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A review of the epidemiology, pathophysiology, and potential treatments for Ebola disease and its associated factors

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Ebola viruses are a group of pathogenic viruses that cause Ebola disease in humans. Over the past several decades, Ebola disease outbreaks had occurred on a vast scale across the African subcontinent, resulting in numerous deaths annually. The three Ebolavirus viz, *Sudan ebolavirus* (SUDV), *Zaire Ebola virus* (ZEBOV), and *Bundibugyo ebolavirus* (BDBV) have proven to be fatal to humans. The disease is severe having mortality rate above 66% among the infected persons. The alarming concerns about the Ebolaviruses are the zoonotic, epizootics, and animals to an animal transmission that could lead to the global pandemics. Fast and reliable diagnosis requires new portable devices and techniques that can offer real-time evaluation in a very short period. Here, we state current knowledge about the Ebola disease and consider different symptomatology and highlight the genome of related viruses. Further, this review describes the pros and cons of the Ebola virus disease and the associated challenges that need proper mitigation.

Keywords: Ebola virus disease; Epidemiology; Mutations; Prevention and treatment; Vaccination.

INTRODUCTION

The *Ebolavirus* belongs to the family *Filoviridae*, of order, *Mononegavirales* (Fig. 1). The *Filoviridae* includes six genera as *Cuevavirus, Dianlovirus, Ebolavirus, Marburgvirus, Striavirus,* and *Thamnovirus* (Vingolo et al. 2015). The genera, *Ebolavirus* contains six different species viz., (i) *Sudan ebolavirus* (SUDV), (ii) *Zaire ebolavirus* (ZEBOV), (iii) *Bundibugyo ebolavirus* (BDBV), (iv) *Tai Forest ebolavirus* (TAFV), (v) *Reston ebolavirus* (RESTV) (Hensley et al. 2004), and *Boumbali ebolavirus* (BOMV). The length of the Ebola virus varies measuring approximately one to 20 μm with a uniform diameter of 80 nm. The first epidemic of Ebola virus disease (EVD) occurred in 1976 in Sudan. The outbreak began in June, and the index patient was a storekeeper of a cotton factory in the Nzara city. The second epidemic of EVD began in the Democratic Republic of the Congo (DRC erstwhile Zaire) in September 1976. Another Ebola outbreak occurred in 2018 in the Equateur Province, Northwest of DRC. The disease began on May 8, 2018, and 17 deaths were reported. The world health organization (WHO) declared the outbreak once the disease was confirmed, one among two people. On July 17, 2019, WHO listed the Ebola outbreak in the DRC as a "public health emergency of international concern". According to statistics collected from 29 health districts on June 21, 2020, there were accumulatively a total of 3470 EVD cases, including 3317 confirmed cases and 153 suspected cases, of which 2287 have died, and the overall case-fatality rate was reported as 66%. During the 2018 EVD epidemic in Equateur province (DRC),

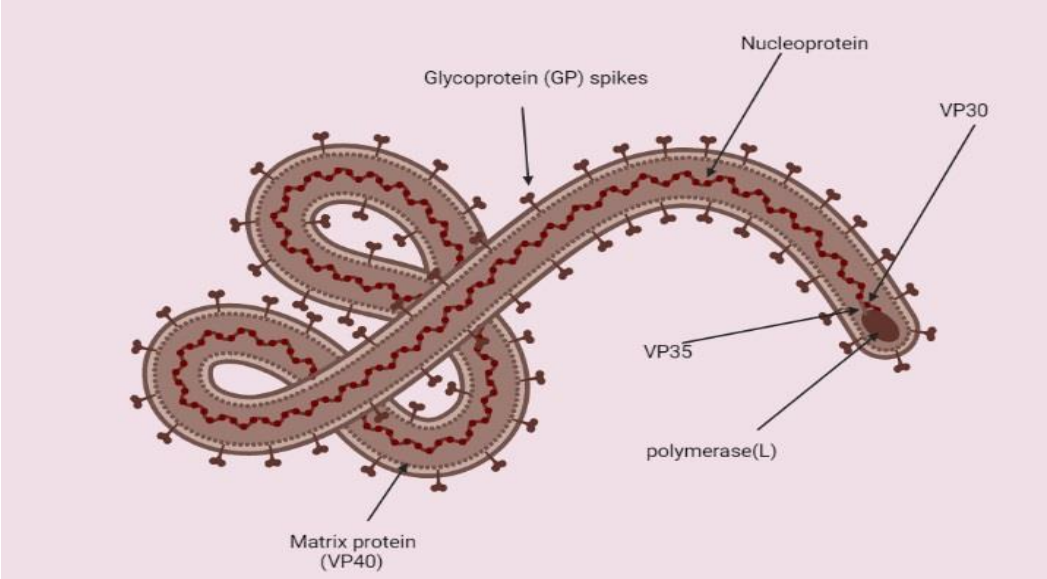

Figure 1: Structure of a typical Ebolavirus

the rVSV-ZEBOV vaccine was used on an emergency basis for the first time against the Ebola virus. In the first response to the epidemic, 3,481 people were vaccinated immediately. Later on, the FDA approved rVSV-ZEBOV as the first Ebola vaccine on December 19, 2019, and it is a single-dose vaccination to prevent the Zaire Ebola virus (WHO, 2019). Currently, medical practices are encouraging to prevent and cure the Ebola disease. This article reviews the epidemiology and current measures applied to treat and prevent Ebola virus disease. Further, we have also highlighted the mechanism of pathogenicity and transmission of Ebola virus disease for its potential management to prevent further outbreaks in the future.

