

# Ebola Outbreak: An Evolving Epidemic- A Review

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## Abstract

Ebola hemorrhagic fever is a severe and often deadly illness that can occur in humans and primates (e.g. monkeys, gorillas). It is some of most virulent pathogens of humans, causing severe hemorrhagic fever that resembles fulminant septic shock. Recent outbreak of Ebola in West Africa has threatened the whole world, because of the high mortality (80-90%). No approved therapy is available for the treatment of these diseases, but progress has been made in new experimental approaches to post exposure prophylaxis and/or treatment that are effective in laboratory primates. Prevention is the best tool. Now WHO has also declared Ebola as a “public health emergency of international concern”. It can also be misused as a bioterrorism agent.

**Key words:** Ebola, hemorrhagic disease, mortality

## Introduction

The ongoing Ebola outbreak in West Africa is the largest, most complicated and most lethal that the world has even seen. It is some of most virulent pathogens of humans, causing severe hemorrhagic fever that resembles fulminant septic shock. It is affecting four countries in West Africa: Guinea, Liberia, Nigeria, and Sierra Leone. The current outbreak, which began in December 2013 is the largest ever, was first detected in March 2014, when cases were recognized in southern Guinea [1]. Liberia, Sierra Leone, and Nigeria are now also involved in the epidemic. Now it has been declared a “public health emergency of international concern” by the World Health Organization [2].

## Epidemiology

The first cases of filovirus hemorrhagic fever were reported in 1967 in Germany and the former Yugoslavia (now Serbia & Montenegro), and the causative agent was identified as Marburg virus, when three laboratory workers, during preparing primary cell culture for polio vaccine production, were exposed to the blood and tissues (kidney) of African green monkeys (*Ceropithecus aethiops*) imported from Uganda [14,17,27]. Since that time, with the exception of a few

accidental laboratory infections, all cases of filoviral disease have occurred in sub-Saharan Africa. The frequency of recognized outbreaks has been increasing since 1990. The first recorded human outbreak of Ebola virus was in 1976, when two epidemics occurred almost simultaneously in Zaire, Sudan and Yambuku, Democratic Republic of Congo. The latter was in a village situated near the Ebola River, from which the disease takes its name. There was substantial secondary transmission through reuse of unsterilized needles and syringes, and nosocomial contacts.

These two epidemics were caused by two distinct species of Ebola virus, Sudan Ebola virus and Zaire Ebola virus, a fact not recognized until years later [15]. Since then, more than 20 outbreaks have occurred, mostly in Equatorial Africa and most due to Ebola (EBOV), these were usually sporadic, isolated and fatal.

Although most previous Ebola outbreaks occurred in Central Africa, this outbreak started in the West African nation of Guinea in late 2013 and was confirmed by the World Health Organization in March 2014 [1,30]. The outbreak subsequently spread to Liberia, Sierra Leone, and Nigeria.

The disease has had an aggregated case-fatality rate of 78% [5]. Ebola virus is now considered a category A

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pathogen that could be misused as a bioterrorism agent [8]. Till 22 August 2014, total of 2615 suspected and confirmed cases (1528 of which are laboratory-confirmed) and 1427 deaths have been reported for a mortality rate of approximately 55%. Attack rates have been highest in the birth-1 year old and 15-50 years old age group. It is one of the world's most deadly diseases. It is a highly infectious virus that can kill up to 90 percent of the people who catch it, causing terror among infected communities.

Ebola hemorrhagic fever (Ebola) is a deadly but rare zoonosis caused by a virus of family filoviridae. Filoviridae family has two genera, Marburg virus and Ebola virus. Ebola virus includes 5 viruses: Ebola (EBOV), Sudan (SUDV), Tai Forest (TAFV), Bundibugyo (BDBV) and Reston (RESTV), all of which are pathogenic to humans except RESTV, which is only pathogenic to nonhuman primates [3].

