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Ebola Virus Disease: A Biological and Epidemiological Perspective of a Virulent Virus

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Abstract

Understanding factors for the re-emergence of Ebola viral disease (EVD), its pathogenesis as well as understanding the biology of Ebola virus in its natural reservoir is one of the most difficult scientific problems facing scientists today. Knowledge gaps exist for this disease that is yet to be fully understood. The virus is endemic in the sub-Saharan Africa where it causes major as well as minor epidemics. Mitigation strategies have not been well understood because of the easy transmission of disease among humans. There are no approved drugs for treatment while vaccines are being tested for human safety. Studying and understanding the pathogen has proved to be a difficult phenomenon because it's virulent form needs level IV biosafety laboratories that are difficult to access in many developing as well as some developed countries. This review aims at discussing the biology, epidemiology, risk factors as well as the pathogenesis of the disease in the hope demystifying the disease.

Keywords: Ebola virus; Ebola viral disease; Epidemiology; Pathogenesis; Risk factors

Introduction

The Ebola virus belongs to the family Filoviridae, genus Ebola virus, the virus is in circulation in the sub-Saharan Africa where it causes large outbreaks of the Ebola viral disease (EVD) that results to Ebola haemorrhagic fever (EHF) in its terminal stages. The fatality rates of this disease are very high due to its fast transmission modes as well as fast pathogenesis [1]. The virus' natural reservoir is unknown although there has been a suspicion of pteropodidae bats being the natural carriers [2]. According to the world health organization, the average fatality rate due to EVD is 50% though figures have kept on varying from 25% to 90% since the Ebola cases were first reported.

Ebola disease is acute, serious and often fatal if no treatment and preventive measures are put in place. The first emergence of the disease was when it appeared simultaneously in Sudan and the Democratic Republic Congo in 1976. Its name "Ebola" was derived from the river Ebola in the Democratic Republic of Congo around which the virus occurred [3].

The virus genome is non-segmented, negative-sense with single-stranded RNA resembling the rhabdoviruses and the paramyxoviruses in genome organization as well as replication mechanisms. The family name Filoviridae is taken from the Latin word "filum," that means thread-like. The virus has a filamentous structure. The haemorrhage due to the disease occurs in a small percentage of Ebola patients when they are in the terminal phase of the disease and in shock [4,5].

Ebola genus is subdivided into five species i.e., Zaire, Ivory Coast, Sudan, Reston and Bundibugyo [6]. Four species have been known to cause disease in humans:

i.) The Zaire virus that was first reported in the year 1976 has been causing large EVD outbreaks in Central Africa with fatality rates being reported at being from 55% to 88%. The Ebola epidemic of the year 2014-2015 in West Africa was caused by this species [7-10].

ii.) The Sudan virus whose first and second epidemics were reported in 1970s, the third epidemic occurred in Uganda in the year 2000 with the fourth and last one to be reported happening in Sudan again in the year 2004. The fatality rates have been documented as being at 50% for the four epidemics [11-15].

iii.) The Ivory Coast virus has only caused an illness in one person who ended up surviving [16].

iv.) The Bundibugyo virus whose first emergence was in 2007 in Uganda. This virus had a lower fatality rate of 30%. The genomic sequences reveal that the virus has close relations with the Ivory Coast species [17].

The Reston virus is maintained in an animal reservoir in Philippines and has not been reported in Africa. This species first caused an outbreak in macaques that were imported in the United States in the year 1989 [18,19]. The latest reports of Reston virus were reported in pigs in 200820.

Reservoir of Ebola virus

Identification of the natural reservoirs of Ebola virus has remained a major challenge. This challenge has proved to be an obstacle when it comes to devising ways to treat and prevent viral transmission to humans. Ebola viral sequences have been detected in fruit bat samples of the family pteropodidae collected from Central Africa [21,22]. Documented data suggests that these bats may be among the natural reservoirs of the virus in Africa [23].

Transmission and Risk Factors for Transmission

Risk factors for transmission

The risk of infection with Ebola virus is associated with three behaviours which are, close contact with an infected person in the later stages of infection; caring for a person with an Ebola infection or when preparing the deceased for a decent burial. There is no risk of infection with asymptomatic persons as well as a very low risk of infection during the incubation period and a low risk of infection during the first week of symptomatic illness. The high risk of transmission in funerals occurs when one touches the body of a diseased person [24].

