

## EBOLA THREAT: WHEN NIGHTMARE BECOMES REALITY

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The Ebola virus is a cause of the serious disease that causes hemorrhagic fevers — illnesses marked by severe bleeding (hemorrhage), organ failure and, in many cases, death. The virus is native to Africa, where sporadic outbreaks have occurred for decades. The current outbreak is the largest and there have been more cases of deaths in this outbreak than all others combined. Various degrees of hepatocellular necrosis have been reported in infected people and non-human primates; however, the hepatocellular lesions are generally not serious enough to explain the cause of death. Importantly, hemorrhagic tendencies could be related to decreased synthesis of coagulation and other plasma proteins because of severe hepatocellular necrosis. Supportive care with hydration with oral or intravenous fluids - and treatment of specific the symptoms improves the survival. There is as yet no proven treatment available for EVD. *Acta Medica Medianae* 2015;54(3):78-83.

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### Introduction

The Ebola virus is a serious disease that causes hemorrhagic fevers — illnesses marked by severe bleeding (hemorrhage), organ failure and, in many cases, death. Virus is native to Africa, where sporadic outbreaks have occurred for decades. Scientists initially detected the Ebola virus disease (EVD) in 1976 in Sudan and the Democratic Republic of Congo. Researchers named the disease after the Ebola River that flows through Congo. Ebola virus lives in animal hosts, and humans can contract the viruses from infected animals. After the initial transmission, the viruses can spread from person to person through contact with body fluids or contaminated needles.

No drug has been approved to treat virus. People diagnosed with Ebola or Marburg virus receive supportive care and treatment for complications. Scientists are coming closer to developing vaccines for these deadly diseases. Although the Ebola virus has been present for more than 35

years, an outbreak that occurred in March in 2014 began in West Africa. This outbreak was more deadly, severe, and widespread than previous outbreaks. The current outbreak is the largest one and there have been more cases of deaths in this outbreak than all others combined. It has also spread between countries starting from Guinea then across land borders to Sierra Leone and Liberia; one passenger travelled by air to Nigeria, and one by land to Senegal. The most severely affected countries - Guinea, Sierra Leone and Liberia, which have very weak health systems, lacking human and infrastructural resources, have only recently emerged from long periods of conflict and instability. On August 8<sup>th</sup>, the WHO Director-General declared this outbreak a Public Health Emergency of International Concern (1-3).

### Etiology

The Ebola virus belongs to the virus family Filoviridae, also known as Filovirus. The virus family Filoviridae includes three genera: Cueva virus, Marburg virus, and Ebola virus. These virus types cause hemorrhagic fever or profuse bleeding inside and outside the body accompanied by a very high fever. Ebola can be further divided into subtypes that are named for the location they were identified. These include:

- Bundibugyo
- Reston
- Sudan
- Taï Forest (previously known as Ivory Coast)
- Zaire.

The virus causing the 2014 West African outbreak belongs to the Zaire species (4).

### **Epidemiology**

The first cases of filovirus haemorrhagic fever were reported in 1967 in Germany and the former Yugoslavia, and the causative agent was identified as Marburg virus (4).

Ebola was the second known Filovirus. In the late 1970s, the international community was again startled, this time by the discovery of Ebola virus as the causative agent of major outbreaks of hemorrhagic fever in the Democratic Republic of the Congo (DRC) and Sudan. EVD outbreaks in Africa were the largest and included 318 cases (5, 6).

The current outbreak started in Guinea, West Africa during December 2013 and spread into Liberia in March, Sierra Leone in May, and Nigeria in late July. The World Health Organization (WHO) was officially notified of the rapidly evolving EVD outbreak on March 23, 2014. It is the largest known EVD outbreak and is expanding exponentially (7).

