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A Review on Ebola

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HUMAN

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ABSTRACT

Ebola virus disease (EVD), formerly known as Ebola haemorrhagic fever, is a severe, often fatal illness in humans. The virus is transmitted to people from wild animals and spreads in the human population through human to human transmission. The average EVD case fatality rate is around 50%. Case fatality rates have varied from 25% to 90% in past outbreaks. The first EVD outbreaks occurred in remote villages in Central Africa, near tropical rainforests, but the most recent outbreak in West Africa has involved major urban as well as rural areas. Community engagement is key to successfully controlling outbreaks. Good outbreak control relies on applying a package of interventions, namely case management, surveillance and contact tracing, a good laboratory service, safe burials and social mobilization. Early supportive care with rehydration, symptomatic treatment improves survival. There is as yet no licensed treatment proven to neutralize the virus but a range of blood, immunological and drug therapies are under development. There are currently no licensed Ebola vaccines but 2 potential candidates are undergoing evaluation.

INTRODUCTION

Ebola virus disease (**EVD**), **Ebola hemorrhagic fever** (**EHF**), or simply **Ebola** is a disease of humans and other primates caused by an ebola virus. Symptoms start two days to three weeks after contracting the virus, with a fever, sore throat, muscle pain, and headaches. Typically, vomiting, diarrhea, and rash follow, along with decreased function of the liver and kidneys. Around this time, affected people may begin to bleed both within the body and externally.

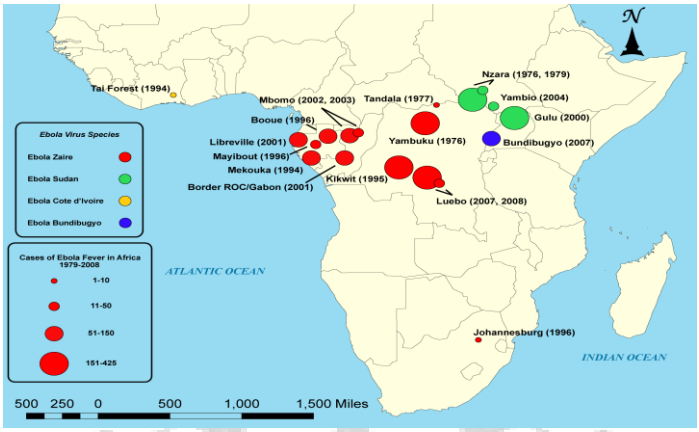
The virus may be acquired upon contact with blood or other bodily fluids of an infected human or other animal. Spreading through the air has not been documented in the natural environment. Fruit bats are believed to be a carrier and may spread the virus without being affected. Once human infection occurs,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

Outbreak control requires community engagement, case management, surveillance and contact tracing, a good laboratory service, and safe burials. Prevention includes decreasing the spread of disease from infected animals to humans. This may be done by checking such animals for infection, 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 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.

No specific treatment for the disease is yet available. Efforts to help those who are infected are supportive and include giving either oral rehydration therapy (slightly sweet and salty water to drink) or intravenous fluids. This supportive care improves outcomes. The disease has a high risk of death, killing between 50% and 90% of those infected with the virus. EVD was first identified in an area of Sudan that is now part of South Sudan, as well as in Zaire (now the Democratic Republic of the Congo).

The disease typically occurs in outbreaks in tropical regions of sub-Saharan Africa. From 1976 (when it was first identified) through 2013, the World Health Organization reported a total of 1,716 cases. The largest outbreak to date is the ongoing 2014 West African Ebola outbreak, which is affecting Guinea, Sierra Leone, Liberia, and Nigeria[1].

HISTORY



Cases of ebola fever in Africa from 1979 to 2008.

The first recorded outbreak of EBD occurred in Southern Sudan in June 1976. A second outbreak soon followed in the Democratic Republic of the Congo (then Zaire).] Virus isolated from both outbreaks was named "Ebola virus" after the Ebola River, located near the Zaire outbreak. Reports conflict about who initially coined the name: either Karl Johnson of the American CDC teamor Belgian researchers. Although it was assumed that the two outbreaks were connected, scientists later realized that they were caused by distinct species of filoviruses, Sudan virus and Ebola virus. In late 1989, Hazelton Research Products' Reston Quarantine Unit in Reston, Virginia suffered a mysterious outbreak of fatal illness (initially diagnosed as Simia Heamorrhagic Fever Virus (SHFV)) among a shipment of crab-eating macaque monkeys imported from the Philippines. Hazelton's veterinary pathologist sent tissue samples from dead animals to the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) at Fort Detrick, Maryland, where a laboratory test known as an ELISA assay showed antibodies to Ebola virus. An electron microscopist from USAMRIID discovered filoviruses similar in appearance to Ebola in the tissue samples sent from Hazelton Research Products' Reston Quarantine Unit.

