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Review Article

Ebola Virus Disease and Its Antecedents in West African Countries: Challenges, the Current Trend and the Way Forward

Bakarey AS[1] and Olayiwola JO[2]*

[1]*Institute for Advanced Medical Research & Training, University of Ibadan, Nigeria*
[2]*Department of Biological Sciences, Ajayi Crowther University, Nigeria*

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***Corresponding author**

Olayiwola JO, Department of Biological Sciences, Ajayi Crowther University, Nigeria, Tel: +234 7035683076; Email: olusolajohn97@yahoo.com

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In 2017, Democratic Republic of Congo, a West African country experienced another outbreak of Ebola Virus Disease (EVD) since the largest outbreaks in history were last reported in 2015 in the region. Ebola virus disease is a severe, often fatal illness, with a death rate as high as 90% and caused by Ebola virus. The victims become infected with the pathogen either through contact with infected animals or via direct contact with the bodily fuids of infected humans. The virus responsible for this outbreak, the Zaire Ebola Virus (EBOV), from the genus Ebolavirus in conjunction with the genus Marburgvirus forms the Filoviridae family. Ebola virus is one of the most deadly and highly virulent pathogens among the viral haemorrhagic fevers resulting in case fatality rates of close to 90% as earlier documented. Multi-organ failure and severe bleeding complications have been responsible for the high mortality usually reported. In the recent past, a total of 5335 cases (confirmed, suspected and probable) with 2622 deaths, with a case fatality rate of around 50% have been documented. Laboratory confirmation through the use of RT-PCR molecular technique remains the gold standard for diagnosis. Although as at today, there is no licensed vaccine against the virus, however, under an agreement between GAVI and Merck, the developer of an Ebola vaccine known as rVSV-ZEBOV is now available. Therefore, various hygienic and preventive measures have been advocated for Ebola control and prevention. This review summarizes the drifts and pattern of Ebola outbreaks and its antecedents in West African region including other aspects of diagnosis and prevention and what is the current trend as a guide against future control.

Introduction

The current epidemic of Ebola virus disease began in March, 2017 in the Democratic Republic of Congo (DR Congo). At least three persons have died from the Ebola virus in the Democratic Republic of Congo according to the World Health Organization (WHO) and the country's Health Ministry. DR Congo is located on the Atlantic coast of West Africa. The last outbreak of the disease killed at least 11,300 people in West Africa [1,2]. Tests on nine people who came down with a hemorrhagic fever in the northeast of the country confirmed the presence of the virus. Three people have died from fever. Other samples were being tested, and six people remained hospitalized. This is the 8th outbreak to hit the Congo, that's more than any other country [1,3,4]. The deadly virus was first detected in its dense tropical forests in 1976 in Zaire (now Dr Congo) between September and October [5-8]. The outbreak was more deadly than that earlier reported in Sudan (between June and November 1976) [9].It was reported that a 44 year old teacher who just returned from northern Congo became the first victim. He was said to have been misdiagnosed for Malaria in Yambuku Mission Hospital.

At the heat of the DR Congo Ebola outbreak on May 11, 2017, the Ministry of Public Health of the Democratic Republic of the Congo informed international public health agencies of a cluster of suspected cases of Ebola Virus Disease (EVD) in the Likati health zone of the province of Bas Uélé. The first report indicated 8 suspected cases, including two deaths, with a third death reported on May 12. Testing of samples was carried out by the Institut National de Recherche Biomedicale (INRB) in Kinshasa, with two samples testing positive for Ebola Zaire by Reverse Transcription Polymerase Chain Reaction (RT-PCR) test. International agencies such as CDC, WHO, MSF (Doctors without Borders), and others provided support to the Ministry of Public Health's epidemiologic, diagnostic, clinical, and communications efforts to respond to the outbreak. There was a lot of challenging logistical obstacles faced, including the remoteness of the area and limited services. Mobile diagnostic laboratories assisted in testing of samples in the affected areas. Subsequent to a period of 42 days since the second negative laboratory diagnostic test of the last confirmed patient, WHO declared that the outbreak was over on 2nd July, 2017.

The use and re-use of needles for injection between patients and poor hygiene aided the spread of Ebola in the hospital among staff and patients, affecting 318 people of which 280 had died including 11 out of 17 hospital staff with a case fatality rate of 88% [10,11]. This hospital was later shut down while all hospitalized Ebola victims were isolated after the infection had spread for about

Table 1: Ebola Outbreak in some West African Countries (2014 Episodes).

Country	Areas affected by Ebola virus Disease
Liberia	Nimba, Lofa, Margibi, Bong, Grand Cape Mount, Grand Bassa, Grand Gedeh,Monterrado, Gbarpolu, RiverCess, Sinoe and River Gee
Sierra Leone	Bombali, Tonkolili, Kailamun, Kenema, Port Loko, Bo, Pujehum, Kono, Kambia, LeoneWestern area, Bonthe
Nigeria	Lagos and PortHarcourt
Senegal	Dakar
Guinea	Tetimede, Dabola, Kissidongou, Dioguiraya, Pita, Nzerekore, Macenta, Conakry, Coyah, Yomou, Forecariah,Kerouane, Boffa, Gueckedou and Kouroussa

4 weeks. Ebola Zaire strain is highly pathogenic and mostly deadly among other strains isolated in Yambuku village along the course of Ebola river which took its route from Congo River [12,13]. The virus was therefore named after Ebola River. Other countries that have experienced Ebola outbreak in Africa include Senegal, Guinea, Sierra Leone, Liberia and Nigeria [14]. However, occasional Ebola outbreaks have been reported outside African region in countries such as United States, Russia and the Philippines and such outbreaks were due to contaminations from the laboratory and from primates (Monkeys) imported from quarantine facilities [4,9].

The 2014 episode of Ebola outbreak affected some African countries spreading from one part of the region to another (Table 1 and Figure 1) as result of free migration and poor sanitary measures [15]. As a result of laboratory contamination, the infection was also reported in other African regions such as South and East Africa while Philippines, Russia, USA, Viriginia and Pennsylvania were not spared of the infection (Table 2). For now, there has not been any report of Ebola outbreak since WHO has declared DR Congo free of the current outbreak, this review seeks to look at the antecedents of this scourge with a view to address the challenges and the way forward.

