Review Article


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INTRODUCTION

Ebola virus (EBOV) is the causative agent of Ebola virus disease (EVD), which is a severe and often fatal haemorrhagic disease and was thus previously known as Ebola haemorrhagic fever. While the outbreak of EVD is infrequent but dates back to 1976 in Sudan and Zaire; it is a global concern because of the associated high infectivity and fatality, with the propensity of spread as an exotic virus. The 2014–2015 Ebola outbreak which is the largest in history is a clear evidence of this, as the outbreak went beyond the traditional East Africa countries of previous outbreaks and spread to Nigeria, Spain, United States of America, England and Italy.

The Ebola epidemic in West Africa destroyed lives and devastated communities with an astounding total no of cases and deaths reported at 28,603 and 11,301, respectively as at the end of February 2016. On the 8th August 2014, the World Health Organization (WHO) had declared the Ebola epidemic in West Africa as a Public Health Emergency of International Concern. Sequel to this, the organisation declared the end of Ebola transmission in Guinea on 29 December 2015, in Liberia on 14 January 2016, and in Sierra Leone on 17 March 2016 (after a flare-up in February 2016). However according to WHO on the 18th March 2016, a flare-up of Ebola cases was reported in a rural village in the region of Nzérékoré, Guinea. As such, the 2014–2015 EVD epidemic may not yet be over as it has extended into 2016 with flare-ups.

METHODOLOGY

Data and relevant information were extracted from the review of majorly relevant publications/papers about the Ebola epidemic in West Africa and other previous outbreaks of EBOV. A consensus meeting of the reviewers was held to determine and harmonise the appropriate section titles and contents.

Key Words: Ebola virus disease, Filoviridae, index case, outbreak, West Africa

EBOLA VIRUS CLASSIFICATION

Ebola virus is a non-segmented negative sense single stranded RNA virus classified as belonging to the genus Ebola virus in the family Filoviridae (order Mononegavirales). The family Filoviridae presently consists of three genera; the Ebola virus, Marburg virus (MARV) and cuevavirus. Five distinct species of the genus Ebola virus are known: Zaire Ebola virus (EBOV), Sudan Ebola virus, Taï forest Ebola virus, Bundibugyo Ebola virus and Reston Ebola virus. On the other hand, there is one known species of MARV, consisting of two viruses, MARV and Ravn virus. The rather new genus - cuevavirus is known to have only one species - Lloviu cuevavirus (LLOV). However, this novel filovirus detected also in bats is biologically uncharacterised, since infectious LLOV has not been isolated yet.

The Zaire species of Ebola virus (EBOV) was the causative agent of the 2014 epidemic in West Africa, as the high degree of sequences similarity and the epidemiologic links suggest a single introduction of the virus into the human population, which was likely to have occurred in December 2013 with its sequel spread [Figure 1].

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RESERVOIRS AND TRANSMISSION

It is clear that EBOV is a zoonotic pathogen that can cause epidemic, lethal haemorrhagic outbreaks among humans and non-human primates. However, the natural reservoirs of filoviruses have remained elusive for decades. Reports suggest that bats (order Chiroptera) are the primary natural hosts, including old world insectivorous bats (genera Rhinolophus and Miniopterus) and frugivorous bats (family Pteropodidae) and fruit bats of the genus Rousettus. However, Ebola viruses have not yet been isolated by viral culture from bats except for the molecular and sero-epidemiologic evidence of infection.

Transmission to humans is always initially through direct contact with bats or their excretions, secretions or contact with other end hosts, such as the great apes and other primates. Human to human transmission is usually a sequel to this by direct contact with the bodily fluids of symptomatic infected persons, this accounts for the high rate of infection of health workers and subsequently nosocomial infection.

Various traditional practices in this region, such as washing and other rituals performed on the dead bodies also promote transmission of Ebola virus from infected contacts; this is exemplified by the first person reported to have been infected in Sierra Leone who was a tribal healer who had been treating Ebola patients from across the nearby border with Guinea. She died on 26 May 2014 and according to tribal tradition, her body was washed for burial, and this appears to have led to infections in persons that participated in her burial.

