Clinical aspects of Ebola virus disease: a review

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SUMMARY

Ebola Virus Disease (EVD), also known as Ebola Hemorrhagic Fever (EHF), initially emerged over 40 years ago in the Democratic Republic of Congo. Endemic to Africa, outbreaks have been recorded in six African countries since its detection in 1976. Fruit bats are believed to be the natural hosts of Ebola viruses (EBoV), with humans and other mammals serving as accidental hosts. Transmission of EBoV has been reported in various ways, including human to human transmission through close contact with blood and bodily fluids. The virus has an incubation period ranging from two to twenty-one days, followed by a multitude of clinical manifestations such as the sudden onset of high fever, chills and myalgia depicting a flu-like syndrome. It is usually diagnosed based on several clinical symptoms such as the sudden onset of illness, high fevers for less than three weeks, and at least two hemorrhagic symptoms despite no predisposing factors. This generally provides enough evidence for clinicians to consider EHF and begin supportive treatment until the virus is confirmed through laboratory findings. Management of patients involves supportive care such as maintaining fluid along with electrolyte balance, blood pressure and oxygen saturation. This also includes treating complications arising from secondary infections. The main options include: prophylactic strategies, anti-viral therapy for EVD, immunotherapies, vaccines, and ZMapp. Finally, the key to managing EBoV epidemics is to stop the transmission of disease in the most severely affected population, as prevention has become of utmost importance to alleviate the significant physical and economic burden.

Keywords: Ebola virus; outbreaks; Ebola hemorrhagic fever; filovirus.

INTRODUCTION

Ebola Virus Disease (EVD), also known as the Ebola Hemorrhagic Fever (EHF), initially emerged in 1976 with a deadly infectious epidemic characterized by acute viral hemorrhagic fever. This outbreak constituted of 318 cases and a high mortality rate of 88% (280 deaths) in Yambuku; hence, it was named Ebola after the Ebola River in the Democratic Republic of Congo (DRC) [1]. The genus Ebola virus belongs to the family *Filoviridae*, along with the genus Marburg virus. This highly virulent virus consists of a characteristic filamentous or branching convoluted shape and is enveloped containing linear non-segmented, negative-sense single-stranded RNA genome [2]. There are five species of this virus, with each subtype having different biologic characteristics and virulence [2, 3]. Fruit bats belonging to the Pteropodidae family are thought to be responsible for the dissemination of this zoonotic virus, believed to be the natural hosts of Ebola viruses (EBoV), with humans and other mammals serving as ac-

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cidental hosts [4]. Transmission of the EBoV has been reported in various ways, including human to human transmission through close contact with blood and bodily fluids such as saliva, breast milk, urine and semen from another infected human or animal, either by direct contact or indirectly from contaminated objects like needles and syringes. Moreover, it is not spread through aerosol droplets or by water and food contamination [5].

Since the original case of this life-threatening disease in DRC, the majority of the outbreaks of EBoV disease have been reported in Africa. The 2014-2016 outbreaks emerged in the rural setting of southeastern Guinea which eventually spread to the crowded urban areas and across borders thus becoming a global epidemic. These outbreaks were declared as a Public Health Emergency of International Concern (PHEIC) by World Health Organization (WHO) resulting in more than 28,600 cases and 11,325 deaths. Furthermore, due to widespread transmission, countries including Guinea, Senegal, Nigeria, and United States amongst others were also affected during the epidemic [6]. The EBoV has an incubation period ranging from two to twenty-one days, followed by a multitude of clinical manifestations such as the sudden onset of high fever, chills and myalgia depicting a flu-like syndrome [2, 7].

In 2018-2019, the tenth and largest EVD outbreak occurred in the DRC since Zaire Ebola virus was first discovered there in 1976. This epidemic involved 1600 patients with a case fatality rate of 67%. The outbreak was first reported as a cluster of cases of acute hemorrhagic fever in North Kivu following which EVD was also detected in Ituri province and important commercial hubs close to Uganda mainly due to travel and health care transmission mechanisms. Additionally, the non-specific clinical manifestations of EVD including vomiting, diarrhea, sweating, dehydration, and hypovolemic shock coupled with undifferentiated symptoms of headache and fatigue further complicated the diagnosis due to a simultaneous high burden of other febrile infectious diseases. A concurrent wave of malaria cases was reported in Beni which enhanced the difficulty of diagnosis and increased the number of people exposed to Ebola in overcrowded health care facilities with inadequate infection prevention and control measures. Eventually, the Ministry of Health in support of WHO developed a government-led Consolidation and Stabilization Plan for long term Ebola survivor care following the end of the outbreak declaration to strengthen the emergency response capacity and preparedness, and overall resilience of the health systems [8, 9]. Despite several warnings and discussions, regular outbreaks of EVD have been noticed in the past decade, making this disease crucial for physicians and infectious diseases specialists to tackle. However, the question arises: when this will stop? Therefore, to answer this question, this narrative review was designed to highlight the clinical aspects associated with EVD, along-with its diagnostic and management approach.

METHODS

For this review, a literature search was conducted using PubMed and Google Scholar from inception to September 2019. The following search string was used: "Ebola" OR "Ebola virus" OR "Ebola outbreak" OR "Ebola virus pathogenesis" OR "Ebola transmission" OR "Ebola diagnosis" OR "Ebola management." Articles in languages other than English were excluded.