Potential drivers of Ebola viral disease outbreaks

Investigation of different EVD outbreaks reveals that there are factors that trigger outbreaks and enhance spread of the disease. Some of the factors include, epizootic challenges, increasing anthropogenic activity (linked to population expansion and poverty), climate change, inadequate health care practices of some members of the a%icted communities, water and sanitation challenges, burial practices and corpse management capacity in poor-resource settings, porous border sand weak port health services, strong cross-border cultural and socio-economic challenges. These are common variables not only for Ebola affected countries but other nations that are at risk of emerging infectious diseases.

The potential role of climate change in triggering Ebola viral disease outbreaks and other emerging diseases is vital. A number of studies have reported the impact of climate change in the migratory patterns of fruit bats [16,17] and the outbreaks EVD in Africa [18]. Reduced precipitation, increasing temperatures and desertification have caused a large number of fruit bats to migrate from their ecological niches in the equatorial rain forest to other areas where

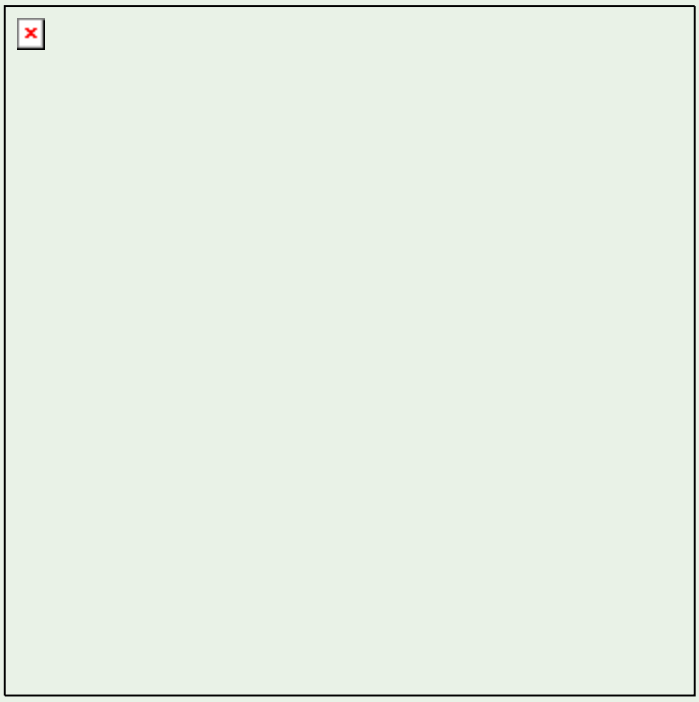

Figure 1: EBOLA Virus Disease: Virulence in each outbreak.
Key: Rectangles are outbreaks, labeled with year. Size is number of disease cases. Color is virulence, the case fatality rate from 0% yellow to red 100%.
(**Data:** WHO / CC BY: JV Chamary / Source: http://onforb.es/Y3YjoG).

Table 2: Ebola outbreaks virus disease between 1976 and 2014, adapted from WHO (2015; 2017).

Year	Country, Village	EboV subtype	Number of human cases	Number of deaths	Mortality	Source and spread of infection
1976	Sudan, Nzara and Marida	Sudan virus	284	151	53%	Spread by close contact within hospitals, many hospital staff were infected
1976	Zaire, Yambuku	Ebola virus	318	280	88%	Contaminated needles and syringes in hospitals
1976	England	Sudan virus	1	0		Laboratory infection, accident-stick of contaminated needles
1977	Zaire, Tandala	Sudan virus	1	1	100%	Noted retrospectively
1979	Sudan, Nzara and Marida	Sudan virus	34	22	65%	Recurrent outbreak at the same site as the 1976
1989	USA, Viriginia and Pennsylvania	Restone virus	0	0		EboV was introduced in to quarantine facility by monkeys from the Philippines
1989-1990	Philippines	Restone virus	3	0		Source: macaques from USA. Three workers (animal facility) developed antibodies, did not get sick
1990	USA, Viriginia	Restone virus	4	0		The same to 1989
1994	Gabon	Ebola virus	52	31	60%	Initially thought to be yellow fever, identified as Ebola in 1995
1994	Cote d'Ivoire	Tai Forest virus	1	0		Scientist become ill after autopsy on a wild chimpanzee (Tai Forest)
1995	Democratic Republic of Congo (Zaire)	Ebola virus	315	250	81%	Case-patient worked in the forest, spread through families and hospitals
1996	Gabon	Ebola virus	37	21	57%	Chimpanzee found dead in the forest was eaten by hunters, spread in family members
1996-1997	Gabon	Ebola virus	60	45	74%	Case-patient was a hunter from forest camp, spread by cloth contact
1996	South Africa	Ebola virus	2	1	50%	Infected medical professional traveled
1996	Russia	Ebola virus	1	1	100%	Laboratory contamination
2000-2001	Uganda	Sudan virus	425	224	53%	Providing medical care to Ebola case patient without using adequate personal protective measures
2001- 2002	Gabon	Ebola virus	65	53	82%	Outbreak occurred over border of Gabon and Republic of the Congo
2002- 2003	Republic of the Congo	Ebola virus	143	128	89%	Outbreak in the districts of Mbomo and kelle in Cuvette Ouest Department
2003	Republic of the Congo	Ebola virus	35	29	83%	Outbreak in villages located in Mbomo district, Cuvette Ouest Department
2004	Sudan, Yambio	Sudan Virus	17	7	41%	Outbreak concurrent with an outbreak of measles, and several cases were later reclassified as measles
2004	Russia	Ebola virus	1	1	100%	Laboratory infection
2007	Democratic republic of the Congo	Ebola virus	264	187	71%	The outbreak was declared over November 20. Last death on October 10
2007-2008	Uganda	Bundibugyo virus	37	149	25%	First reported occurrence of a new strain
2008	Philippines	Reston virus	6	0		Six workers (pig farm) developed antibodies, did not become ill
2008-2009	Democratic republic of the Congo	Ebola virus	32	15	37%	Not well identified
2011	Uganda	Sudan Virus	1	1	100%	The Uganda Ministry of Health informed the public a patient with suspected Ebola died on May 6, 2011
2012	Uganda, Kibaale	Sudan virus	11	4	36%	Laboratory tests of blood samples were conducted by the UVRI and the CDC
2012	Democratic Republic of the Congo	Congo Bundibugyo virus	36	13	36%	This outbreak had no link to the contemporaneous Ebola outbreak in the kibaale, Uganda
2012-2013	Uganda	Sudan virus	6	5	50%	CDC assisted the ministry of Health in the epidemiology and diagnosis of the outbreak
2014	Democratic republic of the Congo	Zaire virus	66	49	74%	The outbreak was unrelated to the outbreak of West Africa
2014	Guinea	Ebola virus	3548	2346	66.1%	CDC assisted the ministry of Health in the epidemiology and diagnosis of the outbreak