Its emergence in the major cities such as Conakry (Guinea), Freetown (Sierra Leone), Monrovia (Liberia), and Lagos (Nigeria) raised the specter of increasing local and international dissemination. As of September 14, 2014, a total of 4.507 confirmed and probable cases of Ebola virus disease (EVD), as well as 2.296 deaths from the virus, have been reported from five countries in West Africa — Guinea, Liberia, Nigeria, Senegal, and Sierra Leone. In terms of reported morbidity and mortality, the current epidemic of EVD is far larger than all previous epidemics combined. The true numbers of cases of deaths are certainly higher. There are numerous reports on symptomatic persons evading diagnosis and treatment, or laboratory diagnoses that have not been included into national databases, and of persons with suspected EVD who were buried without a diagnosis having been made (8).

It is thought that fruit bats of the Pteropodidae family are natural Ebola virus hosts. 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 (2, 9). Ebola then spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. Most human infections in outbreaks seem to occur by direct contact with infected patients or cadavers. Infectious virus particles or viral RNA have been detected in semen, genital secretions and in the skin of infected patients (9).

Healthcare workers have frequently been infected while treating patients with suspected or confirmed EVD. This has occurred through close

contact with patients when infection control precautions are not strictly practiced. Laboratory exposure through needlestick and blood has been reported. The reuse of contaminated needles played an important role in the 1976 outbreaks of Ebola virus in Sudan and Zaire. Although proper cooking of foods should inactivate infectious Ebola virus, ingestion of contaminated food cannot wholly be ruled out as a possible route of exposure in natural infections. 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. The role of aerosol transmission in outbreaks is unknown, but is thought to be rare.

In human beings, the route of infection seems to affect the disease course and outcome (10).

### **Pathogenesis**

Information about the pathology and pathogenesis of Ebola virus infections in men is sparse. This shortcoming is partly attributable to the inaccessibility of the geographical regions in which these natural infections appear. However, comprehensive studies have been done in animals. Rodents such as guinea pigs and mice have been used to study Ebola haemorrhagic fever, though the disease pathogenesis recorded in rodents is less accurate in representation of the human disorder than is the disease recorded in non-human primates (11).

Ebola virus has a broad cell tropism, infecting a wide range of cell types. In situ hybridization and electron microscopic analyses of tissues from patients with fatal disease or from experimentally infected non-human primates show that monocytes, macrophages, dendritic cells, endothelial cells, fibroblasts, hepatocytes, adrenal cortical cells, and several types of epithelial cells all lend support to replication of these viruses (12). Monocytes, macrophages, and dendritic cells infected with Ebola virus migrate out of the spleen and lymph nodes to other tissues, thus disseminating the infection. Although the endothelium is thought to play an important part in the pathogenesis of Ebola virus, studies defining the molecular mechanisms of endothelial impairment are incomplete (12, 13).

Together with the macrophage-rich lymphoid tissues, the liver and the adrenal gland seem to be important targets for filoviruses, and this tropism probably has an equally important role in the disease pathogenesis. Various degrees of hepatocellular necrosis have been reported in infected people and non-human primates; however, the hepatocellular lesions are generally not serious enough to explain the cause of death. Importantly, haemorrhagic tendencies could be related to decreased synthesis of coagulation and other plasma proteins because of severe hepatocellular necrosis. Adrenocortical infection and necrosis have also been reported in humans and non-human primates

infected with Ebola virus. The adrenal cortex plays an important part in the control of blood pressure homeostasis. Impaired secretion of enzymes that synthesize steroids leads to hypotension and sodium loss with hypovolaemia, which are important elements that have been reported in nearly all cases of Ebola hemorrhagic fever (12, 13).

During infection with Ebola virus, lymphoid depletion and necrosis are often noted in the spleen, thymus, and lymph nodes of patients with fatal disease and in non-human primates that are experimentally infected. Although lymphoid tissues are the primary sites of Ebola virus infection, there is usually little inflammatory cellular response in these or other infected tissues. Despite the large die-off and loss of lymphocytes during infection, the lymphocytes themselves are not infected. The mechanism for the underlying apoptosis and loss of bystander lymphocytes during the course of Ebola hemorrhagic fever are unknown but are thought to be provoked through several different agonists or pathways. These pathways or processes might include the TNF-related apoptosis-inducing ligand (TRAIL) and Fas death receptor pathways, impairment of dendritic cell function induced by Ebola virus infection, abnormal production of soluble mediators such as nitric oxide that have proapoptotic properties, or possibly by direct interactions between lymphocytes and Ebola virus proteins (11-13).