1.1 Pathophysiology of the Ebola virus disease

The trimeric-encapsulated glycoprotein (GP) spikes of the filoviruses are involved in entry to host cells by the process of endocytosis. In the lysosome of the host, cysteine protease (cathepsins) cleaves filoviral GP1 protein and creates an intermediate structure consisting of N-terminal GP1 and GP2 (Mohan et al. 2015). Beneath the viral lipid envelope, the matrix protein is composed of viral protein 40 (VP40). The genome of the virus is single-stranded RNA, which is coated by viral nucleoprotein (NP). Viral nucleoprotein is associated with capsid, and other viral proteins like VP24, VP30, and VP35, along with large protein (LP). The large protein (LP) acts as an RNA-dependent RNA polymerase (Gordon et al. 2020; Mitchell et al. 2014). Ebola virus is a non-segmented, lipid enveloped negative-strand RNA virus. The high viral load in the blood of EVD patients indicates a positive correlation with the severe consequences of the disease. Ebola virus enters human skin through mucous membranes and broken skin (Hofmann-Winkler et al. 2012). The pathways of transmission have an impact on the prognosis of the disease. In non-human primate (NHP) models, intramuscular injection of the Ebola virus showed faster progression than those that received only aerosols (Geisbert et al. 2008). Some experimental studies have demonstrated that the Ebola virus can infect epithelial cells, endothelial cells, immune cells (monocytes and macrophages), fibroblasts, hepatocytes, and adrenal tissues (Olejnik et al. 2011; Feldmann et al. 2011). The Ebola virus prefers mononuclear cells showing rapid replication in the early stages of infection (Ward et al. 2020; Wong et al. 2014).

The utmost levels of the Ebola virus replication ensure the capability to respond to the host immune efficiency. Consequently, it shows resistance to interferon (IFN), and the IFN is an essential innate immune response for viral infection (Basler et al. 2009). The viral proteins VP24 and VP35 inhibit type I interferon immune response. Furthermore, the Ebola virus infects dendritic cells and cutting down their function and subsequently escaping from innate immunity and causes immunosuppression. The release of

cytokines from the first infected monocytes recruits other monocytes and extent the apoptosis of mononucleoblasts (Wauquier et al. 2010; Falasca et al. 2015). The Ebola virus causes acute lymphocytic apoptosis due to the decrease in the number and function of macrophages and dendritic cells. The experimental finding in the monkey models revealed that the Ebola virus caused apoptosis of bystanders CD4 and CD8 lymphocytes and NK cells (Haque et al. 2015). Multifocal necrosis is also observed in the testicles, ovaries, kidneys, spleen, and liver of infected persons (Schindell et al. 2018; Ansari et al. 2014). During infection, a dramatic increase in the inflammatory cytokines in the animal models and the plasma samples of EVD patients was also reported. Ebola virus infection triggers the condition of "cytokine storm" and enhances vasodilatation (Bixler et al. 2015; Gatherer et al. 2014). The immune evasion ability of the virus activated acute immunity reaction and increased the level of cytokines.

In the middle of the advanced phases of the disease, the inflammatory molecules cause blood vessel dilation that leads to external and internal bleeding. The clotting system becomes impaired due to liver and hepatocyte damage (Antoniak et al., 2014). These impairments in the body organs and systems appear in hemorrhagic symptoms in the mucous membrane, skin, and visceral organs and result in the effusions of body cavity fluid. The virus dissemination and uncontrolled replication leads to organ failure and secondary bacterial infections. As a result of these multiple reasons, the patient eventually dies (Wong et al. 2014; Hill-Batorski et al. 2015).

2. EBV genome sequences associated with animal

Typically, viruses consist of genetic material, either RNA or DNA, with high mutation rates (Sanjuán and Domingo-Calap, 2016). During the grossed examination of EBV genome data in the Virus Pathogen Database and Analysis Resource (ViPR), it was summarized that thirty-seven whole-genome sequences were represented from animals. These virus sequences belonged to the *Bombali ebolavirus*, *Reston ebolavirus*, and *Zaire ebolavirus* (Fig. 2). Sixteen whole genome sequences (WGS) of the *Reston Ebola* virus were found in animals, and four WGSs of the *Bombali Ebola virus* were found in bats (Table 1). Among 16 WGS *Reston ebolavirus*, 8 and 7 were detected in macaque and swine, respectively, and while one from monkey (Table 2). The last category was the *Zaire ebolavirus*, composed of 16 genomes; among them, 14 WGS were isolated from macaque, two from monkey (Table 2).

Bombali ebolavirus (BOMV) is an Ebola-like virus detected from tailless bats found in Sierra Leone (Goldstein et al. 2018). The discovery of the bat's nest from inside the residential houses suggested potential transmission to humans might be possible. In August 2018, the *Bombali ebolavirus* (B241) was reported from the oral and fecal swab of the tailless insectivorous bat in southeastern Kenya (Fig. 3). The high viral load in the lung tissue confirms that BOMV can infect the bats also (Goldstein et al. 2018).