2014	Sierra Leone	Ebola virus	12,206	3857	31.6%	CDC assisted the ministry of Health in the epidemiology and diagnosis of the outbreak
2014	Liberia	Ebola virus	10,042	4486	44.7%	CDC assisted the ministry of Health in the epidemiology and diagnosis of the outbreak
2014	Nigeria, Lagos and Portharcourt	Ebola virus	20	8	40%	This outbreak had link to the contemporaneous Ebola outbreak in Liberia
2017	Democratic Republic of the Congo	Zaire virus	29	3	10.3%	Not well identified

environmental conditions are more favorable for survival. Studies conducted using satellite telemetry [19] and isotopic labeling [20] have shown that during periods of low fruit abundance in the equatorial forest, large colonies of fruit bats migrate long distances to take advantage of fruit pulses in other regions of the continent [21]. Stopovers during migration have been noted in certain regions of Uganda and DRC (formerly known as Zaire) where major outbreaks of EVD have occurred [19,22]. These stopovers observed in the migratory activity of the fruit bats provide a unique opportunity for local populations to massively hunt bats, either for food or commercial purposes that places the mat great risk of zoonotic infections.

In 2007, outbreak of EVD in DRC was traced to massive bat hunting due to an influx of fruit bats in the Occidental Kasai Province during a peak fruit season [22]. Similarly, the current West African outbreak is traceable to hunting of two species of bats: *Hypsignathus monstrosus* and *Epomops franqueti* that are believed to have migrated from Central Africa http://www.theguardian. This claim was supported by molecular investigation, which indicates that the causative agent of the West African outbreak diverged from the Central African ZEBOV strain about a decade ago [23]. Similarly, antibodies against ZEBOV have been detected in migratory bats in distant geographical areas, including Bangladesh [24] and Ghana, [25] indicating the potential of Central African migratory fruit bats to introduce the virus into other geographical areas. Clearly, the effects of climate change on the migration of fruit bats, particularly from their ecological niches in the equatorial forest of Central Africa to other geographical areas, may have a future global health consequence(s). This is because there is a potential of migratory fruit bats, which are known to harbor over 66 viruses [17] and introduce deadly viruses into different geographic areas. Indeed, there are global concerns that these animal-borne viruses may trigger a broad range of emerging infectious diseases in future.

Ebola virulence experience in each outbreak

The average Ebola virulence is about 61%, which claimed the lives of 2603 out of 4235 victims since records began (Table 2). The word virulence is referred to as the 'case fatality rate', that is the percentage of cases that resulted to death. Color represents virulence from yellow (0% fatality) to red (100%) in the chart represented in the (Figure 1) below. For instance, the 2014 epidemic representing outbreak 25 has claimed the lives of more people than any other outbreak in history according to records (Table 2) [9,15]. However, it is not still regarded as the most fatal, although it claimed the highest death toll and accounted for 44% of recorded cases. It has only killed 55% of infected persons (1013/1848) and hence painted orange on the chart.

With a case fatality rate of 90%indicated as (128/143), the epidemic of 2003 in Congo referred to as outbreak 14 [8]; it is known as the most virulent up to date painted red on this chart. Whether something is 'deadly' is usually defined by the likelihood of dying from it, not the total number it kills. The 2003 Ebola epidemic is the deadliest outbreak based on the interpretation of the word 'deadly' which in general term is defined by the likelihood of victims dying from such disease or the total number it that dies from it. The Uganda scenario is labeled as the least virulent outbreak which occurred in 2007. Its fatality rate was 25% (37/149) and is given yellow colour on this chart. Nevertheless, the most and least virulent outbreaks leave out three cases of 100% fatality in which each claimed the life of one person and an outbreak where the only infected person did not die from the onslaught. This is therefore given as red and yellow lines found in the top-left corner.

Ebola was first reported in 1976 with two simultaneous outbreaks [12]. The first one took place in Sudan and claimed the lives of 53% (151/284). The second outbreak known as the 3rd largest and has the 2nd highest virulence rate of 88% (280/318) labeled with red color on this chart. The Ebola virus disease was named after the Ebola River in the Democratic Republic of Congo which was the site of this outbreak [7,8].

Methodology

The literature search used by the authors for this review was based on keywords of the thrust of the paper, therefore search terms such as Ebola Virus Disease, Ebola antecedents, Ebola outbreak, Clinical syndromes, Treatments, Prevention and Control in West Africa were used. Literature search on cross-sectional, observational and randomized control studies published on the Ebola between 1976 and 2017 provided main sources of information. All these were obtained from the commonly used Medical databases such as Web of Science, Embase, PubMed and Google scholar. Literature search for systematic reviews using Cochrane Library provided a lot of information in addition to websites of international organization which served as data sources for updates and contributions on the subject matter from experts.

