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# Updated Review on Ebola Virus and its Therapeutic Development

**Imad uddin*[1], Mohammed mubeen[1], Rubeena Naaz[1], Yousuf Syed[1], Rafiq shaik[1]**
*1. Department of pharmacology, MAKCollege of Pharmacy, Moinabad, RR dist.*

## ABSTRACT

Ebola hemorrhagic fever (EHF) is an acute viral syndrome that presents with fever and an ensuing bleeding diathesis that is marked by high mortality in human and nonhuman primates. Due to its lethal nature, this filovirus is classified as a biological class 4 pathogen. The natural reservoir of the virus is unknown. As a result, little is understood about how Ebola virus(EBOV) is transmitted or how it replicates in its host. Although the primary source of infection is unknown, the epidemiologic mode of transmission is well defined. A variety of tests have proven to be specific and useful for Ebola virus identification. There is no FDA-approved antiviral treatment for EHF. Since there is no specific treatment outside of supportive management and palliative care, containment of this potentially lethal virus is paramount. The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. But now, the virus seems to have enthralled the global interest due to its lethal prospective. EHF outbreaks have a case fatality rate of up to 90%. The research is ongoing on development of making vaccine to curb this virus yet licensed success or specific treatment is not achieved. Severely ill patients require intensive supportive care. In this article we discussed the recent approaches for the treatment of EHF.

**Keywords:** Ebola hemorrhagic fever, Ebola virus, *Marburgvirus*, ELISA.

*Corresponding Author Email: imadpharma111@gmail.com
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# INTRODUCTION

Ebola virus (figure 1) is one of at least 30 known viruses capable of causing viral hemorrhagic fever syndrome. Although agents that cause viral hemorrhagic fever syndrome constitute a geographically diverse group of viruses, all of those identified to date are RNA viruses with a lipid envelope, all are considered zoonoses, all damage the microvasculature which result in increased vascular permeability. The family Filoviridae resides in the order Mononegavirales and contains the largest genome within the order. This family contains 2 genera: *Ebolavirus* (containing 5 species) and the antigenically distinct *Marburgvirus* (containing a single species).Studies have demonstrated that patients who die of Ebola viral infection do not develop a humoral immune response. However, in survivors neutralizing antibody can be detected. It is likely that a broad humoral immune response can increase the likelihood of an infected patient surviving Ebola. Currently, no specific therapy is available for treatment of Ebola hemorrhagic fever, and there are no commercially available Ebola virus vaccines. General medical support is critical. Care must be administered with strict attention to barrier isolation. Because the source of Ebola virus is unknown, education and prevention of primary cases is problematic. Education of communities at risk, especially healthcare workers, can greatly reduce the number of secondary person-to-person transmissions.

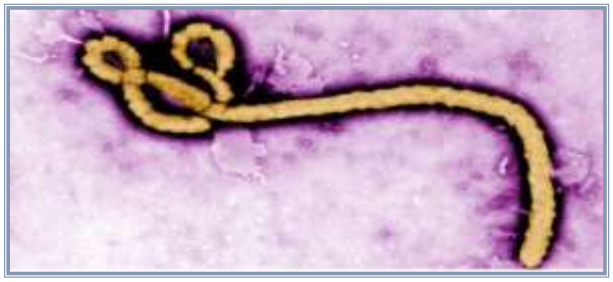

**Figure 1: Ebola virus**

## Pathophysiology

The known members of the family Filoviridae are the genera *Ebolavirus* (Ebola virus) and *Marburgvirus* (Marburg virus). According the 2012 virus taxonomy of the International Committee onTaxonomy of Viruses, *Ebola virus* is classified into the following 5 separate species:

1. *Sudan ebolavirus*
2. *Zaire ebolavirus*
3. *Tai Forest ebolavirus*
4. *Reston ebolavirus*
5. *Bundibugyoebolavirus*

