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An overview on Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF)

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ABSTRACT

Ebola virus disease (EVD), also known as Ebola haemorrhagic fever, is a severe, often fatal illness in humans. EVD outbreaks have a case fatality rate of up to 90%. EVD outbreaks occur primarily in remote villages in Central and West Africa, near tropical rainforests. The virus is transmitted to people from wild animals and spreads in the human population through human-to-human transmission. Fruit bats of the *Pteropodidae* family are considered to be the natural host of the Ebola virus. Severely ill patients require intensive supportive care. No licensed specific treatment or vaccine is available for use in people or animals.

Key words: Ebola virus disease (EVD), Ebola hemorrhagic fever (EHF), Viral haemorrhagic fever.

INTRODUCTION

In Africa, fruit bats, particularly species of the genera *Hypsignathus monstrosus, Epomops franqueti* and *Myonycteris torquata*, are considered possible natural hosts for Ebola virus. As a result, the geographic distribution of Ebola viruses may overlap with the range of the fruit bats.

Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF) is the human disease caused by the Ebola virus. Symptoms typically start two days to three weeks after contracting the virus, with a fever, sore throat, muscle pains, and headaches. Typically nausea, vomiting, and diarrhea follow, along with decreased functioning of the liver and kidneys. At this point, some people begin to have bleeding problems. (EVD Factsheet WHO)

The virus may be acquired upon contact with blood or bodily fluids of an infected animal (commonly monkeys or fruit bats). *(EVD Factsheet WHO)* Spread through the air has not been documented in the natural environment. Fruit bats are believed to carry and spread the virus without being affected. Once human infection occurs, the disease may spread between people as well. Male survivors may be able to transmit the disease via semen for nearly two months. In order to make the diagnosis, typically other diseases with similar symptoms such as malaria, cholera and other viral hemorrhagic fevers are first excluded. To confirm the diagnosis blood samples are tested for viral antibodies, viral RNA, or the virus itself. (EVD Factsheet WHO)

Prevention includes decreasing the spread of disease from infected monkeys and pigs to humans. This may be done by checking such animals for infection and killing and properly disposing of the bodies if the disease is discovered. Properly cooking meat and wearing protective clothing when handling meat may also be helpful, as are

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wearing protective clothing and washing hands when around a person with the disease. Samples of bodily fluids and tissues from people with the disease should be handled with special caution. (EVD Factsheet WHO)

There is no specific treatment for the disease; efforts to help persons who are infected include giving either oral rehydration therapy (slightly sweet and salty water to drink) or intravenous fluids. (EVD Factsheet WHO) The disease has high mortality rate: often killing between 50% and 90% of those infected with the virus. (EVD Factsheet WHO)(C.M.Fauquet) EVD was first identified in Sudan and the Democratic Republic of the Congo. The disease typically occurs in outbreaks in tropical regions of Sub-Saharan Africa. (EVD Factsheet WHO)

Ebola virus in animals

Although non-human primates have been a source of infection for humans, they are not thought to be the reservoir but rather an accidental host like human beings. Since 1994, Ebola outbreaks from the EBOV and TAFV species have been observed in chimpanzees and gorillas. RESTV has caused severe EVD outbreaks in macaque monkeys (Macaca fascicularis) farmed in Philippines and detected in monkeys imported into the USA in 1989, 1990 and 1996, and in monkeys imported to Italy from Philippines in 1992.Since 2008, RESTV viruses have been detected during several outbreaks of a deadly disease in pigs in People's Republic of China and Philippines. Asymptomatic infection in pigs has been reported and experimental inoculations have shown that RESTV cannot cause disease in pigs.

