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A Review- Widespread epidemic of Ebola virus disease throughout the world

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Abstract

Ebola virus disease (formerly called Ebola Hemorrhagic Fever) caused by Ebola virus of the family Flaviviridae, is a severe and fatal disease in humans and primates. First outbreak occurred in Democratic Republic of the Congo (formerly Zaire) and then in several African countries. Compared to the cumulative sum of past cases in 36 years (1976-2012), 2,232 infected people and 1,503 deaths counted which is now over ten times the total number infections and over six times the total number of deaths. One of the reasons that why Ebola is so dangerous is that its symptoms are varied and appear quickly, which resembles to that of hemorrhagic fever and not rapidly diagnosed. Ebola Virus Disease (EVD) can be transmitted between humans through direct contact with bodily fluids (e.g., blood, sweat) from an infected person or sharing contaminated objects. The vaccines cAd3-ZEBOV and rVSV has proved to an extent against primates but human beings are still the subject under consideration.

Keywords: Aedes mosquito, Ebola virus disease, Ebola hemorrhagic fever, epidemic,World.

Introduction

Delwart (2016) stated that viruses inhabit in and around us, are distributed widely may be sometimes harmless to us but certain viruses may underlie mysterious, and causes unexplained diseases. Knowing how these newly discovered viruses affect humans will determine whether they are to be prevented and treated. Researchers can now identify viruses using metagenomic analysis achieved easily by comparing the genetic information from next-generation sequencing of clinical samples to that of the viruses whose complete genome is known. These small sized organism called viruses infect all branches of life, like humans, plants, and bacteria.

Shears (2015) summarized that the virus was first appeared in the Democratic Republic of the Congo (formerly Zaire) in the summer of 1976. Since the first outbreaks in Sudan and Zaire occurred many years ago, transmission health facilities affected the healthcare workers and acted as amplifiers which have spread this disease into the community level. Thippeswamy (2015) continued by noting that that several African countries, including Sierra Leone, Guinea, and Liberia also reported the outbreak of Ebola viruses in the year 2014.

The years from 1976 to 2014, Equatorial Africa verified twenty-four epidemics of Ebola virus disease (EVD). Although the number of cases reported were very small but it has received the attention throughout the world higher death rate (approximately 50-90% due to multi-organ

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failure) were noticed during this period due to Ebola virus infection (Shears, 2015; Karunakar et al., 2013).

According to Johnson and Breman (1978) Ebola virus was isolated from the patients in both epidemics and named Ebola virus after a small river situated in north western area of Zaire. The 2014 Ebola Virus Disease outbreak in West Africa caused by Zaire Ebola Virus (ZEBOV) which was the longest, largest, deadliest, and the most complex viral infection in the history. It was due to fact that in February 2015, there were 22,859 Ebola Virus Disease cases and a total of 9,162 deaths reported (Shears, 2015; Krejcova et al., 2015; WHO, 2014[a]). Gostin and Friedman (2015) found that this outbreak in West Africa has been affected more to the community due to weak health care systems and prior has no experience with Ebola infection.

Generally, the sudden onset of symptoms follows an incubation period of 2-21 days and is characterized by high fever, usually higher than 38°C. The major symptoms of infection indicates multisystem involvement; gastrointestinal disorders such as nausea, vomiting, diarrhea, respiratory indicators like (chest pain, cough) and neurological manifestations. These symptoms are sometimes falsely mistaken with malaria, typhoid fever, dysentery, influenza or various bacterial infections. After these initial symptoms, the fever often progresses to cause more serious symptoms bleeding from mucous membranes results in vomiting blood, coughing blood or the presence of blood in the stool. Some of the patients rarely showed bleeding into the whites of the eyes. Internal and external hemorrhage from orifices, such as the nose, mouth and anus may also occur. Progression of the virus, can lead to bleeding in the brain which may cause severe depression in the patient (CDC, 2010). Whereas aerosol infection has not been reported clinically, despite it has been demonstrated in experimental infection in monkeys (Peters and LeDuc, 1999; CDC, 2014[a]).