Visiting and caring for Ebola cases in hospitals raises transmission risks during major outbreaks [25-28]. This can be attributed to higher viral loads during the periods when the disease is severe as well as inadequate protection measures. However, earlier hospitalization with long hospital stays with sufficient isolation and protective measures can reduce the duration and burden of Ebola outbreak [29].

The Ebola ecological niche can impact on some risk factors for infection such as occupation [30]. The large secondary to primary case ratios in outbreaks negates any chance of ecological niches having a greater influence on calculated risk ratios though [31].

Adulthood increases the risk of disease. Risk of illness does not depend on total viral loads. The higher risk associated with adulthood is because adults are primarily carers thus would be inclined to take care of those infected with EVD [28].

The risks of transmission to family members is higher in those who take care of their loved ones until death and much higher if care is being done at home [25]. Risks of infection are also high among healthcare workers taking care of the sick, in laboratories due to accidents or due to contact with wildlife [25].

Contacts with wildlife are important in Ebola epidemiology as outbreaks are almost always linked to wild animals. However, due to lack of enough data on contacts with wildlife that do not result in to disease, it is difficult calculate the risk of disease due to contact [24].

The risk of transmission is high if contact with fluids from an infected person whose developed signs and symptoms occur through broken skin surfaces or unprotected mucous membranes. The world health organization reckons that blood, feces and vomit are the most infectious body fluids [36-38].

Transmission

Transmission from animals: It is alleged that fruit bats of the family Pteropodidae are the natural hosts of Ebola virus. In the human population, Ebola is introduced through close contact with secretions, blood, organs or other body fluids of infected wildlife such as gorillas, chimpanzees, fruit bats, antelopes, monkeys and porcupines that may be dead or ill in rainforests [3]. There can be accidental infection of laboratory workers in any Biosafety Level 4 facilities where the Ebola virus is being studied or if the virus is used as a biological weapon by terror groups [32,33].

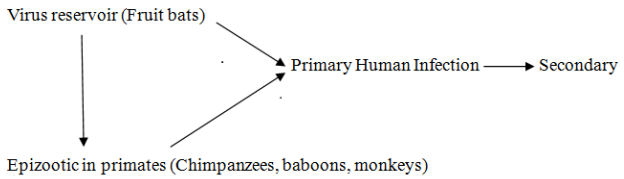

Figure 1: Hypothesis of Ebola virus transmission at the human-animal interface.

Human to human transmission: Human to human transmission is connected to direct contact with individuals who are symptomatic of the Ebola disease or contact with those who've died from the disease. Transmission also occurs via direct contact with body fluids from those who are infected with the disease [34-36]. Infection has a direct correlation with the type of body fluid as well as the viral amount in the fluid.

Among the infectious fluids include semen, urine, vaginal fluid, saliva, breast milk, aqueous humor, blood, vomit and feces. Through Reverse-transcriptase polymerase chain reaction, viral RNA has also been identified in tears and sweat. The RNA can persist in these fluids even when the virus is no longer detectable in the body [39-42].

Transmission through direct skin-skin contact is possible even though the risk of developing infection is lower than fluid contact [36]. Ebola virus on the skin surface might be due to viral replication in dermal and epidermal structures and/or contamination with blood or other body fluids. Contact with contaminated surfaces can result to viral transmission. The Centres for Disease Control (CDC) indicate that the virus on different surfaces can remain infectious from hours to days [43,44].

Viral pathogenesis: Data on disease pathogenesis has been obtained from laboratory studies that employ nonhuman primates such as monkeys, baboons and other animals such as mice. The West African outbreak of 2014-2015 has also provided data on disease pathogenesis through case reports and large scale observational studies [41,45].

Entry into the body is through the mucous membranes, breaks on the skin surface or through mother to child (parenteral infection). Different cell types are infected by the virus especially the macrophages and dendritic cells where replication is done leading to cell necrosis [5,46]. The virus the spreads systematically by suppressing type I interferon responses. It spreads to the lymph nodes where they replicate further. The virus enters the bloodstream then enters the dendritic cells, macrophages in the liver, spleen, thymus as well as other lymphoid tissues. Other cell types such as endothelial cells, hepatocytes, fibroblasts, adrenal cortical cells, and epithelial cells can also be infected. Fatal infection occurs when there is a multifocal necrosis in tissues like the spleen and the liver [47].

Patients then suffer from vomiting and diarrhoea that can result in acute volume depletion, hypotension as well as shock. The gastrointestinal dysfunction has yet to be tied to a direct result of viral infection of the gastrointestinal tract or whether it is because of circulating cytokines [1,48,49]. Infection with the virus then induces systemic inflammatory syndrome by initiating the release of chemokines, cytokines and other proinflammatory mediators from cells such as macrophages and others [5,46].

Tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, macrophage chemotactic protein (MCP)-1, and nitric oxide (NO) are then released from infected macrophages50. The coagulation defects in Ebola virus disease are induced through the host inflammatory response. Viral infected macrophages synthesize cell surface tissue factor (TF), prompting the extrinsic coagulation pathway, proinflammatory cytokines also induce macrophages to produce TF51. The two stimuli explain the rapid development and severity of coagulopathy in Ebola virus infection. D-dimers are also seen in Ebola infected monkeys within 24 hours after infection.

The impaired dendritic cell functions as well as T lymphocyte apoptosis in infected individuals result in the impairment of adaptive immunity resulting to the onset of fatal illness [4].

Ebola infection disables antigen-specific immune responses. Replication majorly occurs in dendritic cells which are responsible for initiating adaptive immune responses. In vitro studies show that infected cells fail to undergo maturation and thus are unable to present antigens to naive lymphocytes, potentially explaining why patients dying from Ebola virus disease may not develop antibodies to the virus [5,14,51,52]. Adaptive immunity is impaired by the viral infection due to apoptosis induced by inflammatory mediators and loss of support signals from dendritic cells. This phenomenon occurs in septic shock too.

Epidemiology of Ebola viral disease

The 2013–2015 epidemic of EVD in Western Africa was the largest and most widespread to date and case fatalities far exceed the total from all previous EVD emergences. This outbreak was caused by the Zaire species of Ebola and it was the first in urban settings with high population densities where sustained transmission occurred. Previous outbreaks were majorly due to nosocomial transmissions of the disease and risks associated with funeral practices.

The large size of the 2013–2015 epidemic was unmatched by adequate clinical capacity resulting in community based care rather than hospitalization of cases [53].

Three Ebola virus species are responsible for the Ebola outbreaks in sub-Saharan Africa: EBOV, Sudan ebolavirus and Bundibugyo ebolavirus. Epidemics have happened in the Democratic Republic of Congo, Sudan, Gabon, Republic of Congo, and Uganda [54,55].

The first recognition of Ebola virus was when two concurrent outbreaks occurred in Zaire and Sudan in 19761. An epidemic due to the Zaire species resulted in several hundred cases in 1995 in Kikwit, DRC, while the Sudan virus infected over 400 people in Gulu, Uganda in 2000. The Ebola virus is not restricted to humans and it has been known to spread to wild nonhuman primates because of their contact with unidentified reservoirs. This has led to reduction by death of some primates such as Chimpanzees and Gorillas in Central Africa. Human epidemics have also occurred due to handling of these sick or dead animals in search for food [56-60].

The 2014-2015 Ebola outbreak in West Africa

The biggest Ebola epidemic thus far. This epidemic began in Guinea in late 2013 and was confirmed by WHO in March 2014. The first case of the outbreak was a 2-year-old child who died in Meliandou in Guéckédou prefecture on December 6, 2013 after developing fever, vomiting, and black stools without haemorrhage [10,61]. Due to person-person contact, the virus spread to other West African countries such as Liberia, Sierra Leone, Nigeria, Senegal and finally Mali [62-65].

According to WHO, about 28,500 cases attributed to Ebola have been identified, with over 11,000 deaths. Among them were 881 healthcare workers who had also been infected with about 60% of them dying. In countries where transmission was limited such as Nigeria and Senegal, the disease was eliminated early while in areas where there was widespread transmission, the disease slowed significantly in 2015 [66].

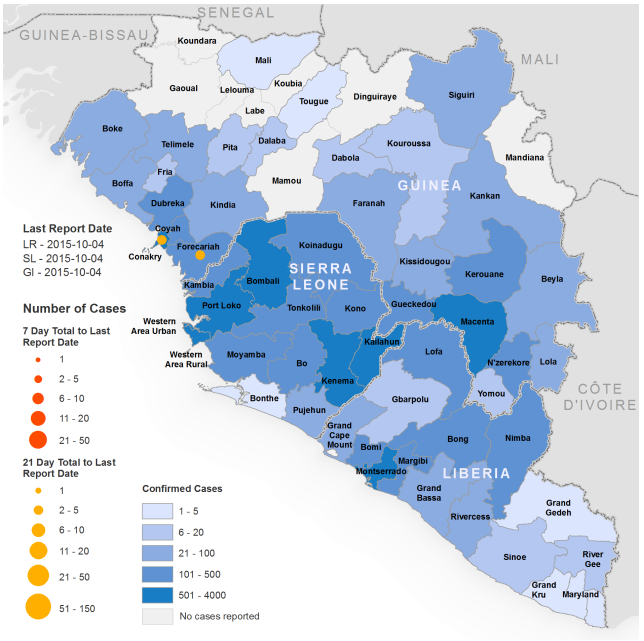

Figure 2: Major West African countries affected by the Ebola viral disease. Adapted from http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html