Virology

Genome

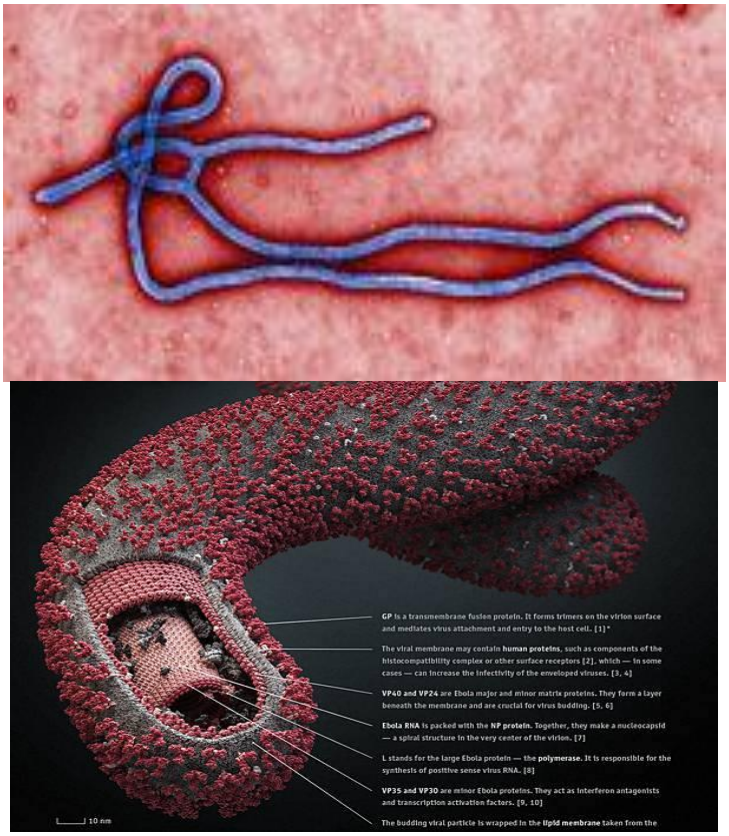


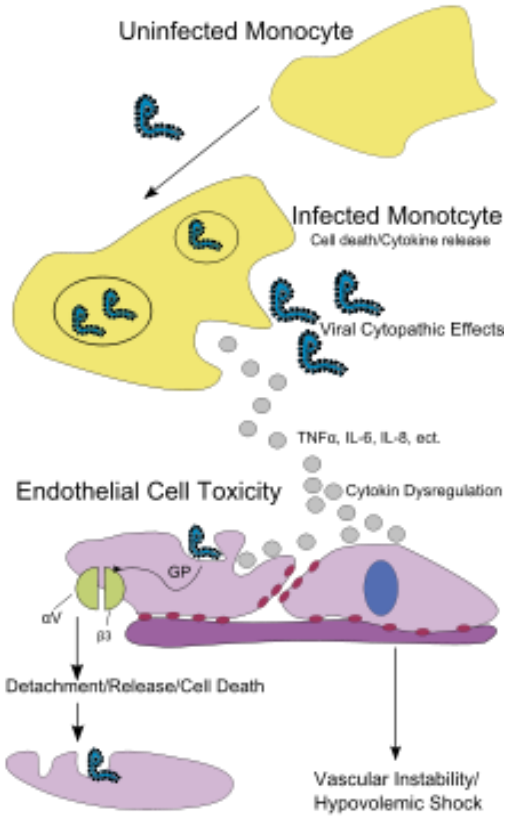
Fig: 1 Electron micrograph of an Ebola virus virion

Structure

Like all filo viruses, ebolavirions are filamentous particles that may appear in the shape of a shepherd's crook or in the shape of a "U" or a "6", and they may be coiled, toroid, or branched.(Kiley MP) In general, ebolavirions are 80 nm in width, but vary somewhat in length. In

general, the median particle length of Ebola viruses ranges from 974 to 1,086 nm (in contrast to marburgvirions, whose median particle length was measured at 795–828 nm), but particles as long as 14,000 nm have been detected in tissue culture. (Geisbert TW)

Pathophysiology



Source: WHO

Fig 2: Pathogenesis schematic

Pathogenesis schematic

Endothelial cells, mononuclear phagocytes, and hepatocytes are the main targets of infection. After infection, a secreted glycoprotein (sGP) known as the Ebola virus glycoprotein (GP) is synthesized. Ebola replication overwhelms protein synthesis of infected cells and host immune defenses. The GP forms a trimeric complex, which binds the virus to the endothelial cells lining the interior surface of blood vessels. The sGP forms a dimeric protein that interferes with the signaling of neutrophils, a type of white blood cell, which allows the virus to evade the immune system by inhibiting early steps of neutrophil activation. These white blood cells also serve as carriers to transport the virus throughout the entire body to places such as the lymph nodes, liver, lungs, and spleen. (Smith, Tara)