Epidemiology of Ebola Virus Disease

The disease typically occurs in outbreaks in tropical regions of Sub-Saharan Africa. From 1976 (when it was first identified) to 2013, the World Health Organization reported 1,716 confirmed cases. The largest outbreak to date was occurred in 2014 in West Africa due to Ebola virus that affected the regions Guinea, Sierra Leone, Liberia, Mali, and Nigeria. As of 18 January 2015, 21,724 suspected cases and 8,641 deaths had been reported (CDC, 2014[e]).

Sudan outbreak

The data presented by Peterson et al. (2004) reveals that the first known outbreak of EVD was identified between June and November, 1976 in Nzara, South Sudan, and was caused by Sudan virus (SUDV). The Sudan outbreak infected 284 people and killed 151. The first identifiable case in Sudan occurred on 27 June in a storekeeper working in a cotton factory in Nzara, who was hospitalized on 30 June and died on 6 July.

Zaire outbreak

A second outbreak of EVD began in Yambuku, a small rural village in Mongala District in northern Zaire on 26 August, 1976. This outbreak was caused by EBOV, formerly designated Zaire Ebola virus, which is a different member of the genus Ebola virus than in the first Sudan outbreak (WHO

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1978[b]). The second major outbreak occurred in Zaire (now the Democratic Republic of the Congo) in 1995, affected 315 and killed 254 people. In 2000, Uganda had an outbreak that has affected 425 people and killed 224; in this case the Sudan virus was found to be the Ebola species responsible for the outbreak (WHO, 2014[a]).

In the Republic of the Congo (2003) an outbreak was noticed that has affected 143 and killed 128, a death rate of 90 percent, the highest death rate of a genus Ebola virus outbreak to till date. In 2004 a Russian scientist died from Ebola after sticking herself with an infected needle. Between April and August 2007, a fever epidemic in a four-village region of the Democratic Republic of the Congo was confirmed in September to have cases of Ebola (NewScientist, 2007).

The WHO reports two small outbreaks in Uganda in 2012. The first outbreak affected 7 people and resulted in the death of 4 and the second outbreak affected 24, resulted in the death of 17. The Sudan variant was responsible for both outbreaks. On 17 August 2012, the Ministry of Health of the Democratic Republic of the Congo reported an outbreak of the Ebola-Bundibugyo variant in the eastern region (Thippeswamy, 2015).

West African outbreak from 2013 to 2015

In March 2014, the WHO reported a major Ebola outbreak in Guinea, a western African nation. Researchers traced out the infection of Ebola in a two-year old child who died in December 2013. Then it was noticed that the disease rapidly spreads to the neighboring countries such as Liberia and Sierra Leone. It was the largest Ebola outbreak that has ever documented (Baize et al., 2014).

As of 23 September, in the three hardest hit countries, Liberia, Sierra Leone and Guinea, only 893 treatment beds were available even though the current need was 2122 beds. According to the statement given by WHO (2014[c])- "The Ebola epidemic ravaging parts of West Africa is the most severe acute public health emergency seen in modern times. As of 18 January 2015, 21,724 suspected cases and 8,641 deaths had been reported; however, the WHO has said that these numbers may be vastly underestimated (WHO, 2014[d]).

Classification

Ebola virus, formerly designated Zaire Ebola virus coming under five known viruses within the genus Ebola virus, family Filoviridae, and order Mononegavirales (CDC, 2014[b]). Tiaji (2014) discussed that in the order Mononegavirales, Filovirus outbreak is considered as one of the most fatal viral diseases distributed worldwide in the host (humans and primates). Therefore, EBOV is now ranked as category A agent according to CDC and level 4 pathogen (Bio-safety) as far as bioterrorism is concerned.

