REVIEW ARTICLE

Ebola Hemorrhagic Fever: Re-Emerging Infectious Disease

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Received: 21 June 2017/Revised: 23 August 2017/Accepted: 26 October 2017

ABSTRACT- Ebola can cause disease in humans and non-human primates like chimpanzees, gorillas, and monkeys). The spring of 2014 has brought a new calamity, the exotic infectious disease: Ebola Hemorrhagic Fever, which is caused by the highly contagious and pathogenic virus, transmitted directly from interpersonal contact or indirectly by common usage of the objects. The epidemic which occurred in Guinea tended to expand to neighboring countries; 83 deaths have been reported on April 1st 2014. Genetic analysis has revealed that the virus that causes this epidemic is similar in a proportion of 98% to Ebolavirus Zaire (EBOV) species that were responsible for the epidemic in the Democratic Republic of Congo, in 2008. The Ebola virus belongs to the Filoviridae family and genus Ebolavirus. Each species of the genus Ebola virus has one member virus, and four of these cause Ebola virus disease (EVD) in humans, a type of hemorrhagic fever having a very high case fatality rate up to 90% in humans. There are five identified Ebola virus species Bundibugyo Ebolavirus (BDBV), Ebolavirus Zaire (EBOV), Reston Ebolavirus (RESTV), Sudan Ebolavirus (SUDV), and Tai Forest Ebolavirus (TAFV). Ebola viruses are present in numerous African countries. The four of the five virus strains occur in an animal host native to Africa.

Key-words- Ebola Virus (EBOV), Ebola Virus Disease (EVD), Emerging Infectious Disease (EID), Viral Hemorrhagic Fevers (VHFs),

INTRODUCTION

Ebola, previously known as 'Ebola hemorrhagic fever', is a rare and deadly disease caused by infection with one of the Ebola virus species. Ebola can cause disease in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). Outbreak of Ebola virus in West Africa could be described as most severe public health emergency in modern times. Before the current situation, outbreaks have appeared sporadically in Africa. EVD (Ebola hemorrhagic fever) first appeared in 1976 with two concurrent outbreaks of acute viral hemorrhagic fever involving 284 cases (151 deaths [53%]) centered in Nzara, Sudan [1], and 318 cases (280 deaths [88%]) in Yambuku (near the Ebola River), Democratic Republic of Congo (DRC) [2]. Since these original cases, there have been approximately 20 other outbreaks occurring through until 2013, involving nearly 2500 cases in the Democratic Republic of Congo, Sudan, Gabon, Cote d'Ivoire, Uganda and the Republic of the Congo [3].

Access this article online	
Quick Response Code	Website: www.ijlssr.com
	DOI: 10.21276/ijlssr.2017.3.6.12

Ebola in India- Ebola is the new threat the world is currently fighting with no defense mechanisms. With the disease taking lives and the danger of it in India has been given many sleepless nights. On 18th November 2014, one of the headlines of 'The Times of India' was "India's first ebola patient has been quarantined". The 26-year-old man, travelling from Liberia to India is being isolated in a facility at Delhi's Indira Gandhi International airport. The infected male arrived at New Delhi airport from Liberia on November 10. He was admitted in a health facility in Liberia on September 11 and was discharged on September 30. Three blood samples from him were tested at National Centre for Disease Control (NDC), Delhi from November 10 to 13. Even as the blood tests were found to be negative for EVD, as has been reported in the past, the virus may continue to be positive in secretions like urine and semen for a longer time. His semen and urine samples were sent to NDC for reconfirmation tests. His semen sample tested positive for EBOV. The tests for semen samples were repeated at the National Institute of Virology, Pune, on Nov 17, 2014, which was also tested positive.

Ebola Virus (EBOV)- EBOV is zoonotic filovirus and belongs to the Filoviridae family, along with the genus *Marburg virus* comprised of envelope, non-segmented negative-stranded RNA. Up to now five species have

been identified: *Zaire ebolavirus*, *Bundibugyo ebolavirus*, *Tai Forest ebolavirus* (formerly known as Cote d'Ivore), *Sudan ebolavirus*, and *Reston ebolavirus* (found in the Western Pacific, highly pathogenic in nonhuman primates) [4,5]. The former three have been responsible for the large outbreaks that have occurred in Africa, whereas the Reston ebolavirus has been observed in animals in Asia but not as a cause of human disease [6]. The natural reservoir host of Ebola virus still remains unknown. However, on the basis of verification and the environment of similar viruses, researchers believe, the virus is animal-borne and that fruit bat bats are the most likely reservoir. Four of the five virus strains occur in an animal host native to Africa. Fruit bats of the *Pteropodidae* family, including the species *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*, are believed to be the natural hosts of Ebola viruses, with humans and other mammals serving as accidental hosts [7].