The presence of viral particles and cell damage resulting from budding causes the release of cytokines (to be specific, TNF-α, IL-6, IL-8, etc.), which are the signaling molecules for fever and inflammation. The cytopathic effect, from infection in the endothelial cells, results in a loss of vascular integrity. This loss in vascular integrity is furthered with synthesis of GP, which educes specific integrins responsible for cell adhesion to the inter-cellular structure, and damage to the liver, which leads to coagulopathy. (Sullivan N)

Transmission

Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals. In Africa, infection has been documented through the handling of infected

chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rainforest.

Ebola then spreads in the community through human-to-human transmission, with infection resulting from direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated with such fluids. 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. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness.

Health-care 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.

Among workers in contact with monkeys or pigs infected with Reston Ebola virus, several infections have been documented in people who were clinically asymptomatic. Thus, RESTV appears less capable of causing disease in humans than other Ebola species.

However, the only available evidence available comes from healthy adult males. It would be premature to extrapolate the health effects of the virus to all population groups, such as immuno-compromised persons, persons with underlying medical conditions, pregnant women and children. More studies of RESTV are needed before definitive conclusions can be drawn about the pathogenicity and virulence of this virus in humans.

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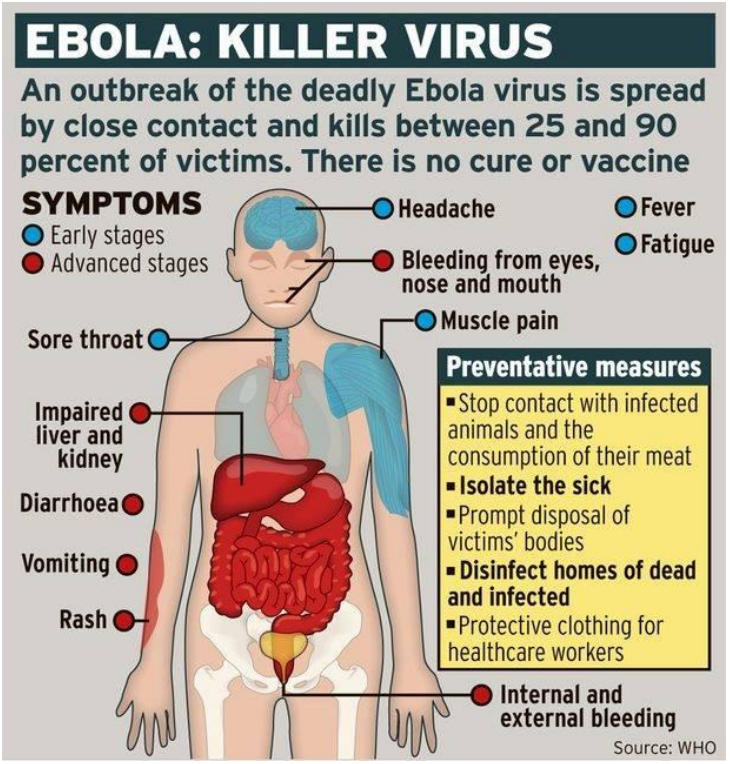
Signs and symptoms

Signs and symptoms of Ebola usually begin suddenly with a flu-like stage characterized by fatigue, fever, headaches, and joint, muscle, and abdominal pain.(Gatherer D)(CDC) Vomiting, diarrhea and loss of appetite are also common.(CDC) Less common symptoms include the following: sore throat, chest pain, hiccups, shortness of breath and trouble swallowing. (CDC) The average time between contracting the infection and the start of symptoms is 8 to 10 days, but it can vary between 2 and 21 days.(CDC) Skin manifestations may include a maculopapular rash (in about 50% of cases).(Hoenen T) Early symptoms of EVD may be similar to those of malaria, dengue fever, or other tropical fevers, before the disease progresses to the bleeding phase.(Gatherer D) 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