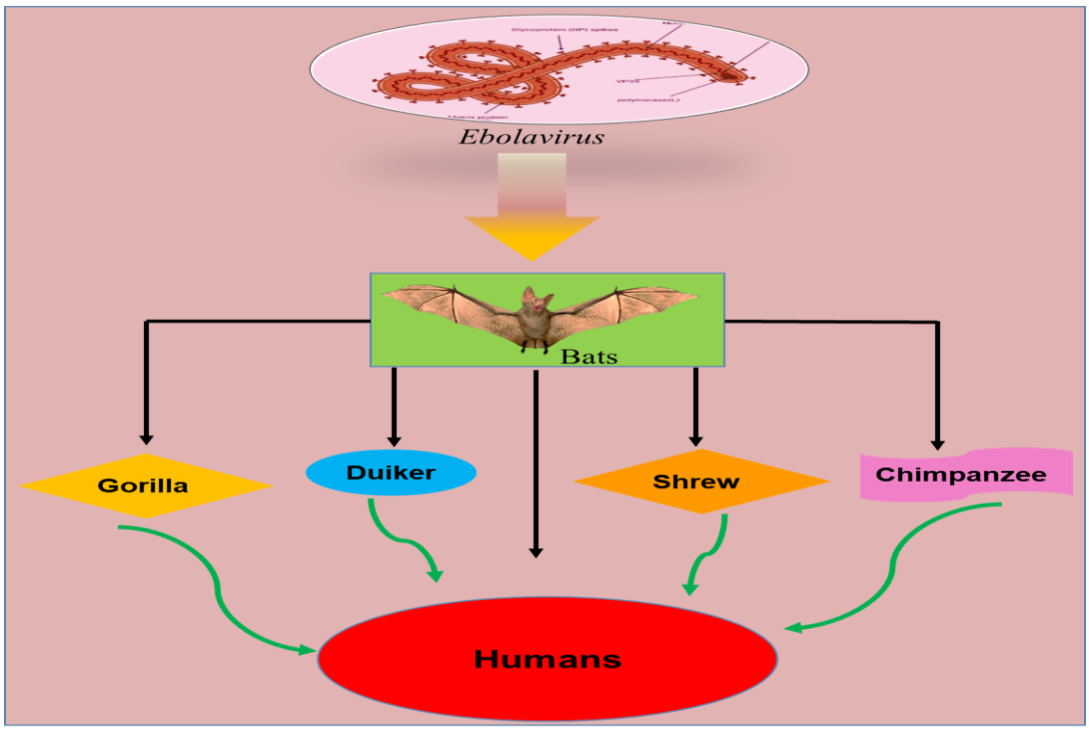

Figure 2: Possible transmission routes of the ebolaviruses to humans.

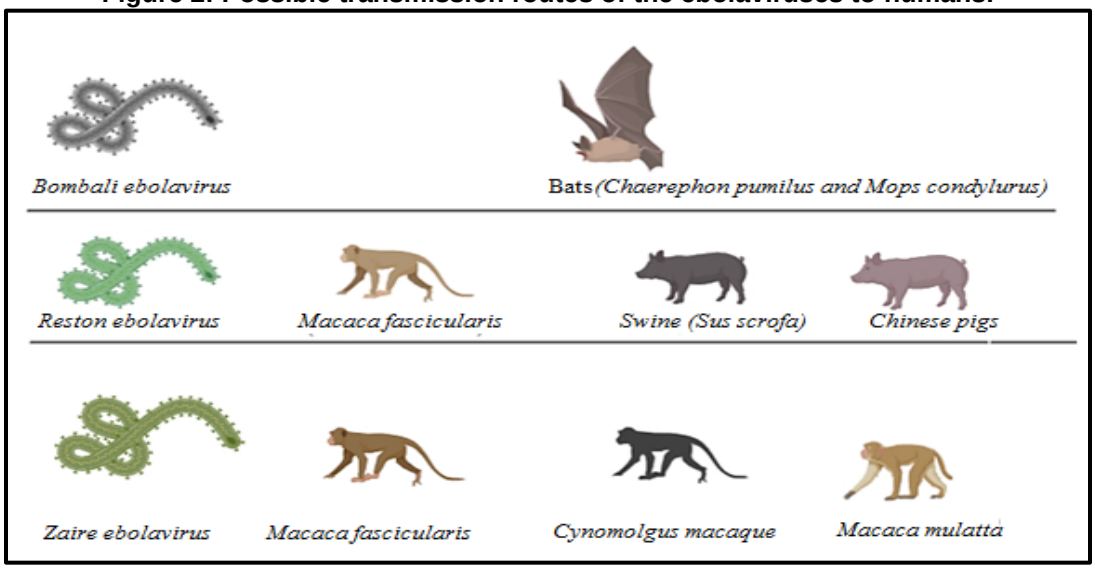

Figure 2: Some examples of the possible animal reservoirs of different Ebolaviruses.

Table 1: *Bombali* ebolavirus reported from bats.

Collection date	Causative agent	Bat-species	Country of epidemics	GenBank accession
2016	*Bombali ebolavirus*	*Chaerephon pumilus*	Sierra Leone	MF319186
		Mops condylurus		NC_039345
				MF319185
2018			Kenya	MK340750

Table 2.: Reports of the *Reston* and *Zaire ebolaviruses* from different wild animals.

Collection Date	Virus Species	Animal -species	Country	GenBank Accession
1989	*Reston ebolavirus*	*Macaca fascicularis*	USA	KY008770, KY798004, KY798005
1992	*Reston ebolavirus*	*Macaca fascicularis*	Italy	KY798007
			Philippines	KY798008
1996	*Reston ebolavirus*	Monkey, *Macaca fascicularis*	USA	JX477166 KY798009
2008	*Reston ebolavirus*	Swine	Philippines	FJ621583, FJ621584, FJ621585
2008	*Reston ebolavirus*	*Sus scrofa*	Philippines	KY798010, KY798011
2009	*Reston ebolavirus*	*Sus scrofa*	Philippines	KY798012
2009	*Reston ebolavirus*	Swine	Philippines	JX477165
2015	*Reston ebolavirus*	*Macaca fascicularis*	Philippines	MF540571, MF540570
2001	*Zaire ebolavirus*	*Macaca fascicularis*	Gabon	KY785939, KY785940, KY785945, KY785947, KY785948, KY785949, KY785965, KY785969, KY785970, KY786007, KY786017
2012	*Zaire ebolavirus*	*Macaca mulatta*	DRC	KU321146, KU321099
2015	*Zaire ebolavirus*	*Cynomolgus macaque*	Gabon	KY471125, KY471095, KY471122

In 1989, the *Reston ebolavirus* (RESTV) was first time detected in the United States from some macaques imported from the Philippines. The RESTV is responsible for hemorrhagic fever in macaques (Rougeron et al. 2015; Jahrling et al. 1999). Later during 2008-2009, it was also reported from the domestic pigs (*Sus scrofa*) of the Philippines. Correspondingly, it was detected from the Chinese pigs in 2011, although the symptoms of EVD were not detected in the pigs (Albariño et al. 2017; Pan et al. 2014). In 1989, it was also reported from human cases with no sign of the disease. However, the developments of antibodies detected against the RESTV in human cases (Cornish et al. 2017). Human pathogenic ebolaviruses include *Sudan Ebolavirus***,** *Tai Forest Ebolavirus*, *Zaire Ebolavirus*, and *Bundibugyo Ebolavirus*. The *Sudan Ebolavirus* causes EVD in humans and non-human primates. The *Tai Forest ebolavirus* was initially called "Côte d'Ivoire Ebola virus" and Later in 2010 it was renamed as "*Tai Forest ebolavirus*" (Kuhn et al. 2010). *Tai Forest ebolavirus* was discovered from the researcher's body in 1994, which might have transferred during the dissection of a dead chimpanzee at Thai Forest National Park, Côte d'Ivoire. The *Bundibugyo Ebolavirus* was discovered by CDC, Georgia, in November 2007, from the samples of Uganda (MacNeil et al. 2010). However, the *Zaire Ebolavirus* prevalence is very high as compared to other strains. The alarming concerns about *Zaire Ebolaviruses* are zoonotic, epizootics, and