Types of Ebola Virus-

Ebola Virus Disease in human is caused by four out of five viruses of the genus Ebola Virus. The four viruses are Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV) and Ebola virus (EBOV, formerly Zaire Ebola virus) of which EBOV is the most dangerous, and is responsible for the largest number of outbreaks. The fifth virus, Reston virus (RESTV), is not thought to cause disease in humans, but it may be virulent to other primates (Hoenen et al., 2012; Kuhn et al., 2010).

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1. Ebola virus or Zaire Ebola Virus

As suggested by Johnson et al., (1977) it is the most fatal disease causing virus and the highest fatality rate may reach up to 90% in most epidemic areas infected with Ebola Virus Disease (EVD). It causes severe hemorrhagic fever in humans and the symptoms of Zaire Ebola virus resemble to that of malaria patients; sometimes treated with quinine.

2. Sudan virus (SUDV)

This virus also caused threatened effect among the people in Nzara, Sudan, when first case was reported in a worker exposed to a potential natural reservoir working in cotton factory (WHO 1978[a]).

3. Tai Forest virus (TAFV) or Ivory Coast Ebola Virus

Kuhn et al. (2010) referred that the Tai Forest virus is also known as Ivory Coast Ebola virus and Tai Ebola virus which was first discovered among chimpanzees from the Tai Forest in Cote d Ivoire, Africa. The source of contamination was thought to be the meat of infected Western Red Colobus monkeys, upon which the chimpanzees preyed.

4. Bundibugyo virus (BDBV)

Smith et al., (1982) stated that this virus is a close relative of Ebola virus (EBOV) and the name of the virus Bundibugyo was given after the first case was discovered from the town of Ugandan, Bundibugyo District.

5. Reston virus (RESTV)

Barrette et al. (2009) explained that it is non pathogenic to humans but sometimes hazardous in monkeys. Reston Ebola virus disease was found in primates and also in peoples with reproductive and respiratory disease syndrome. Changula et al. (2014) discussed that Ebola Hemorrhagic Fever (EHF) typically appears in sporadic outbreaks coinciding with the rainy season, and is usually spread in humans within a poor health-care setting.

Virology

Klenk and Feldmann (2004) stated that the genome of Ebola virus consists of a linear, negative-sense single stranded RNA of the family. The tubular Ebola virions are generally 80 nm in diameter and 14000 nm in length. Ebola Virus Genome may be cylindrical or tubular, and contains viral envelope, matrix, and nucleocapsid components. The overall tubular structure has a virally encoded glycoprotein (GP) projects as 7-10 nm long spikes from its lipid bilayer surface.

Bagherani et al., (2015) add on to this by stating that Ebola virus expands its gene function by forming more proteins. About nine proteins have been known to be translated, which includes glycoprotein (GP), soluble glycoprotein (sGP), small soluble glycoprotein (ssGP), nucleoprotein (NP), the polymerase cofactor viral protein (VP35), the major matrix protein (VP40), transcription activator (VP30), the minor matrix protein (VP24), and viral RNA-dependent RNA polymerase (L).

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GP, the surface glycoprotein inserted into the viral membrane which plays a vital role during the entry of the virus into the host cell by binding to its receptor and fuses with the cell membrane.

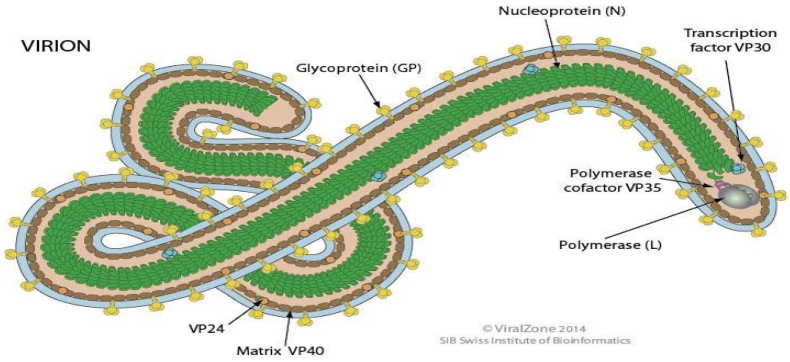

Figure 1: Structure of Ebola Virus (Microbiologyinfo, 2014).

