

Review Article

A Comprehensive review of Ebola Virus Disease & It's futurism in India

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ABSTRACT

Ebola virus disease (EVD) formerly known as Ebola haemorrhagic fever is a severe fatal illness caused by infection with Ebola virus. Ebola virus disease first identified in 1976 in 2 simultaneous outbreaks, one in Nzara, Sudan, and the other in Yambuku, Democratic Republic of Congo, in a village near the Ebola River, from which the disease takes its name. The natural reservoir host of Ebola viruses has not yet been identified, however fruit bats are considered primary source of infection by spillover events. Ebola virus enters the patient through broken skin, mucous membranes or parenterally. EVD symptoms can appear from 2 to 21 days post exposure and are characterized by the sudden onset of fever, intense weakness, muscle pain, fatigue, severe headache, sore throat, diarrhoea, vomiting, abdominal pain and unexplained haemorrhage. No FDA-approved vaccine or medicine is available for Ebola. Management is based on symptomatology by providing intravenous fluids, electrolyte balancing, vitals monitoring and treating other infections. Several vaccines are being developed and the two most advanced vaccines identified based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and recombinant chimpanzee adenovirus expressing an Ebola virus protein (ChAd-EBOV) - are currently being tested in humans for safety and efficacy and trials were started. Scientists are working on variety of vaccines and antiviral drugs for Ebola viruses till then prevention of disease spreading by public awareness and community engagement are keys to control the outbreaks of Ebola virus disease.

Keywords: Ebola virus disease (EVD), Ebola virus protein (VSV-EBOV), Phospho-morpholino oligonucleotides (PMOs), Bundibugyo virus (BDBV)

INTRODUCTION

Ebola virus disease (EVD) formerly known as Ebola haemorrhagic fever is a acute severe, often-fatal illness in humans and nonhuman primates (monkeys, gorillas, and chimpanzees). The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks. Ebola virus is a RNA virus of Filoviridae family. EVD in humans is caused by four of five viruses of the genus Ebolavirus. The four are Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV) and Zaire Ebola virus (EBOV). The fifth, Ebola-Reston, has caused disease in nonhuman primates, but not in humans. EBOV, species Zaire Ebola virus, is the most dangerous of the known EVD-causing viruses, and is responsible for the largest number of outbreaks. The exact origin, locations, and natural reservoir of Ebola virus remain unknown.

The EBOV genome is a single-stranded RNA approximately 19,000 nucleotides long. It encodes

seven structural proteins: nucleoprotein (NP), polymerase cofactor (VP35), (VP40), GP, transcription activator (VP30), VP24, and RNA polymerase (L) [1]. Ebola virus virions are filamentous particles that may appear in the shape of a shepherd's crook, of a "U" or of a "6," and they may be coiled, toroid or branched with 80 nanometers (nm) in width and may be as long as 14,000 nm.

Figure 1: Electron micrograph of an Ebola virus virion



EPIDEMIOLOGY

Ebola virus disease (EVD) first appeared in 1976 in 2 simultaneous outbreaks, one in Nzara, Sudan, and the other in Yambuku, Democratic Republic of

Congo with a case fatality rate of 88%. The latter occurred in a village near the Ebola River, from which the disease takes its name [2]. EVD outbreaks occur intermittently in tropical regions of sub-Saharan Africa between 1976 and 2013, the World Health Organization reports a total of 24 outbreaks involving 1,716 cases. The largest outbreak is the ongoing epidemic in West Africa with onset in early February 2014, still affecting Guinea and Sierra Leone. It has also spread between countries starting in Guinea then spreading across land borders to Sierra Leone and Liberia, by air (1 traveller) to Nigeria and USA (1 traveller), and by land to Senegal (1 traveller) and Mali (2 travellers). As of 24 May 2015, this outbreak has 27,049 reported cases resulting in 11,149 deaths. The first cases were reported from the forested region of south-eastern Guinea near the border with Liberia and Sierra Leone. The Ebola viral aetiology was confirmed on 22 March 2014 by the National Reference Centre for Viral Haemorrhagic Fevers (Institute Pasteur, INSERM BSL4 laboratory, Lyon, France). Sequencing of part of the outbreak virus L- gene has shown that it is 98% homologous with an EBOV last reported in 2009 in Kasai-Occidental Province of the Democratic Republic of Congo. This Ebola virus species has been associated with a high case-fatality during previous outbreaks. Cases have been reported from Conakry, Guéckédou, Macenta, Kissidougou, and from Dabola and Djingaraye prefectures. On 8 August 2014, the WHO Director-General declared the West Africa outbreak a Public Health Emergency of International Concern under the International Health Regulations (2005) [3]. This is the largest outbreak of Ebola Virus Disease (EVD) ever documented and the first recorded in West Africa. The death rate in some Ebola outbreaks can be as high as 90%, but in this outbreak it is currently around 55%—60%.