Filoviruses such as Ebola virus share a characteristic filamentous form, with a uniform diameter of approximately 80 nm but a highly variable length. Filaments may be straight, but they are often folded on themselves.Ebola virus has a non-segmented negative-stranded RNA genome containing 7 structural and regulatory genes. The Ebola genome codes for 4 virion structural proteins (VP30, VP35, nucleoprotein, and a polymerase protein [L]) and 3 membrane-associated proteins (VP40, glycoprotein [GP], and VP24). The GP gene is positioned fourth from the 3′ end of the 7 linearly arranged genes. Most filovirus proteins are encoded in single reading frames; the surface GP is encoded in 2 frames (open reading frame [ORF] I and ORF II). The ORF I (amino-terminal) of the gene encodes for a small (50-70 kd), soluble, nonstructural secretory glycoprotein (sGP) that is produced in large quantities early in Ebola virus infection[1]. The sGP binds to neutrophil CD16b, a neutrophil-specific Fc g receptor III, and inhibits early neutrophil activation. The sGP also may be responsible for the profound lymphopenia that characterizes Ebola infection. Thus, sGP is believed to play pivotal roles in the ability of Ebola to prevent an early and effective host immune response. One hypothesis is that the lack of sGP production by Marburg virus may explain why this agent is less virulent than African-derived Ebola virus. A detailed study of these infected but asymptomatic individuals revealed that they had an early (4-6 days after infection) and vigorous immunologic response with production of interleukin (IL)–1β, IL-6, and tumor necrosis factor (TNF), resulting in enhanced cell-mediated and humoral-mediated immunity. In patients who eventually died, proinflammatory cytokines were not detected even after 2-3 days of symptomatic infection. A second, somewhat larger (120-150kd) GP, transmembrane glycoprotein, is incorporated into the Ebola virion and binds to endothelial cells but not to neutrophils. Ebola virus is known to invade, replicate in, and destroy endothelial cells. Destruction of endothelial surfaces is associated with disseminated intravascular coagulation, and this may contribute to the hemorrhagic manifestations that characterize many, but not all, Ebola infections.

**Mechanism**

African-derived filovirus infections are characterized by transmission from an unknown host (possibly bats) to humans or nonhuman primates, presumably via direct contact with body fluids such as saliva or blood or other infected tissues. Evidence in nonhuman primates indicates that *Sudan ebolavirus* and *Zaire ebolavirus* may be transmitted by contact with mucous membranes, conjunctiva, pharyngeal and gastrointestinal (GI) surfaces; through small breaks in the skin; and, at least experimentally, by aerosol[2]. Dogs have been shown to acquire asymptomatic Ebola virus infections, possibly by contact with virus-laden droplets of urine, feces, or blood of unknown

hosts.[3] Human infection with African-derived strains has often occurred in caregivers (either family or medical) and in family members who have prepared dead relatives for burial. Late stages of Ebola virus disease are associated with the presence of large numbers of virions in body fluids, tissues, and, especially, skin. Individuals who are exposed to patients infected with Ebola without proper barrier protection are at high risk of becoming infected. However, the Reston species has repeatedly been demonstrated to spread among nonhuman primates and possibly from primates to humans via the respiratory route. Fortunately, although the Reston species has been documented to be capable of infecting in humans, it does not appear to be pathogenic to humans.

**Pathogenesis**

Cell entry and tissue damage: After entering the body through mucous membranes, breaks in the skin, or parenterally, Ebola virus infects many different cell types. Macrophages and dendritic cells are probably the first to be infected; filoviruses replicate readily within these ubiquitous "sentinel" cells, causing their necrosis and releasing large numbers of new viral particles into extracellular fluid[4]. Infected macrophages produce tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, IL-6, macrophage chemotactic protein (MCP)-1, and nitric oxide (NO)[5]. Gastrointestinal dysfunction: Patients with Ebola virus disease commonly suffer from vomiting and diarrhea, which can result in acute volume depletion, hypotension, and shock. Coagulation defects: The coagulation defects seen in Ebola virus disease appear to be induced indirectly, through the host inflammatory response. The simultaneous occurrence of these two stimuli helps to explain the rapid development and severity of the coagulopathy in Ebola virus infection. Impairment of adaptive immunity — Failure of adaptive immunity through impaired dendritic cell function and lymphocyte apoptosis helps to explain how filoviruses are able to cause a severe, frequently fatal illness[6]. Ebola virus acts both directly and indirectly to disable antigen-specific immune responses. In vitro studies have shown that infected cells fail to undergo maturation and are unable to present antigens to naive lymphocytes, potentially explaining why patients dying from Ebola virus disease may not develop antibodies to the virus[7].

**Epidemiology**

As of 14 December (9 December for Liberia), a total of 18,603 clinically compatible cases (CCC) of Ebola virus disease (EVD), including 6,915 deaths, have been reported in the five currently affected countries (Guinea, Liberia, Sierra Leone, the US and Mali) and three previously affected countries (Nigeria, Senegal and Spain) since December 2013. On November 21, 2014, the WHO reported that 42 days had passed since the last case tested negative twice and

was discharged from a hospital in the Democratic Republic of the Congo. Out break of ebola virus is depicted in Table 1.