The genome of Ebola virus consists of 18,959 nucleotides with seven Open Reading Frames (ORFs). The 3′ terminal end is neither polyadenylated nor the 5′ terminal end is capped. This viral genome codes for seven structural proteins and one non-structural protein. The gene order is 3′ – leader – NP – VP35 – VP40 – GP/sGP – VP30 – VP24 – L – trailer – 5′. The leader and trailer are non-transcribed regions, which carry important signals to control transcription, replication, and packaging of the viral genomes into new virions (Taylor et al., 2010 & 2014; Belyi et al., 2010).

Figure 2: Genome structure of Ebola Virus (Wikipedia, 2016)

Pathogenesis

Chertow et al. (2014) found that the pathology of Ebola Virus (EBOV) is not yet completely understood. But most of the studies suggest that the variation in the incubation period depends upon the type of exposure (i.e. six days for pre-cutaneous infection and ten days for contact exposure). The WHO reported that the mean incubation period is 11.4 days while the symptoms usually may appear in approximately 8-10 days.

The transfer of Ebola Virus (EBOV) from an animal to a human usually occurs through small cutaneous lesions. The early symptomatic stage is usually between 4-10 days where symptoms of a viral illness appear which is gradually progress with hemorrhagic fever, impaired immunity, and organ failure. (Gebretadik et al., 2015) Sanchez et al. (2001) explored that the Ebola virus replicates at an unusually high rate that overwhelms the protein synthesis apparatus of infected cells and host immune defenses.

As the adaptive immune and inflammatory systems both simultaneously responds against infection, some cell types specially the monocytes and macrophages, are targets relevant to disease pathogenesis. This feature of the infection was initially suggested by the immunohistochemical localization of Ebola virus in vivo in the endothelial cells, mononuclear

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phagocytes, and hepatocytes which are the main targets of infection (Baskerville et al., 1978; Baskerville et al., 1985; Zaki et al., 1999).

Clinical Symptoms

Karunakar et al. (2013) explored that the symptoms usually begin with a sudden flu-like symptoms; like quickly on-coming fever, mayopathy, and headache, which are soon followed by bloody vomit and diarrhea, nausea and vomiting, anorexia (loss of appetite), body weakness, abdominal pain, arthralgia (neurologic pain in joints), back pain, mucosal redness of the oral cavity, dysphasia (difficult in swallowing), conjunctivitis and rashes on the body.

Chertow et al. (2014) focused on the early symptoms of EVD with high fever (temperature up to 40°C), malaise, fatigue, and body aches. The fever persists, by 3 to 5 days of illness; gastrointestinal symptoms typically begin, with epigastric pain, nausea, vomiting, and diarrhea.

According to Woldu et al. (2014) after some days of infection (five to seven days) the first symptoms can begin to bleed through the eyes, nose, or mouth. Hemorrhagic rashes are also reported in some patients on their whole body followed by muscle pain and enlargement of the pharynx. In the case history of West Africa during the current outbreak showed symptoms in maximum patients: fever (87%), fatigue (76%), vomiting (68%), diarrhea (66%), and loss of appetite (65%). Unexplained bleeding has been reported from only 18% of patients, most often blood in the stool (about 6%).

Transmission

The natural reservoir for Ebola virus has not been identified until today. However, fruit bats are considered to the most likely to spread Ebola virus species. There are three types of fruit bats (Hypsignathus monstrous, Epomops franqueti and Myonycteris torquata) were found to be possibly the carrier of Ebola virus without causing any sickness in them as stated by Thippeswamy (2015).