SOURCE

The natural reservoir for Ebola has yet to be confirmed however fruit bats of the Pteropodidae family are considered natural reservoir for Ebola virus. Three types of fruit bats *Hypsignathus monstrosus*, *Epomops franqueti* and *Myonycteris torquata* were found to possibly carry the virus without getting sick. As a result, the geographic distribution of Ebola viruses may overlap with the range of the fruit bats [4].

Although non-human primates have been a source of infection for humans, they are not thought to be the reservoir, but are an accidental host like human beings. Ebola is introduced into the human population through close contact with the blood,

secretions, organs or other bodily fluids of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rainforest. Traces of EBOV were detected in the carcasses of gorillas and chimpanzees during outbreaks in 2001 and 2003, which later became the source of human infections.

TRANSMISSION

Ebola is introduced into the human population through close contact with the blood, secretions, organs, or other bodily fluids of infected animals. Body fluids that may contain Ebola viruses include saliva, mucus, vomitus, feces, sweat, tears, breast milk, urine and semen. According to WHO only people who are very sick are able to spread Ebola disease in saliva, and whole virus has not been reported to be transmitted through sweat. Most people spread the virus through blood, faeces and vomitus. Entry points for the virus include the nose, mouth, eyes, open wounds, cuts and abrasions. Ebola may be spread through large droplets; however, this is believed to occur only when a person is very sick. This can happen if a person is splashed with droplets. Contact with surfaces or objects contaminated by the virus, particularly needles and syringes, may also transmit the infection. The virus is able to survive on objects for a few hours in a dried state, and can survive for a few days within body fluids. The Ebola virus may be able to persist for more than 3 months in the semen after recovery, which could lead to infections via sexual intercourse. Ebola may also occur in the breast milk of women after recovery, and it is not known when it is safe to breastfeed again. There is no evidence of live Ebola virus in vaginal secretions [5].

Ebola then spreads in the community through human-to-human transmission, with infection resulting from direct contact through broken skin or mucous membranes with the blood, secretions, organs, or other body fluids of infected, symptomatic persons, and indirect contact with environments contaminated with such fluids. Transmission does not occur during the incubation period and only occurs once an infected person presents with symptoms. Burial ceremonies in which mourners have direct contact with the body of the deceased person can also play a role in the transmission of Ebola.

Healthcare providers caring for Ebola patients and family and friends in close contact with Ebola patients are at the highest risk of getting sick because they may come in contact with infected blood or body fluids.

During outbreaks of Ebola, the disease can spread quickly within healthcare settings (such as a clinic or hospital). Exposure to Ebola can occur in healthcare settings where hospital staffs are not wearing appropriate personal protective equipment.

Ebola is not spread through the air, by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bush meat (wild animals hunted for food) and contact with infected bats. There is no evidence that mosquitoes or other insects can transmit Ebola virus [6].

LIFE CYCLE & PATHOGENESIS

Ebola virus enters the patient through broken skin, mucous membranes or parenterally and infects many cell types, including monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells and epithelial cells. Macrophages are the first cells infected with the virus, and this infection results in apoptosis. The incubation period may be related to the infection route from 2 to 21 days. Although not infected by Ebola virus, lymphocytes undergo apoptosis resulting in decreased lymphocyte counts. This contributes to the weakened immune response seen in those infected with EBOV. Ebola virus migrates from the initial infection site to regional lymph nodes and subsequently to the liver, spleen and adrenal gland. Viral replication triggers the release of high levels of inflammatory chemical signals and leads to a septic state [7]. Hepatocellular necrosis occurs and is associated with dysregulation of clotting factors and subsequent coagulopathy. Adrenocortical necrosis also can be found and is associated with hypotension and impaired steroid synthesis. Endothelial cells may be infected within 3 days after exposure to the virus. The dysfunction in bleeding and clotting commonly seen in EVD has been attributed to increased activation of the extrinsic pathway of the coagulation cascade due to excessive tissue factor production by macrophages and monocytes. Ebola virus appears to trigger a release of pro-inflammatory cytokines with subsequent vascular leak and impairment of clotting ultimately resulting in multi-organ failure and shock. Ebola viral infection also interferes with proper functioning of the innate immune system [8].