Table 1: Pathological Features of Hemorrhagic Fever Ebola virus

Agent	Major Pathologic Features
Ebola virus	Wide hepatocellular necrosis with intracytoplasmic viral inclusions Necrosis linking macrophages, parenchymal cells, and endothelial cells in main organs Follicular necrosis with necrotic debris in spleen as well as lymph nodes Apoptosis of lymphocytes along with lymphoid depletion Myocardial edema Microvascular infection as well as wound

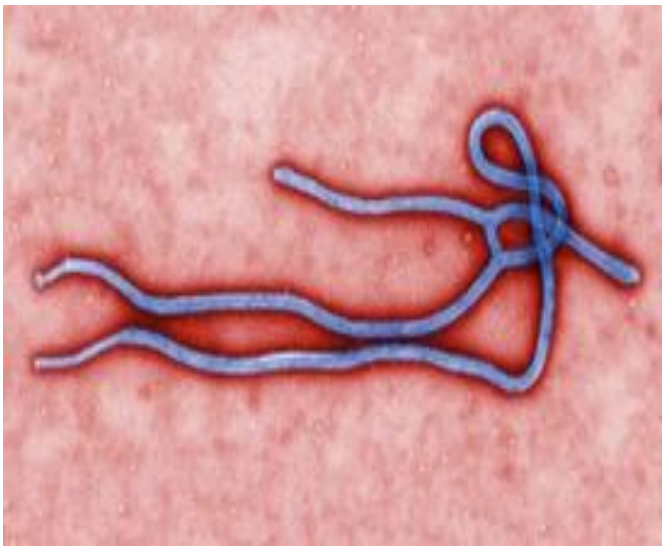

Fig. 1: Ebola Virus (Microscopic observation)
Source: https://vision-life-sl.de/en/facts-about-sierra-leone/

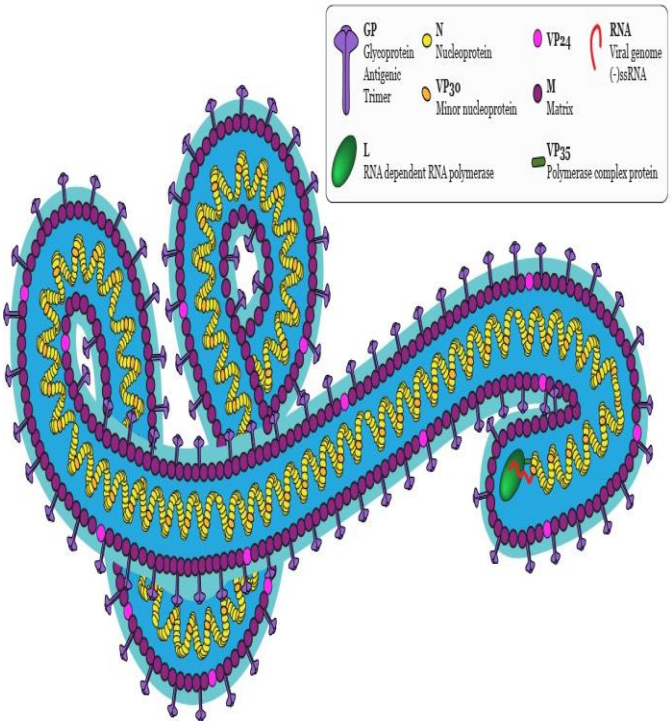

Fig. 2: Structure of a virion belonging to the genus Ebolvairus (An Ebola virus)
Source: https://www.nap.edu/read/18975/chapter/2

Viral Hemorrhagic Fevers (VHFs)- Viral hemorrhagic fevers (VHFs) are caused by four families of viruses (Bunyaviridae, Arenaviridae, Flaviviridae, and Filoviridae) with several genera and species causing illness (Table 2). All four viral families are single-stranded RNA viruses that have a lipid envelope, which makes them susceptible to detergents and environments with low pH; however, they are stable in blood and cold storage [8]. The four families of viruses are zoonoses, with reservoirs recognized for all species except for Ebola virus (EBOV). Fruit bats are assumed to be the reservoir, but only serological evidence and viral sequences of EBOV have been detected [9]. Are naviruses, Crimean-Congo hemorrhagic fever virus (CCHFV), and filoviruses can be transmitted from human to human by contact with blood and other body fluids, potentially expanding exposed individual cases into epidemic outbreaks, including the current EBOV disease outbreak in western Africa [10].

