus*
14 February 2021	19 June 2021	Guinea	23	12	*Zaire ebolavirus*
1 June 2020	18 November 2022	DRC	130	55	*Zaire ebolavirus*
1 August 2018	25 June 2020	DRC and Uganda	3,470	2,287	*Zaire ebolavirus*
8 May 2018	24 July 2018	DRC	54	33	*Zaire ebolavirus*
11 May 2017	2 July 2017	DRC	8	4	*Zaire ebolavirus*
26 July 2014	7 October 2014	DRC	69	49	*Zaire ebolavirus*
23 March 2014	June 2016	Guinea, Liberia, Sierra Leone (West African Epidemic) *	28,610	11,308	*Zaire ebolavirus*

*West African EVD epidemic has ended in June 2016. During this large epidemic, EVD cases were also reported in Italy (one case, no death), Mali (eight cases, six deaths), Nigeria (20 cases, eight deaths), Senegal (one case, no death), Spain (one case, no death), UK (one case, no death), US (four cases, one death). The causative species of West African EVD epidemic was *Zaire ebolavirus*.

EVD outbreaks in Uganda and DRC - 2022

On 20 September 2022, an EVD outbreak was declared by health authorities in Uganda (Mubende district) [19]. The index case was a young male although there had been six previous unexplained deaths in the same district earlier in September 2022. The 24-year-old male patient presented to a healthcare facility with symptoms of high-grade fever, bloody vomiting and diarrhea, and sore throat. The symptoms started on 11 September 2022; blood samples from 18 September 2022, surprisingly indicated infection with *Sudan ebolavirus*. The victim died on 19 September 2022 [20] and additional eight suspected cases were identified, isolated and contact tracing initiated [19,21]. There have been seven previous outbreaks of *Sudan ebolavirus*: three in Sudan, and four in Uganda (the last one in 2012) [21]. In a new 2022 outbreak, a total of 136 confirmed cases, 53 confirmed deaths have been reported in Uganda to 7 November 2022, including 18 cases with seven deaths among HCWs [22]. Additionally, 1386 contact cases are actively under surveillance [22].

In contrast, the outbreak in the DRC declared in the North Kivu province by health authorities on 22 August 2022 [23], had the *Zaire ebolavirus* as the causative agent. The single patient was a middle-aged woman who was hospitalized in the period 23 July to 15 August 2022 suffering from non-specific flu-like symptoms. The woman died on 15 August 2022 [24]. Unfortunately, the deceased woman was discovered to have EDV after the body was returned to her family for funeral arrangements. The laboratory confirmation of EVD was received on 16 August 2022. Contact tracing has identified 60 health care workers and 74 patients as close contacts to the deceased woman, in addition to nine family members [24]. On 27 September 2022, the health authorities in the DRC has declared the end of the current outbreak [25].

An additional EVD outbreak was declared in the DRC, Equateur province, on 23 April 2022 [18]. This EVD outbreak was managed with a robust response from the concerned health authorities, and the DRC declared its end on 4 July 2022.

Preventive measures and vaccination

Preventive and precautionary measures have a pivotal role in controlling EVD outbreaks. The pillars of Ebola preventions include reducing the risk of animal to human transmission, reducing the risk of human-to-human transmission, reducing the risk of sexual transmission, as well as outbreak mitigation and control measures. As the routes of transmission, whether animal to human or human to human, are well-known; thus, the public has a paramount responsibility to adopt and maintain hygienic measures. Apart from isolating EVD patients for proper management and contact tracing, many measures should be taken into consideration by the public. Some of these measures include avoiding direct contact with blood, secretions, and body fluids of individuals who are sick, avoiding oral, vaginal, and anal sexual practices with men recovered from EVD, until the confirmation of a complete viral clearance from the body and semen, avoiding direct contact with virally contaminated inanimate objects, as well as ensuring the highest precautionary standards in funerals of EVD victims. As the primary natural source of the Ebola virus is thought to be bats and nonhuman primates, it is recommended to avoid direct contact with these. Travelers to zones that are known to suffer from EVD outbreaks should be also aware of EVD symptoms and preserve the highest preventive measures.