Wild reservoir of this virus is still unknown but fruit bats of the Pteropodidae family are believed to be the natural reservoir, because they have been present in large numbers at the sites of several filovirus outbreaks and are known to maintain other pathogenic RNA viruses, such as rabies. Fruit bat can support replication and circulation of high titers of Ebola virus without showing overt illness, suggesting that they could play some role in the natural history of filoviruses [4,18].

Epidemiologic data also suggest a strong link between exposure to bats and subsequent filoviral disease. Ebola virus has also been spreading among wild nonhuman primates, resulting to a marked reduction in chimpanzee and gorilla populations [28,29].

Case Definition for Ebola Virus Disease (EVD) [27] (<http://www.cdc.gov/vhf/ebola/hcp/case-definition.html>)Compartir

Early recognition is critical for infection control. Health care providers should be alert for and evaluate any patients suspected of having Ebola Virus Disease (EVD).

Person under Investigation (PUI)

**A person who has both consistent symptoms and risk factors as follows:**

1. Clinical criteria, which includes fever of greater than 38.6 °C or 101.5 °F and additional symptoms such as severe headache, muscle pain, vomiting, diarrhea, abdominal pain, or unexplained hemorrhage; AND
2. Epidemiologic risk factors within the past 21 days before the onset of symptoms, such as contact with blood or other body fluids or human remains of a

patient known to have or suspected to have EVD; residence in—or travel to—an area where EVD transmission is active or direct handling of bats or non-human primates from disease-endemic areas.

**Probable Case-** A person under investigation (PUI) whose epidemiologic risk factors include high or low risk exposure(s) (see below)

**Confirmed Case-** A case with laboratory-confirmed diagnostic evidence of Ebola virus infection

**Exposure Risk Levels-** Levels of exposure risk are defined as follows:

**1. High risk exposures-** A high risk exposure includes any of the following:

- Percutaneous (eg-needle stick) or mucous membrane exposure to blood or body fluids of EVD patient
- Direct skin contact with or exposure to blood or body fluids of an EVD patient without appropriate personal protective equipment (PPE)
- Processing blood or body fluids of a confirmed EVD patient without appropriate PPE or standard bio-safety precautions
- Direct contact with a dead body without appropriate PPE in a country where an EVD outbreak is occurring

**2. Low risk exposures-** A low risk exposure includes any of the following:-

- Household contact with an EVD patient
- Other close contact with EVD patients in health care facilities or community settings. Close contact is defined as-
  - a. Being within approximately 3 feet (1 meter) of an EVD patient or within the patient's room or care area for a prolonged period of time (eg- health care personnel, household members) while not wearing recommended personal protective equipment (i.e.-standard, droplet, and contact precautions)
  - b. Having direct brief contact (eg- shaking hands) with an EVD case while not wearing recommended personal protective equipment.
- Brief interactions, such as walking by a person or moving through a hospital, do not constitute close contact

**3. No known exposure**

Having been in a country in which an EVD outbreak occurred within the past 21 days and having had no high or low risk exposures

## Transmission

Ebola isn't as contagious as other common viruses like colds, influenza, or measles. It is introduced into the

human body through close contact with the blood, secretions, organs or other bodily fluids of infected animals. It spreads to people by-

1. Contact with the skin or bodily fluids of an infected animal, like a monkey, chimp, or fruit bat.
2. Person to person with infected body fluids.
3. Those who care for a sick person or bury someone who has died from the disease often get it.
4. By touching contaminated needles or surfaces.
5. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness.

Ebola isn't spread by-

1. From air, water, or food.
2. A person who has Ebola but has no symptoms can.
3. Insect bite

### Risk factors

For most people, the risk of getting Ebola is low. The risk increases if person:-

1. Travel to endemic area like Africa.
2. Conduct animal research especially with monkeys imported from Africa or the Philippines.
3. Provide medical or personal care, if care takers don't use protective gear, such as surgical masks and gloves.
4. Prepare people for burial, because bodies of people who have died of Ebola hemorrhagic fever are still contagious.
5. Family members, as they care for sick relatives.