Leroy et al. (2005) add on this by stating that the bats show no clinical signs of disease, which is considered the evidence that these bats are the reservoir species of Ebola Virus (EBOV). In a survey which was conducted in the year 2002-2003, among 1,030 animals 679 bats from Gabon and the Republic of the Congo and 13 fruit bats showed the presence of Ebola Virus (EBOV). Apart from bats, other wild animals sometimes infected with Ebola Virus includes, several monkey species, chimpanzees, gorillas, baboons and duikers (Public Health Agency of Canada, 2018).

The Body fluids such as saliva, mucus, vomit, feces, sweat, tears, breast milk, urine and semen may contain Ebola virus and is mode to spread disease from one person to another. Entry of the virus may includes the nose, mouth, eyes, open wounds, cuts and abrasions. Contact with surfaces or objects contaminated by the virus, particularly needles and syringes, may also transmit the infection (WHO, 2014[b]).

It was reported by CDC (2015) that the human being infected with Ebola virus may retain virus for up to 8 weeks in the semen after they have recovered, which may transmit virus during sexual intercourse, breast feeding females to their child, dead bodies of the infected person (Chan,

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2014), health–care workers engaged in treating the infected persons (Tiaji, 2014). Weingartl et al. (2012) offers that air borne transmission may also occur from pigs to primates.

The risk of infection increases when these workers do not have appropriate protective clothing such as masks, gowns, gloves and eye protectant glasses. This risk is particularly common in parts of Africa where health systems function poorly and where the disease mostly occurs. Hospital-acquired transmission has also occurred in some African countries resulted, due to the reuse of needles (Lashley and Durham, 2007; Magill et al., 2013).

Diagnosis

When Ebola Virus Disease (EBD) is suspected in a person, their travel history, exposure to wildlife, any family history are considered as some of the important factors for further diagnosis.

1. **Non specific laboratory testing**

Thippeswamy (2015) reported that the patients infected with Ebola virus showed possible laboratory indicators such as low platelets count, higher level of the liver enzymes alanine-aminotransferase (ALT) and aspartate aminotransferase (AST). The other indices are low level of WBC count initially followed by higher WBC count, abnormal blood clotting mechanism (bleeding period, partial or prolonged prothrombin time period) with disseminated intravascular coagulation (DIC).

2. **Specific laboratory testing**

Goeijenbier et al. (2014) conclude that the diagnosis of EVD after preliminary test may be confirmed by isolation of virus, its culture, viral RNA detection by PCR, and protein detection by enzyme-linked immunosorbent assay (ELISA) are most widely used techniques. The antibody detection from blood against EBOV is the most reliable method to detect its presence in late stages of disease and in those who has recovered. IgM antibodies are detectable two days after symptom onset and IgG antibodies can be detected 6 to18 days after symptom onset.

3. **Differential Diagnosis**

As indicated by Bagherani et al. (2015) early symptoms sometimes resemble other tropical infectious diseases like influenza, malaria, typhoid fever, meningococcal septicemia and various forms of encephalitis, leptospirosis, relapsing fever, anthrax, typhus, non typhoidal salmonellosis, Dengue fever, Chikungunya fever, yellow fever, Lassa fever, Marburg fever, fulminant viral hepatitis, which are also prevalent in these countries. Confusing noninfectious syndromes with hemorrhage such as acute leukemia, lupus erythematous, idiopathic thrombocytopenic purpura, and hemolytic uremic syndrome also fall into the differential diagnosis

Treatment

Woldu et al. (2014) conclude that there is no approved treatment available for Ebola Virus Disease (EVD). Instead, some vaccines are based on relatively new approaches that have been made possible with the advancement of molecular biology and recombinant genetic technologies introduced during the last 10-20 years (Jocelyn, 2014; Hampton, 2014). The first vaccine is cAd3-ZEBOV developed by GlaxoSmithKline and tested by the US National Institute of Allergy and

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Infectious Diseases (NIAID). The second is the rVSV tested by the New Link Genetics Corporation after being licensed from the Public Health Agency of Canada. Both vaccines demonstrated promising rates of efficacy in primates, but the translation of these results to human subjects has not yet been accomplished (Cheepsattayakorn and Cheepsattayakorn 2015; West, 2014).
Clinical management focus on supportive care of complications, such as hypovolemia, electrolyte abnormalities, hematologic abnormalities, refractory shock, hypoxia, hemorrhage, septic shock, multi-organ failure may be monitored. Kalra et al. (2014) reported that many experiments were conducted to achieve antiviral therapies against EBOV during the 2014 outbreak in West Africa. Although, the efficacy of antiviral are still not clear but in current status it is the active area. In addition, the availability of these drugs is limited.