RISK OF TRANSMISSION THROUGH DIFFERENT BODY FLUIDS

According to WHO, the most infectious body fluids are blood, faeces, and vomit. The molecular method has also been used to demonstrate viral RNAs in urine, semen, saliva, aqueous humour, vaginal fluid and breast milk for the persistent and extended period after the infection. Specifically, evidence suggestive of persistent Ebola viruses in semen has been found in five different Ebola outbreaks, including the current epidemic. A case from Kikwit, Congo had the longest semen positivity described, with a positive virus detection of EBOV on day 82 post-onset. However, in a study of 100 male survivors of EVD in Sierra Leone 2014 outbreak, the semen of 26 of forty (65%) who had a specimen obtained 4–6 months after onset still tested positive to EBOV. The contribution of this to flare-up is under evaluation by a number of investigators. Be that as it may, proper post-Ebola infection counselling should be rendered all Ebola survivors on body fluids and risk of transmission.

OUTBREAKS

Ebola was first recognised in 1976 when two epidemics occurred almost simultaneously near the Ebola River in the Democratic Republic of the Congo (then known as Zaire) and in a region of Sudan, with a mortality rate of 88% and 53%, respectively. Active surveillance revealed that the index case in Zaire received an injection of chloroquine for presumptive malaria at the outpatient clinic at Yambuku Mission Hospital. Several other persons that received injections at the hospital also suffered from Ebola haemorrhagic fever like the index case.

Baron Peter Piot and his team while working at the Institute of Tropical Medicine, Antwerp, Belgium received blood sample that had been taken from a Belgian missionary who had died during the 1976 Zaire outbreak. They described the virus as Marburg-like because of its thread-like nature and was later named EBOV. While the outbreaks were clearly documented, further insight into the nature of the pathogen was alluded by the publication of Emond et al. in November 1976, an investigator at the Microbiological Research Establishment accidentally inoculated himself while processing material from patients in Africa. He developed an illness closely resembling Marburg disease, and a virus was isolated from his blood that resembled MARV but was distinct serologically. The course of the illness was mild and may have been modified by treatment with human interferon and convalescent serum. Convalescence was protracted; there was evidence of bone-marrow depression and the virus was excreted in low titre for some weeks. Recovery was complete.

Since then, sporadic and smaller outbreaks have erupted over the succeeding years. More than 25 known outbreaks have
been reported, mostly in Equatorial Africa and frequently due to EBOV.\cite{34}

The 2014–2015 Outbreak

The 2014–2015 outbreak of Zaire Ebola virus in West Africa [Figure 2] with its subsequent spread to Nigeria, Spain, United States, England, and Italy exemplifies the virulence and communicability of EVD.\cite{8} As of April 13th 2016, the WHO updated cases of EVD was 28,670 with 11,325 deaths [Table 1 for break down].\cite{6} This outbreak in West Africa was first reported during early March 2014 in the 3 South-Eastern prefectures of Guinea (Gueckedou, Macenta, and Kissidougou), which border Liberia and Sierra Leone;\cite{17} a report by Baize et al., however dates back the outbreak to December 2013. Although their report still identifies Gueckedou as the initial phase and geographic origin of the EBOV outbreak.\cite{11} Sequence analysis of viruses isolated from patients in Sierra Leone indicated that the epidemic resulted from sustained person-to-person transmission, without additional introductions from animal reservoirs.\cite{26}

The epidemic was concentrated in the West African nations of Liberia, Guinea and Sierra Leone, with minor outbreaks elsewhere [Table 1]. It caused significant mortality, with reported case fatality rates of up to 67%. As of 2016, with the epidemic under control, the WHO has warned that flare-ups of the disease are likely to continue for some time as recently occurred in Sierra Leone and on-going in Guinea.\cite{5}