Results and Discussion

Epidemiology

Two main suggested modes of transmission of Ebola Virus (EBOV) into human populations are either direct contact to a reservoir or contact to other wildlife that also contracts EBOV via the reservoir [26]. Ebola virus (EBOV) transmission in human population occurs by direct contact with infected blood, or other bodily fluids including saliva, sweat, semen, milk and tissues from dead or living infected persons [27]. Epidemiologic observations have demonstrated that chimpanzees were the source of one human case in two previously described outbreaks in Coˆte d'Ivoire in 1994 and Gabon in 1996 (Table 2) [28]. Transmission through inanimate objects contaminated with infected bodily fluids has also been reported while the principal mode of transmission in human outbreaks is human-to-human transmission through direct contact

with a symptomatic or dead EVD case or with contaminated surfaces and materials (bedding, clothing) [29,30]. In the early stage of human disease (prodromal phase), the risk for transmission is lower but viral loads in blood and secretions increase so rapidly during the course of illness, with the highest levels of virus shedding noticed very late during the course of illness of severely ill patients [30,31]. Nevertheless, handling of dead bodies during burial ceremonies plays an important role in transmission. Augmented transmission takes place in hospitals involving nearly one quarter of cases occurring among health care workers [32].

Ebola virus (EBOV) can also infects human, non-human primates and some other mammalian regarded as host, but reservoir of Ebola viruses was for a long period in latent form. However, intensive efforts were expended to identify the natural reservoir [27]. Some researchers previously suggested that rodents and bats could play vital role as reservoir animals of EBOV [33,34]. The detection of antibodies and viral RNA in three bats species was the first verification about EBOV infected bats [35,36] and this was a proof that bats are involved in circulation of EBOV in nature [37]. Ebola virus (EBOV) transmission to humans in sub-Saharan Africa was believed to be the contact with dead or living infected animals (non-human primates, antelopes and bats), although some reports [38,39] have linked the cases to the skinning and butchering of carcasses. In previous outbreaks (Table 2), hunting and butchering of chimpanzee including fruit bats have been known as a potential source of Ebola infection [40,41]. According to a report Leroy et al., [42] the human outbreaks is made up of multiple simultaneous epidemics resulting from different viral strains, and each epidemic came as a result of the handling of a distinct gorilla, chimpanzee, or duiker carcass [39]. In this regard, surveillance of wildlife health and monitoring of their mortality may help to envisage and prevent subsequent Ebola outbreaks.

Replication of Ebola Virus

Life cycle and pathogenicity of Ebola virus in humans: Ebola virus (EBOV) is an encapsulated single-stranded (ss) negative RNA virus from the family Filoviridae. This article reviews the structure of the virus and the known function of its components so as to understand the life cycle and pathogenicity of the virus in humans.

Molecular and cell biology of Ebola Virus: Studies by electron microscopy reveal that the EBOV has a filamentous appearance typically 800 nm long and 80 nm in diameter. Each viral particle or virion is made up of a nucleocapsid which in turn consists of the negative ssRNA genome covered by the nucleoprotein NP, the virus specific transcription activator VP30, the polymerase cofactor VP35 and the viral RNA polymerase L proteins (Figure 1). An outer viral envelope forms a capsule round the nucleocapsid which originates from the host cell membrane with characteristic 10 nm long viral Glycoprotein (GP) spikes. The matrix sandwiching the outer viral envelope and the nucleocapsid is occupied by the VP40 and VP24 viral proteins [43].The virus genome is 19 kb in length, and encodes seven structural and one non-structural protein. Figure 2 below shows the virus genome with the gene order.

The viral RNA polymerase binds at the leader end to initiate sequential transcription of each gene. The newly transcribed mRNAs are capped and polyadenylated by the L protein during this process. Of note, the primary mRNA transcribed from the GP gene encodes a small, non-structural, soluble protein called sGP which is secreted from the infected host cells into blood. The fully functional glycoprotein is a result of RNA editing and this protein is expressed on the cell surface as GP spikes [44]. These GP spikes, help in anchorage and membrane fusion of the virion to the host cell, and are a crucial factor for Ebola virus pathogenicity.

The matrix protein VP40 is important for maintaining the structural integrity of the virion. It is also associated with endocytosis and virus budding and has the ability to release itself from the cells even in the absence of other viral proteins [45]. The second matrix protein VP24 suppresses interferon production in the host cell [44,46]. In addition, VP24 is also important for the correct assembly of a functional nucleocapsid along with VP35 and NP proteins [47]. The remaining proteins namely NP, VP35, VP30 and L proteins form the structural components of the nucleocapsid. Moreover, these proteins also catalyse genome transcription and replication [47].

Transmission of Ebola Virus: Bodily fluids contact of infected humans or animals is primarily responsible for the Ebola virus (EBOV) outbreak although it is not clear how the virus spreads in humans. However, fruit bats are the natural reservoirs of EBOV. Figure 3 clearly describes the likely method of virus transmission from bats to humans and the outcome of such method.

Life-Cycle of Ebolavirus:

(i) Host immune system attack: The monocytes and the macrophages of the host immune system are the early targets of EBOV. The dendritic cells, liver cells, and endothelial cells are the other target cells. The virus makes use of different mechanisms to interfere with or even overlook the host immune system completely. EBOV structural proteins attack nearly all host immune system processes. An example of such mechanism is referred to the Antibody-Dependent Enhancement (ADE) in which the host Antibodies (Abs) aid or augment the attachment of EBOV to the host cells thereby increasing infection in such cells. The antibodies bind to antibody receptors at their Fc sites whereas the virus binds to the antigen-binding site at the free end of the Abs [48]. In vitro studies indicated Ebola virus activates the classical pathway of the complement system. Firstly, the EBOV binds to its receptor at the surface of the host cell. Subsequently antibodies bind to the glycoprotein (GP) spikes of the virus, and the C1q component of the complement system in turn binds to the Ab-GP complex. The C1q component enhances the Ab-GP complex so as to bind to C1q ligands on the surface of the host cell thereby increasing the interaction of EBOV with its receptor on the host cell

Figure 2: Diagrammatic representation of the Ebola virus genome. The leader and the trailor regions are untranscribed sequences which regulate transcription, replication and packaging of genomes into new virions.
Source: Viral Zone (ExPASy).

surface. In this manner the GP spikes on EBOV make use of the host immune system (Abs and the complement components) to augment its attachment to the target cells [49].

Further to ADE, EBOV protein VP35 blocks the immune system's Interferon (IFN) pathways consisting of various cytokines which exert anti-viral responses. EBOV protein VP35 blocks IFN response by competing with the proteins for example Retinoic acid-Inducible Gene 1 (RIG1) protein to activate the IFN pathway [50]. Together with VP35, VP24 also blocks IFN pathway activation. VP24 blocks transcription factors such as STAT1 that regulate transcription of the immune system genes [46].