Epidemiology and outbreaks

In June 1976, an individual from a rural area in Sudan, worked in a factory in the township of Nzara presented with complaints of headache, chest pain and fever. The patient developed epistaxis, bleeding from the mouth and bloody diarrhea the next day. After infecting several of his colleagues and family members, the patient died on July 6, four days after his admission to the hospital. According to the WHO, the characteristics of the disease were found to be similar to those in patients in Marburg, Germany, nine years ago. After lasting for five months from June-November 1976 and infecting 284 people, the epidemic was brought under control, with the mortality being 53% [10].

Endemic to Africa, 36 outbreaks have been recorded in 6 African countries since its detection in 1976. While outbreaks and isolated cases have also been reported in the United States, United Kingdom, Canada, Spain, and Thailand, however, they have been reported as intermittent imported cases [11]. Table 1 and Figure 1 outline Ebola outbreaks from 1976 to 2018 in various parts of the world, constituting of mainly Africa [12].

The largest outbreak to date has been reported

between the years 2013 and 2016 in West Africa, notably in Guinea, Sierra Leone, and Liberia [13]. Liberia has accounted for roughly 11,000 cases, and over 4,800 deaths out of the unmatched globally reported 28,616 cases and 11,310 casualties [11]. This outbreak included both rural and urban areas with a very high incidence and mortality. Nonetheless, the actual burden might have been markedly greater, owing to under-reporting [13].
Most recent outbreaks were recorded in a remote area in the provinces of Equateur and the North Kivu in the DRC in May and June 2018, respectively. According to the reports, most of these outbreaks have been recorded in remote rural areas, but the outbreak in Gulu, Uganda, in 2000 was in a semi-urban area.
The Figure 2 outlines the most recent outbreak in Democratic Republic of Congo and Uganda [14]. Nevertheless, small outbreaks might not have been identified as such. According to various

Table 1 - Outbreaks of Ebola virus from 1976-2020 [12].

#	*Year*	*Country*	*Species*	*Cases reported*	*Deaths Reported*
1	1976	Sudan	Sudan ebolavirus	284	151 (53%)
2		Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	318	280 (88%)
3	1979	Sudan	Sudan ebolavirus	64	22 (65%)
4	1989	Philippines	Reston ebolavirus	3	0 (0%)
5	1990	United States of America	Reston ebolavirus	4	0 (0%)
6	1994	Gabon	Zaire ebolavirus	51	31 (61%)
7	1995	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	315	254 (81%)
8	1996	South Africa	Zaire ebolavirus	2	1 (50%)
9		Gabon	Zaire ebolavirus	60	45 (95%)
10	2000	Uganda	Sudan ebolavirus	425	224 (53%)
11	2001	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	59	44 (75%)
12		Gabon	Zaire ebolavirus	65	53 (81%)
13	2003	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	143	128 (89%)
14	2004	Sudan	Sudan ebolavirus	17	7 (41%)
15	2005	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	12	10 (83%)
16	2007	Uganda	Bundibugyo ebolavirus	131	42 (32%)
17		Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	264	187 (71%)
18	2008	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	32	15 (47%)
19		Philippines	Reston ebolavirus	6	0 (0%)
20	2012	Uganda	Sudan ebolavirus	6	3 (50%)
21		Democratic Republic of the Congo (formerly Zaire)	Bundibugyo ebolavirus	38	13 (34%)
22		Uganda	Sudan ebolavirus	11	4 (36%)
23	2014	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	69	49 (71%)
24		Guinea, Liberia, Sierra Leone (West African Epidemic)	Zaire ebolavirus	28610	11,308 (39%)
25		Mali	Zaire ebolavirus	8	6 (75%)
26		Nigeria	Zaire ebolavirus	20	8 (40%)
27		United States of America	Zaire ebolavirus	4	1 (25%)
28	2017	Democratic Republic of the Congo (formerly Zaire)	Zaire ebolavirus	8	4 (50%)
29	2018-20	Democratic Republic of the Congo (formerly Zaire), Uganda	Zaire ebolavirus	3310	2264 (68.4%)

