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Editorial Open Access

Re-Emergence of Zaire Ebola Virus Disease: Lessons to be Learnt

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Editorial

Ebola virus disease or Ebola hemorrhagic fever is a zoonotic disease with a very high fatality rate affecting humans and other primates. Symptoms starts after 8-10 day of incubation that include fever, headache, vomiting, diarrhoea, rash and people may begin to bleed both within the body and externally. Fruit bats are initially responsible for spread of infection or virus may be acquired through body fluids of an infected animal. Once human infection occurs virus may spread between people. Since Ebola virus infection is highly contagious in nature with high mortality rate it is listed highest priority of biological weapon agents and recommended to handle in biosafety level 4 laboratories.

Outbreaks between 1976 and 2013 caused by viruses of the genera Ebolavirus represent a major public health issue in sub-Saharan Africa, with a case fatality rate depending on the virus species is 30 to 90%. Till date World Health Organization reported 1716 confirmed cases of Ebola virus disease starting from the first identified case of 26th Aug 1976 near Ebola River valley in Zaire (now known as Democratic Republic of Congo) through 2013. Poor health infrastructure, socio-economic and illiteracy in Africa facilitate the spread of the disease from human to human. Most of the epidemics have occurred in the Democratic Republic of Congo, Sudan, Gabon, Republic of Congo and Uganda. Out of five *Ebolavirus* species, three have caused large outbreaks in sub-Saharan Africa: Sudan *Ebolavirus, Bundibugyo Ebolavirus* and one called simply Ebola virus formerly known as Zaire *Ebolavirus*. Ebola virus is the only member of Zaire Ebola virus species, the most dangerous of known EVD causing viruses and is responsible for largest number of out breaks. Reston *Ebolavirus* caused disease in nonhuman primates but not in humans and circulates in the Philippines. The fifth species, Tai Forest *Ebolavirus* was reported to involve a single human infection in Ivory Coast caused by the contact with an infected chimpanzee from the Tai forest. Ebola virus is RNA virus, belongs to order Mononegi virales, family filovoviridae. The five Ebola viruses are closely related to Marburg virus, another genus of filoviridae causing similar hemorrhagic fever with comparative less fatality (30%).

On March 10, 2014, hospitals and public health services (Ministry of Health of Guinea) was reported about a mysterious disease characterized by fever, severe diarrhoea, vomiting and also progresses to bleeding phase with an apparent high fatality rate. For epidemiologic investigations and virology analysis blood samples were collected and sent to the biosafety level 4 laboratories in Lyon, France and Hamburg, Germany. As of April 10th 2014, WHO declared as is the largest ever documented EVD outbreak affecting Guinea, Liberia and Sierra Leone. On 8th Aug, 2014 the WHO declared the epidemic as an international public health emergency as countries that affected do not have capacity to manage outbreak of this size and requested international community to provide support on the most urgent basis possible. Researchers traced the outbreak originated from the two year child who died on 6th Dec 2013 followed by the death of relatives and medical attendee. As of 15th August 2014 WHO reported 2127 suspected cases which has taken 1145 lives. WHO reported17th Sept (Wedenesdaydeath toll in West Africa Ebola epidemic is 2,630 and 5762The EBOV in samples obtained from three patients of recent outbreak was completely sequenced and all three sequences of 18,959 nucleotides in length were found identical with the exception of a few polymorphisms at positions. The present Guinean EBOV strain showed 97% identity to EBOV strains isolated from the Democratic Republic of Congo and Gabon earlier.

The virus is a filamentous negative sense single stranded RNA virus with genome size of 19kb. In general Ebola virions are 80 nm in width but length may vary in the range of 976 to 1086 nm that may appear in shape of U or 6 shaped and may be coiled, toroid or branched. The genome of Ebola virus is continuous (non-segmented) and contain seven structural genes, namely, NP (nucleoprotein or nuclear capsid protein), VP35 (virion protein 35 or polymerase complex), VP40 (virion protein 40 or matrix protein), Gp/sGP (glycoprotein or trans membrane/secretory protein), VP30 (virion protein 30 or transcription regulatory protein), VP24 (virion protein 24 or matrix associated of unknown function) and L (RNA dependent RNA polymerase) with UTR sequences at both 3' and 5' ends. The genes at 3' end of the genome are transcribed in a greater abundance compared with the genes located at 5' end. Viral RNA polymerase binds to the single promoter located at the 3' end of the genome which transcribed viral RNA into positive strand mRNA that then this translated into structural and non-structural proteins.

In a study, fruit bats were found to contain Ebola viral RNA fragments and considered as natural reservoir as there are no signs of Ebola infection reported in bats. As such no link of transmission of virus between natural reservoir and human is established, however outbreaks from handling of carcass of gorilla, chimpanzee or duiker are reported. Eating of fruit bats by the people in West Africa may be considered another reason for eruption of the outbreak. High lethality in gorillas and chimpanzees from Ebola virus infection is the reason to not consider them as natural reservoir. In Sub-Saharan region comprises of world's poorest countries and majority of the population depend on bush meat that make them vulnerable to repeated outbreaks.Poor health care infrastructure fans the spread of disease from human to human.