### Pathogenesis

Ebola virus is an aggressive pathogen that causes a highly lethal hemorrhagic fever syndrome in humans and nonhuman primates. Yet there are still no satisfactory biological explanations to account for its extreme virulence.

The pathogenesis of the disease is not well understood. Studies in nonhuman primates have shown that Ebola virus replicates in monocytes, macrophages, and dendritic cells [31]; however, in situ hybridization and electron microscopy have also shown the presence of virus in endothelial cells, fibroblasts, hepatocytes, and adrenal cells [33].

The virus disseminates to lymph nodes and spleen also. The available data suggest that the envelope glycoprotein and the interaction of some viral proteins with the immune system are likely to play important roles in the extraordinary pathogenicity of this virus. Ebola virus replicates at an unusually high rate that overwhelms the

protein synthesis apparatus of infected cells and host immune defenses [16].

The rapid progression of Ebola virus infection has further complicated the control of this disease, affording little opportunity to develop acquired immunity. Ebola virus infections are characterized by immune suppression and a systemic inflammatory response that causes impairment of the vascular, coagulation, and immune systems, leading to hepatocellular necrosis, cytokine storm, complement activation, multi-organ failure, disseminated intravascular coagulation, hemorrhage and shock, and thus, in some ways, resembling septic shock [3]. There is significant lymphocyte apoptosis, which leads to lymphopenia and seems to be a marker of prognosis.

### What Are the Symptoms of Ebola?

Diagnosis of Ebola can be difficult initially because the symptoms can be confused with those of diseases that are more common, such as malaria, typhoid fever, bacterial meningitis, or Lassa fever. Signs and symptoms typically begin abruptly within 5-10 days of infection, but can range 2-21 days. Initial clinical symptoms are non specific with sudden onset of fever (greater than 101.5 F), chills, severe headache, intense weakness, loss of appetite, joint and muscle pain, malaise and weight loss.

This is followed by flu-like symptoms (nasal discharge, cough, shortness of breath, chest pain, red eye and rashes); gastrointestinal symptoms (diarrhea, nausea, vomiting, stomach pain and abdominal pain); eye swelling, genital swelling and finally, hemorrhagic symptoms in the most severe cases. Bleeding, usually from the eyes and bruising (people near death may bleed from other orifices, such as ears, nose and rectum) and later internal bleeding. Ultimately, it causes levels of blood-clotting cells to drop.

This leads to severe, uncontrollable bleeding. As the virus spreads through the body, it damages the immune system and organs. Poor prognosis is associated with the development of shock, encephalopathy, coma, seizure, delirium, jaundice, multi organ failure, DIC and extensive hemorrhage [11,12]. One reason the viruses are so deadly is that, they interfere with the immune system's ability to mount a defense, but scientists don't understand why some people recover from Ebola and others don't.

For people who survive, recovery is slow. It may take months to regain weight and strength, and the viruses remain in the body for weeks. People may experience hair

loss, sensory changes, weakness, fatigue, headaches, eye inflammation, testicular inflammation and hepatitis.

### Diagnosis

Ebola fever is difficult to diagnose in early stage, because early signs and symptoms resemble those of many common illness like malaria, typhoid fever, shigellosis, cholera, leptospirosis, plague, rickettsiosis, relapsing

fever, meningitis, hepatitis and other viral hemorrhagic fevers. When the diagnosis is suspected, reverse transcriptase polymerase chain reaction and antigen detection by enzyme-linked immunosorbent assay are the most useful tests, but unfortunately these tests are available in referral center only. In suspected case, depending on time of interaction, following tests can be advised to quickly identify the virus.