animal to animal transmission (Fig. 2). It was reported from different hosts, including humans, macaque, monkeys (Table 2). In 1996, two EVD outbreaks were reported in Gabon, first in the spring and the second in the autumn. The leading cause of the 1996 first epidemic was a sick chimpanzee. The outbreak infected 31 individuals and caused 21 deaths. The second epidemic led to 60 confirmed cases with 45 deaths, while again, the chimpanzees were considered the source of infection (Georges et al. 1999). In 2007 Ebola epidemic began with an accident of eating freshly killed fruit bats by the index case. The epidemic developed more than 260 infected cases, with a 71 % fatality rate (Leroy et al. 2009). In the 2014 EVD outbreak, the index patient was a child from Guinea, and he was supposed to be infected by a bat (Marí Saéz et al. 2015).

3. Epidemiology

The first epidemic of Ebola virus disease was reported in 1976 in Sudan. The outbreak began in June, and the index patient was a storekeeper of a cotton factory in the Nzara city. The symptoms like severe headache, fever, and chest pain established by 27th June. The patient was admitted to Nzara Hospital on 30th June, and on the next day (accumulatively fifth day of the disease), he developed bleeding symptoms and subsequently expired on 6th July. The upcoming victims of the disease were two colleagues of the first patient and many other contacts, who attained the patient in the hospital or at home. The epidemic also spread to Maridi hospital (about 128 km away from Nzara city) and spread around Maridi township by hospital contamination. The *Sudan ebolavirus* was involved in the epidemic and 284 individuals infected, claiming 151 deaths; thus, the case fatality rate was 53% (Tseng et al. 2015; Gałas et al. 2014). The second epidemic of EVD began in Zaire (now DRC) in September 1976. Most of the cases occurred around the Yambuku, located in the northwest of DRC. The first confirmed patient was a male instructor at a mission school who faced the challenge of high fever, and unknown sickness thought to be malaria. The patient was admitted to Yambuku Church Hospital on 26th August 1976. During treatment, a chloroquine injection is administered by the parental route. Unfortunately, the syringes and needles were reused that infected 318 people with 280 deaths. In this epidemic, the hospital was the primary source of transmission, and the *Zaire ebolavirus* was the causative agent of the disease (Lamunu et al. 2004). In 1979 EVD epidemic re-emerged in the city of Nzara, Sudan. It occurred on 31st July and then 6th October 1979, through nosocomial transmission and contact among family members were the main spreading mode. The epidemic infected 34 individuals, out of which 22 were reported dead (Table 3, Baron et al. 1983).

In an outbreak, there are often several secondary cases and very few tertiary levels. In the epidemiological study of the family circle, most secondary cases became infected via direct physical contact with blood, organs, and other body fluid (MacNeil et al. 2011). The whole transmission tree, constructed from the Nigeria outbreak 2014, revealed that the index patient was a person from Liberia. The EVD was diagnosed within three days, followed by strategic control and specific prevention measures. Therefore, the epidemic situation was over within weeks. In this response, a total of 898 contacted were under observation, and 2% of all contacts established EVD (Fasina et al. 2014). The transmission of EVD through air contamination raised the public health concern, a study of three healthy *Rhesus macaques*, placed three meters apart from the cage of the infected reservoir, revealed; only two of them became infected (Jaax et al. 1995). Sometimes instead of bloody droplets, non-bloody aerosol or droplet suddenly desiccates and becoming suspended in the air and contributes to the transmission of the disease (Alimonti et al. 2014). The main problem of the Ebola Virus transmission in humans is assessing the minimal infectious dose. However, it is challenging to evaluate how much blood or body fluids are enough for developing the disease.

In the episodic outbreaks, both recurrence and reinfection phenomena are involved and challenges for controlling the disease. Many aspects of the EVD, particularly infection and transmission routes, have been well studied, such as the rate and chances of sexual transmission. During the 1995 EVD epidemics of Kiewit, DRC, the transmission occurred within family members in the initial phases, while later turned into a hospital-acquired infection. The number of deaths was 254 out of 315 confirmed patients (including 80 health care workers). Mysteriously, in 2014 an EVD epidemic took place in the Equateur Province, which infected 66 individuals and killed 49 people. This epidemic was caused by the *Zaire Ebolavirus* but was not related to the big West Africa epidemic and was closely related to the 1995 Kikwit outbreak.

In addition to the recurrence cases among

the survivor, there is some evidence regarded as reinfection (Coltart et al. 2017). The evidence of recurrence and reinfection of EVD is also necessary to highlight its impact on the EVD episodic outbreak. Reinfection is theoretically possible due to weakening or partial immunity and facing the challenges of high viral load during the convalescence stages or the combination of all mentioned factors. Studies have shown that in some survivors, the antibodies level decline after few years. However, the level of antibodies needed for optimal protection or immune memory is still unknown, despite a slight defense is rendered by cell-mediated immunity. There is no documented evidence that the new outbreak arises from the EVD survivors (MacIntyre et al. 2016). But the probability of new outbreaks from the EVD survivors should not be neglected because the disease is not leaving Africa and continuously re-emerging after suppression.