Additionally, prevention through vaccination is vital. There are currently three approved Ebola virus vaccines from nine Ebola vaccine candidates. In 2019, a single-dose vaccine (Ervebo®) was approved by the US Food and Drug Administration (FDA) for individuals who are 18 years and older, against *Zaire ebolavirus*. Ervebo®, a vesicular stomatitis virus (VSV)-based vector vaccine (rVSV-ZEBOV), is a live attenuated recombinant vaccine. It contains the vesicular stomatitis virus in which the gene encoding the envelope glycoprotein (GP) has been modified with that of the *Zaire ebolavirus* [26]. It is not possible to contract EVD infection from the vaccine because the vaccine only contains a gene from the Ebola virus, not the whole virus. Ervebo® vaccine's approval is supported by a cluster-randomized ring vaccination study conducted in Guinea during the 2014–2016 outbreak in people aged 18 years or more [27]. Ervebo® safety was evaluated in approximately 15,000 people in Africa, Europe, and North America. The most frequently reported side effects were pain, headache, fever, swelling and redness at the injection site, joint and muscle aches, and fatigue [28]. Ervebo® is currently registered in DRC and some other Ebola-prone African countries [14].

Recently a combination vaccine regimen of Zabdeno® (Ad26.ZEBOV) and Mvabea® (MVA-BN-Filo) has been marketed for protection against *Zaire ebolavirus* [26]. This combined vaccine regimen is given as an initial dose, with a booster dose after an eight-week gap. Although it is not yet FDA-approved for routine use [4], the European Medicines Agency and the European Commission have granted marketing authorization as a pre-exposure prophylaxis for individuals aged one year and older, especially among high-risk groups in Europe (e.g., HCWs) [29]. However, it is reported that this two-agent combined vaccine regimen is still not registered in African countries [14], possibly as, in an EVD outbreak, immediate protection and immunological response is necessary [29]. The efficacy of the combined vaccine was evaluated in 3,367 individuals including children, adolescents, and adults in five clinical trial sites in Europe, Africa, and the USA [29]. The reported side effects were similar to that of Ervebo®.

Occupational risks of EVD outbreaks

As EVD is a highly contagious and deadly infection, it carries a high risk of healthcare-associated infection (HCAI). HCAI occur whether among patients attending a healthcare facility or among HCWs as an occupational infection. In general, HCAI are higher in low- and middle-income settings due to limited resources and infrastructure [30]. In the context of EVD, HCWs involved in managing/treating patients with confirmed or suspected EVD, and those who are involved in outbreak response and surveillance are recommended to maintain the highest infection control and prevention (IPC) measures. This can be facilitated through the implementation of the WHO multi-modal infection prevention and control (IPC) strategies [31], including, training of healthcare staff on IPC measures and PPE usage, sufficient supplies of PPE, monitoring of compliance, feedback and evaluation, capacity building for promotional materials, and enhancing the culture of safety aiming at facilitating the organizational climate to adopt IPC measures successfully.

Psychological impacts of EVD outbreaks

Infectious diseases outbreaks are not only considered a threat to human's physical wellbeing, but also to psychological wellbeing. For instance, outbreaks such as severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and coronavirus disease 2019 (COVID-19) pandemic have been associated with significant mental health and social impacts [32–34]. This is partly due to fear of contracting infection, but also psychological impacts may arise from the accompanied isolation, stigmatization, shortage of resources, and the uncertainty that accompanies the crisis [35–39]. Also, psychological distress amid infectious diseases outbreaks and epidemics can affect anyone regardless of sex, ethnicity, religion, occupation, and health status. Even people with no previous psychiatric history can be severely afflicted by such outbreaks [40].

Therefore, not surprisingly, significant burden on mental health caused by EVD outbreaks has been reported [41,42]. For example, during the West African EVD epidemic in 2014–2016, a widespread fear, post-traumatic stress symptoms, and anxiety-depression were found among patients, survivors and even those who did not contract the disease [42–44]. On top of that, stigmatization was an issue that may have caused under-reporting of symptoms or even unwillingness to seek medical help when needed [43]. Therefore, mental health and psychosocial support (MHPSS) should be considered an essential component of an infectious disease outbreak response.