Bleeding

All people infected show some symptoms of circulatory system involvement, including impaired blood clotting. (Hoenen T) In 40–50% of cases, bleeding from puncture sites and mucous membranes (e.g. gastrointestinal tract, nose, vagina and gums) has been reported. (Medscape)

In the bleeding phase, internal and subcutaneous bleeding may present itself through reddening of the eyes and bloody vomit. (Gatherer D) Bleeding into the skin may create petechiae, purpura, ecchymoses, and hematomas (especially around needle injection sites). Types of bleeding known to occur with Ebola virus disease include vomiting blood, coughing it up or blood in the stool. Heavy bleeding is rare and is usually confined to the gastrointestinal tract. (Hoenen T)(Fisher-Hoch SP) In general, the development of bleeding symptoms often indicates a worse prognosis and this blood loss can result in death. (Gatherer). The incubation period, that is, the time interval from infection with the virus to onset of symptoms is 2 to 21 days.

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.

Samples from patients are an extreme biohazard risk; testing should be conducted under maximum biological containment conditions.

Vaccines

No licensed vaccine for EVD is available. Several vaccines are being tested, but none are available for clinical use. (EVD Factsheet WHO)(Hoenen T)(Choi JH) The most promising candidates are DNA vaccines (65) or vaccines derived from adenoviruses, (Sullivan NJ) vesicular stomatitis Indiana virus (VSIV) (Geisbert TW) or filovirus-like particles (VLPs) (Warfield KL) because these candidates could protect nonhuman primates from Ebola virus-induced disease. DNA vaccines, adenovirus-based vaccines, and VSIV-based vaccines have entered clinical trials. (Oplinger)(Martin JE)(Bush))

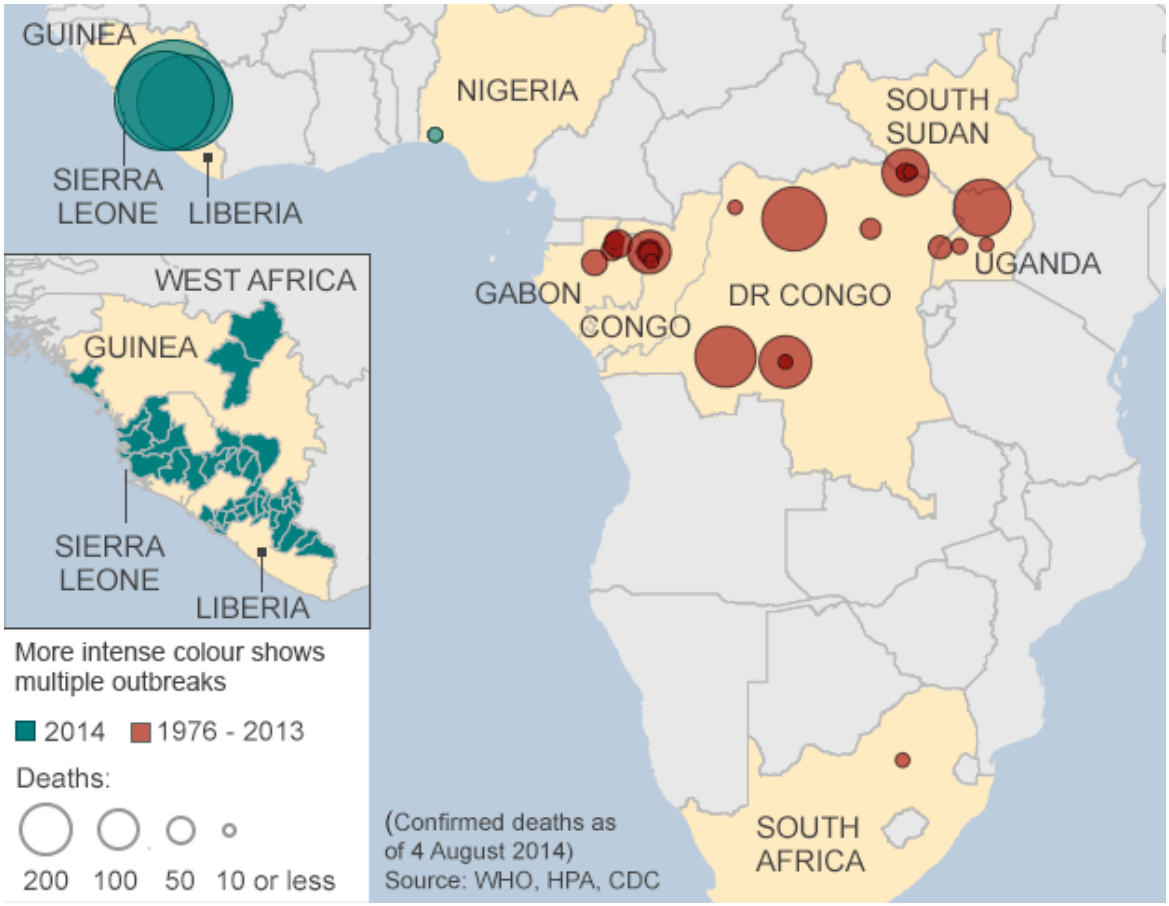
Vaccines have protected nonhuman primates. Immunization takes six months, which impedes the counter-epidemic use of the vaccines. Searching for a quicker onset of effectiveness, in 2003 a vaccine using an adenoviral (ADV) vector carrying the Ebola spike protein was tested on crab-eating macaques. Twenty-eight days later they were challenged with the virus and remained resistant. (Sullivan NJ) A vaccine based on attenuated recombinant vesicular stomatitis virus (VSV) vector carrying either the Ebola glycoprotein or the Marburg glycoprotein in 2005 protected nonhuman primates,(Jones SM)) opening clinical trials in humans.(Oplinger) The study by October completed the first human trial, over three months giving three vaccinations safely inducing an immune response. Individuals for a year were followed, and, in 2006, a study testing a faster-acting, single-shot vaccine began; this new study was completed in 2008. Trying the vaccine on a strain of Ebola that more resembles one that infects humans is the next step. On 6 December 2011, the development of a successful vaccine against Ebola for mice was reported. Unlike the predecessors, it can be freeze-dried and thus stored for long periods in wait for an outbreak.