Shortly afterward, a US Army team headquartered at USAMRIID went into action to euthanize the monkeys which had not yet died, bringing those monkeys and those which had already died of the disease to Ft. Detrick for study by the Army's veterinary pathologists and virologists, and eventual disposal under safe conditions. Blood samples were taken from 178 animal handlers during the incident. Of those, six animal handlers eventually seroconverted, including one who had cut himself with a bloody scalpel. When the handlers did not become ill, the CDC concluded that the virus had a very low pathogenicity to humans.

The Philippines and the United States had no previous cases of Ebola infection, and upon further isolation, researchers concluded it was another strain of Ebola, or a new filovirus of Asian origin, which they named Reston ebolavirus (REBOV) after the location of the incident.

POINTS REGARDING EBOLA VIRUS

1. What is Ebola virus disease?

Ebola virus disease (formerly known as Ebola haemorrhagic fever) is a severe, often fatal illness, with a death rate of up to 90%. The illness affects humans and nonhuman primates (monkeys, gorillas and chimpanzees).

Ebola first appeared in 1976 in two simultaneous outbreaks, one in a village near the Ebola River in the Democratic Republic of Congo, and the other in a remote area of Sudan.

The origin of the virus is unknown but fruit bats (Pteropodidae) are considered the likely host of the Ebola virus, based on available evidence.

2. How do people become infected with the virus?

In the current outbreak in West Africa, the majority of cases in humans have occurred as a result of human to human transmission. Infection occurs from direct contact through broken skin or mucous membranes with the blood, or other bodily fluids or secretions (stool, urine, saliva, semen) of infected people. Infection can also occur if broken skin or mucous membranes of a healthy person come into contact with environments that have become contaminated with an Ebola patient’s infectious fluids such assoiled clothing, bed linen, or used needles.

More than 100 health care workers have been exposed to the virus while caring for Ebola patients. This happens because they may not have been wearing personal protection equipment or were not properly applying infection prevention and control measures when caring for the patients. Health care providers at all levels of the health system – hospitals, clinics, and health posts – should be briefed on the nature of the disease and how it is transmitted, and strictly follow recommended infection control precautions.

WHO does not advise families or communities to care for individuals who may present with symptoms of Ebola virus disease in their homes. Rather, seek treatment in a hospital or treatment centre staffed by doctors and nurses qualified and equipped to treat Ebola virus victims. If you choose to care for your loved one at home, WHO strongly advises you to notify your local public health authority and receive appropriate training, equipment (gloves and personal protective equipment [PPE]) for treatment, instructions on proper removal and disposal of PPE, and information on how to prevent further infection and transmission of the disease to yourself, other family members, or the community. Additional transmission has occurred in communities during funerals and burial rituals. Burial ceremonies in which mourners have direct contact with the body of the deceased person have played a role in the transmission of Ebola. Persons who have died of Ebola must be handled using strong protective clothing and gloves and must be buried immediately. WHO advises that the deceased be handled and buried by trained case management professionals, who are equipped to properly bury the dead.

People are infectious as long as their blood and secretions contain the virus. For this reason, infected patients receive close monitoring from medical professionals and receive laboratory tests to ensure the virus is no longer circulating in their systems before they return home. When the medical professionals determine it is okay for the patient to return home, they are no longer infectious and cannot infect anyone else in their communities. Men who have recovered from the illness can still spread the virus to their partner through their semen for up to 7 weeks after recovery. For this reason, it is important for men to avoid sexual intercourse for at least 7 weeks after recovery or to wear condoms if having sexual intercourse during 7 weeks after recovery. Generally, a person must come into contact with an animal that has Ebola and it can then spread within the community from human to human.

3. Who is most at risk?

During an outbreak, those at higher risk of infection are:

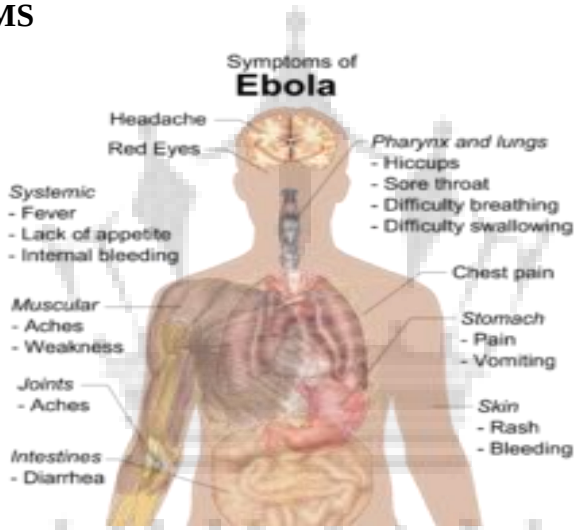
1. Health workers;

2. Family members or others in close contact with infected people; and

3.Mourners who have direct contact with the bodies of the deceased as part of burial ceremonies.