West (2014) added to this by stating that there are no approved medications for the treatment of Ebola virus disease or for post-exposure prophylaxis in persons who have been exposed to the virus but have not yet become ill.

Prevention

Protective equipments and clothing should be used by the person who is handling the cases of Ebola virus patients. In 2014, the CDC began recommending that medical personal protective equipment (PPE); in addition, a designated person should appropriately trained in biosafety.

Strict infection control measures and the proper use of personal protective equipment are essential to prevent further transmission to healthcare workers. The patients suffering from EBV should be monitored regularly and the person nearby infected person or exposed to infection should be kept in surveillance for early detection and diagnosis of a disease. This virus can be eliminated if heated for 30-60 minutes at 60°C or boiled for 5 minutes. To disinfect surfaces, some lipid solvents such as some alcohol-based products, detergents, sodium-hypochlorite (bleach) or calcium hypochlorite (bleaching powder), and other suitable disinfectants may be used at appropriate concentrations (Ethiopian Public Health Institute, 2014; Peters, 1998; Baron et al., 1983). Certain burial rituals, which may have included making various direct contacts with a dead body, require redevelopment such that they maintain a proper protective barrier between the dead body and the living (CDC, 1998).

Isolation is a mode of barrier which isolates or separates the infected person from non infected person. Quarantine refers to separating those individuals which have already been exposed to a disease but either not showing any sign of the disease from the community. During the 2014 Ebola disease outbreak, schools in Liberia was closed (CDC, 2014[c] ; Lewis, 2014).

Kortepeter et al., (2011) and CDC (2014[d]) reported that breastfeeding and infant care should be needed as Ebola Virus can be transmitted by close contact of an infected mother to a child. Jamieson et al. (2014) presented a fact that during pregnancy, strict infection control precautions must be used while caring the pregnant women to protect them from Ebola Virus diseases because there is a high risk for foetal death and pregnancy associated hemorrhage.

As it was earlier discussed that virus present in certain body fluids (e.g. urine, semen, vaginal secretions, and breast-milk) even if virus undetectable in the blood diagnosis. Therefore, Kilmarx

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et al. (2014) showed that the risk of secondary transmission to EBOV is still a threat to the population.

Conclusion

Ebola virus is classified as a biosafety level 4 agent, as well as a Category A bioterrorism agent by the Centers for Disease Control and Prevention according to MacNeil and Rollin (2012). Salvaggio and Baddley (2004) considered that it has the potential to be weaponized for use in biological warfare, and were investigated by Bio preparat (which was the biological warfare agency of Soviet Union) for such use, but might be difficult to prepare as a weapon of mass destruction because the virus becomes ineffective quickly in open air (Geoffrey 2013).

EBOV is a highly pathogenic virus that has caused an increasing number of outbreaks in Central Africa with largest outbreak ever documented in 2014. Because of its high fatality rate and potential use as a bioweapon, it is very important to understand its mechanisms of pathogenesis and, ultimately, to develop vaccines and therapeutics. Although there are currently no approved vaccines or treatments for EHF, but rNAPc2 and at least two recombinant virus vaccine approaches have shown promise in the NHP model (Thippeswamy, 2015).

These alliances, termed by WHO as "Surveillance" are defined as the "the systematic ongoing collection, careful examination and analysis of data for public health purposes and the timely dissemination of public health information for assessment and public health response as necessary" as given in International Health Regulation, 2005 (Harrison, 2017).

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