**Table 1: Known Cases and Outbreaks of Ebola Virus Disease, in Reverse Chronological Order.**

| Year(s) | Country | Ebola subtype | Reported number of human cases | Reported number of deaths among cases |
|---|---|---|---|---|
| August-November 2014 | Democratic Republic of the Congo | Zaire virus | 66 | 49 |
| March 2014-Present | Multiple countries | Zaire virus | 17942 | 6388 |
| November 2012-January 2013 | Uganda | Sudan virus | 6* | 3 |
| June-November 2012 | Democratic Republic of the Congo | Bundibugyo virus | 36* | 13 |
| June-October 2012 | Uganda | Sudan virus | 11* | 4* |
| December 2008-February 2009 | Democratic Republic of the Congo | Ebola virus | 32 | 15 |
| December 2007-January 2008 | Uganda | Bundibugyo virus | 149 | 37 |
| 2007 | Democratic Republic of the Congo | Ebola virus | 264 | 187 |
| 2004 | Russia | Ebola virus | 1 | 1 |
| 2004 | Sudan (South Sudan) | Sudan virus | 17 | 7 |
| November-December 2003 | Republic of the Congo | Ebola virus | 35 | 29 |
| December 2002-April 2003 | Republic of the Congo | Ebola virus | 143 | 128 |

On 10 October, 2014, ahealthcare worker at the Texas Health Presbyterian Hospital who attended the Ebola patient developed a fever on 10 October. The healthcare worker is in isolation, and confirmatory testing will be carried out by the CDC. Everyone who has had contact with the person since the onset of symptoms is under surveillance. The confirmed case was a healthcare worker who had onset of disease on 11 September 2014 while working at Mengo Hospital, Kampala. The case presented to Mpigi District Health Center on 17 September 2014, and transferred to Mengo Hospital, Kampala, on 23 September 2014. On admission the case presented with symptoms including fever, headache, abdominal pain, vomiting and diarrhoea and died on 28 September 2014.

**Transmission**

Epidemics of Ebola virus disease are generally thought to begin when an individual becomes

infected through contact with the meat or body fluids of an infected animal(Fig 2). Once the patient becomes ill or dies, the virus then spreads to others who come into direct contact with the infected individual's blood, skin, or other body fluids. Studies in laboratory primates have found that animals can be infected with Ebola virus through droplet inoculation of virus into the mouth or eyes[8,9], suggesting that human infection can result from the inadvertent transfer of virus to these sites from contaminated hands.


**Figure 2: Animals susceptible to EBOLA Virus of transmission of Ebola virus may be described as involving 3 stages, from primates or bats to humans**

**Person-to-person**: Person-to-person transmission occurs through direct contact with blood, body fluids, or skin of patients with Ebola virus disease, including those who have died from the infection[10,11]. As examples:

The ritual washing of Ebola victims at funerals has played a significant role in the spread of infection in past outbreaks, and has contributed to the epidemic in West Africa.

**Risk of transmission through different body fluids:** Transmission is most likely to occur through direct contact of broken skin or unprotected mucous membranes with virus-containing body fluids from a person who has developed signs and symptoms of illness[12]. According to the World Health Organization, the most infectious body fluids are blood, feces, and vomit[13]. Infectious virus has also been detected in urine, semen, saliva, breast milk, tears and sweat[14,15]. Infectious virus or viral RNA can persist in some of these fluids even after it is no longer detected in blood; however, the risk of transmission from persistent virus at these sites is not well established. As examples. A study of patient samples collected during the outbreak of Ebola Sudan virus disease in Gulu, Uganda in 2000 detected virus in the breast milk of a patient, even after virus was no longer detectable in the bloodstream[16]. Two children who were breastfed by infected mothers died of the disease. Risk of transmission through contact with contaminated surfaces — Ebola virus may be transmitted though contact with contaminated surfaces and

objects. The Centers for Disease Control and Prevention (CDC) indicates that virus on surfaces may remain infectious from hours to days[17,18]. There are no high-quality data to confirm transmission through exposure to contaminated surfaces, but it is clear that the potential risk can be greatly reduced or eliminated by proper environmental cleaning.

**Risk of airborne transmission:** There is no evidence that Ebola virus can spread from person to person by the respiratory route[19]. However, laboratory experiments have shown that Ebola virus released as a small-particle aerosol is highly infectious for rodents and nonhuman primates[20,21].