In 2014 West African EVD outbreak and the index was a small child from Guinea. The age of the patient was 18-month, and he was supposed to be infected by bats. Then five fatal cases of diarrhea were reported in the area, and an official medical alert was issued to regional health officials. Due to the poor infrastructure and weak surveillance strategies, the virus quickly spread to the surrounding countries like Sierra Leone and Liberia. The epidemic soon extended from the rural area to the populated urban communities when the epidemic situation became more deteriorating in West Africa. In this response on 8th August 2014, WHO declared public health emergency of international concern (PHEIC). During this epidemic, the disease spread to seven more countries: Italy, Spain, Nigeria, Mali, Senegal, United Kingdom, and the United States. On 13th April 2014, WHO updated the statistic of the West Africa EVD outbreak, the number of confirmed cases and deaths in each country followed a trend, Guinea (2544 death out of 3814 confirmed cases), Liberia (4810 death out of 10678 confirmed cases) and Sierra Leone (3956 death out of 14124 confirmed cases). All 11310 individuals died out of 28616 confirmed cases during the West Africa epidemic (Kaner et al. 2016).

The 2018 Ebola outbreak occurred in the Equateur Province, the northwest of DRC. It began on 8th May 2018, and 17 people believed to die from Ebola near the Bikoro town in the Equateur province. Once the disease was confirmed in two individuals after that, the World Health Organization declared the outbreak. Furthermore, from 17th May to 24th July, there were confirmed 53 patients, out of which 33 died. Another outbreak began on 1st August 2018, documenting four positive Ebola cases in the Kivu, the eastern region of DRC. On 13th August, the Ituri province was affected by this outbreak. In this outbreak, the first-time vaccine rVSV-ZEBOV was used against Ebola. A total of 3,481 people were vaccinated in the first response to the epidemic.

Furthermore, the EVD extended to Uganda in June 2019 with the entry of an infected 5-year-old Congolese boy and his family. A confirmed case in Goma stimulated the WHO for an emergency committee for the fourth time. On 17th July 2019, WHO declared that the Ebola epidemic in DRC as a “Public Health Emergency of International Concern.” By mid-October 2019, the spread of the virus had dropped significantly. Since 17th February 2020, there are no new cases of the Ebola virus. On 4th March 2020, after the recovery and release of the last patient from the Ebola treatment center, the WHO declared that the EVD epidemic was over. This could be possibly due to the emergence of the COVID-19 pandemics which restricted the movement of people all over the world. According to the data on 21st June 2020, based on 29 health zone, there was an accumulative total of 3470 EVD cases, including 3317 confirmed cases and 153 probable cases; of the accumulative total, 2287 led to death. The overall case-fatality rate was 66%. Of the total 3470 EVD cases, 57 % (1970) were female and 29% (1002) were children (under 18 years of age), while 5% (171) were health workers (Table 4).

Table 3: Some of the epidemic events of the ebolaviruses have happened from 1979 to 2014.

Year	Virus strain	Country	Deaths	No. of patient	Fatality rate
1976	Sudan ebolavirus	Sudan	151	284	53%
1976	Zaire Ebolavirus	Zaire	280	318	88%
1979	Sudan ebolavirus	Sudan	22	34	65%

1994	Zaire ebolavirus	Gabon	29	49	59 %
1995	Zaire ebolavirus	Kiewit	254	315	81 %
1996 Spring	Zaire ebolavirus	Gabon	21	31	68%
1996 Autumn	Zaire ebolavirus	Gabon	45	60	75%
2000	Sudan ebolavirus	Uganda	224	425	53%
2001-2002	Zaire ebolavirus	Gabon	53	65	82%
2001-2002	Zaire ebolavirus	Congo	44	59	75%
2003	Zaire ebolavirus	Congo	157	178	88%
2004	Sudan ebolavirus	Sudan	7	17	41%
2005	Zaire ebolavirus	Congo	10	12	83%
2007	Zaire ebolavirus	Uganda	187	264	71 %
2007	Bundibugyo ebolavirus	Uganda	37	149	25%
2008	Zaire ebolavirus	DRC	15	32	46 %
2012	Zaire ebolavirus	Uganda	17	24	71 %
2012	Sudan ebolavirus	Uganda	4	7	57
2012	Bundibugyo ebolavirus	DRC	29	57	51%
2014	Zaire ebolavirus	DRC	49	66	74%

Table 4:Two biggest epidemic of *Zaire ebolavirus*.

1- West African EVD Epidemic 2014-2016							
Guinea		**Liberia**		**Sierra Leone**		**Overall**	
Death	Total case	Death	Total case	Death	Total case	Total Death	Total case
2544	3814	4810	10678	3956	14124	11310	28616
2 - EVD outbreak 2018-2019, DRC							
Confirmed cases		Probable cases		Accumulative total		Total death	Fatality rate
3317		153		3470		2287	66%.

4. Treatment and prevention

The treatment of suspected and confirmed cases comprises standard quarantine, supportive, and symptomatic treatment. The supportive treatment usually provided including rehydration, fluid replacement, management of secondary infection, and psychological counseling. The rehydration encounters hypovolemia and maintenance of electrolyte balance; oral rehydration is highly recommended along with anti-emetic and anti-diarrheal for the symptomatic patient of diarrhea. There is no approved antiviral therapy for the treatments of EVD. Although, during the 2018-2019 DRC epidemic in the ethical context, the health authorities and WHO developed a road map for the recommendation to access the unregistered anti-Ebola therapies, which included three monoclonal antibodies (MAb114, ZMapp, and RE-EB3) and an antiviral drug (Remdesivir) (Damon et al. 2018; Kiiza et al. 2020). In the randomized controlled trial (n=681), the safety and efficacy of the three products (MAb114, Remdesivir, and REGN-EB3) were contrasted in Ebola patients undergoing optimized supportive treatment with the control drug ZMapp. The trial was terminated early after MAb114 and REGN-EB3 were better than ZMapp, reducing the 28-day mortality rate (Kiiza et al. 2020). ZMapp is a cocktail of three chimeric monoclonal antibodies targeting a surface epitope of glycoprotein on the *Zaire ebolavirus*, and 3 doses of 50 mg/kg/body weight administered IV, every 3 days in the latest DRC outbreak 2018-2019. The morality of patients (with Ct value <22) in the ZMapp group was 24.5% (24/98), while that of critically ill patients (Ct-value > 22) was 84.5% (60/70) (Kiiza et al. 2020; Davey et al. 2016; Lee et al. 2019). Remdesivir GS-5734 is a small molecular nucleotide prodrug having antiviral activity against *Bundibugyo ebolavirus, Sudan ebolavirus,* and *Zaire ebolavirus*. It does not have any side effects, but it slightly increases the levels of AST/ALT. A single high dose provides high concentration and rapid bioavailability, neutralizing Ebola viremia and clearing viruses from the immune-protected site. The mortality rate in the Remdesivir group was 53.1% (93/175), while it was 49.7 % in the