Ebola virus infection triggers the expression of several inflammatory mediators including interferons; interleukins 2, 6, 8, and 10; interferon-inducible protein 10; monocyte chemoattractant protein 1; regulated upon activation normal T cell expressed and secreted; TNF $\alpha$ ; and reactive oxygen and nitrogen species (14).

Results from studies of various primary human cells in vitro also show that infection of Ebola virus can trigger the production of many of these inflammatory mediators. Overall, virus-induced expression of these mediators seems to result in an immunological imbalance that partly contributes to the progression of disease. Pro-inflammatory responses recorded in fatal cases of Ebola hemorrhagic fever are dysregulated, whereas early and well-regulated inflammatory responses have been associated with recovery (15).

Inhibition of the type I interferon response, initially noted by studies of endothelial cells infected with Zaire Ebola virus, seems to be a key feature of filovirus pathogenesis. The Ebola virus VP35 functioned as a type I interferon antagonist by blocking activation of interferon regulatory factor 3 and possibly by preventing transcription of interferon  $\beta$ . Additionally, other studies suggest that expression of VP24 of the Ebola virus interferes with type I interferon signaling; mutations in VP24 have been linked to adaptation of Zaire Ebola virus to produce lethal disease in mice and guinea pigs (16).

Results from several studies show an important role for reactive oxygen and nitrogen species in pathogenesis of Ebola hemorrhagic fever. In-

creased concentrations of nitric oxide in blood were reported in non-human primates experimentally infected with Zaire Ebola virus and were noted in patients infected with Zaire Ebola virus and Sudan Ebola virus. Increased blood concentrations of nitric oxide in patients were associated with mortality. Abnormal production of nitric oxide has been associated with several pathological disorders including apoptosis of bystander lymphocytes, tissue damage, and loss of vascular integrity, which might contribute to virus-induced shock. Nitric oxide is an important mediator of hypotension, and hypotension is a prominent finding in most of the viral haemorrhagic fevers including those caused by Ebola virus (17).

Defects in blood coagulation and fibrinolysis during Ebola virus infections are manifested as petechiae, ecchymoses, mucosal haemorrhages, congestion, and uncontrolled bleeding at venepuncture sites. However, massive loss of blood is infrequent and, when present, is mainly limited to the gastrointestinal tract. Even in these cases, the amount of blood that is lost is not substantial enough to cause death. Thrombocytopenia, consumption of clotting factors, and increased concentrations of fibrin degradation products are other indicators of the coagulopathy that characterizes Ebola virus infections. Results from clinical laboratory data strongly suggest that the coagulation abnormalities that occur during human Ebola hemorrhagic fever are generally consistent with disseminated intravascular coagulation. The mechanism responsible for triggering the coagulation disorders that typify Ebola hemorrhagic fever are not wholly understood (18).

In sum, the data so far suggest that an impaired and ineffective host response leads to high concentrations of virus and proinflammatory mediators in the late stages of disease, which is important in the pathogenesis of hemorrhage and shock. The prevailing hypothesis at this time is that infection and activation of antigen-presenting cells is fundamental to the development of Ebola hemorrhagic fever. The release of proinflammatory cytokines, chemokines, and other mediators from antigen presenting cells, and perhaps other cells, causes impairment of the vascular and coagulation systems leading to multiorgan failure and a syndrome that in some ways resembles septic shock (18).

