



## **Ebola virus disease: Getting to know a new emerging foe!**

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### **Abstract:**

Viral hemorrhagic fevers have been at the top of the severity scale in terms of morbidity and mortality among human beings. Many of the viruses have their reservoirs in animal kingdom and from time to time they get introduced to humans and cause sporadic outbreaks and epidemics. Thousands of people from the Western African region have already succumbed to the complications due to Ebola virus infection.

The South East Asian region including India has been affected by several outbreaks of communicable diseases like SARS, bird flu, swine flu etc. The current outbreak has been a global concern due to its spread beyond the African continent. WHO has declared EVD as an international health emergency and worldwide efforts have been enhanced to escalate research to find a vaccine or cure for the disease.

**Key words:** Ebola Virus, WHO, Africa, Fruit bats, Wild animals, South Asia, Haemorrhage

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**Introduction:**

Among all the tropical diseases, viral hemorrhagic fevers have been at the top of the severity scale in terms of morbidity and mortality among human beings. Many of the viruses have their reservoirs in animal kingdom and from time to time they get introduced to humans and cause sporadic outbreaks and epidemics.<sup>1,2,3</sup> Among the viral hemorrhagic fevers, Ebola virus poses severe challenges to the health systems of many countries, especially those of the developing countries.<sup>1</sup> Thousands of people from the Western African region have already succumbed to the complications due to Ebola virus infection.<sup>4</sup> This can also spread to various countries across the borders in addition to the country of origin.<sup>1,2</sup>

In 1976, Ebola virus disease (EVD) made its first appearance in the villages near Ebola River, in Democratic Republic of Congo (due to which the disease got the name Ebola) and Sudan. The current West African outbreak (2014) is the largest in history in terms of numbers and mortality. It has also spread to several countries starting in Guinea then spreading to Sierra Leone & Liberia and then by air to Nigeria, by land to Senegal.<sup>3,4,5</sup> These countries do not have a health system which is ready to tackle this burden due the lack of human and infrastructural resources, and these countries have just come out of long periods of political unrest. The current African case toll has crossed fourteen thousand.<sup>7</sup> Outbreaks are also reported from Boende, Equateur, and an isolated part of the Democratic Republic of Congo, which were not linked to the original West African outbreaks.<sup>3,6,7</sup>

The South East Asian region including India has been affected by several outbreaks of communicable diseases in the recent past, wherein several countries witnessed the morbidity and deaths of high

number of their citizens. Examples include SARS, bird flu, swine flu etc. The current outbreak has been a global concern due to its spread beyond the African continent and few confirmed cases from United States of America.

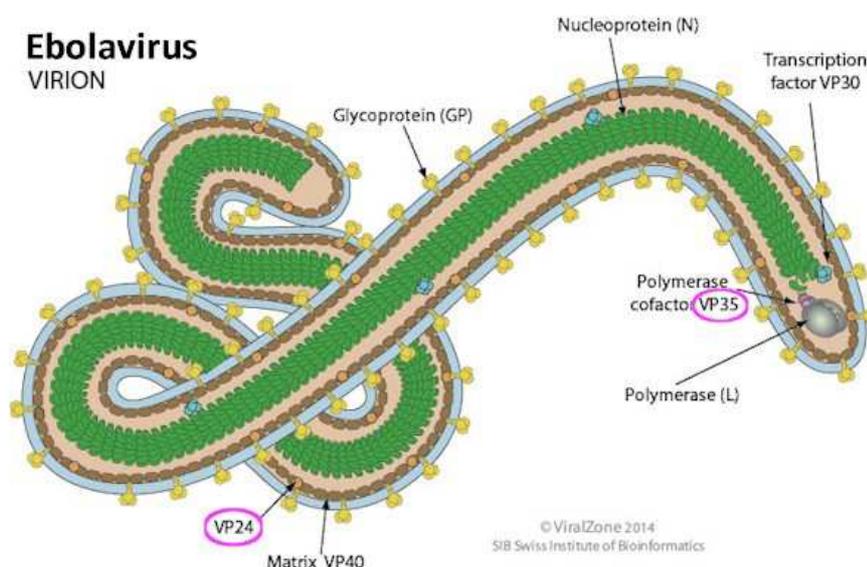
The sparse knowledge regarding the virulence factors and host responses have hampered the development of treatment modalities and vaccine against Ebola Virus Disease (EVD). WHO has declared EVD as an international health emergency and worldwide efforts have been enhanced to escalate research to find a vaccine or cure for the disease.