Reasons for the Persistence of the 2014–2015 Epidemic

The 2014 Ebola outbreak persisted for several reasons: It occurred in a region of Africa in which Ebola had never before been reported. This was because the governments of the countries involved had never witnessed the social and economic mayhem that can accompany an outbreak of this nature. Populations could not understand what hit them or why. According to WHO, cities including the capitals of all three major countries with the Ebola epidemics have been epicentres of intense virus transmission.\cite{27} This demonstrated how swiftly the virus could move once it reached urban settings and densely populated slums. Several other factors necessitated the persistence of this virus in this West-African epidemics as reported by the WHO,\cite{27} which includes but not restricted to the following:

**Damaged Public Health Infrastructures and Lack of Awareness of Ebola Symptoms**

This particularly relates to Guinea, Liberia, and Sierra Leone, which are among the poorest countries in the world, had only lately emerged from years of civil war and turbulence that left basic health infrastructures severely damaged or destroyed and created a regiment of young adults with little or no education.\cite{27} Road systems, transportation services and telecommunications are weak in all the three countries, especially in rural settings. The difficulties for healthcare workers to promptly identify Ebola as the cause of infection, since early symptoms are similar to endemic diseases such as malaria, shigellosis, and salmonellosis, inadequate personal protective equipment (PPE), insufficient numbers of hospital beds and lack of basic amenities were also responsible for the quick spread of the virus.\cite{17,22,24}

<table>
<thead>
<tr>
<th>Country</th>
<th>End of outbreak</th>
<th>Cases</th>
<th>Deaths</th>
<th>Case fatality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liberia</td>
<td>14th January 2016</td>
<td>10,678</td>
<td>4810</td>
<td>45</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>17th March 2016, after a flare-up in February, 2016</td>
<td>14,142</td>
<td>3956</td>
<td>28</td>
</tr>
<tr>
<td>Guinea</td>
<td>2 new cases/5 deaths reported 18th March 2016 outbreak ended 19th October 2014</td>
<td>3814</td>
<td>2544</td>
<td>67</td>
</tr>
<tr>
<td>Nigeria</td>
<td>20th October 2014</td>
<td>20</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Mali</td>
<td>21st December 2014</td>
<td>8</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>United States</td>
<td>20th July 2015</td>
<td>4</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Italy</td>
<td>10th March 2015</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>10th March 2015</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Senegal</td>
<td>17th October 2014</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spain</td>
<td>2nd December 2014</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>18th March 2016</td>
<td>28,670</td>
<td>11,325</td>
<td>40</td>
</tr>
</tbody>
</table>

Source: WHO Updates, 2016
The Liberian was a 40-year-old Diplomat of the

This was after an index case of an acutely

The high degree of population movement across exceptionally porous borders, driving to a large extent by poverty contributed to the persistence of EBOV. This mobility creates two significant weaknesses to control. First, as noted early on, cross-border contact tracing is difficult. Second, as the situation in one country began to improve, it attracted patients from neighbouring countries, thus reigniting transmission chains.\[22\]

Severe shortage and industrial strikes of health care workers

Earlier before the outbreaks, the three countries (Guinea, Liberia, and Sierra Leone) had a ratio of only one to two doctors per nearly 100,000 populations.\[27\] That inadequate personnel has been further diminished by the unparalleled number of health care workers infected during these outbreaks. Another critical issue was the reduction in numbers of health workers by being absent without leave because of the fear of being infected.\[8\] Strikes by hospital staff and burial teams have further impeded control efforts. Most strikes occurred after staff were not paid for weeks or months, did not receive promised hazard pay, or were asked to work under unsafe conditions associated with the deaths of many colleagues.\[27\]

Cultural beliefs and behavioural practices

High-risk behaviours experienced in these recent outbreaks have been shown to be similar to what has been seen during previous Ebola outbreaks, with adherence to the ancestral funeral and burial rites singled out as driving large eruptions of new cases.\[27\] Another deep-rooted cultural trait in West Africa is compassion. This allowed Ebola virus to spread through the webs that bind societies together in a culture that stresses compassionate care for the ill and ceremonial care for their bodies after death.\[27\]