**Nosocomial transmission:** Transmission to healthcare workers may occur when appropriate personal protective equipment is not available or is not properly used, especially when caring for a severely ill patient who is not recognized as having Ebola virus disease. During the 2014 outbreak in West Africa, a large number of doctors and nurses have become infected with Ebola virus in Sierra Leone .Several factors have accounted for these infections, including incorrect triage and/or failure to recognize patients and corpses with Ebola virus disease; delayed laboratory diagnosis; limited availability of appropriate personal protective equipment and hand washing facilities; and inadequate training

**Transmission from animals:** Human infection with Ebola virus can occur through contact with wild animals (eg, hunting, butchering, and preparing meat from infected animals)[22,23]. In Mayibou, Gabon in 1996, for example, a dead chimpanzee found in the forest was butchered and eaten by 19 people, all of whom became severely ill over a short interval[24]. Direct transmission of Ebola virus infection from bats to wild primates or humans has not been proven. However, Ebola RNA sequences and antibodies to Ebola virus have been detected in bats captured in Central Africa[25,26,27].

**Management**

General principles of care are as follows:

- Supportive therapy with attention to intravascular volume, electrolytes, nutrition, and comfort care is of benefit to the patient
- Such therapy must be administered with strict attention to barrier isolation; all body fluids contain infectious virions and should be handled with great care
- No specific therapy is available that has demonstrated efficacy in the treatment of Ebola hemorrhagic fever
- There are no commercially available Ebola vaccines; however, neutralizing antibodies have been studied that may be useful in vaccine development or as passive prophylactic agents

At present, no specific anti-*Ebolavirus* agents are available. Agents that have been studied for the treatment or prevention of Ebola virus disease include the following:

- Ribavirin (possesses no demonstrable anti-*Ebolavirus* activity in vitro and has failed to protect *Ebolavirus* -infected primates)
- Nucleoside analogue inhibitors of S-adenosylhomocysteine hydrolase (SAH)
- Interferon beta
- Horse- or goat-derived immune globulins
- Human-derived convalescent immune globulin preparations
- Recombinant human interferon alfa-2
- Recombinant human monoclonal antibody against the envelope glycoprotein (GP) of Ebola virus
- DNA vaccines expressing either envelope GP or Nucleocapsid protein (NP) genes of Ebola virus
- Activated protein C[28]
- Recombinant inhibitor of factor VIIa/tissue factor[29]

**Signs And Symptoms**

EVD external bleeding. Laboratory findings include low white blood cell and platelet counts and elevated liver enzymes.is a severe acute viral illness often characterized by the sudden onset of fever, intense weakness, muscle pain, headache and sore throat. This is followed by vomiting, diarrhoea, rash, impaired kidney and liver function, and in some cases, both internal and People are infectious as long as their blood and secretions contain the virus. Ebola virus was isolated from semen 61 days after onset of illness in a man who was infected in a laboratory.*The incubation period, that is, the time interval from infection with the virus to onset of symptoms is 2 to 21 days.

**Main Symptoms**

**Figure 3: Symptoms of EHF**

As shown in Figure 3 main symptoms are Malaise, Myalgia, Severe headache, Conjunctival injection Pharyngitis, Abdominal pain, Vomiting, Diarrhea that can be bloody, Bleeding not related to injury (e.g., petechiae, ecchymosis, epistaxis), Unexplained hemorrhage, Erythematous maculopapular rash on the trunk.

**Diagnosis**

- Other diseases that should be ruled out before a diagnosis of EVD can be made include: malaria, typhoid fever, shigellosis, cholera, leptospirosis, plague, rickettsiosis, relapsing fever, meningitis, hepatitis and other viral haemorrhagic fevers.
- Ebola virus infections can be diagnosed definitively in a laboratory through several types of tests:
- Antibody-capture enzyme-linked immunosorbent assay (ELISA)

+antigen detection tests

- Serum neutralization test
- Reverse transcriptase polymerase chain reaction (RT-PCR) assay
- Electron microscopy
- Virus isolation by cell culture.

**Prevention**

It is not always possible to identify patients with Ebola early because initial symptoms may be non-specific. For this reason, health-care workers apply standard precautions consistently with all patients – regardless of their diagnosis.

When cases of the disease do appear, health care workers must be able to recognize a case of Ebola and be ready to employ practical viral hemorrhagic fever isolation precautions or barrier nursing techniques which include:

• Wearing of protective clothing (such as masks, gloves, gowns, and goggles)

• The use of infection-control measures (such as complete equipment sterilization and routine use of disinfectant)

• Isolation of ebola patients from contact with unprotected persons

The aim of all of these techniques is to avoid contact with the blood or secretions of an infected patient. If a patient with Ebola dies, it is equally important that direct contact with the body of the deceased patient be prevented.