Special Pathogens Branch (SBP) divides viral hemorrhagic fever into following:

BSL-4 (Biosafety level 4) pathogen: Arenaviruses, Filoviruses, Buniaviruses

Non BSL-4 pathogen: Dengue hemorrhagic fever, Yellow fever

Table 2: Viral Families causing Viral Hemorrhagic Fever [11]

Virus Family	Disease (Virus)	Natural Distribution	Usual Source of Human Infection	Incubation (Days)
		Arenaviridae		
Arenavirus	Lassa fever	Africa	Rodent	5-16
	Argentine HF (Junin)	South America	Rodent	7-14
	Bolivian HF (Machupo)	South America	Rodent	9-15
	Brazilian HF (Sabia)	South America	Rodent	7-14
	Venezuelan HF (Guanarito)	South America	Rodent	7-14
		Bunyaviridae		
Phlebovirus	Rift Valley fever	Africa	Mosquito	2-5
Nairovirus	Crimean-Congo HF	Europe, Asia, Africa	Tick	3-12
Hantavirus	Hemorrhagic fever with renal syndrome, Hantavirus pulmonary syndrome	Asia, Europe, worldwide	Rodent	9-35
		Filoviridae		
Filovirus	Marburg and Ebola	Africa	Fruit bat	2-216
		Flaviviridae		
Flavivirus	Yellow fever	Tropical Africa, South America	Mosquito	3-6
	Dengue HF	Asia, Americas, Africa	Mosquito	Unknown for dengue HF, 5-7 for dengue

Epidemiology- On March 23, 2014, the World Health Organization (WHO) notified of an outbreak of EVD in Guinea [12]. The initial source of the recent outbreak appears to be a tiny village called Meliandou in southern Guinea where an index-case, a two-year old boy name Emille developed a hemorrhagic fever and died on 6th December 2013 [13]. Soon after that, the infection spread to Liberia and Sierra Leone. Outbreak of Ebola virus in West Africa could be described as most severe public health emergency in modern times. The number of potential cases ranges from thousands to millions with a high mortality rate.

According to Ebola situation report by WHO as of October 28, 2015. The Ebola virus disease (EVD) epidemic occurring in West Africa is unprecedented in its duration and scale, a total of 28,575 suspected, probable and confirmed cases, including 11,313 deaths had been reported [14].

WHO Ebola response roadmap situation report' reported the progression of the epidemic of EBOV after outbreak occurred in Nigeria. There were 20 cases found and 7 cases found in Mali. Four other countries (Senegal, Spain, the United Kingdom and the United States of America) also reported cases imported from West Africa [15-17]. WHO presented the data on 31st March 2015, after one year of outbreak, the total number of cases were in excess of 25,000 with over 10,000 deaths [18]. After all, on 14th Jan 2016, the previously infected countries had been declared Ebola-free.

Transmission- Transmission to humans required the contact with animal tissues or body fluids, including handling and ingestion of animal tissues, or ingestion of

plants or water contaminated with bats faces or bodily fluids [18]. A range of animal accidental hosts have been documented and Ebola virus has been implicated as one of the major causes of decline of African chimpanzee and gorilla populations in recent decades [19,20]. The ebola virus is transmitted to humans through close contact with blood and bodily fluids from another infected human or animal, either by direct contact or indirectly from a contaminated environment.