Reliance on traditional healers

In Africa, traditional medicine has a long history. Poor access to and delays in operations in government owned health facilities made care by traditional healers or self-medication the preferred health care option for many, especially the poor. At the beginning of the outbreaks, the high case fatality rate encouraged the opinion that hospitals were places of contagion and death. This further reinforced the defiance to the advice to seek early medical attention. However, despite the unprecedented number of cases, it is believed that the official numbers of cases and deaths are thought to be underestimates, as some Ebola victims were not cared for in health care facilities, and their illnesses and deaths have not been documented due to reliance on the traditional healer.\[6,27,28\]

Community resistance

There were multiple reasons why control efforts were disrupted. First, fear and misconceptions about an unfamiliar disease have been well documented. Individuals and their lineages had been living in the same ecological milieu for many centuries, hunting the same wild animals in the same forest areas, and had never before seen a disease like Ebola. These unfamiliar response measures, like disinfecting houses, setting up barriers and fever checks, and the invasion by non-nationals dressed in what looked like spacesuits, who took people to hospitals or barricaded tent-like wards from which few returned. A second cause of resistance arose from the inability of ambulance and burial teams to respond quickly to calls for help, with bodies sometimes left in the community for as long as 8 days propagating the transmission of Ebola.\[27\]

Public health messages that powered hopelessness and despair

Initially, there were early and persistent denial that Ebola was real and health messages issued to the public repeatedly emphasised that the disease was extremely serious, deadly, and had no vaccine, treatment or cure. These had opposite effect on the populace.

For unknown reasons that may include the stigma that surrounds Ebola, the practice of hiding patients in homes continued in some areas.

Spread by international air travel

The importation of Ebola into Lagos, Nigeria and Dallas, Texas marked the first times the virus entered a new country via air travellers. These events theoretically placed every city with an international airport at risk of an imported case.\[1,27\]

Possible change in clinical and epidemiological features of Ebola virus

Virological analyses have determined that the virus circulating in West Africa is genetically distinct from Zaire viruses seen in past outbreaks. This virus takes a different clinical course and epidemiological consequences, although these differences do not affect the infectious period, case fatality rate, or modes of transmission.\[27\]

On the whole, supportive treatment and the experimental use of blood plasma from recovered Ebola patients appeared to improve survival rates in patients in the United States and Europe, but these treatments were not feasible for many patients in the hardest hit countries in West Africa.\[24,29,30\] Beyond the death toll, the disease had notable social and economic impact on the mostly affected countries.\[3\] Several children being orphaned, schools were closed, travel restrictions were put in place, markets were shut down and sources of income were significantly diminished.\[31\] The cumulating effect of all these is a social epidemic on its own which can lay the platform for other infectious diseases of poverty.

The Nigeria Outbreak

Nigeria’s feat for curtailing EVD was acknowledge globally, and the country was declared EVD free by the WHO on the 20th October 2014. This was after an index case of an acutely ill traveller from Liberia via Accra, Ghana, to Lomé, Togo, arrived at the Lagos International Airport on the 20th of July, 2014.\[22,33\] The Liberian was a 40-year-old Diplomat of the Economic Community of West African States (ECOWAS), his status allowed air travel protocols to be broken and was taken and directly attended to in a private clinic in Obalende,
Lagos.\textsuperscript{[34]} He infected two ECOWAS associates and health workers at the hospital that attended to him which led to a cascade of secondary transmission. One of the ECOWAS associates died in Lagos on 12\textsuperscript{th} August 2014, while the other travelled to Port Harcourt for medical attention. Four persons were reported to have contacted EVD in Port Harcourt including the doctor that attended to the ECOWAS associate, his wife, sister and an elderly woman. The Port Harcourt doctor and the elderly woman later died, while the others recovered and survived the infection. On the other hand, one of the nurses that contacted EVD in the hospital that attended to the index case in Lagos travelled to Enugu and caused 25 persons to be placed on surveillance at Enugu. None of them developed EVD and good enough, the nurse also recovered.\textsuperscript{[32]}