ZMapp group (84/169) (Kiiza et al. 2020; Mulangu et al. 2019; Gaudinski et al. 2019). REGN-3470-3471-3479 is a combination of 3 human antibodies for the *Zaire ebolavirus* non-overlapping epitopes. The immunogenic response to REGN-3470-3471-3479 was nil, and the headache is the common side-effect. At 25 °C, it was stable for six months, and three months at 45 °C. In the latest REGN-3470-3471-3479 therapy was a single 150 mg/kg infusion dose, the overall mortality rate in the REGN-3470-3471-3479 group was 33.5 % (52/155) against 51.3 % (79/154) in the ZMapp group (Kiiza et al. 2020; Mulangu et al. 2019; Gaudinski et al. 2019). Another compound, MAB114, is primarily a monoclonal human IgG1 antibody that targets the GP *Zaire Ebola virus*. Anti-drug antibody reactions have not been documented so far, although few cases have reported adverse effects of nausea, myalgia, and pain in the joints. MAB114 is a frozen powder preparation that can be stable at 40 °C for up to six months and stored without cooling. In the current trial of DRC, a single dose comprising 50 mg/kg of MAb114 was used as a single infusion. In the MAB114 group, among patients with a Ct-value >22, the mortality rate was 9.9%, while the critical patient (Ct value ≤ 22) was 69.9%. In the MAb114 group, overall mortality was 35.1 % (61/174) vs 49.7 % (84/169) in the ZMapp control group (Kiiza et al. 2020; Mulangu et al. 2019; Gaudinski et al. 2019). Besides the above anti-ebola therapy, several other new drug candidates have been developed worldwide. The antiviral Favipiravir (T-705) previously used against influenza showed effectiveness against the EBOV (Smither et al. 2014; Zhang et al. 2017; Dhama et al. 2018). Fleximers is a novel flexible nucleoside that demonstrated efficacy against the recombinant EBOV in Huh7 cells (Zhang et al. 2017; Dhama et al. 2018). Lamivudine is an anti-retroviral drug, which was administered to 15 EVD patients among the 13-patient demonstrated recovery. However, two separate studies conducted on the Guinea pig and Vero E6 cells revealed no significant antiviral activity of Lamivudine (Zhang et al. 2017). The antiviral compound, Ribavirin delayed the death and enhanced the survival rate in the monkey and mouse model but was associated with extreme side effects (Zhang et al. 2017).

5. Vaccination

Hitherto, many approaches have been developed for vaccination against the Ebola virus; however, most of the vaccines are not licensed and currently unavailable. First-time vaccine rVSV-ZEBOV used against Ebola in 2018 Equateur Province EVD outbreak of the DRC (Monath et al. 2019). A total of 3,481 people were vaccinated in the first response to the epidemic. On 19th December 2019, FDA approved the rVSV-ZEBOV as the first Ebola vaccine; it is a single-dose vaccine that prevents *Zaire ebolavirus* (Monath et al. 2019). According to a WHO report, the “rVSV-ZEBOV” vaccine has been inoculated to a total of 101,195 persons. Of the total vaccinated people, 26,613 were contacts, while 74,367 were the secondary contacts of Ebolavirus infections. Among the total vaccinated people 29,688 were health care workers, and 26,361 were children, ages ranging from 1 to 6 years old. During 2019 combat against the Ebola epidemic in DRC, another vaccine was developed and introduced under the research protocol. This vaccine was a component of two different vaccines (MVA-BN-Filo and Ad26.ZEBOV). This vaccine required two initial doses and a second “booster” after 56 days (WHO). The Rhabdovirus vector vaccine provides a unique platform for producing specific immunity and cross-protective immunity for both filoviruses and rhabdoviruses. Attenuated rVSV (recombinant vesicular stomatitis virus) vector-based expression of filovirus glycoprotein instead of SVS glycoprotein has shown promising results. These vectors give complete protection against homologous virus strains and partial protection against the heterologous excellent in infected macaques (Yates et al. 2017; Geisbert et al., 2011). These candidate vaccines provide significant rapid protection when administered into post-exposure non-human primates. The main advantages of these vector vaccine platforms are the excellent immune response and minimal pre-existing immunity against VSV in the human population (Geisbert et al. 2011; Monath et al. 2019).

CONCLUSION

In the recent outbreaks of the Ebola virus, the number of infections among the general population and health care workers increased dramatically compared to past events. Eight health care workers died during the 2014 outbreak in the DRC. While in the West Africa EVD outbreak, more than 890 health care workers became infected with a 57% fatality rate. In the 2018-2019 epidemic, 171 health workers were infected, which was 5% of the total infected cases. The inhibiting of the transmission chain should be one of the top priorities for EVD outbreak

management and prevention. Regular training should be provided to health workers, which is critical to strengthening the overall health care system to improve the safety of the medical staff in high-risk countries. In the past, EVD pathogens had received little attention; however, being an emerging potential threat for public and animal health concerns these pathogens are attracting the interest of scientists worldwide. Currently, the utmost consideration of EVD to enhance the recovery of the infected patient and minimize the death ratio. Although in the 2018-2019 epidemic, effective vaccine was available, and the fatality rate dropped to 66%, which is still high. Emphasis should be given to prevent the entry of viruses into the most populated cities. If the Ebola virus challenges the modern world in terms of a pandemic, it may appear as a big disaster for the human population.