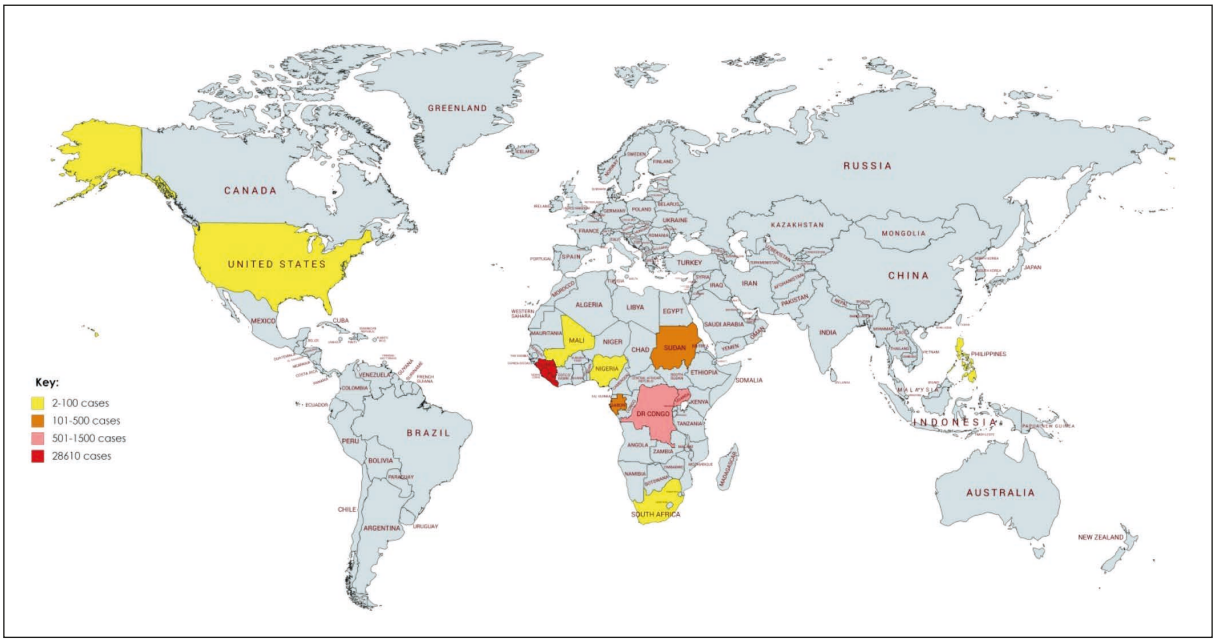


Figure 1 - Global distribution of EBoV from 1976-2018.

studies, EVD is mainly endemic to African countries, with some spread to its neighboring countries [13].

Pathogenesis

EBoV, formerly known as *Zaire* EBoV, belongs to the Filoviridae family. This species is associated with the greatest number of outbreaks and the highest case-fatality rates among the other four viruses sharing the EBoV genus. The other viruses include Sudan ebolavirus (SUDV), Bundibugyo ebolavirus (Bundibugyo virus), Taï Forest ebolavirus (Taï Forest virus), and finally Reston ebolavirus (Reston virus (RESTV) (Figure 3).

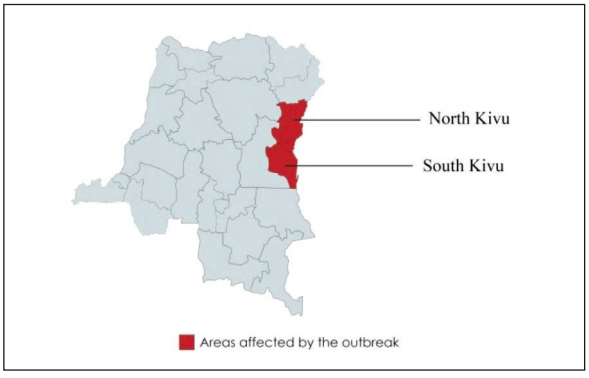


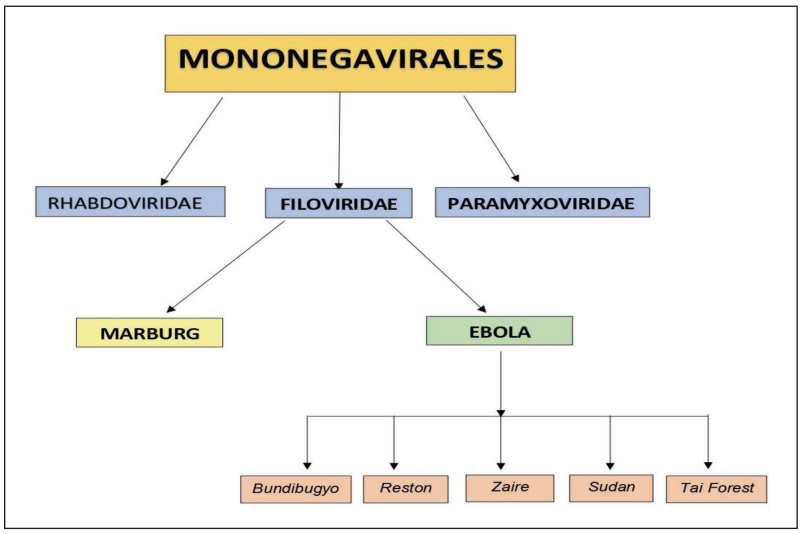
Figure 2 - EBoV from 2018-2020.

The EBoV virion is a single-stranded, non-segmented, negative-sense RNA that is approximately 19,000 nucleotides long, consisting of 7 genes and 9 proteins [15]. Unlike most of the viral infections, EBOV has high pathogenicity with debilitating complications, and fatal outcome [16].

This pathogenicity is primarily related to its structure, as EBoV is a lipid-enveloped virus that aids the virus into entering the host cell. The viral envelope glycoprotein (GP) essentially binds to the receptor and binds the viral envelope with the host membrane [17]. Initially, the virus turns off the immune system by affecting the macrophages and dendritic cells (antigen-presenting cells), causing their replication. This leads to modulation of the genes, which then undergo apoptosis and release viral particles to extracellular tissues [18]. However, later it may affect other several types of cells such as Kupffer cells, hepatocytes, fibroblasts, adrenal gland cells leading to the spread of disease, and causing vascular damage and multi-organ failure [19].

The virus disrupts the immune system by suppressing the maturation of dendritic cells, which leads to disruption in the production of inflam-

Figure 3 - Taxonomy of Ebola Virus.



matory cytokines that impairs their ability to activate T-cells [2, 19, 20]. *In vitro* studies indicate that VP35 is involved in blocking the host interferons production and signaling by suppressing the activation of T-cells and expression of cytokines when activated by a RIGI-like receptor signaling. While, VP24 directly inhibits Interferon a/b and Interferon g (IFN) signaling by inhibiting the dimerization of phosphorylated STAT1, ultimately blocking the transcription of anti-viral genes [15, 21]. Additionally, IFNs also upregulate expression of major histocompatibility complex on host cell surfaces' which generally plays an essential role in innate immune response [2].