The outbreak was curtailed in Nigeria by the initial action of the Medical Consultant (Dr. Stella Adadevoh) that attended to the index case at the private hospital where he was hospitalised. He presented with high fever, lymphadenopathy and sore throat and was treated for malaria and typhoid fever until he later developed diarrhoea, vomiting and microscopic haematuria. The culmination of the clinical presentations and his epidemiological link to Liberia raised the suspicion for haemorrhagic fever. She suspected EVD when the patient did not respond to these earlier treatments prescribed and went on to further put herself in arms way by refusing the patient self-discharge and pressures to discharge. His specimens were subjected to viral investigations and within few hours of receiving samples at the Virology Research Laboratory Unit of the Central Research Laboratory of the College of Medicine, University of Lagos, due to the availability of prompt diagnostic technique, EVD was confirmed in Nigeria. These were the fulcrum of activities peculiar to Nigeria alone, leading to the rapid response to the outbreak. In Nigeria, it is worth noting that the decision of the index case to obtain medical care in a private instead of a government health facility and the on-going strike in the government health facilities during the outbreak might have limited further spread.\textsuperscript{[33]}

After that, the Federal Ministry of Health through the Nigeria Center for Disease Control (CDC), with the Lagos State Government and International partners; activated an Ebola Incident Management Centre as a precursor to an Emergency Operations Center (EOC) to rapidly respond to the outbreak.\textsuperscript{[32,33] The focal points of the control interventions were public awareness jingles/programmes, case isolation, PPE for healthcare workers, contact tracing and surveillance.\textsuperscript{[33]} The EOC had in membership professionals who had relevant expertise in the management of similar outbreaks, such as lassa fever, influenza, major lead poisoning and recent experience with polio eradication reporting to an incident manager, who in turn was responsible to deliver accountable results to the respective co-ordinating institutions as shown in Figure 3 below. The EOC also collaborated with the Nigeria public and international organisations such as WHO, doctors without borders, and the US CDC and prevention.\textsuperscript{[34]}

In all, Nigeria had 894 contacts identified and followed during the response and a case fatality rate of 40% - twenty cases of EVD and eight deaths, which included medical professionals whose heroics will never be forgotten by the country.\textsuperscript{[6,28,32]}

**PATHOGENESIS OF EBOOLA VIRUS DISEASE**

As aforementioned, Ebola virus is an extremely virulent pathogen that causes a highly lethal haemorrhagic fever syndrome in humans with preferential binding of Ebola virus glycoprotein (GP) to the endothelium.\textsuperscript{[35]} Specifically, GP facilitates the introduction of the virus into its early targets which are monocytes and the macrophages of the host immune system. Other target cells include dendritic cells, liver cells and endothelial cells.\textsuperscript{[36]}

While the pathogenicity of Ebola virus is principally an immune-pathogenic one, the cascade of destruction is elicited basically by four mechanisms namely: Cell entry and tissue damage, impairment of adaptive immunity, systemic inflammatory response and coagulation defects.\textsuperscript{[37-40]}

**LABORATORY DIAGNOSIS OF EBOOLA VIRUS**

The prompt and accurate diagnosis of EVD is paramount to the curtailing of an outbreak, because the virus is an acute viral syndrome which can mimic other infectious agents of acute onset.\textsuperscript{[41]} More so, the virulence and contagious nature of EVD makes rapid laboratory support more essential. This support is required to aid contact tracing, confirm for quarantine or discharge suspected cases, guide clinical decisions and facilitate the early detection of cases in people with an exposure history.\textsuperscript{[42]}

Specific laboratory testing for EVD include virus isolation, real time-polymerase chain reaction targeting viral nucleic acid, antigen-capture enzyme-linked immunosorbent assay (ELISA), antigen detection by immunostaining, and IgG- and IgM-IFA or ELISA using specific virus antigens.\textsuperscript{[43]} Diagnosis by detection of virus antigens is suitable for patients in the early stage of illness, while serological diagnosis by the detection of specific IgM and IgG antibodies is suitable for patients in recovery or relatively late stage of illness.\textsuperscript{[44]} Meanwhile, antigen detection by immune-histochemical analyses is a post-mortem histological techniques used for patients who die before an antibody response is mounted.\textsuperscript{[45]}