**Structural features and Pathogenesis: (S.B)**

Ebola and Marburg viruses are the only members of family Filoviridae in the order Mononegavirales<sup>8</sup>. Filoviruses are linear, enveloped, non-segmented and single stranded, negative sense RNA viruses. Ebola virus has a diameter of 80 nm but the length varies upto 14000nm assuming a shape of '6' or hairpin. It has seven genes which code for the various viral proteins- VP 34, VP30, VP24, VP 40, RNA dependent RNA polymerase, glycoprotein and nucleoprotein (Figure I<sup>9</sup>). All are monocistronic i.e. code for one single protein except the gene coding for glycoprotein which codes for two proteins- GPI and GPII, both linked with disulphide bonds. The ribonucleoprotein complex consists of the RNA genome surrounded by the nucleoprotein.

**Pathogenesis:**

Ebola virus disease is considered to be a classic zoonosis with persistence in a reservoir which is present in the endemic areas. . In Africa, a particular variety of fruit bat is considered the reservoir of infection for Zaire Ebola virus. Detection of virus RNA and antibodies have been found in three species of tree roosting bats- *Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*.<sup>10</sup>



**Figure I:** Structure of Ebola virus<sup>9</sup>

However, no reservoirs have been found for the other three African Ebola viruses. Apes, humans and other mammalian hosts are susceptible to infection and are considered end hosts. Bats are thought to directly transmit the infection to humans or indirectly by infecting other susceptible animals which are hunted for meat<sup>1, 4</sup>. Human to human infection is through close contact.

The possible mode of infection include close contact with blood, secretions, body fluids or organs of infected and dead animals, consumption of bush meat from infected animals, touching objects that have come in contact with the virus and parenteral transmission. Reuse of needles played an important part in the transmission of infection in the 1976 outbreak of Zaire and Sudan Ebola virus. The virus gains entry through the mucous membranes and abrasions in skin. There is no airborne transmission.

Ebola has a broad cell tropism and infects a wide range of cells<sup>8</sup>. They infect monocytes, macrophages, dendritic cells, fibroblasts, hepatic cells, adrenal cortical cells and endothelial cells, though monocytes, macrophages and dendritic cells are the early and preferred replication

sites. After infecting these cells, infection spreads to the regional lymph nodes through the lymphatics and to the liver and spleen through the blood. From these organs, the monocytes and macrophages migrate out and infect other organs and tissues disseminating the infection.

Ebola virus is taken up into the endosome, where they are exposed to a low-pH environment. Two endosomal proteases cathepsin B and cathepsin L can individually cleave Ebola virus GP1 to yield an approximately 18-kD N-terminal fragment, which is further digested by cathepsin B, leaving only GP2. This causes fusion between the viral envelope and the endosomal membrane leading to the release of the viral genome into the cytoplasm<sup>11</sup>.

Though Ebola virus can infect the endothelial cells, the damage resulting in haemorrhages has been attributed to the hepatocellular necrosis resulting in decreased synthesis of coagulation and plasma proteins. Due to infection of the adrenal cortex, there is impaired secretion of enzymes that synthesize steroids leading to hypotension and sodium loss with hypovolemia, both leading to shock, a feature commonly seen in end stage Ebola

virus hemorrhagic fever<sup>8</sup>. Although lymphocytes are not infected by Ebola virus there is large scale depletion in the spleen, thymus and lymph nodes of infected patients. This is mainly due to apoptosis which is triggered by the aberrant release of inflammatory mediators and cytokines like interleukin-1b (IL-1b), tumour necrosis factor- $\alpha$  (TNF $\alpha$ ), IL-6, IL-15, IL-16, IL-1 receptor antagonist, IL-10, NO-, IL-8, by the infected macrophages and monocytes- the so called 'Cytokine Storm'. The TNF and NO- are also responsible for the increasing endothelial permeability, decreased vascular tone and disseminate intravascular coagulation<sup>10</sup>. The various viral proteins especially VP35 cause inhibition of type I IFN response which is crucial for the Ebola virus survival.

### Clinical features: (S.M.)

Ebola virus disease (EVD) is a public health emergency of international concern and the outcome is frequently fatal.