Furthermore, the virus further suppresses the immunity by causing apoptosis of bystander lymphocytes, most probably via FasL/FasR receptor binding (extrinsic pathway), and possibly via upregulating TNF-α production inducing viral damage to the surrounding tissue (intrinsic pathway) [2, 22, 23]. In addition to weakening the immune system, the release of vast amounts of cytokines and chemokines, results in increased activation of coagulation cascade causing damage to the vascular integrity and permeability. This damage in the vessels may lead to hypovolemic shock, and subsequently, disseminated intravascular coagulation plays a huge role in the mortalities associated with EHF [19, 20, 23].

Vectors, transmission and reservoirs

Members of the *Pteropodidae* family, Fruit bats, are considered as the most likely natural reservoir of EBoV [24]. With an incubation period of 4 to 10 days, EBoV has a biosafety level 4 and category A bioterrorism pathogen with a significant transmission probability throughout the nation [11]. Liquid or dried material both can help the virus survive for many days [25].

Blood, feces, and vomit are considered as most infectious bodily fluids, according to WHO [26]. Such fluids are considered as highly transmittable by direct contact from dead or living infected persons. Non-animal objects contaminated with infected bodily fluids (fomites) may also transmit the disease [25]. However, the relative infectivity of the various body fluids of patients with EVD has not been established yet. Although well documented, the risk associated with sexual transmission remains low [24].

So far, direct contact with a symptomatic or dead EVD case is the major route of transmission [25]. Humans can also get infected with EBoV via contact with wild animals in situations such as hunting and preparing meat from infected animals [26].

Along with no documentation of airborne transmission, attempts to culture virus from the amniotic fluid have not been reported either. Furthermore, high levels of viral RNA in amniotic fluid of pregnant women infected with EVD and on the placenta and fetus right after delivery. These factors, along with elevated in utero fetal and neonatal fatality rates, are strong indicators of vertical transmission of EVD [24, 25].

Clinical manifestations

With an incubation period ranging from 2 to 21 days - high fever, fatigue, malaise, body aches, and chills represent EVD as a flu-like syndrome. The disease also commonly manifests as gastrointestinal (abdominal pain and anorexia), respiratory (chest pain and dyspnea), vascular (postural hypotension and edema), and rarely neurologic (headache, delirium, confusion and coma) disorders [2, 13]. Furthermore, low serum concentrations of potassium, sodium and calcium have also been commonly reported in EVD patients, proving them to be important causes of death along with dehydration [27]. Although discretely visible on patients with dark skin, a maculopapular rash has also been reported as one of the findings [13]. If pregnant, such women have a high probability of transmitting the disease to their infants either by breast milk or by close contact. Such women also have an increased risk of miscarriage, and as suggested by clinical findings, high children of infected mothers have a high mortality rate [2].

Death typically occurs between days 6 and 16, even though the patients with the fatal disease develop clinical manifestation during early infection. The causes of death include hypovolemic shock and multiorgan failure [2]. Although in certain cases, sudden death can occur due to cardiac arrhythmias. Nevertheless, if patients survive the stage of shock, there is a possibility of gradual recovery. Even though several studies tried to identify clinical manifestations for EVD, their diagnostic accuracy was too little to rely upon, rendering them inaccurate to be included in clinical triage systems [13].

Diagnosis

The EVD presents with clinical manifestations depicting a flu-like syndrome, and many differential diagnoses must be considered to eliminate the possibility of diseases including malaria, typhoid fever and meningococcal meningitis. Hence, it is imperative for clinicians to consider the travel and exposure history when treating a suspected patient returning from an endemic area of EVD [2, 7]. In accordance with a study conducted by Collier et al., abnormal laboratory findings in an EVD involves leukopenia (as low as 1000 cells/L) with a left shift, thrombocytopenia (50,000-100,000 cells/L) prolonged bleeding time and prothrombin time, hyperproteinemia and hematuria [28]. Moreover, the EHF presents with early non-specific symptoms and a high index of suspicion is needed in diagnosis. However, identification of the EBoV is not required for the initial diagnosis of EHF. It is usually diagnosed based on multiple virologic consequences such as sudden onset of illness, high fevers (>101°F) for less than three weeks, at least two hemorrhagic symptoms (*e.g.*, epistaxis, bloody stools, or hemoptysis) despite no predisposing factors for hemorrhagic manifestations generally provides ample evidence to the clinicians to consider EHF and begin supportive treatment until confirmation of the virus is provided by the laboratory findings [29].

The specific diagnosis of EHF and EVD requires laboratory evidence that should be performed in a well-equipped laboratory with biosafety level 4 bio-contaminant facilities keeping in view the high biohazardrisk associated with testing [30]. Serologic testing for the Ebola viral antibodies includes enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), radioimmunoprecipitation assay (RIPA), and Western blot analysis which is an immunoassay of viral proteins separated by polyacrylamide gel electrophoresis and transferred to a paper medium [31]. RIA is a sensitive radioimmunoassay that uses 125I-Ia-beled staphylococcal protein A and was utilized by Douglas and Cleveland to distinguish between the two strains of the Ebola virus from the 1976 outbreaks of acute hemorrhagic fever in southern Sudan (SUDV) and northern Zaire (EOBV) [32]. The RIPA and the Western blot analysis measure antibody responses to individual viral proteins, thus showing molecular specificity to response and are used as secondary confirmatory serologic tools. The most sensitive serologic tool to detect antibodies to EBoV is the ELISA used for both primates and humans. It is favorable in epidemiological studies and on-going surveillance programs. Immunoglobulin (Ig) M antibodies to Ebola virus appear as early as six days after symptoms begin and disappear in less than 90 days while IgG antibodies appear more slowly after symptom onset but persist for many months (>400 days) [31]. IgM and IgG antibodies do not develop in all fatal cases and can only be used in a fraction of symptomatic patients, requiring seroconversion or a substantial increase in antibody titer for unambiguous diagnosis. However, it is the method utilized by clinicians to diagnose asymptomatic