REPLICATION

Viruses use the machinery and metabolism of a host cell for replication and they assemble in the cell. The virus attaches to host cell by specific surface receptors such as C-type lectins, DC-SIGN, or integrins, which is followed by fusion of the viral

envelope with cellular membranes. The virions endocytosed into macropinosomes in the host cell then travel to acidic endosomes and lysosomes where the viral envelope glycoprotein GP is cleaved. This processing appears to allow the virus to bind to cellular proteins enabling it to fuse with internal cellular membranes and nucleocapsid is released into the cytoplasm [9]. Encapsidated, negative-sense genomic ssRNA is used as a template for the synthesis (3' →5') of polyadenylated, monocistronic mRNAs. Using the host cell's machinery translation of the mRNA into viral proteins occurs. Viral proteins are processed, glycoprotein precursor (GPO) is cleaved to GP1 and GP2, which are heavily glycosylated. These two molecules assemble, first into heterodimers, and then into trimers to give the surface peplomers. Secreted glycoprotein (sGP) precursor is cleaved to sGP and delta peptide, both of which are released from the cell. As viral protein levels rise, a switch occurs from translation to replication. Using the negative-sense genomic RNA as a template, a complementary +ssRNA is synthesized; this is then used as a template for the synthesis of new genomic (-)ssRNA, which is rapidly encapsidated. Newly synthesized structural proteins and genomes self-assemble and accumulate near the inside of the cell membrane. Virions bud off from the cell, gaining their envelopes from the cellular membrane from which they bud from. The mature progeny particles then infect other cells to repeat the cycle [10].

SIGNS AND SYMPTOMS

The incubation period, that is, the time interval from infection with the virus to onset of symptoms is 2 to 21 days but the average is 8 to 10 days. Symptoms usually begins with influenza like stage characterized by sudden onset of high grade fever, intense weakness, decrease appetite, fatigue, muscle pain, headache and sore throat, This is followed by vomiting, diarrhoea, abdominal pain, shortness of breath, chest pain, confusion, maculopapular rash, impaired kidney and liver function, and in some cases, both internal bleeding (hematemesis, hemoptysis, malena) and external petechiae, purpura, ecchymoses or hematomas[11]. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes. Humans are not infectious until they develop symptoms. People are infectious as long as their blood and secretions contain the virus. Recovery from Ebola depends on good supportive clinical care and the patient's immune response. People who recover from Ebola infection develop antibodies that last for at least 10 years. Recovery may begin between 7 and 14 days after first

symptoms. Death, if it occurs, follows typically 6 to 16 days from first symptoms and is often due to low blood pressure from fluid loss. Bleeding often indicates a worse outcome, and blood loss may result in death [12].

EXPOSURE RISK LEVELS

Table 1: Levels of risk of transmission of Ebola virus according to type of contact with an infected patient

Risk level	Type of contact
Very low or no recognized risk	Casual contact with a feverish, ambulant, self-caring patient, Examples: sharing a sitting area or public transportation; receptionist tasks.
Low risk	Close face-to-face contact with a feverish and ambulant patient. Example: physical examination, measuring temperature and blood pressures
Moderate risk	Close face-to-face contact without appropriate personal protective equipment (including eye protection) with a patient who is coughing or vomiting, has nosebleeds or who has diarrhoea.
High risk	Percutaneous, needle stick or mucosal exposure to virus-contaminated blood, bodily fluids, tissues or laboratory specimens in severely ill or known positive patients

DIAGNOSIS

It is difficult to diagnose EVD in prodromal phase because the early symptoms are not specific and often seen in patients with more commonly occurring diseases, such as malaria, meningitis and typhoid fever. If a person has symptoms of Ebola and had history of exposure with blood or body fluids of a person sick with Ebola or with objects that have been contaminated with blood or body fluids of a person sick with Ebola, or with an infected animal, the patient should be isolated and public health professionals notified. Samples from the patient can then be collected and tested to confirm infection by using following investigations:

- Antibody-capture enzyme-linked immunosorbent assay (ELISA)
- Antigen-capture detection tests
- Serum neutralization test
- Reverse transcriptase polymerase chain reaction (RT-PCR) assay
- Electron microscopy
- Virus isolation by cell culture.

Samples from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples

should be conducted under maximum biological containment conditions [13].