The incubation period, i.e. the time interval from infection caused by the virus to the onset of symptoms is 2-21 days. Humans are not infectious until they develop symptoms.<sup>12</sup>

#### Symptoms:<sup>8, 13</sup>

Non-specific symptoms – abrupt onset of fever, chills, malaise followed by anorexia, headache, myalgia, arthralgia, sore throat.

Gastrointestinal symptoms – Nausea, vomiting, epigastric and abdominal pain and diarrhoea occurs in first few days.

Respiratory symptoms – chest pain, shortness of breath, cough, nasal discharge.

Vascular symptoms – conjunctival injection, symptoms of postural hypotension and oedema.

Neurological symptoms – headache, confusion and coma.

Haemorrhagic manifestations – haemorrhage seen in about 50% of the patients arise during the peak of illness and

include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal haemorrhages and post-mortem evidence of visceral haemorrhagic effusions.

A maculopapular rash associated with varying severity of erythema and desquamation can often be noted by day 5-7 of illness. This symptom is a valuable differential diagnostic feature and is usually followed by desquamation in survivors.

#### Initial evaluation<sup>13</sup>

Clinical criteria: fever  $> 38.6^{\circ}\text{C}$  [ $> 101.5^{\circ}\text{F}$ ] with additional symptoms listed above.

#### Epidemiological risk factors:

- Contact within previous 3 weeks with blood or other body fluids of patient with known or suspected EVD.
- Residence in or travel to area with active EVD transmission.
- Participation in funeral and burial rituals in disease endemic areas.
- Direct handling of bats, rodents, or primates from disease endemic areas.

Use personal protective equipment to examine patients with suspected infections.

Isolate patients immediately to prevent transmission.

#### Physical examination:<sup>14</sup>

Body temperature – temperature of  $39^{\circ}\text{C}$ - $40^{\circ}\text{C}$  early in the disease course is frequently observed. Wide swings in body temperature during the course of the illness, with drops below normal have been described.

Blood pressure – initially the haemodynamic parameters may be normal. Fatally infected patients are known to proceed through hypotension and shock to death.

Pulse – it has been noted that relative bradycardia is a common finding. As the disease progresses, in fatal cases there could be severe tachycardia.

Respiratory rate – it increases in fatal disease.

Rash – in a number of outbreak reports, rash was seen in 25%-52% of individuals. It is frequently described as being non-pruritic, erythematous, and maculopapular, sometimes beginning focally, and then becoming diffuse, generalised and confluent.

Haemorrhage – patients often develop multiple foci of mucosal hemorrhage, most evident in the conjunctiva, together with easy bruising and persistent bleeding from injection or venipuncture sites. However, hemorrhage is not seen in all patients, and massive bleeding is usually observed only in fatal cases when it is typically localized to the gastrointestinal tract. Intracranial haemorrhage has been described.

Other findings – there could be pharyngeal erythema with a complaint of sore throat, enlarged lymph nodes and tender hepatomegaly.

#### **Course of the disease:**

Non-fatal cases may improve around day 6-11.<sup>13</sup> In few patients, convalescence is extended and often associated with sequelae such as myelitis, recurrent hepatitis, psychosis or uveitis. Pregnant women have an increased risk of miscarriage, and clinical findings suggest a high death rate for children of infected mothers as the transmission could be through breast feeding or through close contact<sup>14</sup>.

Patients with fatal disease develop clinical signs early during infection and die typically between day 6 and 16 with hypovolemic shock and multi-organ failure<sup>8</sup>.

#### **Differential diagnosis**<sup>15</sup>

Malaria, Typhoid fever, Shigellosis, Cholera, Leptospirosis, Plague, Rickettsiosis, Relapsing Fever, Meningitis, Hepatitis and other viral haemorrhagic fevers.

#### **Laboratory diagnosis: (S.B)**

Any person who fits the definition of a case under investigation should be

subjected to a laboratory investigation for Ebola virus infection<sup>16</sup>. A case under investigation is defined as any person who has travelled to or stayed in a country that has reported at least one confirmed case of EVD, within a period of 21 days before the onset of symptoms, and who presents with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, diarrhoea, anorexia/loss of appetite, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, hiccup or inexplicable bleeding/haemorrhaging or who died suddenly and inexplicably<sup>17</sup>.

Specimens for molecular detection should ideally be taken when a patient exhibits symptoms that meet the case definition of EVD. Specimens should be collected with strict infection prevention and control measures adhered to throughout the process, including waste disposal and disinfection.