More research is needed to understand if some groups, such as immune compromised people or those with other underlying health conditions, are more susceptible than others to contracting the virus.

SIGNS AND SYMPTOMS



- Fatigue, fever, headaches, joint, muscle, and abdominal pain

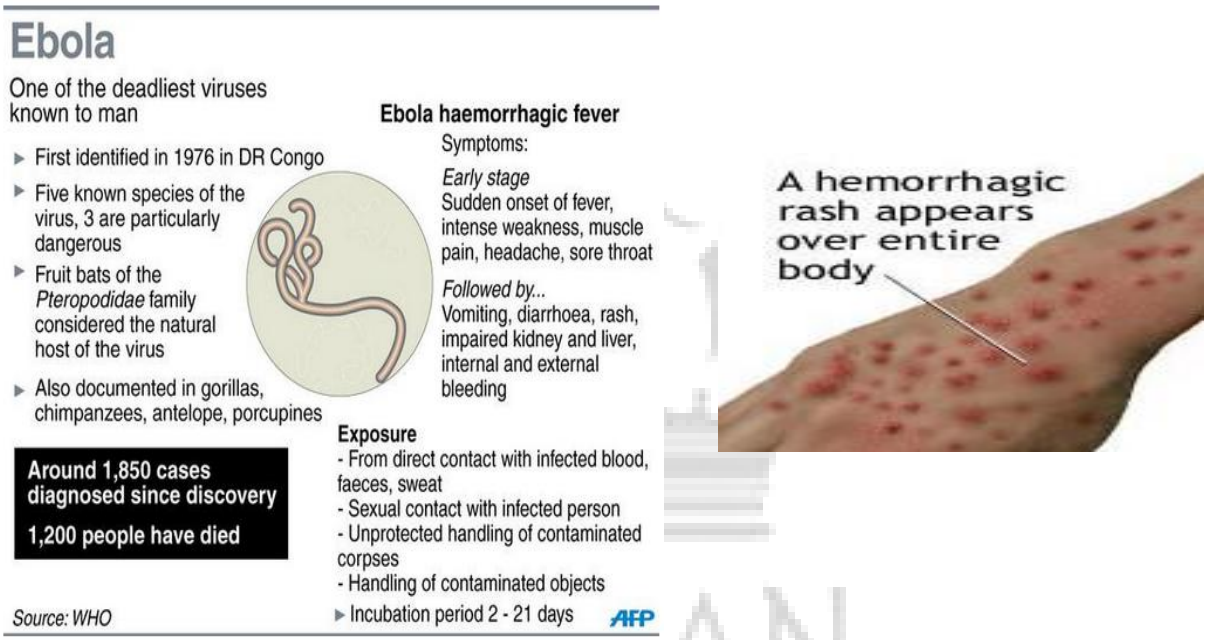
- Vomiting, diarrhea, and loss of appetite

Less common symptoms include the following:

sore throat, chest pain, hiccups, shortness of breath, and trouble swallowing

The average time between contracting the infection and start of symptoms (incubation periods) is 8 to 10 days, but it can vary between 2 and 21 days. 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. In 40–50% of cases, bleeding from puncture sites and mucous membranes (e.g., gastrointestinal tract, nose, vagina, and gums) has been reported. In the bleeding phase, which typically begins five to seven days after first symptoms, internal and subcutaneous bleeding may

present itself in the form of reddened eyes and bloody vomit. Bleeding into the skin may create petechiae, purpura, ecchymosed, and hematomas (especially around needle injection sites). Sufferers may cough up blood, vomit it, or excrete it in their stool. Heavy bleeding is rare and is usually confined to the gastrointestinal tract. In general, the development of bleeding symptoms often indicates a worse prognosis and this blood loss can result in death. All infected people show some signs of circulatory system involvement, including impaired blood clotting. If the infected person does not recover, death due to multiple organ dysfunction syndromes occurs within 7 to 16 days (usually between days 8 and 9 after first symptoms).