Future perspectives

To understand the exact dynamics of the Ebola disease and its transmission, multidisciplinary initiatives with the probable concept of One Health focused on humans, animals, and the environment are immensely important. Primarily, an interdisciplinary collaboration involving public health officials and veterinarians together with academicians, researchers, clinicians, ecologists, and microbiologists/virologists should be prioritized to gain vital information and understand different aspects of the epidemiology of the Ebola disease. Secondly, the diagnostic kits and laboratory equipment should be available to public health laboratories to tests the suspected cases for early confirmation of the outbreak. To accomplish quick and accurate detection of the viruses, easy to handle and sophisticated techniques such as electron microscopy (EM), immuno-serological methods (e.g. ELISA), molecular approaches, and biosensor-based methods should be developed. Even the combinations of test methods might be imperative for early detection of the disease. Alternatively, new procedures may need to be devised because the isolation and initial characterization of the Ebola virus needs biosafety level 4 facilities. For early and successful prevention, outbreak preparedness response infrastructures must be prioritized and specialized training to concerned medical staff. This also necessitates the timely development of vaccines and other targeted drugs for possible prevention of the Ebola virus. The decryption of the reservoir dynamics of Ebola viruses will be pivotal to design strategies and policies for the prevention of the Ebola disease in the future. The source or reservoir of the Ebola disease is still debatable that mandates the surveillance of wildlife, and significant gaps in the information of Ebola disease necessitate better case definitions. Since many potential vaccine candidates are available now, vaccination should primarily start with healthcare workers and veterinarians, and public masses dealing with monkeys.

Further, any mass gathering that increases the transmission rate of the virus should be prevented. Lastly, the viral gene signatures responsible for infections and mortality should be determined from the positive cases. The geographic information systems (GIS)-based tracing of the patients and their contacts may be helpful to assess high-risk areas and subsequent transmissions. Finally, education and public awareness campaigns on cleanliness and food safety must be implemented as soon as possible.

Note: All the figures were created in the online platform; https://biorender.com).

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

K.U performed a comprehensive literature review and drafted the original manuscript. M.D. Conceptualization, Literature review, and writing - review & editing; S.Y provided scientific Conceptualization, Supervision, and helped in writing - review & editing. W.Z provided Supervision and suggest a fruitful direction, AM revealed the obligation to write the review article and also recommend technical and professional support.

REFERENCES

Albariño CG, Wiggleton Guerrero L, Jenks HM, Chakrabarti AK, Ksiazek TG, Rollin PE, Nichol ST. 2017. Insights into Reston virus spillovers and adaption from virus whole genome sequences. PloS one 12: e0178224.

Alimonti J, Leung A, Jones S, Gren J, Qiu X, Fernando L, Balcewich B, Wong G, Ströher U, Grolla A. 2014. Evaluation of transmission risks associated with in vivo replication of several high containment pathogens in a biosafety level 4 laboratory. Scientific reports 4: 1-7.

Alimonti J, Leung A, Jones S, Gren J, Qiu X, Fernando L, Balcewich B, Wong G, Ströher U, Grolla A. 2014. Evaluation of transmission risks associated with in vivo replication of several high containment pathogens in a biosafety level 4 laboratory. Scientific reports 4: 1-7.

Ansari AA. 2014. Clinical features and pathobiology of Ebolavirus infection. Journal of autoimmunity 55: 1-9.

Antoniak S, Mackman N. 2014. Multiple roles of the coagulation protease cascade during virus infection. Blood 123: 2605-2613.

Arima Y, Shimada T. 2015. Epidemiological situation of Ebola virus disease in West Africa. Virus 65: 47-54.

Baron RC, McCormick JB, Zubeir OA. 1983. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. Bulletin of the World Health Organization 61: 997.

Basler CF, Amarasinghe GK. 2009. Evasion of interferon responses by Ebola and Marburg viruses. Journal of Interferon & Cytokine Research 29: 511-520.

Bixler SL, Goff AJ. 2015. The role of cytokines and chemokines in filovirus infection. Viruses 7: 5489-5507.

Coltart CE, Lindsey B, Ghinai I, Johnson AM, Heymann DL. 2017. The Ebola outbreak, 2013–2016: old lessons for new epidemics. Philosophical Transactions of the Royal Society B: Biological Sciences 372: 20160297.

Damon IK, Rollin PE, Choi MJ, Arthur RR, Redfield RR. 2018. New tools in the Ebola arsenal. New England Journal of Medicine 379: 1981-1983.

Ebola virus disease Democratic Republic of Congo: External situation report 94 / 2019. (n.d.). WHO | World Health Organization. https://www.who.int/publications/i/item/10665-332654

Falasca L, Agrati C, Petrosillo N, Di Caro A, Capobianchi M, Ippolito G, Piacentini M. 2015. Molecular mechanisms of Ebola virus pathogenesis: focus on cell death. Cell Death & Differentiation 22: 1250-1259.

Fasina FO, Shittu A, Lazarus D, Tomori O, Simonsen L, Viboud C, Chowell G. 2014. Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014. Eurosurveillance 19: 20920.

Feldmann H, Geisbert TW. 2011. Ebola hemorrhagic fever. The Lancet 377: 849-862.

Food U, Administration D. First FDA-approved vaccine for the prevention of Ebola virus disease, marking a critical milestone in public health preparedness and response. Press Announc 2019.

Gałaś A. 2014. The evolution of Ebola virus disease outbreaks. Folia Medica Cracoviensia 54.

Gaudinski MR, Coates EE, Novik L, Widge A, Houser KV, Burch E, Holman LA, Gordon IJ, Chen GL, Carter C. 2019. Safety, tolerability, pharmacokinetics, and immunogenicity of the therapeutic monoclonal antibody mAb114 targeting Ebola virus glycoprotein (VRC 608): an open-label phase 1 study. The Lancet 393: 889-898.

Geisbert TW, Daddario-DiCaprio KM, Geisbert JB, Reed DS, Feldmann F, Grolla A, Ströher U, Fritz EA, Hensley LE, Jones SM. 2008. Vesicular stomatitis virus-based vaccines protect nonhuman primates against aerosol challenge with Ebola and Marburg viruses. Vaccine 26: 6894-6900.

Geisbert TW, Feldmann H. 2011. Recombinant vesicular stomatitis virus–based vaccines against Ebola and Marburg virus infections. The Journal of infectious diseases 204: S1075-S1081.