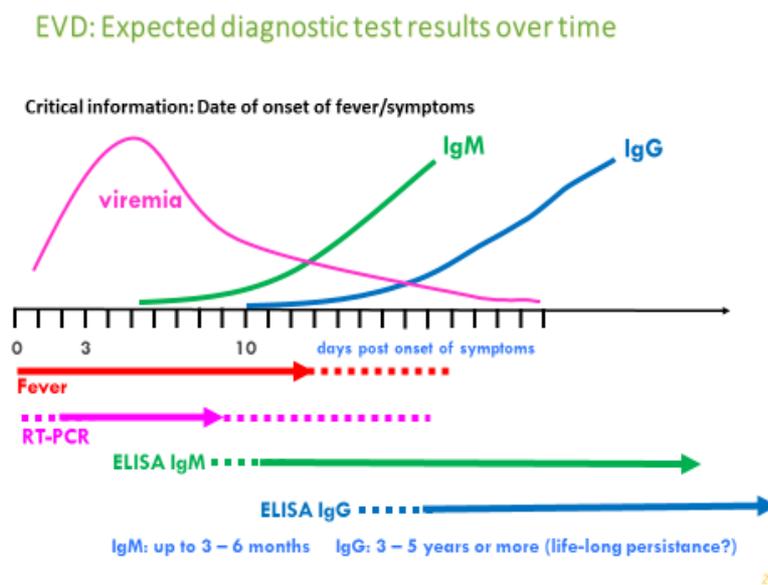
If specimens are collected less than 3 days after onset of symptoms, additional specimens will be needed if the test result on the first specimen is negative. The second specimen should be collected at least 48 hours after the first specimen. Whole blood for serological testing can be collected after 8 days of onset of symptoms (**Figure II**<sup>18</sup>).

At least 4 ml whole blood EDTA is collected for RT-PCR, while for serological tests clotted blood is the ideal specimen. Samples can be stored at room temperature for up to 24 hours, 0-5°C for one week and at -70 °C for long-term storage. They should be shipped on dry ice if the specimen is referred to a WHO Collaborating Centre.

The various tests available (**Table I**) for Ebola virus disease are: RT-PCR, Antigen capture ELISA, IgM and IgG antibody detection, virus isolation, immunohistochemistry

**Table I:** Laboratory tests for Ebola virus disease diagnosis

Investigation	Specimen	When after onset of symptoms	Adv/ Disadv	Biosafety Level
<b>RT-PCR</b>	4 ml EDTA blood	3-16 days	Most sensitive, should be performed in WHO	BSL 3 for non-inactivated specimen BSL 2 for inactivated specimen (inactivated with Guanidine Isothiacyanite)
<b>Antigen detection</b>	Serum sample	3-16 days	Seen early in disease and indicates acute infection	BSL 3 for non-inactivated specimen BSL 2 for inactivated specimen (inactivated with gamma radiation)
<b>IgM ELISA</b>	Serum, blood, tissues	2-30 to 168 days	Monitors immune response in confirmed EVD cases, IgM indicates presumptive diagnosis	BSL 3 for non-inactivated specimen BSL 2 for inactivated specimen (inactivated with gamma radiation)
<b>IgG ELISA</b>	Serum, Blood, Tissues	6/8 days- many years	Monitors immune response in confirmed EVD cases, A rise in titre indicates a presumptive diagnosis	BSL 3 for non-inactivated specimen BSL 2 for inactivated specimen (inactivated with gamma radiation)
<b>Virus Isolation</b>	Tissues, Blood		Can take several days	BSL 4
<b>Immunohistochemistry</b>	Tissues, dead wild animals		Used for retrospective diagnosis, localises viral antigen	BSL 3

**Figure II:** Expected diagnostic test result<sup>18</sup>**Treatment: (S.M.)****Patient management:**<sup>19</sup>

1. Currently, no specific therapy is available that has demonstrated efficacy in the treatment of EVD. In the absence of specific therapy, a number of modalities have been tried/ experimented. None of them have been scientifically validated.
2. General medical support is critical. Such care must be administered with strict attention to barrier isolation. All body fluids (blood, saliva, urine, and stool) contain infectious virions and should be handled with great care.
3. Surgical intervention generally follows a mistaken diagnosis in which Ebola associated abdominal signs are mistaken for a surgical abdominal emergency. Such a mistake may be fatal for the patient and for any surgical team members, who become contaminated with the patient's blood.
4. Survivors can produce infectious virions for prolonged periods. Therefore, strict barrier isolation in a private room away from traffic patterns must be maintained throughout the illness. Patient's urine,

stool, sputum and blood along with any objects that have come in contact with the patient or the patient's body fluids (such as laboratory equipment), should be disinfected with a 0.5% sodium hypochlorite solution.