Ebola virus infections, which are characterized by extremely low viremia and development of IgG and IgM about three weeks after infection [33].
Real-time reverse transcription-polymerase chain (RT-PCR) reaction for clinical blood and oral swab specimens, as well as immunohistochemistry on a skin biopsy, are most used to diagnose *post-mortem* EVD in people who died before hospitalization [34, 35]. RT-PCR was used for the rapid diagnosis of EHF during the largest outbreak in Uganda (2000-2001). After the initial diagnosis of SUDV, viral antigen detection by ELISA and RT-PCR was used to diagnose SUDV infection in suspected patients and proved very useful for detecting the virus in patient serum, plasma, and whole blood. The RT-PCR assay could also detect the Ebola virus 24-48 hours prior to detection by antigen capture in a sample collected during the early phase of infection [36]. RT-PCR was originally developed and implemented during the EHF outbreaks in Gabon in 1996. Due to the high mortality and transmissibility rates, immediate diagnoses using relatively sophisticated techniques were essential for surveillance and control. Since the peripheral blood mononuclear cell (PBMC) is known to be targets for filovirus; this technique was utilized to detect the Ebola virus in these cells. RT-PCR results were also compared with ELISA antigen capture, and Ebola specific IgM and IgG antibody detection [37].
RT-PCR proved to be more sensitive in identifying acute infection and early convalescence as compared to antigen and IgM detection with a sensitivity of 100% and 91%, respectively. The specificity compared with antigen detection and IgM assay combined was 97%. Antigen capture was able to detect only 83% of those viruses identified by PCR, while only 67% of the viruses were identified by IgM [36]. A novel technique of immunohistochemistry (IHC) testing using formalin-fixed postmortem skin specimens (skin biopsy) was used as a diagnostic procedure for the EHF outbreak in the DRC (1995). In the IHC testing, EBoV antigens were seen primarily within endothelial cells, mononuclear phagocytic cells, and hepatic sinusoids, indicating these cells to be the primary target of Filovirus. IHC also showed an association of cellular damage with the viral infection and abundant viral antigens in the skin of EHF patients showed transmission by contact to be responsible for epidemics [38].

Management and treatment
Management of patients suffering from EVD involves supportive care such as maintaining fluid along with electrolyte balance, blood pressure and oxygen saturation. This also includes treating complications arising from secondary infections. However, multiple medical, immunotherapy and nucleic acid therapy approaches have been reported and are under further investigation.

Prophylactic strategies for EVD
In the absence of pre-exposure prophylaxis to prevent the disease through non-pharmacologic means by creating a barrier to transmission, anti-viral agents could be used for post-exposure prophylaxis or treatment to reduce the disease severity, virus transmission, and duration of clinical manifestations. These therapeutic agents are available in different formulations and can be administered via the oral, intramuscular, or intravenous routes. Measurement of end-organ and immune system function, in addition to the frequency and duration of prophylaxis, must all be considered for an effective post-exposure prophylactic agent [39, 40].

Anti-viral therapy for EVD
Due to the requirement of biosafety level 4 facilities in a laboratory, researches have employed reverse genetics to identify new targets within viral genomes of the EBoV for drug and vaccine development. Reverse genetics allows the development of recombinant filoviruses, such as EBoV, containing key gene sequences but are non-replicating and hence non-infective. This technique has been used by Martinez and colleagues to understand gene function in EBoV research to study virus entry, replication and assembly [41]. Ribavirin and lamivudine have been tried as a means to treat EVD. Ribavirin interferes with the capping of the viral mRNA, while lamivudine is a nucleoside analogue that interferes in gene replication. However, ribavirin resulted in reduced mortality in human cases of Lassa fever and monkeys with Rift Valley fever virus but has not been effective in animal models of filoviral and flaviviral infections [42]. Furthermore, no apparent survival benefit was observed with lamivudine treatment [43]. Another anti-viral agent known as T-705 (favipiravir) has undergone animal trials to evaluate its efficacy against EBoV. Although it was initially

developed by Fujifilm, Japan for treating influenza virus infection by inhibiting a viral enzyme, the animal studies have now confirmed that favipiravir is effective in treating animals infected with the aerosolized E718 strain of EBoV [44, 45].

Immunotherapies

Passive immune therapy or convalescent immune plasma for treatment of EVD was originally used in a 1995 outbreak in Kikwit, Zaire. Mupapa and his colleagues utilized this therapy to treat eight patients with EVD, out of which seven survived [46]. This technique uses plasma from recovered EVD patients to neutralize antibodies. WHO issued recent guidelines for the potential use of blood products from EVD survivors. This guideline addressed various issues ranging from identification of suitable blood or plasma donors among EVD survivors, donor consent and selection, donor blood collection, as well as storage of whole blood and plasma along with transportation [47].

Zmapp

This experimental drug was used for some patients during the 2014 West Africa Ebola outbreak, and several people survived. It comprises of a combination of three humanized murine antibodies generated by EBoV infected mice and produced in tobacco plants. This combination of antibodies binds to and inactivates the virus. In animal studies, 43% of infected mice survived with Zmapp treatment. However, no randomized controlled clinical trials exist to investigate whether Zmapp is effective for patients suffering from EVD [43, 44 ,48].