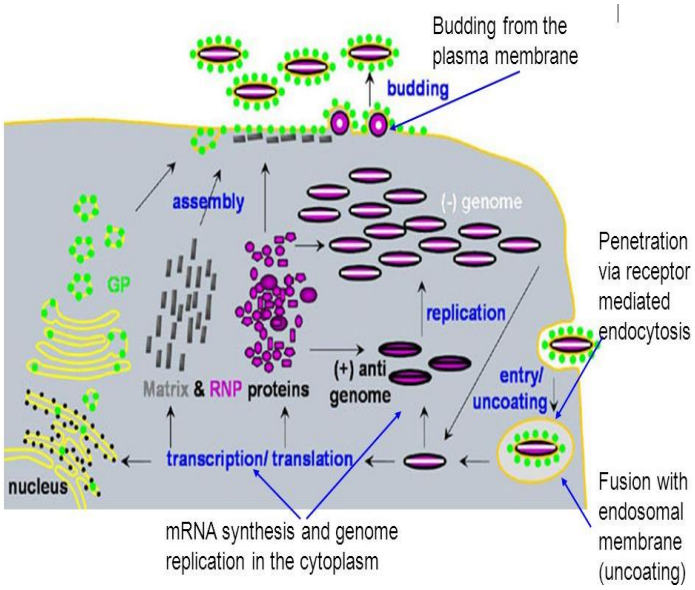

Fig. 3: Ebola virus replication cycle
Source: http://slideplayer.com/slide/8088359/

Clinical presentation- The incubation period for Ebola virus disease ranges from two to 21 days and is characterized by fever, headache, myalgias and gastrointestinal symptoms [3]. Multisystem involvement with hypotension and respiratory, kidney and liver failure may ensue, as well as internal and external bleeding [21]. In one detailed prospective assessment of 26 of 30 hospitalized patients with Ebola virus disease during the 2007-2008 Bundibugyo outbreaks, the median duration of symptoms was nine days from onset to death and 10 days from onset to discharge for survivors [22]. The most common symptoms will fever, nausea/vomiting and diarrhea, abdominal pain and conjunctivitis. The most common clinical features will severe headache, asthenia, myalgia, dysphagia, anorexia and diarrhea. Among the cohort of 26 cases, seven exhibited hemorrhagic features, which included melena, prolonged bleeding at injection sites, hematemesis, bleeding gums, hemoptysis, hematuria and postpartum vaginal bleeding [22]. In severe cases patients are developing hypovolemic shock and multi organ failure, including hepatic damage, kidney and respiratory failure. Seizures and coma can occur as well [4,23,24].

Pathogenesis- EBOV tropism toward antigen presenting cells (APCs) seems to play also an important role in viral pathogenesis [25]. The infected APCs fail to undergo maturation; as such they are unable to present viral antigens to naive lymphocytes. This is followed by massive loss of uninfected lymphocytes due to the bystander effect of which lymphocytes undergo massive apoptosis due to the apoptotic induction of inflammatory mediators or loss of support signals from dendritic cells [18,25,26]. After the infection virus is disseminated within the monocytes, macrophages, dendritic cells to the lymph nodes, and then by the blood to the spleen and liver [18,27]. EBOV entry, which includes an attachment and penetration into the cytoplasm, is mediated by the surface glycoprotein (GP) [5].

It was proved that patients who are able to develop antibodies within the second week of infection have cleared viremia and improved clinical symptoms. Progression of the disease is leading to the vasodilatation and increased vascular permeability, induction of extrinsic coagulation cascade and lymphocyte apoptosis [4,18,28].

Viral Diagnosis- For confirmation of a clinically suspected case of Ebola virus disease, we should perform NGS (new generation sequencing). However, because of the extreme biohazard risk, testing using antigen or antibody-based assays or reverse transcriptase polymerase chain reaction testing in a biosafety level 4 laboratories is required. To establish diagnosis viral RNA by PCR or viral antigen (i.e. NP, VP40 and GP) by immunoenzymatic methods (ELISA) should be detected in the blood or other body fluids. Rapid tests are available. Cell culture can be done in vero cell lines. It must be stressed that EBOV RNA can be detected 3 days after the infection. Laboratory findings include leukopenia, followed by leukocytosis and atypical lymphocytosis. Thrombocytopenia, as well as elevation of aminotransferases (AST & ALT) is a characteristic feature. Prolongation of the partial thromboplastin time and the international normalized ratio (INR) are common abnormality [4,18,24,27,28].

Treatment and Prophylaxis- Still Ebola has no specific treatment. There is also no therapeutics for the prevention or post exposure. Several experimental therapies are under development, but not fully tested in human. About 15 different vaccines were in preclinical stages of development, including DNA vaccines, virus-like particles and viral vectors [29]. However, FDA has approved some experimental treatments for emergency use in patients with Ebola infection [30]. One of them is brincidofovir oral nucleotide analog, which is modified version of cidofovir. In vitro data suggest its activity against Ebola and recently FDA approved it for Phase 2 study [30].