In August of 2014, an outbreak of Ebola virus disease was reported in the Democratic Republic of the Congo. As of November 11, 2014, a total of 66 cases of Ebola virus disease (confirmed and probable), including 49 deaths, had been connected to this outbreak [67-69].

Clinical symptoms and diagnosis of Ebola virus disease

The time interval from infection with the Ebola virus to the onset of symptoms is 2 to 21 days but the average is 8-10 days. Humans are infectious only when they've developed symptoms. The first symptoms are the sudden onset of fever, fatigue, weakness, muscle pain, severe headache and sore throat. These are then followed by vomiting, diarrhoea, rash, abdominal pain, symptoms of impaired kidney and liver function and unexplained haemorrhage. Laboratory tests find low white blood cell and platelet counts as well as elevated liver enzyme levels [70,71].

Distinguishing Ebola Virus Disease from other infectious diseases like malaria, typhoid fever and meningitis is difficult. According to WHO, confirmation of Ebola virus infection is done using; antibody-capture enzyme-linked immunosorbent assay (ELISA), antigen-capture detection tests, serum neutralization test, reverse transcriptase

polymerase chain reaction (RT-PCR) assay, electron microscopy and virus isolation by cell culture [70].

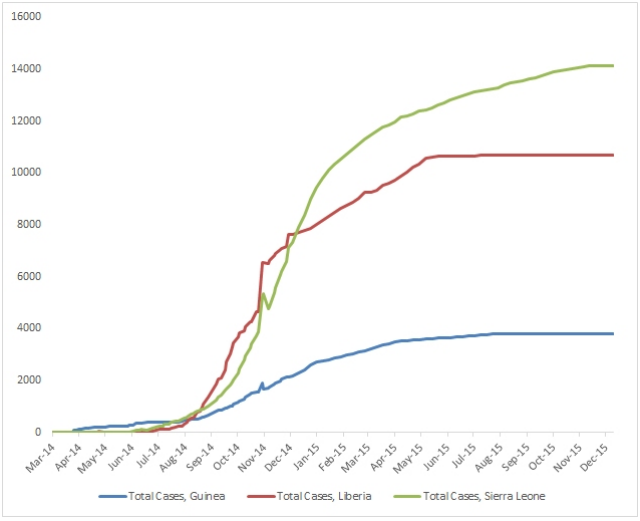

Figure 3: Timeline of Ebola infection In Guinea, Liberia and Sierra Leone. Adapted from http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/index.html

Treatment and vaccines

There is no approved treatment available for Ebola Virus Disease. A range of treatments including immune therapies, blood products and drug therapies are being evaluated. Supportive care rehydration with oral or intravenous fluids and treatment of specific symptoms increases the chances of survival. No licensed vaccines are available yet, but 2 potential ones are undergoing human safety tests [70].

Prevention and control

Prevention and control strategies rely on employing different interventions in case management, surveillance and contact follow-up, provision of good laboratory services as well as safe burials. For the control of outbreaks, there should be community engagement and training to increase awareness on disease risk factors. Primary infection can be controlled by handling animals with gloves and other suitable protective clothing. Animal products for consumption should be well cooked.

Secondary transmission from direct contact with people with Ebola symptoms can be controlled by wearing gloves as well as protective equipment during patient care. Hands should be washed regularly after patient care. Reducing the risk of sexual transmission involves abstinence from sex for men and women who've recovered from Ebola disease; if not possible, protective measures such as condom use should be recommended.

Healthcare workers should mind hand hygiene, respiratory hygiene, use of protective equipment and safe injection practices. Train laboratory staff on proper handling of samples collected for Ebola investigative tests.

In conclusion, the risk of Ebola infections primarily follows from only close personal contact when symptoms have manifested. Patient care is risky especially in domestic settings. There should be more studies to correlate the contexts, timing as well as the intimacy of contacts after disease onset. Due to the severe nature of the disease, preventive and control strategies should be placed in endemic areas, especially sub-Saharan Africa as treatment options are sought.

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