Vaccination and prevention

Despite the discovery of the EBoV in 1976, it was not until 2014 the world saw the virus's destructive potential. The epidemic outbreak of Ebola in West Africa leading to unprecedented numbers of cases and deaths, heralded the scientific communities throughout the world to work on the development of the Ebola vaccine, ideal for use in an outbreak setting. WHO and a number of other public health experts, trial centers, funders, global stakeholders and agencies collaborated for this cause. Various clinical trials were rapidly initiated in Africa and Australia, while the United States, Europe, and Asia started designing and manufacturing new vaccines. Regulatory and ethical reviews of clinical trial protocols were immediately done in Europe, North America, and Africa [49].

Anti-Ebola Virus vaccine efforts have been in progress for the past 2 decades, culminating in over 12 different vaccine candidates that have been placed into several clinical trials [50]. However, it was not until December 19th, 2019 when finally the U.S. Food and Drug Administration approved the Ebola vaccine rVSV-ZEBOV. The rVSV-ZEBOV vaccine is a single dose injection, and is a live, attenuated vaccine that has been genetically engineered to contain a protein from the Zaire ebolavirus.

The approval of rVSV-ZEBOV is supported by a study conducted in Guinea during the 2014-2016 outbreak in individuals 18 years of age and older. This study was an open-label, cluster-randomized phase III trial using an innovative ring vaccination protocol [51, 52]. The phase III clinical trial study reported promising results providing significant protection against EBOV-mediated disease and no new cases reported in either randomized or non-randomized clusters of contacts around confirmed EBOV virus disease patients.

Disease control

The key to managing EBoV epidemics is to stop the transmission and interrupt the spread of disease in the most affected population. This is possible through early case identification/intervention, rapid isolation, clinical management, public awareness and support, and transversal coordination. Insufficient resources and lack of awareness played a major role in the 2014 Ebola outbreak. It was an alarming situation highlighting the weakened and understaffed health care system. Hence, in August 2014, a partnership between WHO, Ministries of Health, Centers for Disease Control and Prevention (CDC) and others was established to uplift the infection prevention and control practices in health care facilities [13, 53].

Rapid identification requires aggressive surveillance systems for the anticipation of outbreaks in areas at risk. Advanced technology and reliable laboratory testing techniques are vital for the immediate detection of the EBoV and other hemorrhagic fever viruses. The advantages of novel diagnostic technologies and rapid laboratory response are highlighted in managing the EBoV outbreak in the DRC in 2018 [54].

Isolation of the suspected case and monitoring of the contacts is the next major step to interrupt the chains of transmission. Establishment of Ebola treatment centers (ETCs) where quality care and well-equipped staff are provided for the patients, is crucial in order to achieve this. These treatment centers should be located close to the affected communities and should be designed in a way that families can get involved in the care of their close ones and visit their affected family members. Efficient transportation facilities should also be available to move the patient quickly [55-57].

Setting up these ETCs in time, especially in remote areas where the virus usually emerges, requires the importation of equipment, supplies, and experts in medical professionals along with logistical support for proper planning of the infrastructure. For this to happen, we need global organizations that provide rapid comprehensive epidemic support and the resources that are required for clinical management [58]. Medical professionals and the healthcare workers involved in patient transport and cleanup of infectious material should be vaccinated. Moreover, they should use personal care equipment to safeguard themselves and avoid contact with blood and body fluids of Ebola patients [59].

Public awareness, in order to gain the public support, is essential to limit the spread of the disease. Various strategies like contact tracing, burial practices, quarantine/restriction of the movements have the potential to curtail an outbreak. However, resistance from the community is a significant hindrance to the implementation of these strategies, primarily because of the people's perception regarding their social and cultural values being violated. Contact tracing includes identification, listing, and monitoring of the contacts of patients with the EBoV. A survey in Liberia during 2014-2015 highlighted the success of this strategy as it helped in detecting 3-6% of new cases [60]. Although scarcity of resources like ambulances and skilled human force might restrict the practice of contact tracing, effective community involvement and reciprocity will allow contact tracing even when the resources are limited. Additionally, enforcement of safe burial practices is a major contribution to control of the EBoV outbreak. However, practices such as the use of plastic bags without burial clothes and prayers face a massive backlash from the community as they are against their honor and traditions. Therefore, improving these procedures by making them more flexible in accordance with the community traditions and ensuring all the essential safety precautions can significantly increase the compliance of safe burial activities. Also, female members should be a part of the burial team to bury female bodies [57]. Implementation of all the interventions mentioned above will not be possible without international aid and funds, a high level of coordination and acceptance from the community. Nonetheless, if all the mentioned approaches are successfully implemented, there is a pronounced likelihood of controlling the spread of the disease.

CONCLUSION

Frequent outbreaks of EBoV have caused numerous mortalities and morbidities. Since the virus may lead to a pandemic, its prevention has become of utmost importance as it is highly capable of causing significant physical and economic burden. Hence, there is a dire need to conduct clinical trials on EBoV to establish possible treatment regimens to prevent any further outbreaks.