CAUSES

EVD is caused by four of five viruses classified in the genus Ebola virus, family *Filoviridae*, order *Mononegavirales*. The four disease causing viruses are Bundibugyo virus (BDBV), Sudan virus (SUDV), Taï Forest virus (TAFV), and one called, simply, Ebola virus (EBOV, formerly Zaire Ebola virus). Ebola virus is the sole member of the *Zaire ebola virus* species and the most dangerous of the known Ebola disease causing viruses, as well as being responsible for the largest number of outbreaks. The fifth virus, Reston virus (RESTV), is not thought to be disease causing in humans. These five viruses are closely related to the Marburg viruses.

Transmission

Human to human transmission can occur via direct contact with blood or bodily fluids from an infected person (including embalming of an infected dead person) or by contact with objects contaminated by the virus, particularly needles and syringes. Their body fluids with Ebola virus include saliva, mucus, vomit, feces, sweat, tears, breast milk, urine, and semen.

Entry points include the nose, mouth, eyes, or open wounds, cuts and abrasions. The potential for widespread EVD infections is considered low as the disease is only spread by direct contact with the secretions from someone who is showing signs of infection. The symptoms limit a person's ability to spread the disease as they are often too sick to travel. Because dead bodies are still infectious, traditional burial rituals may spread the disease. Nearly two thirds of the cases of Ebola in Guinea during the 2014 outbreak are believed to be due to burial practices.

Semen may be infectious in survivors for up to 7 weeks. It is not entirely clear how an outbreak is initially started. The initial infection is believed to occur after ebola virus is transmitted to a human by contact with an infected animal's body fluids.

One of the primary reasons for spread is that the health systems in the part of Africa where the disease occurs function poorly. Medical workers who do not wear appropriate protective clothing may contract the disease. Hospital transmission has occurred in African countries due to the reuse of needles and lack of universal precautions. Some healthcare centers caring for people with the disease do not have running water. Airborne transmission has not been documented during EVD outbreaks. They are, however, infectious as breathable 0.8–1.2 m laboratory-

generated droplets. The virus has been shown to travel, without contact, from pigs to permits, although the same study failed to demonstrate similar transmission between non-human primates.

Bats drop partially eaten fruits and pulp, then land mammals such as gorillas and duikers, feed on these fallen fruits. This chain of events forms a possible indirect means of transmission from the natural host to animal populations, which has led to research towards viral shedding in the saliva of bats. Fruit production, animal behavior, and other factors vary at different times and places that may trigger outbreaks among animal population

Reservoir

Bush meat being prepared for cooking in Ghana, 2013. Human consumption of equatorial animals in Africa in the form of bush meat has been linked to the transmission of diseases to people, including Ebola.

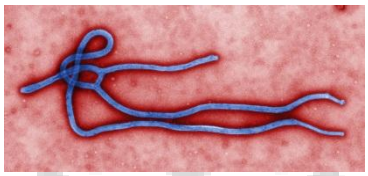
Bats are considered the most likely natural reservoir of the EBOV. Plants, arthropods, and birds were also considered. Bats were known to reside in the cotton factory in which the first cases for the 1976 and 1979 outbreaks were observed, and they have also been implicated in Marburg virus infections in 1975 and 1980. Of 24 plant species and 19 vertebrate species experimentally inoculated with EBOV, only bats became infected. The absence of clinical signs in these bats is characteristic of a reservoir species. In a 2002–2003 survey of 1,030 animals including 679 bats from Gabon and the Republic of the Congo, 13 fruit bats were found to contain EBOV RNA fragments. As of 2005, three types of fruit bats (*Hypsignathus monstrous*, *Epomops franqueti*, and *Myonycteris torquata*) have been identified as being in contact with EBOV. They are now suspected to represent the EBOV reservoir hosts. Antibodies against Zaire and Reston viruses have been found in fruit bats in Bangladesh, thus identifying potential virus hosts and signs of the filoviruses in Asia. Between 1976 and 1998, in 30,000 mammals, birds, reptiles, amphibians and arthropods sampled from outbreak regions, no *ebolavirus* was detected apart from some genetic traces found in six rodents (*Mus setulosus* and *Praomys*) and one shrew (*Sylvisorex ollula*) collected from the Central Africa Republic. Traces of EBOV were detected in the carcasses of gorillas and chimpanzees during outbreaks in 2001 and 2003, which later became

the source of human infections. However, the high lethality from infection in these species makes them unlikely as a natural reservoir.

Transmission between natural reservoir and humans is rare, and outbreaks are usually traceable to a single case where an individual has handled the carcass of gorilla, chimpanzee or duiker. Fruit bats are also eaten by people in parts of West Africa where they are smoked, grilled or made into a spicy soup.