5. Steroid therapy has no role.

6. There is no role for antibiotics unless there is evidence of secondary bacterial infection.

**Supportive Care:**

1. Supportive therapy with attention to intravascular volume, electrolytes, nutrition and comfort care is of benefit to the patient. Intravascular volume replenishment is one of the most important supportive measures.
2. For high grade fever, patient should be treated with only Paracetamol. No other analgesic, antipyretic and in particular Aspirin should be given in this case as these drugs may increase chances of bleeding. Tepid sponging should be done repeatedly to bring down the temperature immediately in case of high grade fever.
3. Due to repeated vomiting and diarrhoea patient may present with shock and electrolyte imbalance. Without vomiting and diarrhoea, patient also may have shock due to capillary leakage and

haemoconcentration may be observed in this case. Plenty of oral fluids may be advised in mild hypotensive cases or those who have no vomiting and diarrhoea.

4. There may be transient bone marrow suppression and patient may present with leucopenia and thrombocytopenia for which patient may develop bleeding from different sites and may also have superadded infection. Patient should be transfused with platelets when the count is below 20,000 cells/cu.mm or bleeding from any sites irrespective of platelet count.

5. In case of severe shock and vomiting, patient may be treated with intravenous fluids with crystalloids or colloids. Intravenous fluid therapy should be carefully monitored to avoid fluid overload as most of the deaths are associated with it due to rapid correction of fluid in severe shock. Blood transfusion may be required in those who have severe gastrointestinal bleeding and shock. Management should include replacement of coagulation factors and heparin if disseminated intravascular coagulation develops.

6. Patient may present with different organ involvement commonly liver and kidney. Patient may present with jaundice due to liver impairment and acute renal failure due to acute tubular necrosis in case of profound shock or direct renal involvement by Ebola virus. Patient may require dialysis in severe case of renal failure.

7. Patient should be carefully managed by gastroenterologist in case of severe liver dysfunction.

8. Patient may require ICU support for breathlessness due to lung involvement or critical condition.

9. High morbidity and mortality is associated with different co-morbid illnesses; therefore, EVD should be carefully treated in patients of hypertension, diabetes, coronary artery diseases and pregnancy. In particular, in those patients who are on anti-platelet therapy, drugs should be temporarily

stopped as these may increase chance of bleeding.

10. Co-infection with EVD should be immediately treated with proper antibiotics. In the early stage, if co-infection is not treated properly patient may develop sepsis and septic shock which may lead to fatal outcome.

#### **Diet and Activity:**

Nutrition is complicated by the patient's nausea, vomiting, and diarrhoea. Good hydration is to be ensured with good amount of protein supplements.

#### **Recovery:**

Recovery often requires months and delays may be expected before full resumption of normal activities. Weight gain and return of strength are slow. Ebola virus continues to be present for many weeks after resolution of the clinical illness. Semen from men recovering from Ebola infection has been shown to contain infectious virus and Ebola has been transmitted by sexual intercourse involving recovering men and their sex partners. Any individuals who were exposed to infected patients should be watched closely for signs of early Ebola virus disease.

#### **Other aspects:**

##### **Disposal of Dead Body**

Safe disposal of dead body must be done with proper precautions for prevention of transmission of EVD. Ebola virus is present in almost all kinds of body fluids like blood, saliva, urine, vomit, stool, nasal secretion, gastrointestinal secretion. Therefore, it is mandatory that one should not come in contact with these kinds of potentially infectious material. Relatives should be counselled properly regarding the mode of transmission of EVD and to adopt safe practices for the disposal of dead bodies. Ritual activities after death should be strictly avoided. Those persons who are dealing with the disposal of dead bodies require proper protection for prevention of transmission of Ebola virus. Dead body should be packed with

impermeable leak proof body bags for safe disposal and to prevent contamination.