Funding
None

Conflict of interest
None to declare

REFERENCES

[1] Report of an International Commission. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ.* 1978; 56 (2), 271-93.
[2] H. Feldmann, T.W. Geisbert. Ebola haemorrhagic fever. *Lancet.* 2012; 377 (9768), 849-62.
[3] J.H. Kuhn, S. Becker, H. Ebihara, et al. Proposal for a revised taxonomy of the family Filoviridae: classification, names of taxa and viruses, and virus abbreviations. *Arch Virol.* 2010; 155 (12), 2083-2103.
[4] Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature.* 2005; 438 (7068), 575-6.
[5] Groseth, H. Feldmann, J.E. Strong. The ecology of Ebola virus. *Trends Microbiol.* 2007; 15 (9), 408-16.
[6] Centers for Disease Control and Prevention. 2014-2016 Ebola Outbreak in West Africa. Retrieved from https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html. Last accessed March 16, 2020.
[7] Sanchez TW, Feldmann GH. Filoviridae. Marburg

and Ebola viruses, *In D.M. Knipe, P.M. Howley (Eds.), Fields virology.* Lippincott Williams & Wilkins, Philadelphia; 1985; 1409-48
[8] Kalenga OI, Moeti M, Sparrow A et al. The Ongoing Ebola Epidemic in the Democratic Republic of Congo, 2018-2019. *N Engl J Med.* 2019; 381, 373-83.
[9] World Health Organization. Ebola virus disease – Democratic Republic of the Congo. Disease outbreak news 25 July 2018. Retrieved from https://www.who.int/csr/don/25-july-2018-ebola-drc/en/ Last accessed March 16, 2020.
[10] Murray MJ. Ebola Virus Disease: A Review of Its Past and Present. *Anesth Analg.* 2015; 121(3), 798-809.
[11] Hasan S, Ahmad SA, Masood R, et al. Ebola virus: A global public health menace: A narrative review. *J Family Med Prim Care.* 2019; 8 (7), 2189-2201.
[12] Centers for Disease Control and Prevention. 40 Years of Ebola Virus Disease around the World. 2019. Retrieved from https://www.cdc.gov/vhf/ebola/history/chronology.html. Last accessed December 25, 2019.
[13] Malvy D, McElroy AK, de Clerck H. *Lancet*. 2019; 393 (10174), 936-48.
[14] Medecins Sans Frontieres. DRC Ebola outbreaks, Crisis update – March 2020. Retrieved from: https://www.msf.org/drc-ebola-outbreak-crisis-update. Last accessed March 10, 2020
[15] Kiley MP, Bowen ET, Eddy GA, et al. Filoviridae: a taxonomic home for Marburg and Ebola viruses? *Intervirology.* 1982; 18, 24-32.
[16] Zhang L, Wang H. Forty years of the war against Ebola. *J Zhejiang Univ Sci B.* 2014; 15 (9), 761-5.
[17] Yang Z, Duckers HJ, Sullivan NJ, et al. Identification of the Ebola virus glycoprotein as the main viral determinant of vascular cell cytotoxicity and injury. *Nat Med*. 2000; 6 (8), 886-9.
[18] Fowler RA, Fletcher T, Fischer WA 2nd, et al. Caring for critically ill patients with ebola virus disease. Perspectives from West Africa.*Am J Respir Crit Care Med.* 2014; 190 (7), 733-7.
[19] Furuyama W, MarziA.Ebola Virus: Pathogenesis and Countermeasure Development. *Annu Rev Virol.* 2019; 6 (1), 435-58.
[20] Bociaga-Jasik M, Piatek A, GarlickiA.Ebola virus disease - pathogenesis, clinical presentation and management. *Folia Med Cracov.* 2014; 54 (3), 49-55.
[21] Yen B, Mulder LCF, Martinez O, et al. Molecular basis for Ebolavirus VP35 suppression of human dendritic cell maturation. *J Virol.* 2014; 88 (21), 12500-10.
[22] Bradfute SB, Swanson PE, Smith MA, et al. Mechanisms and consequences of ebolavirus-induced lymphocyte apoptosis. *J Immunol.* 2010; 184 (1), 327-35.
[23] Wauquier N, Becquart P, Padilla C, et al. Human fatal Zaire ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. *PLoSNegl Trop Dis.* 2010; 4 (10), e837.
[24] Vetter P, Fischer WA, Schibler M, et al. Ebola Virus Shedding and Transmission: Review of Current Evidence. *J Infect Dis.* 2016; 214 (Suppl. 3), S177-S184.
[25] Rewar S, Mirdha D. Transmission of Ebola virus disease: an overview. *Ann Glob Health* 2014; 80 (6), 444-51.
[26] Gebretadik FA, Seifu MF, Gelaw BK. Review on Ebola Virus Disease: Its outbreak and current status. *Epidemiology.* 5, 204.
[27] Roberts I, Perner A. Ebola virus disease: clinical care and patient-centred research. *Lancet*. 2014; 384, 2001-2.
[28] Collier L, Balows A, Sussman M. *Topley and Wilson's microbiology and microbial infections, 9th ed.* Oxford University Press, New York; 1998.
[29] Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biologicalweapons—medical and public health management. *JAMA*. 2002; 287 (18), 2391-405.
[30] Ebola Virus Infection. Taiwan Centers for Disease Control. Available at: https://www.cdc.gov.tw/. Last accessed January 5, 2020.
[31] Ksiazek TG, West CP, Rollin PE. ELISA for the detection of antibodies to Ebola viruses. *J Infect Dis.* 1999; 179 (Suppl. 1), S192-8.
[32] Richman DD, Cleveland PH, McCormick JB, et al. Antigenic Analysis of Strains of Ebola Virus: Identification of Two Ebola Virus Serotypes. *J Infect Dis.* 1983; 147 (2), 268-71.
[33] Leroy EM, Baize S, Volchkov VE, et al. Human asymptomatic Ebola infection and strong inflammatory response. *Lancet.* 2000; 355, 2210-2215.
[34] Erickson BR, Sealy TK, Flietstra T, et al. Ebola virus disease diagnostics, Sierra Leone: analysis of real-time reverse transcription-polymerase chain reaction values for clinical blood and oral swab specimens. *J Infect Dis.* 2016; 214, S258-S262.
[35] Zaki SR, Shieh WJ, Greer P, et al. A novel immunohistochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. Commission de Lutte contre les Epidemies a Kikwit. *J Infect Dis.* 1999; 179, S36-S47.
[36] Towner JS, Rollin PE, Bausch DG, et al. Rapid diagnosis of Ebola hemorrhagic fever by reverse transcription-pcr in an outbreak setting and assessment of patient viral load as a predictor of outcome. *J Virol*. 2004; 78 (8), 4330-41.
[37] Leroy E, Baize S, Lu C, et al. Diagnosis of Ebola haemorrhagic fever by RT-PCR in an epidemic setting. *J Med Virol.* 2000; 60, 463-7.
[38] Sherif RZ, Wun-JuShieh, Patricia W, et al. A novel immunohistochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever. *J Infect Dis.* 1999; 179(1), S36-S47.
[39] Mupapa K, Mukundu W, Bwaka MA, et al. Ebola hemorrhagic fever and pregnancy. *J Infect Dis.* 1999a; 179(Suppl. 1), S11-2.