Virology

Genome



Electron micrograph of an Ebola virus virion

Like all mononegaviruses, ebolavirions contain linear non segmented, single-strand, non-infectious RNA genomes of negative polarity that possesses inverse complementary 3' and 5' termini, do not possess a 5' cap, are not polyadenylated, and are not covalently linked to a protein Ebolavirus genomes are approximately 19 kilobase paired long and contain seven genes in the order 3'-UTR-*NP*-*VP35*-*VP40*-*GP*-*VP30*-*VP24*-*L*-5'-UTR. The genomes of the five different ebolaviruses (BDBV, EBOV, RESTV, SUDV, and TAFV) differ in sequence and the number and location of gene overlaps.

Structure

Like all filoviruses, 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. In general, ebolavirions are 80 nm in width, but vary somewhat in length. In general, the median particle length of ebolaviruses 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.

Replication

The ebola virus life cycle begins with virion attachment to specific cell-surface receptors, followed by fusion of the virion envelope with cellular membranes and the concomitant release of the virus nucleocapsid into the cytosol. The viral RNA polymerase, encoded by the L gene, partially uncoats the nucleocapsid and transcribes the genes into positive-strand mRANs, which are then, translates into structural and nonstructural proteins. Ebolavirus RNA polymerase (L) binds to a single promoter located at the 3' end of the genome. Transcription either terminates after a gene or continues to the next gene downstream. This means that genes close to the 3' end of the genome are transcribed in the greatest abundance, whereas those toward the 5' end are least likely to be transcribed. The gene order is, therefore, a simple but effective form of transcriptional regulation. The most abundant protein produced is the nucleoprotein, whose concentration in the cell determines when L switches from gene transcription to genome replication. Replication results in full-length, positive-strand antigenomes that are, in turn, transcribed into negative-strand virus progeny genome copy. Newly synthesized structural proteins and genomes self-assemble and accumulate near the inside of the cell membrane. Virions bud off from the cell, gaining their envelopes from the cellular membrane they bud from.

PATHOPHYSIOLOGY

Endothelial cells, macrophages, monocytes, and liver cells 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 trimetric complex, which binds the virus to the endothelial cells lining the interior surface of blood vessels. The SGP forms a diametric 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.

DIAGNOSIS

The travel and work history along with exposure to wild life are important to consider when the diagnosis of EVD is suspected. The diagnosis is confirmed by isolating the virus, detecting its

RNA or proteins, or detecting antibiotics against the virus in a person's blood. Isolating the virus by cell culture, detecting the viral RNA by polymerase chain reaction (PCR) and detecting proteins by enzyme linked immunosorbent assay (ELISA) works best early and in those who have died from the disease. Detecting antibodies against the virus works best late in the disease and in those who recover.

During an outbreak, virus isolation is often not feasible. The most common diagnostic methods are therefore real-time PCR and ELISA detection of proteins, which can be performed in field or mobile hospitals. Filovirions can be seen and identified in cell culture by electron microscopy due to their unique filamentous shapes, but electron microscopy cannot tell the difference between the various filoviruses despite there being some length differences.

Differential Diagnosis

The symptoms of EVD are similar to those of Marburg virus disease. It can also easily be confused with many other diseases common in Equatorial Africa such as other viral hemorrhagic fever, falciparum malaria, typhoid fever, shigellosis, rickettsial diseases such as typhus, cholera, negative septicemia, borrelis is such as relapsing fever or EHEC enteritis. Other infectious diseases that should be included in the differential diagnosis include the following: leptospirosis, scrub typhus, plague, Q fever, candidiasis, histoplasmosis, trypanosomiasis, visceralleishmaniasis, hemorrhagic smallpox, measles, and fulminant viral hepatitis.

PREVENTION

Infection Control and Containment

The risk of transmission is increased among those caring for people infected. Recommended measures when caring for those who are infected include isolating them, sterilizing equipment and surface, and wearing protective clothing, including masks, gloves, gowns, and goggles. If a person with Ebola dies, direct contact with the body of the deceased patient should be avoided. In order to reduce the spread, World Health Organization recommends raising community awareness of the risk factors for Ebola infection and the protective measures individuals can take. These include avoiding contact with infected people and regular hand washing using soap and water. Traditional burial rituals, especially those requiring washing or embalming of bodies,

should be discouraged or modified. Social anthropologists may help find alternatives to traditional rules for burials. Airline crews are instructed to isolate anyone who has symptoms resembling Ebola virus. The Ebola virus can be eliminated with heat (heating for 30 to 60 minutes at 60 °C or boiling for 5 minutes). On surfaces, some lipid solvents such as some alcohol-based products, detergents, sodium hypochlorite (bleach) or calcium hypochlorite (bleaching powder), and other suitable disinfectants at appropriate concentrations can be used as disinfectants.