### Symptoms of EVD

The incubation period, that is, the time interval from infection with the virus to the onset of symptoms is 2 to 21 days. Humans are not infectious until they develop symptoms. The first symptoms are the sudden onset of fever, fatigue, joint and muscle pain, severe headache, chills, weakness and sore throat. This is followed by nausea and vomiting, diarrhea (may be bloody), severe weight loss, raised rash, red eyes, chest pain and cough, symptoms of impaired kidney and liver function, and in some cases, both internal

and external bleeding (e.g. oozing from the gums, blood in the stools). Hemorrhagic manifestations arise during the peak of the illness and include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal hemorrhages, and post-mortem evidence of visceral hemorrhagic effusions. A macropapular rash associated with varying severity of erythema and desquamation can often be noted between days 5–7 of the illness; this symptom is a valuable differential diagnostic feature and is usually followed by desquamation in survivors. Abdominal pain is sometimes associated with hyperamylasaemia and true pancreatitis. In later stages, shock, convulsions, severe metabolic disturbances, and, in more than half the cases, diffuse coagulopathy supervene (12, 18, 19).

Laboratory variables are less characteristic, but the following findings are often associated with Ebola hemorrhagic fever: early leucopenia (as low as 1000 cells per  $\mu\text{L}$ ) with lymphopenia and subsequent neutrophilia, left shift with atypical lymphocytes, thrombocytopenia (50 000–100 000 cells per  $\mu\text{L}$ ), highly elevated serum aminotransferase concentrations (aspartate aminotransferase typically exceeding alanine aminotransferase), hyperproteinaemia, and proteinuria. Prothrombin and partial thromboplastin times are extended and fibrin split products are detectable, indicating diffuse intravascular coagulopathy. In a later stage, secondary bacterial infection might lead to raised counts of white blood cells (12, 19).

### Diagnosis

It can be difficult to distinguish EVD from other infectious diseases such as malaria, typhoid fever and meningitis. Confirmation that symptoms are caused by Ebola virus infection are made using the 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 (20).

Samples from patients are an extreme biohazard risk; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions (20).

### Treatment and vaccines

Supportive care - rehydration with oral or intravenous fluids and treatment of specific symptoms, improves the survival. There is as yet no proven treatment available for EVD. However, a range of potential treatments including blood pro-

ducts, immune therapies and drug therapies are currently being evaluated. No licensed vaccines are available yet, but two potential vaccines are undergoing human safety testing (21).

### Prevention and control

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 mobilization. Community engagement is key to successful control of 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.

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

### Conclusion

WHO aims to prevent Ebola outbreaks by maintaining surveillance for Ebola virus disease and supporting at-risk countries to develop preparedness plans. The document provides the overall guidance for control of Ebola and Marburg virus outbreaks. When an outbreak is detected, WHO responds by supporting surveillance, community engagement, case management, laboratory services, contact tracing, infection control, logistical support and training and assistance with safe burial practices.

WHO has developed detailed advice on the prevention and control of Ebola infection.

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## OPASNOST OD EBOLE: KADA NOĆNA MORA POSTANE STVARNOST

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Virus ebole je uzročnik opasne bolesti koja uzrokuje hemoragijsku groznicu – oboljenje koje se karakteriše teškim krvarenjem, organskom disfunkcijom i smrtnim ishodom u velikom broju slučajeva. Virus potiče iz Afrike, odakle se decenijama javljaju sporadične epidemije. Aktuelna epidemija je do sada najveća, sa najvećim brojem smrtnih slučajeva. Do sada je zapaženo nekoliko stepena hepatocelularne nekroze kod inficiranih ljudi i nehumanih primata. Ipak, hepatocelularna oštećenja nisu dovoljno teška da bi se njima objasnio uzrok smrti. Još važnije, hemoragijska dijateza možda nastaje usled smanjene sinteze faktora koagulacije i ostalih plazmatskih proteina zbog teške hepatocelularne nekroze. Potporna terapija, rehidracija oralnim i intravenoznim tečnostima i tretiranje specifičnih simptoma poboljšava preživljavanje. Još uvek nema dokazano uspešne terapije za oboljenje izazvano virusom ebole. *Acta Medica Medianae* 2015; 54(3):78-83.

**Ključne reči:** virus ebole, hemoragija, groznica

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