The laboratory diagnosis of EVD must be sensitive, specific, and reliable because misdiagnosis of the virus may bring huge turmoil to the society. This is of great importance as a false positive EVD result for an individual suggests isolation. This put such an individual at unnecessary risk of infection by the placement of the person in a high-risk environment such as an isolation ward. Furthermore, a false-negative result will allow persons who are infected with EVD to be unrestricted, denied access to isolation and prompt management. Such individual becomes highly contagious and cause person-to-person transmission of these virus in the community.\textsuperscript{[46]}

Our laboratory recently evaluated one of these kits and the result was rather promising and with minor modifications, the kit should soon be available for use. This Regional Directors
Team for EVD will definitely reduce the protracted delay in results of EVD suspected cases and ultimately curb the spread of EBOV in resource limited settings.

**Management of Ebola Virus Disease**

Currently, there is no proven virus-specific treatment or approved vaccine for EVD; as such supportive therapy is the mainstay of treatment for patients with symptomatic EVD, as it is evident that recovery from Ebola depends on good supportive care and the patient’s immune response.[26] Nigeria therefore depended on using known best practices for EVD management, which included screening with non-contact infrared thermometers, hand washing, the use of appropriate PPE, barrier nursing, restriction on corpse movement and proper burial methods for EVD victims.[32]

Despite the use of experimental drugs during the outbreak, which included monoclonal antibodies (ZMapp), the WHO, identified that the reason most patients in American and European hospitals survived was due to the use of intravenous fluids and other supportive therapy, along with adequate monitoring, control of blood chemistry and other parameters.[20] There is however hope for EVD management as researchers announced on 31st July, 2015 that a vaccine trial in Guinea had been completed that appeared to give protection from the virus. The vaccine is a recombinant replication-competent vesicular stomatitis virus-based vaccine, expressing a surface GP of Zaire Ebola virus (rVSV-ZEBOV). Results of an interim analysis of the trial show the vaccine to be highly efficacious, but more conclusive evidence is needed on its capacity to protect populations through herd immunity.

**Lessons Learnt**

Based on the success of Nigeria and other countries who were able to nip Ebola in the bud, here are four key lessons learnt from the outbreaks in West Africa:

1. Trace, isolate, and treat: Tracing all the people who could have caught the disease, isolating them so they can’t pass it on to others, and treating them quickly if they do develop symptoms
2. Detect early, before lots of people can be exposed: Prompt and early diagnosis and the faster the victim can be isolated was key to limit transmission of EBOV. Thus, strengthened laboratory facilities, health systems and skilled human resources were major contributor to EBOV containment
3. Strong leadership is essential. The most critical factor is leadership, engagement from the President (head of state), Minister of Health and national ownership of problems are key to effective management of outbreaks such as EVD
4. The public needs to be part of the solution information campaigns such house-by-house leafleting, messages on local radio stations, and enlisting ‘Nollywood’ stars to deliver health messages were crucial to stopping the disease.

**Conclusion**

The West African EVD Epidemic, 2014–2015 concentrated in the nations of Liberia, Guinea and Sierra Leone is the largest in history. This has made the requirement for specific therapeutic drugs and vaccine more than ever desirous. Till the development and approval of such specific therapy, it is important that the level of supportive care should be enhanced particularly in the affected countries in Africa.
is clear as documented in Nigeria, Europe and the USA, that early presentation of symptomatic EVD contacts and early commencement of supportive care is paramount for good prognosis.

As this may not be the last outbreak of EVD in Africa, there is need to focus on diagnostic and research capacity required to curtail EVD in sub Saharan Africa. Adequate measures for emergency preparedness and support for development for specific therapy and vaccine development should also be pursued rigorously. Finally, the gains of the outbreak, such as improved Port Health Services, public health activities in Nigeria, hand washing practices and burial practices should be strengthened and institutionalised.

**FINANCIAL SUPPORT AND SPONSORSHIP**

Nil.

**CONFLICTS OF INTEREST**

There are no conflicts of interest.

**REFERENCES**


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