In laboratories where diagnostic testing is carried out, biosafety level 4-equivalent containment is required, since Ebola viruses are World Health Organization Risk Group 4 pathogens. Laboratory researchers must be properly trained in BSL-4 practices and wear proper personal protective equipment.

Quarantine

Quarantine, also known as enforced isolation, is usually effective in decreasing spread. Governments often quarantine areas where the disease is occurring or individuals who may be infected. In the United States, the law allows quarantine of those infected with Ebola. During the 2014 outbreak, Liberia closed schools.

Contact Tracing

Contact tracing is regarded as important to contain an outbreak. It involves finding everyone who had close contact with infected individuals and watching for signs of illness for 21 days. If any of these contacts comes down with the disease, they should be isolated, tested, and treated. Then repeat the process by tracing the contacts.

TREATMENT

1. Standard Support

No ebola virus-specific treatment is currently approved. However, survival is improved by early supportive care with rehydration and symptomatic treatment. Treatment is primarily supportive in nature. These measures may include management of pain, nausea, fever and anxiety, as well as rehydration via the oral or by intravenous route. Blood products such as packed red blood

cells, platelets or fresh frozen plasma may also be used. Other regulators of coagulation have also been tried including heparin in an effort to prevent disseminated intravascular coagulation and clotting factors to decrease bleeding. Antimalarial medications and antibiotics are often used before the diagnosis is confirmed, though there is no evidence to suggest such treatment is in any way helpful.

2. Intensive Care

Intensive care is often used in the developed world. This may include maintaining blood volume and electrolytes (salts) balance as well as treating any bacterial infections that may develop. Dialysis may be needed for kidney failure while extracorporeal membrane oxygenation may be used for lung dysfunction.

3. Alternative Medicine

The Food and Drug Administration (FDA) advises people to be careful of advertisements making unverified or fraudulent claims of benefits supposedly gained from various anti-Ebola products. The FDA has already sent out at least one letter of warning to a seller of colloidal silver who made unverified claims of Ebola related benefits, supposedly derived from the use of their products.

PROGNOSIS

The disease has a high mortality rate which varies between 25 percent and 90 percent. As of September 2014, information from WHO across all occurrences to date puts the overall case fatality rate at 50%. The 90% fatality rate was only reported in one outbreak in the Congo in 2003 and this value is widely misreported in mainstream media over many years implying or stating 90% is the average while not mentioning 25% or 50%. There are indications based on variations in death rate between countries that early and effective treatment of symptoms (e.g., supportive care to prevent dehydration) may reduce the fatality rate significantly. 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.

EPIDEMIOLOGY

The disease typically occurs in outbreaks in tropical regions of Sub*Saharan Africa From 1976 (when it was first identified) through 2013, the World Health Organization reported 1,716 confirmed cases. The largest outbreak to date is the ongoing 2014 West Africa Ebola virus outbreak, which is affecting Guinea, Sierra Leone, Liberia and Nigeria. As of 3 October, 7,497 suspected cases have been identified, with 3,439 deaths.

1. 1976 Sudan Outbreak

An outbreak of Ebola virus disease (EVD) occurred between June and November 1976 in Southern Sudan and was caused by Sudan virus, a member of the genus Ebola virus. The Sudan outbreak infected 284 people and killed 151, with the first identifiable case on 27 June. Also in 1976, an outbreak of EVD caused by Ebola virus (formerly called Zaire ebola virus) began in Yambuku, a small rural village in Mongala District in Northern Democratic Republic of the Congo (then known as Zaire), with the first case identified on 26 August. The first victim, and the index case for the disease, was village school headmaster Mabalo Lokela, who had toured an area near the Central African Republic border along the Ebola river between 12–22 August. On 8 September, he died of what would become known as the Ebola virus species of the ebola virus. Subsequently a number of other cases were reported, almost all centered on the Yambuku mission hospital or having close contact with another case. 318 cases and 280 deaths (88% fatality rate) occurred in the DRC. The Ebola outbreak was contained with the help of the World Health Organization and transport from the Congolese air force, by quarantining villagers, sterilizing medical equipment, and providing protective clothing. The virus responsible for the initial outbreak, first thought to be Marburg viruses, was later identified as a new type of virus related to Marburg, and named after the nearby Ebola River.