In addition, psychological distress may also occur amongst HCWs, and their families, who are involved in caring for EVD patients or in contact-tracing. This can be attributed to the stress and fear of contracting the virus, fear of transmitting the virus to family members (in case of contracting it and during the incubation period where no symptoms present), and experiencing the loss of patients due to EVD [41]. Consequently, it is recommended that psychological support strategy be included in any organization's outbreak response. This can be ensured by having a regular mental health screening for all HCWs even before an outbreak or as the disaster occurs, providing adequate PPE supply especially for staff who work in high-risk roles, early screening and detection of mental distress among HCWs during an outbreak response, and timely referral to a mental health specialist service for any needed intervention. The afore-mentioned measures may collectively improve the preparedness of a HCW to be involved in EVD outbreak response, and may reduce the psychosocial distress or preventing it from worsening.

The suggested intervention pillars of MHPSS during infectious disease outbreak response include social considerations in basic services and security, strengthening community and family supports, focused (person-to-person) non-specialized supports, and specialized mental health services [45]. **Figure 1** illustrates the potential candidates for MHPSS during an infectious disease outbreak/epidemic.

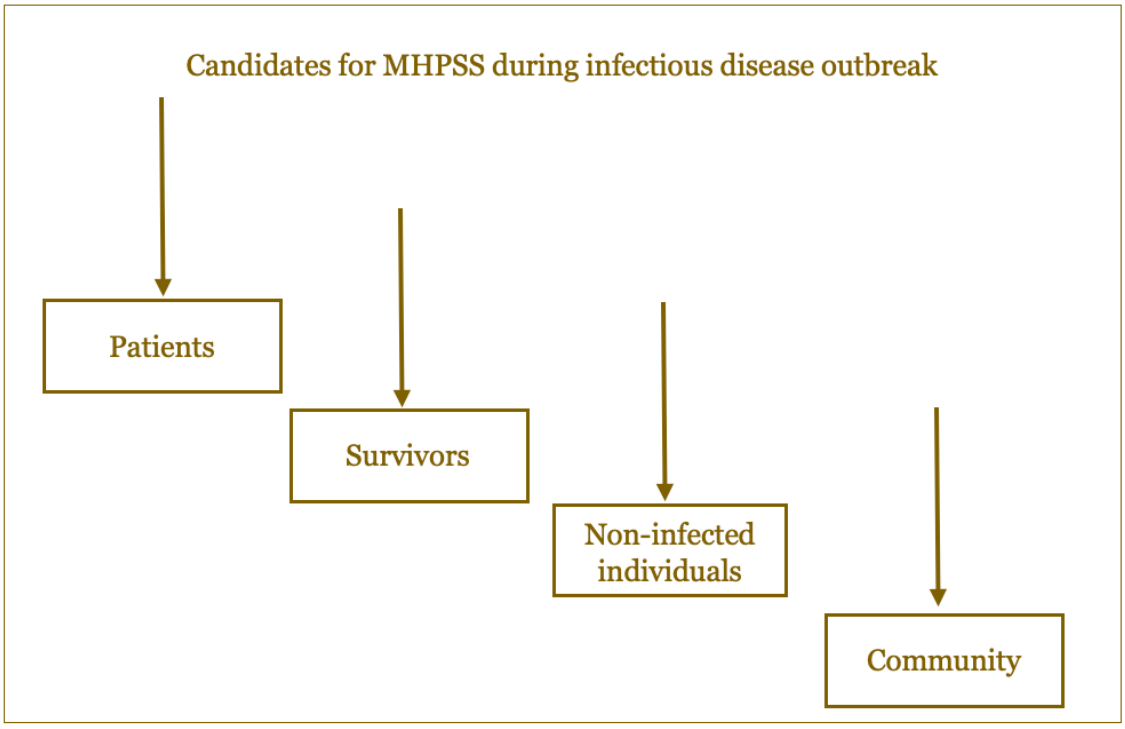

Figure 1. Potential candidates for mental health and psychosocial support (MHPSS) during outbreak response