Treatment

No Ebola virus-specific treatment exists.(Choi JH) Treatment is primarily supportive in nature and includes minimizing invasive procedures, balancing fluids and electrolytes to counter dehydration, administration of anticoagulants early in infection to prevent or control disseminated intravascular coagulation, administration of procoagulants late in infection to control bleeding, maintaining oxygen levels, pain management, and the use of medications to treat bacterial or fungal secondary infections. (Bausch Jeffs) (Bnkoghé) Early treatment may increase the chance of survival. (Sierra Leone) A number of experimental treatments is being studied. (Briggs)

Prognosis

The disease has a high mortality rate: often between 50 percent and 90 percent. (EVD Factsheet WHO)(C.M. Fauquet) If an infected person survives, recovery may be quick and complete. Prolonged cases are often complicated by the occurrence of long-term problems, such as inflammation of the testicles, joint pains, muscle pains, skin peeling, or hair loss. Eye symptoms, such as light sensitivity, excess tearing; iritis, iridocyclitis, choroiditis and blindness have also been described. EBOV and SUDV may be able to persist in the semen of some survivors for up to seven weeks, which could give rise to infections and disease via sexual intercourse. (EVD Factsheet WHO)



Source: WHO, HPA, CDC

Medications

Favipiravir looks like it may be useful in a mouse model of the disease.(Gatherer) Estrogen receptor drugs used to treat infertility and breast cancer (clomiphene and toremifene) inhibit the progress of Ebola virus in infected mice. Johansen Ninety percent of the mice treated with clomiphene and fifty percent of those treated with toremifene survived the tests. Johansen given their oral availability and history of human use, these drugs would be candidates for treating Ebola virus infection in remote geographical locations, either on their own or together with other antiviral drugs.