[<http://www.cdc.gov/vhf/ebola/diagnosis/>]

S. No	Time of investigation	Recommended Test
1.	Within a few days after symptoms begin	1. Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing 2. IgM ELISA 3. Polymerase chain reaction (RT-PCR) 4. Virus isolation by cell culture
2.	Later in disease course or after recovery	M and IgG antibodies
3.	Retrospectively in deceased patients	1. Immunohistochemistry testing 2. PCR 3. Virus isolation

Other supportive test- TLC (leukopenia), platelets counts (thrombocytopenia), aminotransferase (elevated), prothrombin time (elevated), partial thromboplastin times (elevated) and fibrin split products (elevated).

### How Is Ebola Treated?

As there's no cure for Ebola, treatment is essentially symptomatic and supportive and has not changed appreciably since the 1950s [33]. Due to the high risk of person-to-person and nosocomial transmission associated with Ebola hemorrhagic fever, management is based on isolation of patients and institution of protected care [10].

The current standard for treatment in initial stage consists of oral medication, oral fluid rehydration, nutritional supplementation, and psychosocial support. Oral medication includes drugs that alleviate symptoms such as nausea and vomiting (eg, metoclopramide and promethazine), dyspepsia (eg, aluminium hydroxide, cimetidine, ranitidine, and omeprazole), anxiety, agitation, or confusion (eg, diazepam, chlorpromazine), and pain (eg, paracetamol, tramadol, and morphine) when indicated.

In advanced stage treatment includes oxygen, fluid and electrolyte correction, vasopressors, blood and blood components and treatment of other infections. No antiviral drug has been proved to be useful in nonhuman primates when symptoms have already appeared.

Efforts by researchers working in high-containment laboratories are ongoing. Evaluated in nonhuman primates (NHPs) and other animals, some post-exposure prophylaxes have achieved promising results

[3,5,6,7,9,19], Innovative treatment can be divided into following categories:-

- Disease-modifying agents-
  1. Recombinant human activated protein C (rhaPC)
  2. Recombinant nematode anticoagulant protein c2 (rNAPc2)
- Inhibitors of viral replications-
  1. Antisense phosphorodiamidate morpholino oligomers (PMOs)
  2. Short-interfering RNA (siRNA) molecules
- Monoclonal antibodies (mAb)
- Novel broad spectrum nucleoside analogue BCX4430.
- Plasma from patients who have recovered from infections

Recent achievements in post-exposure prophylaxes represent a major breakthrough in filovirus research [20.21]. Although results of these experimental studies are encouraging, but availability of an effective and approved treatment for human testing in an outbreak setting may be years away. Reasons for this are: (1) the development of an innovative treatment has been slow and (2) researchers have yet to evaluate treatment success in Non-human primates [20-26].

Persons having been in close contact with patient should be kept under medical surveillance for 21 days. Recovering patients should use condoms for three

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months. Bodies of deceased patients should be handled by trained teams and buried quickly because traditional funeral and caretaking methods contribute to the spread of the virus and potentiate outbreaks [10].

The occurrence of even a single human infection outside of Africa is a public health emergency requiring immediate investigation, since it could represent the leading edge of an impending outbreak.

**Prognosis**

Approximately 90% of patients die from the disease. Patients usually die from shock rather than from blood loss.

**How Can You Prevent Ebola?**

1. There's no vaccine to prevent Ebola.
2. The best way to avoid catching the disease is by not traveling to endemic areas.
3. Health care workers can prevent infection by wearing masks, gloves, and goggles.

Importation is the major risk of spreading from endemic countries to diseases free countries. Even if cases are imported, the likelihood of further transmission beyond the index patient is near zero because hospital infection control practices are an effective barrier.

However, clinics, hospitals, and emergency departments in worldwide should be prepared to immediately isolate any patient with a recent history (<3 weeks) of travel to West Africa, who presents with compatible signs and symptoms of Ebola.

**Ebola virus vaccine**

As of today there is no vaccine for Ebola virus infections and the development of a preventive vaccine was not a priority until recently. Trials for development of vaccines are going on in nonhuman primate, which closely resemble disease progression in human. Several of them are efficacious against this lethal disease in nonhuman primates attesting that vaccination against Ebola virus infections is feasible [8].