Economic consequences of EVD outbreaks

EVD outbreaks/epidemics impose a significant burden on economies whether through direct or indirect mechanisms. The direct economic impacts are related to the cost of healthcare resources mobilized to mitigate the disease spread, as well as the productivity loss that result from workforce diversion and depletion, especially in large-scale outbreaks and epidemics [46]. Such direct economic costs can be attributed to the impact on HCWs, costs of EVD-related deaths, costs of long-term EVD sequalae, costs of treatment, infection control and screening, and costs of deployment of human resources [47]. Indirect economic impacts are associated with behavioral changes that accompany a contagious disease like EVD. For example, fear of EVD infection can lead to absenteeism of employees, and people displacement from disease zones which can lead to immediate financial loss [46]. Additionally, EVD can negatively affect the economy through its control measures (e.g., stay-at-home orders, border closure, and export/import trade depletion) that may lead to trade reduction. Giving an example on the 2014–2016 West African EVD epidemic, estimates from Nigeria revealed 0.1–3.3% reduction in investment in 2015, and 2–3.4% reduction in exports in 2014, with $3.8–$32.6 billion lost gross domestic product (GDP) in the period 2014–2015 [47]. Additionally, in Liberia, $2.8 billion lost GDP in 2014–2016, and around $550 million lost GDP in nonaffected sub-Saharan African countries in 2015 [47].

EVD-related global health challenges

At a time while most countries in the world are still managing the COVID-19 pandemic with its associated physical, psychological, and socioeconomic impacts [48], in addition to the smaller ongoing human monkeypox outbreak [49], the two separate EVD outbreaks in 2022 in the DRC and Uganda have the potential for adding significantly to the burden on global health. As the world cannot afford further international lockdowns similar to those triggered by COVID-19, extreme vigilance is necessary to avoid cross-border exportation of EVD. As EVD is endemic in Africa, and the African countries that experienced outbreaks are highly prepared, sharing knowledge and experience with other parts of the world, especially countries with limited resources, is very important. Concerning EVD outbreak response, various challenges may

present especially in low-resources settings such as inadequate HCW training, insufficient PPE supplies, lack of diagnostic capabilities, and poor infrastructure of public health system [50].

A timely epidemic preparedness, with collective intelligence and coordination between various sectors and authorities, should be established and strengthened [14]. Although there are currently two available vaccines for EVD, their effectiveness is only against *Zaire ebolavirus*. This in fact imposes a significant public health challenge in case of EVD outbreak by other species (i.e., the current EVD outbreak in Uganda is by *Sudan ebolavirus*). Additionally, the licensing issue of vaccines remains a challenge due to the sporadic nature of EVD outbreaks [26]. Lack of robust research in limited-resource settings, insufficient public health-focused leadership, inequity in vaccines, medications, and PPE distribution, lack of sufficient EVD therapy and vaccines efficacy data, and the uneven power in Ebola medications/vaccines development between partners involved in research development are all contributing factors to the global health challenges of EVD control [14]. Preparedness against infectious disease outbreaks is challenging from a global health perspective, as highlighted by a recent review of EVD which noted 'a typical case of market failure: no treatment, diagnostic, or vaccine was available when a long-expected, major outbreak devastated Guinea, Liberia, and Sierra Leone in 2014–2016' [14]. Public health authorities should augment their multi-faceted response including stringent contact tracing and border control to avoid the catastrophe of the 2014–2016 EVD epidemic, considering that most available FDA-approved therapies are not yet registered in Africa, and only one vaccine against *Zaire ebolavirus* is approved for use and registered in the DRC among few African countries.

Recommendations

Based on lessons learnt from previous outbreaks and epidemics, it is vital for every country to have a well-formulated outbreak response plan for EVD, including countries that have never reported EVD. Taking into consideration the risk of cross-border exportation of EVD, a robust public health response is essential in countries that announce an EVD outbreak. State services, non-governmental organizations (NGOs), as well as the community have a paramount responsibility in providing the needed support to mitigate the risks of EVD outbreak and its associated consequences. In order to be well-prepared and to have a robust immediate outbreak response, immense efforts must be invested in improving healthcare and laboratory infrastructures, augmenting public health preparedness and response, sharing information from credible sources with public, maintaining a sustainable inter-agency collaboration, strengthening of epidemiological surveillance systems, inclusion of MHPSS strategies in the outbreak response, protecting high-risk groups and HCWs, as well as implementing timely non-pharmaceutical interventions.

Ethics approval

Not required.

Acknowledgments

All authors listed have significantly contributed to the development and the writing of this article.

Conflict of interest

All the authors declare that there are no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

How to cite

Al-Tammemi AB, Sallam M, Rebhi A, *et al.* The outbreak of Ebola virus disease in 2022: A spotlight on a re-emerging global health menace. Narra J 2022; 2 (3): e97 - http://doi.org/10.52225/narra.v2i3.97.

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