Moreover, the primary mRNA transcript of the GP gene encodes the soluble sGP which is thought to possess an anti-inflammatory attribute for the duration of infection which further helps EBOV to escape response from host immune system. Nevertheless, sGP possesses many comparable epitopes with GP and so it could have potential to sequester or absorb host Abs in order to block their downstream action [51,52]. Hence, the viral proteins disrupt various components of the immune system in order to bind to the host cell for consequent entry.

(ii) Virus entry into the host cell: Ebola virus (EBOV) and most enveloped viruses use a general mechanism to infect host cells referred to endocytosis. However, the exact mechanism for which EBOV enters host cells still remains a mirage. Reports have it that EBOV makes use of a lipid-dependent, non-clathrin and dynamin-independent endocytic pathway of entry of which Macropinocytosis remains the most likely mechanism employed by the EBOV [53]. Macropinocytosis involves outward extensions of the plasma membrane formed by actin polymerization, which could fold back upon them. The formation of a macriopinosome is as a result of the distal loop ends of these extensions or membrane ru%es can fuse together. This also indicates that actin and its associated polymerising proteins play a major role in virus entry but the exact mechanism through which EBOV induces macropinocytosis is still not clear. It is however suggested that interactions between GP and host cell surface receptors could trigger macropinocytosis to begin viral entry [53].

(iii) Virus replication: EBOV commences transcription at the leader end of the genome with the binding of the polymerase complex immediately after gaining entry into the host cell [47]. The gene VP30 is an important transcription activation factor used for the transcription viral genome while VP24 acts as an inhibitor transcription process. The precise mechanism of VP24-dependent transcription termination is not yet clear. However it appears to be vital for converting the virus from its transcriptional or replication active form to another modified for the assembly virion and outlet from host cell [54].

(iv) Virus budding and exit from host cell: After the replication process, the cell loses its connection with other cells in addition to attachment to its substrate. Nevertheless the newly synthesized genomes are put together into new buds or virions and emerged from the host cell surface with the help of the matrix protein VP40. The gene VP40 interacts with ubiquitin ligase Nedd4 which is a part of

Figure 3: Ebola virus transmission from fruit bats to humans via contaminated body fuids.
Source: Centre for Disease Control, USA.

human ubiquitination enzyme pathway and connects multiple copies of ubiquitin molecules to VP40 [55]. The VP40 on its own is taken to the host cell plasma membrane using the COPII transport system [56]. Immediately it is located into the plasma membrane, EBOV moves through lipid rafts where the final assembly and budding of the virions takes place after which their final removal from the host cell. Despite the fact that the structural components of the virus have been revealed, the precise mechanisms by which EBOV causes human disease are not yet clear. It is therefore a major constraint for treatment and till date, prevention is the best mode of action to avert an Ebola outbreak.

Virology and Pathogenesis of Ebola virus

Ebola virus disease outbreak in West Africa (2013-2016).

An unprecedented outbreak of Ebola virus disease which started in West Africa in December 2013 which affected Guinea, Liberia and Sierra Leone came to an end but the risk of sporadic cases and flare-ups remain unabated [57]. World Health Organization had declared the Ebola epidemic in West Africa a Public Health Emergency of International Concern (PHEIC) on 8 August 2014 [58,59].The same gesture was extended as end of Ebola transmission in Guinea on 29 December 2015, in Liberia on 14 January 2016, and in Sierra Leone on 17 March 2016 [60].

However, the same body (WHO) continues to stress that these countries are still at risk of sporadic transmission of Ebola, largely due to virus persistence in some survivors, and should remain on high alert and ready to respond [57,61]. It was further stated that strong surveillance and emergency response capacity must be maintained, while care, screening and counselling also should be provided for survivors. A flare-up of Ebola cases was reported in a rural village in the prefecture of Nzérékoré, Guinea as at 18 March 2016 [60].

The Biology of Ebola virus

Ebola virus (EBOV) is an envelope, non--segmented, negative-sense, single-stranded RNA virus with genome size of approximately 19 kbp [62]. Its virion is pleomorphic, producing 'U'- shaped, '6'-shaped, or circular forms [40]. The virus may cause Ebola Virus Disease (EVD) in humans as well as in non-human primates. Ebola virus EBOV was firstly described in 1976 and since then five species of the EBOV were described. Four of species namely Sudan Virus (SUDV), Ebola virus (EBOV, known as Zaire), Taï Forest Virus (TAFV) and Bundibugyo Virus (BDBV) cause acute and lethal disease in human population [63,64]. The fifth one Reston Virus (RESTV) which differs from each other was reported to have caused disease only in monkeys, chimpanzees, and gorillas and it is apparently maintained in an animal reservoir in the Philippines but has not been found in Africa [32,41]. Since it was first noticed 1976, over twenty outbreaks of EVD have been reported in Africa [14,65]. The West Africa Ebola Outbreak 2014 (WAEO), first reported by the World Health Organization (WHO) on 22 March 2014 was linked to ZEBOV which has caused for more than ten thousands death [66]. Further to the three most affected countries in sub-Saharan Africa (Guinea, Liberia ad Sierra Leone), EBOV cases have been described in the Great Britain, the United States and Spain [67,68]. The alarming pattern of West Africa Ebola Outbreak (WAEO) made some countries to take a decision to implement special measures for air plane transport of passengers from affected countries [69].

Ebola virus disease

Ebola virus (EBOV) is known to cause severe hemorrhagic fever with high rate of fatal outcome in humans and several species of Non-Human Primates (NHPs) [70]. Human Ebola outbreaks usually take place unexpectedly (without notice) from a vaguely defined source, with subsequent rapid spread via contact of person to person [28]. Long-ago, Ebola viruses were referred to as "hemorrhagic fever viruses", as a result of the clinical manifestations, which include coagulation defects, bleeding, and shock [71,72]. For now such term is no longer used because not all of Ebola patients developed significant hemorrhage symptoms which commonly occur only in the terminal phase of fatal illness [73].