**Vaccines**

Work continues on a vaccine for Ebola virus infection in primates. Sullivan et al reported on the combination of naked DNA vaccine capable of encoding Ebola proteins followed by a booster vaccination with a recombinant adenoviral vector expressing Ebola GP (Z)[30]. In this study, cynomolgus macaques were injected with 3 doses of the DNA vaccine, 1 dose every 4 weeks[31]. Twelve weeks later, the macaques were vaccinated with the recombinant adenoviral vector. After another 12 weeks, unvaccinated macaques and vaccinated macaques were injected with a lethal dose of Ebola virus. All of the unvaccinated macaques died, whereas none of the vaccinated macaques died. This work indicates that primates can be vaccinated against Ebola virus and can develop both a cell-mediated response and a humoral antibody response (thought to be a result of

the recombinant adenoviral vaccine).Although these vaccines protected rodents against an Ebola virus challenge, they did not protect cynomolgus macaques or rhesus macaques against exposure to the virus.

**Sub-unit vaccines (non-viral)**

**In** DNA plasmidEBOV genes are inserted and injecteddirectly into a patient's muscle which elicits immune response. DNA vaccinesgenerates antibody and cytotoxic T lymphocytes[32]. DNA vaccines expressing EBOV antigens NP, VP40, GPor VP35 alone or in combination have been evaluated in mice. Full protection was reported in mice and later in guinea pigs with optimized strategies.[33] In studies using EBOV DNA vaccines, consistently low survival rates have been documented for NHPs.[34]

**Virus-like particles (vlps)**

VLP vaccines are not like viral vaccines and these parts are inactivated by heat, chemical. EBOV-like particles were examined as potentialvaccine candidates and can be generated by the expression ofVP40 alone or along with GP.[35]While these surface proteins assemble much like infectious EBOV particles, VLPs lack NP,VP35, VP30, VP24 and L proteins.

**vector-based vaccines**

when genes encodingantigens of EBOV are inserted and expressed from the viral carrier which can be used as vaccine vectors.

**protease inhibitors**

VP30 is essential for transcription of Ebola and it isphosphorylated at N-terminal serine clusters andthreonine residues at positions 143 and 146. Host cellular Protein Phosphatase 1 (PP1) controls VP30dephosphorylation as expression of a PP1-bindingpeptide cdNIPP1 increased VP30 phosphorylation. 1E7-03 compound targeted at non-catalytic site of PP1inhibited the transcription and replication in cell culture model [36]

Here is a roundup of some of the Ebola treatments and vaccines in the research pipeline

**NIAID/GSK investigational Ebola vaccine**

The first safety tests of this vaccine, developed by scientists at the NIAID and GlaxoSmithKline, began last month in healthy volunteers at the NIH Clinical Center in Bethesda, MD, and in Great Britain. Testing is also expected to begin in a few African countries. Two variations of the vaccine will be tested. Both use a chimp cold virus to deliver segments of the Ebola gene into the volunteers' cells. The cells take the segment and produce an Ebola marker on its surface. A volunteer's immune system sees the marker and attacks. One version of the vaccine uses genetic segments from Zaire Ebola, the virus species causing the current outbreak, and Sudan Ebola. The

other version uses only Zaire Ebola genetic material. The vaccines cannot cause Ebola.

**Newlink genetics vaccine**

One month ago, the FDA gave New Link permission to begin the first clinical trials to test the company's Ebola vaccine, which was developed by Canada's Public Health Agency. Vaccine uses a weakened animal virus to deliver Ebola proteins to the person, triggering an immune response. NewLink spokesman Brian Wiley told WebMD Oct. 2 that the first trial will be done in healthy volunteers at Walter Reed National Military Medical Center in Bethesda, MD, and is expected to begin this month.

## CONCLUSION

Outbreak of EHF was the outcome of complex human behavioral, environmental factors on the public. There are many drugs which are under clinical and at pre-clinical level can target both viral and human host proteins. Development of rapid diagnostic tools should be given priority. Establishment of a system for continuous surveillance of emerging and re-emerging diseases is a need of the hour. The cost effective drugs should have global acceptance, accessibility, affordability. The awareness programmers should be conducted in large scale to eradicate the disease and we need to proceed with sense of urgency.

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