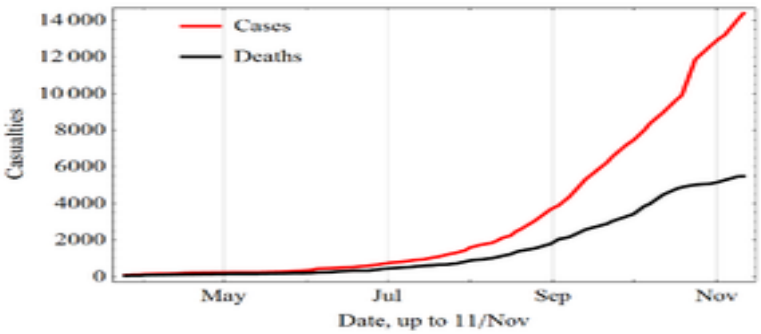
2. 1995 to 2013

The second major outbreak occurred in 1995 in the Democratic Republic of Congo, affecting 315 and killing 254. The next major outbreak occurred in Uganda in 2000, affecting 425 and

killing 224; in this case the Sudan virus was found to be the ebola virus species responsible for the outbreak. In 2003, there was an outbreak in the Republic of Congo that affected 143 and killed 128, a death rate of 90%, the highest to date.

In August 2007, 103 people were infected by a suspected hemorrhagic fever outbreak in the village of Kampungu, Democratic Republic of the Congo. The outbreak started after the funerals of two village chiefs, and 217 people in four villages fell ill. The 2007 outbreak eventually affected 264 individuals and resulted in the deaths of 187.On 30 November 2007, the Uganda Ministry of Health confirmed an outbreak of Ebola in the Bundibugyo District in Western Uganda. After confirmation of samples tested by the United States National Reference Laboratories and the Centers for Disease Control, the World Health Organization confirmed the presence of a new species of Ebola virus, which was tentatively named Bundibugyo. The WHO reported 149 cases of this new strain and 37 of those led to deaths. The WHO confirmed two small outbreaks in Uganda in 2012. The first outbreak affected 7 people and resulted in the death of 4 and the second affected 24, resulting in the death of 17. The Sudan variant was responsible for both outbreaks. On 17 August 2012, the Ministry of Health of the Democratic Republic of the Congo reported an outbreak of the Ebola-Bundibugyo variant in the eastern region. Other than its discovery in 2007, this was the only time that this variant has been identified as the ebola virus responsible for an outbreak. The WHO revealed that the virus had sickened 57 people and claimed 29 lives. The probable cause of the outbreak was tainted bush meat hunted by local villagers around the towns of Isiro and Viadana.

3. 2014 West African outbreak



Increase over time in the cases and deaths during the 2013–2014 outbreak

In March 2014, the World Health Organization (WHO) reported a major Ebola outbreak in Guinea, a western African nation. Researchers traced the outbreak to a two-year old child who died on 28 December 2013. The disease then rapidly spread to the neighboring countries of Liberia and Sierra Leone. It is the largest Ebola outbreak ever documented, and the first recorded in the region. On 8 August 2014, the WHO declared the epidemic to be an international public health emergency. Urging the world to offer aid to the affected regions, the Director-General said, "Countries affected to date simply do not have the capacity to manage an outbreak of this size and complexity on their own. I urge the international community to provide this support on the most urgent basis possible." By mid-August 2014, Doctors without Borders reported the situation in Liberia's capital Monrovia as "catastrophic" and "deteriorating daily". They reported that fears of Ebola among staff members and patients had shut down much of the city's health system, leaving many people without treatment for other conditions. By late August 2014, the disease had spread to Nigeria, and one case was reported in Senegal. On 30 September 2014, the first confirmed case of Ebola in the United States was diagnosed. The patient died eight days later.

Aside from the human cost, the outbreak has severely eroded the economies of the affected countries. A Financial Times report suggested the economic impact of the outbreak could kill more people than the virus itself. As of 23 September, in the three hardest hit countries, Liberia, Sierra Leone, and Guinea, there were only 893 treatment beds available while the current need was 2122. In 26 September statement, the WHO said, "The Ebola epidemic ravaging parts of West Africa is the most severe acute public health emergency seen in modern times. Never before in recorded history has a biosafety level four pathogen infected so many people so quickly, over such a broad geographical area, for so long".

By 3 October 2014, 7,492 suspected cases and 3,439 deaths had been reported; however, the World Health Organization has said that these numbers may be vastly underestimated. The WHO reports that more than 216 healthcare workers are among the dead, partly due to the lack of equipment and long hours[7].

SOCIETY AND CULTURE

Weaponization

Ebolavirus is classified as a biosafety level 4 agent, as well as a category A bioterrorism agent by the Centers for Disease Control and Prevention. It has the potential to be weaponized for use in biological warfare, and was investigated by the Biopreparat for such use, but might be difficult to prepare as a weapon of mass destruction because the virus becomes ineffective quickly in open air.