[40] Jamieson DJ, Uyeki TM, Callaghan WM, et al. What obstetrician-gynecologists should know about ebola: a perspective from the centers for disease control and prevention? *Obstet Gynecol.* 2014; 124 (5), 1005-10.
[41] Martinez MJ, Volchkova VA, Raoul H, et al. Role of VP30 phosphorylation in the Ebola virus replication cycle. *J Infect Dis.* 2011; 204 (Suppl. 3), S934-40.
[42] Huggins JW. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. *Rev Infect Dis.* 1989; 11 (Suppl. 4), S750-S761.
[43] Centers for Disease Control and Prevention. Ebola virus disease Information for Clinicians in U.S. Healthcare Settings. CDC USA Website. Retrieved from http://www.cdc.gov/vhf/ebola/hcp/clinician-information-us-healthcare-settings.html#investigational-vaccines. Last accessed January 4, 2020.
[44] Butler D. Ebola drug trials set to begin amid crisis. *Nature.* 2014; 513, 13-14.
[45] Smither SJ, Eastaugh LS, Steward JA, et al. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. *Antiviral Res.* 2014; 104, 153-5.
[46] Mupapa K, Massamba M, Kibadi K, et al. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. *J Infect Dis.* 1999; 179 (Suppl. 1), S18-23.
[47] World Health Organization. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion as an Empirical Treatment during Outbreaks. Version 1.0. 2014. Retrieved from https://apps.who.int/iris/handle/10665/135591. Last accessed December 6, 2019.
[48] Pettitt J, Zeitlin L, Kim DH, et al. Therapeutic intervention of Ebola virus infection in rhesus macaques with the MB-003 monoclonal antibody cocktail. *Sci Transl Med*. 2013; 5, 199, 199ra-113.
[49] Venkatraman N. Vaccines against Ebola Virus. *Vaccine.* 2017; 36 (36), 5454-59.
[50] Centers for Disease Control and Prevention. Ebola (Ebola Virus Disease), Prevention and Vaccine. Retrieved from: https://www.cdc.gov/vhf/ebola/prevention/index.html?fbclid=IwAR01HUk6eOJ7apF3eqA7j_C6MwF5OeWWfnIbMHN9R8yQX1b0jvQ8wWRgihU. Last accessed March 15, 2020
[51] Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola ÇaSuffit!). *Lancet.* 2017; 389 (10068), 505-18.
[52] Henao-Restrepo AM, Longini IM, Egger M, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *Lancet*. 2015; 386 (9996), 857-66.
[53] Hageman JC. Infection prevention and control for Ebola in health care settings - West Africa and United States. *MMWR supple* 2016; 65 (3), 50-6.
[54] Mbala-Kingebeni P, Villabona-Arenas CJ, Vidal N, et al. Rapid confirmation of the Zaire Ebola virus in the outbreak of the Equateur province in the Democratic Republic of Congo: implications for public health interventions. *Clin Infect Dis*. 2018; 68 (2), 330-3.
[55] Gray N, Stringer B, Bark G, et al. 'When Ebola enters a home, a family, a community': A qualitative study of population perspectives on Ebola control measures in rural and urban areas of Sierra Leone. *PLoS Negl Trop Dis.* 2018; 12 (6), e0006461.
[56] Okware SI, Omaswa F, Talisuna A, et al. Managing Ebola from rural to urban slum settings: experiences from Uganda. *Afr Health Sci.* 2015; 15 (1), 312-321.
[57] Caleo G, Duncombe J, Jephcott F, et al. The factors affecting household transmission dynamics and community compliance with Ebola control measures: a mixed-methods study in a rural village in Sierra Leone. *BMC Public Health.* 2018; 18 (1), 248.
[58] Baseler L, Chertow DS, Johnson KM, et al. The pathogenesis of Ebola virus disease. *Ann Rev Pathol.* 2017; 12, 387-418.
[59] Coltart CE, Lindsey B, Ghinai I, et al. The Ebola outbreak, 2013–2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci.* 2017; 372 (1721), 20160297.
[60] Swanson KC, Altare C, Wesseh CS, et al. (2018). Contact tracing performance during the Ebola epidemic in Liberia, 2014-2015. *PLoS Negl Trop Dis.* 2018; 12 (9), e0006762.