Another antiviral drug favipiravir [30]. TKM Ebola and AVI 6002 are molecules used for blocking of viral replication genes via gene silencing. These drugs have shown effects against EVD in animal model [29]. Z Map is another experimental treatment for EVD. It contains three monoclonal antibodies. Oral fluid replacement with rehydration solutions is preferred [31]. Giving that Ebola is highly contagious through direct contact with bodily fluids, contaminated objects and possibility of its aerosol route of infection isn't definitely excluded it is crucial to

reduce the risk of human-to-human transmission. Isolation of the infected patients, protective clothes and equipment, control protocols, proper waste and sample management are essential to protect medical personnel and prevent spreading of the infection.

Preventive measurement to be taken Ebola in Healthcare providers- During an outbreak, healthcare providers take specific preventive measures to protect themselves and others in the affected areas, called standard and other addition precautions. Risks for Healthcare providers involved in health care and epidemic response to EVD include psychological distress, stigma, violence, long working hours, heat stress and dehydration from using heavy PPE and ergonomic problems from handling bodies and loads. These require specific measures for psychosocial support, security and work organization.

Healthcare providers at all levels of the health system- hospitals, clinics, laboratories, health posts, laundries, transport should be brief and must be trained in infection control and adhere to the universal infection control standard guidelines to facilitate prevention and precaution. All staff handling suspected or confirmed cases of EVD or contaminated specimens and materials should use special personal protective equipment for working with biohazards, and apply hand hygiene measures according to WHO recommendations. If the recommended level of precaution is implemented, transmission of disease should be prevented.

Following these evidences based guidelines are imperative for the stoppage of an outbreak:

- Identify, Isolate, Inform- According to CDC, if someone is suspected of Ebola, the healthcare provider should place the patient in a room with the door closed and call the local health department and does not advise families or communities to care for individuals
- Personal Protective Equipment (PPE)- PPE is all the stuff that healthcare providers put on to protect themselves. PPE consists of the powdered air purifying respirator (PAPR) or high-filtration mask (n95 respirator), fluid resistant medical mask, apron and boots, coveralls with single-use disposable hoods and full-face shields (instead of goggles) and single use disposable nitrile gloves with extended cuffs
- Follow good hygiene
- Clean and maintain work surfaces
- Dispose properly of human remains and medical waste

CONCLUSIONS

The ebola virus disease has mostly affected countries deprived economically as limited resources. We summarized this review with the emphasis on the epidemiology, transmission, clinical manifestations, pathogenesis, diagnosis, prevention and treatment. Ebola vaccine available is critical for global preparedness and Merck's VSV-EBOV vaccine is on path to filing licensure applications. The increasing pressure to alleviate patients' suffering has triggered the use of drug repurposing in the treatment of viral hemorrhagic fevers, and screening programs leading to the discovery of potential drugs have emerged, however, a systematic assessment of the current evidence is warranted to justify their use in specific treatment. The public healthcare system in developing countries must prepare strategies, holding the available resources in mind, to deal with the outbreak before it occurs.

FUTURE PROSPECT

Rapid and wide geographic spread of the EBOV outbreak, the initial non-specific presentation of EVD, high-risk exposure and lack of an effective treatment, WHO declared the EBOV epidemic an international crisis. Recent advances in field testing have made assays for VHF available to those in endemic areas but still require capital investment, highly trained personnel, and advanced technology from outside nations. Future advancements in diagnostic testing may occur as a result of biomarkers or other host signatures that can predict active disease. These approaches will ultimately lead to faster contact tracing and containment of disease outbreaks.

In India, there are lots of scientific and technical capabilities. Infrastructure in the areas of technology, computational biology, bio-informatics, molecular biology, genomics are excellent for research. According to WHO, India has done very well in terms of polio eradication. In the last few years or decades, global pandemics like MERS, SARS, avian influenza, swine flu, Zika and Ebola diseases are becoming global. We can't guess what's going to emerge and from where? We should take the necessary steps now to better prepare and educate ourselves and families from the sequela of such events and provide effective treatment for those whom we will provide care during this and subsequent epidemics

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How to cite this article:
Rai A, Siddiqui AH, Singh S, Negi C, Parveen S: Ebola Hemorrhagic Fever: Re-Emerging Infectious Disease. Int. J. Life Sci. Scienti. Res., 2017; 3(6):1500-1505. DOI:10.21276/ijlssr.2017.3.6.12
Source of Financial Support: Nil, **Conflict of interest:** Nil