Clinical syndromes Ebola disease

Clinical presentations in patients with Ebola Virus Disease (EVD) usually take effect after an incubation period of 4-10 days, of about 2-21 days range [74,75]. Prior to an abrupt onset of 'flu-like' symptoms such as fever, myalgia, chills vomiting and diarrhoea, the EVD can suddenly evolve into a rigorous state with a swift clinical turn down. This phase of the disease is accompanied by potential haemorrhagic problems and multiple organ failure [74,76]. Ebola patients may show clinical presentations relating to gastrointestinal symptoms which include nausea, stomach ache, vomiting and diarrhoea, neurological symptoms such as headache, profound weakness and coma, respiratory symptoms e.g. coughing, dyspnoea and rhinorrhoea, and generalized symptoms closely related to cardiovascular system failure which may end up in shock and oedema [75-77]. Nevertheless, the most common symptoms are fever in together with anorexia, asthenia and a maculopapular rash spanning between day 5 and 7 after the disease commencement, [75-77] closely related to an earlier outbreak characterized with primary clinical presentation such as gastrointestinal. However, clinical symptoms and chemical laboratory tests are used to confirm multi-organ involvement in EVD.

Diagnosis

Current laboratory diagnostics for Ebola virus disease/Ebola haemorrhagic fever: In Ebola Haemorrhagic Fever (EHF) outbreaks, confirmation of infections is carried out by various laboratory diagnostic methods. These methods are virus isolation, reverse transcription-PCR (RT-PCR, including real-time quantitative RT-PCR, antigen-capture Enzyme-Linked Immune Sorbent Assay (ELISA), antigen detection by immunostaining, and IgG- and IgM-ELISA using reliable virus antigens [27,38,39,66,78,79]. Histological techniques such as antigen detection by immunohistochemical analyses are sensitive methods, particularly when required for postmortem diagnosis [78].

During the initial stage of illness, laboratory diagnosis by detection of virus antigens is suitable for patients whereas serological diagnosis by the detection of specific IgM and IgG antibodies is reliable for patients in a relatively late stage of illness. The detection of virus antigens is especially reliable for patients who die prior mounting an antibody response. Diagnostics for viral hemorrhagic fevers such as EHF, must be sensitive, specific, and reliable because problems of misdiagnosis of viral hemorrhagic fevers may result in huge turmoil to society. Hence, the diagnosis of EHF must not be based on any single diagnostic method alone [39].

The risk of misdiagnosis should be extremely reduced a minimum level. In actual EHF outbreak areas, patients with EHF should be isolated [15]. This shows that a false-positive result will place an individual at unnecessary risk of infection thereby putting him/her in a high-risk environment such as an isolation ward. On the other hand, a false-negative result will make individuals who are infected with EBOV to be live in the community with the understanding that they do not have viral hemorrhagic fever, whereas they have the potential to become highly contagious and create person-to-person transmission of these pathogens in the community. Lassa fever and Crimean-Congo hemorrhagic fever are also endemic in Africa. Hence, the diagnosis of viral hemorrhagic fevers should rely on multiple diagnostic assays for viral hemorrhagic fevers in a broad manner [80].

Isolation of Ebola virus: One of the sensitive and basic methods for the diagnosis of EHF, EBOV is virus isolation. The virus grows well in a large variety of cell lines; however Vero cells and Vero E6 cells are commonly used. Blood and other bodily fluids must be sent to BSL-4 laboratories located in developed countries especially from an outbreak area which is usually very remote. The shipment of specimens for virus isolation in ideal conditions such as maintenance of cold chain during the period is generally complex. It is therefore advisable to note that, diagnostic criteria based on virus isolation alone cannot provide an etiologic diagnosis. A panel of monoclonal antibodies specific for recombinants NP of Zaire EBOV, Reston EBOV, Zaire and Sudan EBOV, Zaire and Reston EBOV, and Lake Victoria MARV have been developed [30,81,82]. These antibodies when used became possible to identify the species of EBOV isolates by serology.

RT-PCR and Real-time quantitative RT-PCR: Diagnostic methods using Molecular technique for EHF by RT-PCR have been properly developed and evaluated in the epidemic setting, particularly during EHF outbreaks in the Democratic Republic of Congo in 1995, Gabon in 1996, and Uganda in 2000 [39,42,80]. For the period of the EHF outbreak in Uganda in 2000, a nested RT-PCR using primer sets designed specifically for the NP region of the Sudan EBOV Gulu strain, a causative EBOV responsible for the outbreak was developed [80]. Just of recent, real-time quantitative RT-PCR methods for EHF and MHF have also been developed [27,66,79,80].

The real-time quantitative RT-PCR method developed by Drosten et al, [66] is a one-step RT-PCR with additional DNA-intercalating dye SYBR green I using the primer set. This primer set was designed for the amplification of L genes from both EBOV and MARV [66,39]. Conversely, the real-time quantitative RT-PCR methods developed by other investigators depend on the technology of TaqMan probe-based quantitative RT-PCR, which uses a designated primer set with a fluorogenic TaqMan probe labeled at the 5' end with the reporter dye 6-carboxyfluorescein and at the 3' end with a quencher tag ([27,79,80]. The primer sequences are used for RT-PCR, nested RT-PCR, and real-time quantitative RT-PCR. These molecular diagnostics for EHF and MHF have been found to be sensitive, specific, and e cacious in the diagnosis of filovirus infections. Nevertheless, RT-PCR assaysin particular nested RT-PCR and real-time quantitative RT-PCR is ideal, false-positive and false-negative results should always be removed. There is variation in sensitivities of the RT-PCR systems used in several laboratories [83].

Antigen detection ELISAs for EHF: During fatal infection with EBOV, patients usually pass on before the antibody response. Serological diagnostics have been suggested to be suitable for the diagnosis of infection in patients who survive and not in those consumed by the infection. High titers of infectious pathogens are found in the blood and tissues of patients at the onset of illness, thereby suggesting that the detection of virus antigens is vital for diagnosis of EHF at an early stage. Antigen-capture ELISA was produced for the detection of EBOV antigens and applied in clinical settings e.g. EHF outbreaks in the Democratic Republic of Congo in 1995, Gabon in 1996, and Uganda in 2000 and confirmed to be effective in diagnosis of EHF [38,39,80]. In the antigen-capture ELISA, a pool of monoclonal antibodies to the Zaire and Sudan EBOVs and rabbit sera elevated to the Zaire and Sudan EBOVs were respectively used as capture and detection antibodies [38]. Antigen-capture ELISA systems which detect EBOV antigens have also been produced by many groups [30,81,82,84,85] using target proteins such as NP, VP40, and GP.