### **Epidemiology (P.M.P., B.U., R.T.)**

#### **Agent factors:**

Ebola viruses are part of the family Filoviridae, which have filamentous structures. Family also includes Lassa fever and Marburg Viruses. Their genetic material is a single-stranded non-segmented RNA. So far five species of Ebola Virus have been identified: Zaire, Sudan, Ivory Coast, Bundibugyo and Reston, based on the predominant geographical area they affect.<sup>6</sup> Of these, Reston species are not known to cause disease among humans. The main reservoirs for Ebola virus are fruit bats, which act as subclinical carriers of Ebola virus.<sup>1,2</sup> They can survive for many weeks outside the human body, especially on the contaminated surfaces.

#### **Host factors:**

There is no particular preponderance for the virus towards a particular age group and no gender differences.

#### **Environmental factors:**

In the transmission of Ebola infection, many factors work in combination like fruit production by different trees, behaviour of the animals, drought and rainfall, in addition to the several unknown environmental factors. The presence of infected body fluids in the environment during different occasions can present a potential risk for indirect transmission of the virus.<sup>20</sup>

#### **Transmission:**

The most common speculation by several studies is that fruit bats of Pteropodidae family are the natural hosts of Ebola Viruses. Human beings acquire Ebola infection by close contact with the blood, bodily secretions and organs of the infected animals such as monkeys, fruit bats found ill or dead.<sup>3</sup> Later on, Ebola marks its way through human-to-human transmission occurring via direct contact (e.g. broken skin or mucous membranes)

with the blood, organs or other bodily fluids of infected people, and with contaminated surfaces and materials (e.g. bedding, clothing). Also, health-care workers carry the risk of infection while treating patients with suspected or confirmed EVD, especially when infection control precautions are not strictly practised.<sup>3</sup> Because the natural reservoir host of Ebola viruses has not yet been confirmed, the mechanism by which the virus first appears in a human outbreak is not completely understood. However, previous research findings suggest that the first patient becomes infected through contact with an infected animal.<sup>4</sup>

In Africa, Ebola is believed to spread as a result of handling bush meat (meat of wild animals for eating purpose) and contact with infected bats. So far there is no evidence of vectors like mosquitoes involving in the transmission.<sup>4</sup> During outbreaks of Ebola, healthcare settings like clinics, laboratories and hospitals also get involved and witness faster spread of the virus. Whenever staff in such health care settings do not use appropriate protective equipments like masks, gowns, gloves and goggles, chances of exposure to Ebola increase manifolds.<sup>1,4</sup>

### **Prevention and control (P.M.P., B.U., R.T.)**

#### **In health-care settings:**

Whenever providing patient care, it is preferable to use disposable equipments and/or instruments, by the healthcare personnel. If instruments and equipments are not disposable, they must be sterilized before using them again.<sup>4</sup> In addition to this; during the times of outbreak, healthcare workers should always follow standard precautions regarding hand hygiene, respiratory hygiene, using personal protective equipment, safe injection practices.<sup>4,5</sup> Laboratory samples taken for investigation of Ebola infection should only be handled by the trained staff in suitably equipped laboratories.

Laboratory personnel should apply extra infection control measures to prevent contact with the patient's body fluids and any contaminated articles or surfaces.<sup>3,4,5</sup>

#### **In the community:**

Creating and improving awareness about risk factors for Ebola infection and protective measures is an effective way to reduce transmission in the community. Gloves and appropriate personal protective equipment should be worn when taking care of ill patients at home. Regular hand washing is required during the care of patients at home.<sup>2,3</sup> People who have recovered from the disease can still transmit the virus through their body fluids for up to 7 weeks after recovery.<sup>3</sup> After this period, they can no longer spread the virus.<sup>4</sup> 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.<sup>20, 21, 22, 23</sup>

Thus the contagious nature of the Ebola virus and the presence of the susceptible individuals along with the suitable environmental conditions make way for the high possibility of a pandemic of Ebola virus. This can even include regions like South Asia and Europe which have not reported cases yet.<sup>24</sup> But readiness of the healthcare system cannot be over emphasized. Approaches to curtail the Ebola virus spread should be multipronged i.e. at healthcare setting, community and the travel population. This should alert the healthcare systems of all the countries and call for the regional as well as global co-operation between the health systems of different countries so that the future outbreaks of Ebola virus and other hemorrhagic viral fevers can be prevented. This could also be the first step in reversing the chances of a pandemic.

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