Goldstein T, Anthony SJ, Gbakima A, Bird BH, Bangura J, Tremeau-Bravard A,

Belaganahalli MN, Wells HL, Dhanota JK, Liang E. 2018. Author correction: the discovery of Bombali virus adds further support for bats as hosts of ebolaviruses. Nature microbiology 3: 1486-1486.

Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, Götte M. 2020. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. Journal of Biological Chemistry 295: 6785-6797.

Haque A, Hober D, Blondiaux J. 2015. Addressing therapeutic options for Ebola virus infection in current and future outbreaks. Antimicrobial agents and chemotherapy 59: 5892-5902.

Hensley LE, Jones SM, Feldmann H, Jahrling PB, Geisbert TW. 2005. Ebola and Marburg viruses: pathogenesis and development of countermeasures. Current molecular medicine 5: 761-772.

Hofmann-Winkler H, Kaup F, Pöhlmann S. 2012. Host cell factors in filovirus entry: novel players, new insights. Viruses 4: 3336-3362.

Jaax N, Jahrling P, Geisbert T, Geisbert J, Steele K, McKee K, Nagley D, Johnson E, Jaax G, Peters C. 1995. Transmission of Ebola virus (Zaire strain) to uninfected control monkeys in a biocontainment laboratory. The Lancet 346: 1669-1671.

Jahrling P, Geisbert T, Johnson E, Peters C, Dalgard D, Hall W. 1990. Preliminary report: isolation of Ebola virus from monkeys imported to USA. The lancet 335: 502-505.

Kaner J, Schaack S. 2016. Understanding Ebola: the 2014 epidemic. Globalization and health 12: 1-7.

Kiiza P, Mullin S, Teo K, Adhikari N, Fowler R. 2020. Treatment of Ebola-related critical illness. Intensive care medicine 46: 285-297.

Kuhn JH, Becker S, Ebihara H., Geisbert TW, Johnson KM, Kawaoka Y, et al. 2010. Proposal for a revised taxonomy of the family *Filoviridae*: classification, names of taxa and viruses, and virus abbreviations. Arch. Virol. 155: 2083–2103. https://doi.org/10.1007/s00705-010-0814-x

Lee JS, Adhikari NK, Kwon HY, Teo K, Siemieniuk R, Lamontagne F, Chan A, Mishra S, Murthy S, Kiiza P. 2019. Anti-Ebola therapy for patients with Ebola virus disease: a systematic review. BMC infectious diseases 19: 1-11.

MacIntyre CR, Chughtai AA. 2016. Recurrence and reinfection—a new paradigm for the management of Ebola virus disease. International Journal of Infectious Diseases 43: 58-61.

MacNeil A, Farnon EC, Morgan OW, Gould P, Boehmer TK, Blaney DD, Wiersma P, Tappero JW, Nichol ST, Ksiazek TG. 2011. Filovirus outbreak detection and surveillance: lessons from Bundibugyo. The Journal of infectious diseases 204: S761-S767.

Mitchell WM, Carter WA. 2014. The quest for effective Ebola treatment: Ebola VP35 is an evidence-based target for dsRNA drugs. Emerging microbes & infections 3: e77.

Mohan GS, Ye L, Li W, Monteiro A, Lin X, Sapkota B, Pollack BP, Compans RW, Yang C. 2015. Less is more: Ebola virus surface glycoprotein expression levels regulate virus production and infectivity. Journal of virology 89: 1205-1217.

Olejnik J, Ryabchikova E, Corley RB, Mühlberger E. 2011. Intracellular events and cell fate in filovirus infection. Viruses 3: 1501-1531.

Pan Y, Zhang W, Cui L, Hua X, Wang M, Zeng Q. 2014. Reston virus in domestic pigs in China. Archives of virology 159: 1129-1132.

Rougeron V, Feldmann H, Grard G, Becker S, Leroy E. 2015. Ebola and Marburg hemorrhagic fever. Journal of Clinical Virology 64: 111-119.

Sanjuán, R. Domingo-Calap, P. 2016. Mechanisms of viral mutation. Cell. Mol. Life Sci. 73, 4433–4448.

Schindell BG, Webb AL, Kindrachuk J. 2018. Persistence and sexual transmission of filoviruses. Viruses 10: 683.

Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. 2014. Post-exposure efficacy of oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral research 104: 153-155.

Tseng C-P, Chan Y-J. 2015. Overview of Ebola virus disease in 2014. Journal of the Chinese Medical Association 78: 51-55.

Vingolo EM, Messano GA, Fragiotta S, Spadea L, Petti S. 2015. Ocular manifestations of Ebola virus disease: an Ophthalmologist's guide to prevent infection and panic. BioMed research international 2015.

Ward MD, Kenny T, Bruggeman E, Kane CD, Morrell CL, Kane MM, Bixler S, Grady SL, Quizon RS, Astatke M. 2020. Early detection of Ebola virus proteins in peripheral blood mononuclear cells from infected mice. Clinical proteomics 17: 1-11.

Wauquier N, Becquart P, Padilla C, Baize S,

Leroy EM. 2010. Human fatal zaire ebola virus infection is associated with an aberrant innate immunity and with massive lymphocyte apoptosis. PLoS Negl Trop Dis 4: e837.

WHO|WorldHealthOrganization.https://www.who.int/immunization/sage/meetings/2018/october/2_Ebola_SAGE2018Oct_BgDoc_20180919.pdf

Wong G, Kobinger GP, Qiu X. 2014. Characterization of host immune responses in Ebola virus infections. Expert review of clinical immunology 10: 781-790.

Yates MK, Raje MR, Chatterjee P, Spiropoulou CF, Bavari S, Flint M, Soloveva V, Seley-Radtke KL. 2017. Flex-nucleoside analogues–novel therapeutics against filoviruses. Bioorganic & medicinal chemistry letters 27: 2800-2802.

Zhang T, Zhai M, Ji J, Zhang J, Tian Y, Liu X. 2017. Recent progress on the treatment of Ebola virus disease with Favipiravir and other related strategies. Bioorganic & medicinal chemistry letters 27: 2364-2368.