The primary target of Ebola virus is cells of lymphoid tissues including dendritic cells, monocytes and epithelial cells. However, after initiation of infection in the host the virus can infect all type cells expressing NPC C1 protein. The virus enters into the cytoplasm of host cell through macropinocytosis. Entry of the virus occurs in two phases, at both the phases involving interaction of GP protein of the virus with host receptors. Multiple targets for binding of GP protein on cell

surfaced was found such as intigrins, lectins and TAM. GP1, 2 protein cleaved by cathepsin B and L at the glycosylation rich region GP1 exposing receptor binding domain. Receptor binding site interact with NPC C1 on macropinosome leading to release of viral content into the cytoplasm.The Ebola infection is fast acting, and highly replicating coupled with disturbing host protein synthesis. The rapid multiplication of virus outperforms the cellular protection mechanism leading initial failure of humored immunity to contain infection. The virus releases a secretory form of GP out of the infected cell in abundance which due to epitope cross reactivity to full GP competes to bind with neutralizing anti bodies leading to failed immune response. The same reason is the leading concern in developing vaccine against *Ebolavirus* infection.

On the basis of the preliminary signs and symptoms it is not possible to differentially diagnose the disease by the clinicians as symptoms may be similar to other viral, bacterial and protozoan diseases. For confirmatory diagnosis the most common methods therefore are real-time PCR and detection of viral protein using ELISA. These tests can be carried out in mobile hospitals and virus isolation during the outbreak is not feasible.

There is no FDA approved therapy available for either pre- or post-exposure or vaccine exists for the infection of Ebola Virus. The rapid progression of Ebola virus infection provides little opportunity to develop acquired immunity. Symptomatic supportive care can be given to the individuals including rehydration and supplementing with coagulation factors. The *Ebolavirus* pose high risk of nosocomial transmission and hence biohazard to health care's workers and doctors. Various studies on protection against EBOV infection in non-human primates with monoclonal antibodies and Si RNA against NP and VP40 proteins showed encouraging results. However, very recently an American doctor and his assistant who acquired the infection was given the experimental drug containing monoclonal antibodies against three Ebola virus proteins and both of them recovered from the infection. On 6th August in the meeting of WHO it has recommended that a controlled treatment with experimental drug may be permitted in humans with learned consent as humanitarian crisis over looming over ethics of experimental drug use limited to 2014 Ebola outbreak only. Extreme personal protection is required while handling the infected patients, and contaminated material. WHO and Centers for Disease Control and Prevention, USA recommended personal protection protocol after the recent outbreak includes full impermeable suite (Single use), N95 particulate filter max, impermeable boots, gloves and protective goggles. Minimum handling of the infected patient is recommended and patient care by the relatives may be totally avoided except in case of children with full protection. Frequent hand hygiene with detergent or alcohol based solutions is paramount to protect against infection in health care workers. The virus can be easily get destroyed by 70% alcohol , 0.05% sodium hypochlorite solution, bleaching powder or solution containing 500 ppm chlorine and contaminated materials need to be treated with above solution before disposal. If available incineration of contaminated materials such as clothes, cotton swabs soiled with body fluids should be done. Funeral of dead bodies with confirmed or suspected *Ebolavirus* infection should be strictly adhered to personal protection protocol, un-protected handling of dead bodies must be avoided.

EVD in the Context of Bioterrorism

Viral hemorrhagic fever had been recognized as potential biological weapons long before the terrorist attacks in USA on September 11th, 2001 and the subsequent anthrax cases. VHF viruses have been included in Category A agents list by the Centers for Diseases Control and Prevention of USA. The Working Group in Civilian Biodefense in the USA listed key characteristics of biological agents, that include a. high morbidity and mortality; b. person-to-person transmission; c. highly infectious potential of aerosol dissemination, and can cause large outbreaks; d. vaccine unavailable; e. availability of agent; f. ease of production; g. environmental stability and i. prior research and development as a biological weapon along with potential to cause anxiety in health care worker and public at large. A number of VHFs exhibit these characteristics and pose a serious risk to be used as biological weapons. VHFs list include Ebola, Marburg viruses, Lassa fever, New World arena viruses, Rift Valley fever, yellow fever, Omsk hemorrhagic fever and Kyasanur Forest disease. The absence of an effective antiviral therapy and vaccines makes these viruses too dangerous as biological weapon. The deliberate release of such agents either overt or covert could cause a wide spread illness and death, in any case the release will not be apparent until the first cases is identified. However, the illness due to deliberate release of infectious agents may be more severe and involve larger numbers than the natural outbreak, if the agent has been aerosolized. Several studies revealed Ebola, Marburg, Lassa and Junin viruses could produce lethal infections in non-human primates when administered by aerosol preparations. Recent deadliest outbreak could have been averted if the programme for the development of effective antivirals and vaccine initiated after identification of virus during the initial outbreaks. Effort at the international level should be made to develop vaccine against across the hemorrhagic causing viruses to effectively counter bio-threat.