Saijo et al. developed filovirus antigen detection ELISAs using unique monoclonal antibodies to the rNPs of Zaire EBOV, Reston EBOV, and Lake Victoria MARV [30,81,82]. Despite the fact that monoclonal antibodies were developed by immunizing mice with recombinant NPs, the NP-capture ELISA detected not only the rNPs of these viruses but also that of the authentic EBOV rNPs. Antigen-capture ELISAs were developed for the detection of the NPs of Zaire EBOV, Sudan EBOV, and Reston EBOV [81], that for Reston EBOV alone [30,82]. The antigenic regions on the NPs of EBOV were found to be located in their carboxy-terminal halves. The carboxy-terminal 110 amino acids of the NPs of EBOV have strong antigenicity [86]. All the monoclonal antibodies that may be used as capture antibodies in the antigen-capture ELISA format bound with epitopes within the carboxy-terminal ends of NPs [30,81,82].

The conformational epitopes within the carboxy-terminal ends of NPs is recognized by the monoclonal antibodies designed as capture antibodies for rNPs of EBOV while those for rNP of Reston EBOV acknowledged linear epitopes [30,81,82]. The antigen-capture ELISA with capture monoclonal antibodies to the rNP of Reston EBOV (Res2-6C8 and Res2-1D8) that identify linear epitopes, can detect only rNP of Reston EBOV while that of capture antibody to rNP of Zaire EBOV (3-3D) which recognizes the conformational epitope, can detect both the rNP of Zaire EBOV and that of rNPs of Sudan, Reston, and Ivory Coast EBOVs [30,81] Lucht et al. produced an antigen-capture ELISA using a monoclonal antibody to Zaire EBOV GP as the capture antibody and that of monoclonal antibody to the same antigen as a detector antibody [85]. The production of an ELISA for the detection of Zaire EBOV VP40 by the same group was done using two monoclonal antibodies to Zaire EBOV VP40 as capture and detector antibodies [84]. The EBOV GP-capture ELISA can only detect the GP of Zaire EBOV while that of EBOV VP40-capture ELISA can detect the VP40s of all four EBOV species. It is therefore considered that EBOV antigen detection ELISAs are of use for accurate and rapid diagnosis of EHF. In order to determine the e cacies of these antigen-capture ELISAs, they must be evaluated by using patient specimens in a clinical setting and during outbreaks of EHF.

Treatment

Ebola virus Disease (EVD) is accompanied by haemorrhagic fever which makes it different from malaria which is endemic in West Africa. When EVD is established, general medical support is critical and should include replacement of coagulation factors and heparin if disseminated intravascular coagulation is indicated. It is advisable that this type of care should be administered with strict attention to barrier isolation. It must be noted that all body fluids such as blood, saliva, urine, and stool contain infectious virions and must be handled with utmost care.

Ribavirin and medical support are indicated for the management of Ebola Virus Disease (EVD) when detected early. Ribavirin as a drug of choice has demonstrated to be more effective when given intravenously than oral administration of the anti-viral drug. Early diagnosis will enable the commencement of the drug administration. It has also been proven that if the drug is given before the incubation period of twenty one days, deaths rate may come down by as much as 90%.

For now, no specific therapy is available that has proven e cacy in the treatment of Ebola hemorrhagic fever. Currently, there are no commercially available Ebola vaccines. Nevertheless, a recombinant human monoclonal antibody directed against the envelope GP of Ebola has been proven to possess neutralizing activity. This Ebola neutralizing antibody may be a source of materials in vaccine development and could serve as a passive prophylactic agent and this vaccine research is ongoing.

Prevention and Control (including Vaccine development and at what stage)

Currently, an experimental Ebola vaccine tested on humans in the waning days of the West African epidemic has been proven to provide 100 percent protection against the deadly EVD. However, the vaccine has not yet been approved by any regulatory authority. It is however considered highly effective to the extent that an emergency stockpile of 300,000 doses has already been created for use should there be any outbreak threat again. Right from time Ebola was discovered in the former Zaire in 1976 [14], there have been various attempts to develop vaccines capable of controlling the scourge. All these began with a sense of urgency but frizzled out for lack of financial support. Although throughout those years only about 1,600 people died of EVD with the bizarre nature their deaths characteristic of copious hemorrhaging from every orifice thereby making the disease to possess frightening reputation. Consequently, only the huge, explosive 2014 outbreak which claimed 11,000 lives in Africa and spread overseas, affecting countable number of people in Europe and the United States ultimately gave the political and economic impetus for making possible an effective vaccine.

During the West Africa Ebola outbreak, the vaccine was not ready in time to halt the scourge, which probably began in a hollow, bat-filled tree in Guinea and ravaged Liberia and Sierra Leone before it was put under control. However, the prospect of a vaccine stockpile now has brought optimism among public health experts. A vaccine trial was later conducted in Guinea. According to the World Health Organization, the world can't afford the confusion and human disaster that came with the last epidemic [15]. Although many people lost their lives during West Africa's Ebola epidemic, however with the recent scientific breakthrough the world will never be found wanting again should there be any future Ebola outbreak again. This development on Ebola vaccine opens up new, faster, more e cient ways to handle the virus.

The new vaccine did not come to be without its own challenge(s). It is only potent against one of the two most common strains of the Ebola virus, and may lack long-lasting protection. Some people also complain of side effects such as headaches and joint pains. It is gives a great relief as regards to any new outbreak. A vaccine trial was done on 11,841 residents of Guinea in 2016. Among the 5,837 people who got the vaccine, none came down with Ebola 10 or more days later. There were additional 23 Ebola cases among the thousands of others not immediately vaccinated. The Ebola trial was in the instance of World Health Organization, the Guinean Health Ministry, Norway's Institute of Public Health and other institutions. The vaccine, known as rVSV-ZEBOV, was developed over a decade ago by the Public Health Agency of Canada and the United States Army and is now licensed to Merck.