**Special considerations- Bioterrorism**

Because of their virulence, stability, and high infectivity as small-particle aerosols, Marburg and Ebola virus are classified as Category A bioterror agents by the United States Centers for Disease Control and Prevention (CDC) and the National Institute of Allergy and Infectious Diseases (NIAID) [34].

CDC guideline for travelers to prevent Ebola [<http://wwwnc.cdc.gov/travel/notices/warning/ebola-guinea>]-

There is no vaccine or specific treatment for Ebola, and many people who get the disease die. Therefore, it is important to take steps to prevent Ebola.

If any person is traveling to Nigeria, please make sure to do the following:-

- Practice careful hygiene. Avoid contact with blood and body fluids.
- Do not handle items that may have come in contact with an infected person's blood or body fluids.
- Avoid funeral or burial rituals that require handling the body of someone who has died from Ebola.
- Avoid contact with animals or with raw meat.
- Avoid hospitals where Ebola patients are being treated.
- Seek medical care immediately if develop fever, headache, achiness, sore throat, diarrhea, vomiting, stomach pain, rash, or red eyes.
- Limit your contact with other people when you travel to the doctor. Do not travel anywhere else.
- Pay attention to your health after you return.
- Monitor your health for 21 days if you were in an area with an Ebola outbreak, especially if you were in contact with blood or body fluids, items that have come in contact with blood or body fluids, animals or raw meat, or hospitals where Ebola patients are being treated.
- Tell the doctor about your recent travel and your symptoms before you go to the office or emergency room. Advance notice will help the doctor care for you and protect other people who may be in the office.

Special Recommendation for Health Care Workers [<http://www.who.int/csr/resources/who-ipc-guidance-ebolafinal-09082014.pdf>]-

Health care workers who may be exposed to people with the disease should follow these steps:-

- Wear protective clothing, including masks, gloves, gowns, and eye protection.
- Practice proper infection control and sterilization measures.
- Isolate Ebola patients from unprotected people.
- Avoid direct contact with the bodies of people who have died from Ebola.
- Notify health officials if you have been exposed to someone with Ebola.

Ebola Outbreak: Government Issues Precautionary Guidelines to Airlines-  
[<http://www.ndtv.com/article/india/ebola-outbreak-government-issues-precautionary-guidelines-to-airlines-574974>]

The Directorate General of Civil Aviation (DGCA) has issued directives to all airlines operating on international routes and asked them to take a series of precautionary measures with immediate effect to prevent the entry and spread of the Ebola Virus Disease (EVD) in India.

1. The airlines have been asked to keep first aid and universal precaution kits, including masks, sanitizers and disposal gloves and bags.
2. They would also have to make in-flight announcements for self-reporting by travelers who have any signs or symptoms of Ebola Virus Disease (EVD), ask passengers to fill up special health forms for submitting information regarding visit to any affected country in the last 21 days, among other things.
3. The details of passengers boarding from affected countries should be sent in advance to the station of arrival in India by all Indian and foreign airlines
4. The airlines have been directed to keep a record of all passengers returning to India after staying or visiting West African countries and inform the details to health officials at the concerned airports.

### Other guidelines

CDC, in conjunction with the World Health Organization, has developed a set of guidelines to help prevent and control the spread of Ebola. Guidelines are available at: <http://www.cdc.gov/vhf/ebola>.

### Conclusion

The Ebola virus is among the most virulent human pathogens, causing severe hemorrhagic fever that resembles fulminant septic shock. In view of high mortality and non availability of definitive treatment, it is essential to follow CDC guidelines, standard, contact, and droplet precautions in hospitalized patients with known or suspected Ebola virus disease.

Trials for development of vaccines are going on in nonhuman primate with encouraging results. Finally, we urgently need strategies, financial support, and political will to bring the current developments to the populations of endemic areas in equatorial Africa, who are in primary need for intervention and for whom financial resources are scarce.

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