PREVENTION & CONTROL

There is no FDA-approved vaccine available for Ebola. Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilisation. Community engagement is a key to successfully controlling outbreaks. Raising awareness of risk factors for Ebola infection and protective measures that individuals can take is an effective way to reduce human transmission. Risk reduction messaging should focus on several factors:

Reducing the risk of wildlife-to-human transmission from contact with infected fruit bats or monkeys/apes and the consumption of their raw meat. Animals should be handled with gloves and other appropriate protective clothing. Animal products (blood and meat) should be thoroughly cooked before consumption.

Reducing the risk of human-to-human transmission from direct or close contact with people with Ebola symptoms, particularly with their bodily fluids. Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home. Regular hand washing is required after visiting patients in hospital, as well as after taking care of patients at home.

Reducing the risk of possible sexual transmission, because the risk of sexual transmission cannot be ruled out, men and women who have recovered from Ebola should abstain from all types of sex (including anal- and oral sex) for at least three months after onset of symptoms. If sexual abstinence is not possible, male or female condom use is recommended. Contact with body fluids should be avoided and washing with soap and water is recommended. WHO does not recommend isolation of male or female convalescent patients whose blood has been tested negative for Ebola virus.

Outbreak containment measures, including prompt and safe burial of the dead, identifying people who may have been in contact with someone infected with Ebola and monitoring their health for 21 days, the importance of separating the healthy from the sick to prevent further spread, and the importance of good hygiene and maintaining a clean environment [14].

CONTROLLING INFECTION IN HEALTH CARE SETTINGS

Health-care workers should always take standard precautions when caring for patients, regardless of their presumed diagnosis. These include basic hand hygiene, respiratory hygiene, use of personal protective equipment (to block splashes or other contact with infected materials), safe injection practices and safe burial practices.

Health-care workers caring for patients with suspected or confirmed Ebola virus should apply extra infection control measures to prevent contact with the patient's blood and body fluids and contaminated surfaces or materials such as clothing and bedding. When in close contact (within 1 metre) of patients with EBV, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).

Laboratory workers are also at risk. Samples taken from humans and animals for investigation of Ebola infection should be handled by trained staff and processed in suitably equipped laboratories [15].

TREATMENT AND VACCINES

Supportive care-rehydration with oral or intravenous fluids- and treatment of specific symptoms, improves survival. There is as yet no proven treatment available for EVD. However, a range of potential treatments including blood products, immune therapies and drug therapies are currently being evaluated but they have not yet been fully tested for safety or effectiveness. No FDA-approved vaccine or medicine (e.g.,antiviral drug) is available for Ebola yet, but 2 potential vaccines are undergoing human safety testing. Several vaccines are being developed and the two most advanced vaccines identified based on recombinant vesicular stomatitis virus expressing an Ebola virus protein (VSV-EBOV) and recombinant chimpanzee adenovirus expressing an Ebola virus protein (ChAd-EBOV) — are currently being tested in humans for safety and efficacy in the United States of America and trials were started in Africa and Europe [16]. Timely treatment of Ebola is important but challenging since the disease is difficult to diagnose clinically in the early stages of infection. Because prodromal symptoms are not specific to Ebola viruses, cases of Ebola may be initially misdiagnosed. However, if a person has symptoms of Ebola and had history of exposure, the patient should be isolated [17].

IS INDIA AT RISK?

Availability of favourable factors for Ebola virus replication can increase India's vulnerability .India has some similar factors to west African countries. Tropical climate, burial practices, higher population density, slums, lack of trained health workers, improper biomedical waste disposal and higher immigrants from Ebola prevalent west African countries can transmit the Ebola virus to India. Virus could be spread overseas by unwitting travellers from Guinea, Liberia and Sierra Leone. Up to three Ebola infected people could embark on overseas flights every month from most affected African countries.

India is in top 15 countries where Ebola could reach from Guinea, Liberia and Sierra Leone. However screening of Ebola patients is carried out at entry portals of international airports but screening can miss travellers who don't yet show signs of Ebola Virus Disease. A person can incubate the virus for up to 21 days without exhibiting signs of the disease. The controlling of the outbreak at the source is more important than to prevent the international spread of virus [18].

CONCLUSION

Increasing public awareness and prevention of Ebola virus disease (EVD) spreading are the presently needed essentials for the community. Community engagement is key to successfully controlling outbreaks. Raising awareness of risk factors for Ebola infection and protective measures that individuals can take is an effective way to reduce human transmission. As several clinical studies are under process worldwide, we can expect the development of potent and safe drugs for the treatment of Ebola virus disease (EVD). Almost 45000 Indian s are living in Ebola affected African countries and there is every chance that visiting Indians can bring it to India. In India strict monitoring is essential to keep this severe disease away from country.

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