Various tests in monkeys showed that a shot protected all of them when it was given at least a week before they were given a high dose of Ebola. The shot even protected a few monkeys who received it a day prior being infected with Ebola. There are five known subtypes Ebola virus of which the most common are Ebola-Zaire which caused the West African outbreak, and Ebola-Sudan. This virus is also related to Marburg virus, which is similarly deadly. An ideal vaccine would protect against all Ebola strains and Marburg when given a shot may not be effective against several strains if it is based on the VSV spine because VSV triggers a lot of side effects. It is therefore noted that risks that that are acceptable amidst of a deadly epidemic are not acceptable in a preventive vaccine given to healthy children and adults.

Work is ongoing on a likely candidate for a routine Ebola vaccine which uses two shots: the first has the Ebola surface protein attached to a chimpanzee adenovirus which can infect humans without harming them; the second makes use of a weakened pox virus similar to that used in smallpox vaccine. For now there is no license Ebola vaccine, hence the need to seek approval of from the World Health Organization, which itself requires licensing by a major regulatory agency such as the United States Food and Drug Administration or the European Medicines Agency.

Conclusion

Ebola Virus Disease (EVD) outbreak in West Africa is unpredictable and has always come with different pattern associated with casualties of different degrees; however, the recent outbreak in DR Congo came in a different scenario. Health o cials in the Democratic Republic of the Congo have confirmed one case of Ebola in what appears to be the first new outbreak of the deadly virus since the massive epidemic that ravaged West Africa in 2014-'15 [15]. The first report mentioned 8 suspected cases, including two deaths, with a third death reported on May 12. Latest reports indicated that, nine people in a very remote part of the country recently fell ill with a hemorrhagic fever. According to WHO, three people have died, but only one so far has been confirmed tested positive for Ebola and the case occurred "in a very remote zone, very forested" [60].

Ebola is a virus known to circulate in populations of chimpanzees, gorillas, fruit bats, and a few other animals in the rainforests of West and Central Africa. Occasionally it infects humans who come in contact with those animals' or fellow infected humans' bodily fluids, causing intermittent outbreaks [9,57]. The fever is associated with vomiting and blood loss, and kills around half of all the people it infects. The World Health Organization has deployed health care workers to manage the outbreak and carry out surveillance to track it. In pursuance of this goal, the first teams of epidemiologists, biologists, and experts in the areas of social mobilization, risk communication and community engagement, and also personnel specializing in water, hygiene and sanitation have been deployed to the crisis area.

A sudden surge of Ebola virus disease outbreak in Nigeria in 2014 if not quickly curtailed may have had a spillover effect across West African countries due to so many factors. Ebola has a mean virulence of 61%, killing a total 2603 out of 4235 people since records began. With a 90% case fatality rate (128/143), the 2003 epidemic in Congo (outbreak 14) is the most virulent to date The 2014 epidemic (outbreak 25) has killed more people than any other outbreak in history. But it's not the most fatal: although it has the highest death toll and accounts for 44% of recorded cases, it's 'only' killed 55% of those infected (1013/1848) [4,13]. The wide range of clinical features and unexceptional symptoms that appear early in Ebola infection hinders a diagnosis based strictly on clinical manifestations, even at the expense of experienced physicians [59].

West Africa as a region is seeing a flare-up of the Ebola virus disease, but Zaire where Ebola was first discovered in 1976 -- is experiencing much higher mortality rates than usual. On average, Ebola virus disease is deadly in 50% of all individuals infected, with higher rates of 75% morbidity among people hospitalized for the illness [6,15] but the current outbreak in DR Congo has seen about 10.3% of those affected dying from their infection. Furthermore, a 2014 outbreak of Ebola in Sierra Leone caused more than 12,206 people to become infected, but 3857 deaths, according to the [13]. Despite higher case numbers, the death toll in such outbreak was already considered higher than expected. However in previous outbreaks, some infections went unreported as the disease mainly affects rural areas where populations of poor economic status can be highly infected, but the health authorities were not informed. Furthermore, in the 2014 to 2015 outbreak, more than 11,000 people died, mainly in Sierra Leone, Guinea, and Liberia. According to report [4,9], the DR Congo was spared the worst of the Ebola outbreak with just 49 deaths. The outbreak was declared over in 2016, but the WHO warned of occasional future "flare-ups" of the disease.

Many challenges have been noted which aids the continual outbreaks of Ebola in West Africa and its circulation to other parts of the world through contamination in research laboratories in Europe and America.. Firstly, Ebola has been regarded as a neglected tropical disease has affected countries such as Nigeria, Ivory Coast, Zaire, Guinea, Sierra Leone, Republic of Benin, DR Congo, Uganda, Gabon, South Africa, and Liberia (Tables 1 and 2). The disease has also spread to Philippines, England, Indonesia and USA suggesting asymptomatic infection. The rodent hosts play a pivotal role in maintaining the virus in our environment also survives due to poor hygienic practices in West African countries and its environs [87]. The second challenge is the socioeconomic problem related to Ebola vaccination for which there is no licensed vaccine and this probably remains the biggest obstacles to cross [4]. Those who are at the higher risk of contracting the disease are also the poorest in the above-mentioned endemic West African countries. It has been observed that poor hygiene and sanitation in such countries increases the probability of Ebola virus exposure [88]. Moreover, with the advent of Ebola vaccine (though not yet licensed) many people living in these countries may not be able to pay for vaccination due to poor economic condition. Hence, there is need for massive and continuous surveillance in Ebola endemic region such as West Africa. This will in no doubt provide strong measures for control and prevention including succor for the less privilege against Ebola scourge. We must therefore realize that all epidemics start with one case and no one must take any risks but should take all measures to contain it as a way out of this incessant flare-up scourge in West Africa.

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Authors Contribution

All authors contribute maximally to the success of this review article including drafting of the manuscript and revising it critically for important intellectual content, read and approved the final manuscript version to be published.

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