Antibodies

The researchers looking at slides of cultures of cells that make monoclonal antibodies. These are grown in a lab and the researchers are analyzing the products to select the most promising of them. During an outbreak 1999 in the Democratic Republic of the Congo, seven of eight people who received blood transfusions from individuals who had previously survived the infection survived

themselves. (Mupapa K) However, this potential treatment is considered controversial. (Feldmann) Intravenous antibodies appear to be protective in non-human primates who have been exposed to large doses of Ebola. (Saphire). On July 31, 2014, an experimental drug, ZMapp, was first tested on humans. It was administered to two Americans who had been infected with Ebola. Both people appeared to have had positive results.

Other treatments

Other promising treatments rely on antisense technology. Both small interfering RNAs (siRNAs) and phosphorodiamidate morpholino oligomers (PMOs) targeting the Zaire Ebola virus (ZEBOV) RNA polymerase L protein could prevent disease in nonhuman primates.(Geisbert TW) (Warren TK)TKM-Ebola is a small-interfering RNA compound, currently tested in a phase I clinical trial in people.(Helen Branswell) (Pollackl)

Prevention and control

Controlling Reston Ebola virus in domestic animals

No animal vaccine against RESTV is available. Routine cleaning and disinfection of pig or monkey farms (with sodium hypochlorite or other detergents) should be effective in inactivating the virus. If an outbreak is suspected, the premises should be quarantined immediately. Culling of infected animals, with close supervision of burial or incineration of carcasses, may be necessary to reduce the risk of animal-to-human transmission. Restricting or banning the movement of animals from infected farms to other areas can reduce the spread of the disease. As RESTV outbreaks in pigs and monkeys have preceded human infections, the establishment of an active animal health surveillance system to detect new cases is essential in providing early warning for veterinary and human public health authorities.

Reducing the risk of Ebola infection in people

In the absence of effective treatment and a human vaccine, raising awareness of the risk factors for Ebola infection and the protective measures individuals can take is the only way to reduce human infection and death. In Africa, during EVD outbreaks, educational public health messages for risk reduction 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 in the community arising from direct or close contact with infected patients, particularly with their bodily fluids. Close physical contact with Ebola patients should be avoided. 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.
- Communities affected by Ebola should inform the population about the nature of the disease and about outbreak containment measures, including burial of the dead. People who have died from Ebola should be promptly and safely buried.

Pig farms in Africa can play a role in the amplification of infection because of the presence of fruit bats on these farms. Appropriate biosecurity measures should be in place to limit transmission. For RESTV, educational public health messages should focus on reducing the risk of pig-to-human transmission as a result of unsafe animal husbandry and slaughtering practices, and unsafe consumption of fresh blood, raw milk or animal tissue. Gloves and other appropriate protective clothing should be worn when handling sick animals or their tissues and when slaughtering animals. In regions where RESTV has been reported in pigs, all animal products (blood, meat and milk) should be thoroughly cooked before eating. Some peoples are believing using hot water with salt to take bath can prevent ebola viral fever. But there is no evidence for that.

Conclusion

Human-to-human transmission of the Ebola virus is primarily associated with direct or indirect contact with blood and body fluids. Transmission to health-care workers has been reported when appropriate infection control measures have not been observed. It is not always possible to identify patients with EBV early because initial symptoms may be non-specific. For this reason, it

is important that health-care workers apply standard precautions consistently with all patients – regardless of their diagnosis – in all work practices at all times. These include basic hand hygiene, respiratory hygiene, and the use of personal protective equipment (according to the risk of splashes or other contact with infected materials), safe injection practices and safe burial practices. Health-care workers caring for patients with suspected or confirmed Ebola virus should apply, in addition to standard precautions, other infection control measures to avoid any exposure to the patient's blood and body fluids and direct unprotected contact with the possibly contaminated environment. When in close contact (within 1 meter) of patients with EBV, health-care workers should wear face protection (a face shield or a medical mask and goggles), a clean, non-sterile long-sleeved gown, and gloves (sterile gloves for some procedures).Laboratory workers are also at risk. Samples taken from suspected human and animal Ebola cases for diagnosis should be handled by trained staff and processed in suitably equipped laboratories.

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