RESEARCH

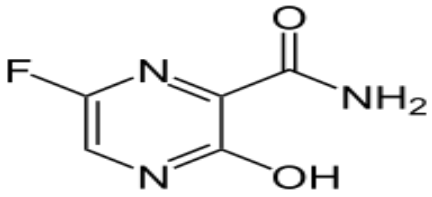
A number of experimental treatments are being studied. In the United States, the Food and Drug Administration (FDA)'s animal efficacy rule is being used to demonstrate reasonable safety to obtain permission to treat people who are infected with Ebola. It is being used because the normal path for testing drugs is not possible for diseases caused by dangerous pathogens or toxins. Experimental drugs are made available for use with the approval of regulatory agencies under named patient programs, known in the US as "expanded access". On 12 August 2014 the WHO released a statement that the use of not yet proven treatments is ethical in certain situations in an effort to treat or prevent the disease.

A. MEDICATIONS

1. Antiviral

A number of antiviral medications are being studied.

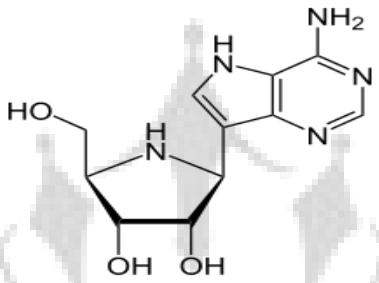
1) Favipiravir, an anti-viral drug approved in Japan for stockpiling against influenza pandemics, appears to be useful in a mouse model of Ebola. On 4 October 2014, it was reported that a French nun who contracted Ebola while volunteering in Liberia was cured with Favipiravir treatment.



Favipiravir

Mechanism of action: The mechanism of its actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase. Favipiravir does not inhibit RNA or DNA synthesis in mammalian cells and is not toxic to them.

2) BCX4430 is a broad-spectrum molecule antiviral developed by BioCryst pharmaceuticals and undergoing animal testing as a potential human treatment for Ebola by USAMRIID. The drug has been approved to progress to Phase 1 trials, expected late in 2014. Brincidofovir, another broad-spectrum antiviral drug, has been granted an emergency FDA approval as an investigational new drug for the treatment of Ebola, after *in vitro* tests found it to be effective against Ebola virus.

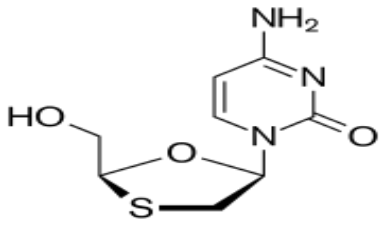


BCX4430

Mechanism of action: BCX4430 (**Immucillin-A**) is an antiviral drug, an adenosine analog (a type of nucleoside analog). It is developed by BioCryst pharmaceuticals with funding from NIAID, originally intended as a treatment for Hepatitis C, but subsequently developed as a potential treatment for deadly filovirus infections such as Ebola virus disease and Marburg virus disease.

3) Lamivudine, an antiviral drug which is usually used to treat HIV/AIDS, was reported in September 2014 to have been used successfully to treat 13 out of 15 Ebola-infected patients by a doctor in Liberia, as part of a combination therapy also involving intravenous fluids and antibiotics to combat opportunistic bacterial infection of Ebola-compromised internal organs. Western virologists have however expressed caution about the results, due to the small number of patients treated and confounding factors present. Researchers at the NIH stated that lamivudine had so far failed to demonstrate anti-Ebola activity in preliminary *in vitro* tests, but that they would continue to test it under different conditions and would progress it to trials if

even slight evidence for efficacy is found. Lamivudine has been used for treatment of chronic hepatitis B at a lower dose than for treatment of HIV. It improves the seroconversion of e-antigen positive hepatitis B and also improves histology staging of the liver.



Lamivudine

Mechanism of action: Lamivudine is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B virus. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

B: Antisense technology

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. TKM-Ebola is a small interfering RNA compound, currently being tested in a Phase I clinical trial in humans. Sarepta Therapeutics has completed a Phase I clinical trial with its Morpholino oligo targeting Ebola.

C: Other

Two selective estrogen receptor modulators used to treat infertility and breast cancer (clomiphene and toremifene) have been found to inhibit the progress of Ebola virus *in vitro* as well as in infected mice. Ninety percent of the mice treated with clomiphene and fifty percent of

those treated with toremifene survived the tests. The study authors conclude that 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.

A 2014 study found that three ion channel blockers used in the treatment of heart arrhythmias, amiodarone, dronedarone and verapamil, block the entry of Ebola virus into cells *in vitro*.

Melatonin has also been suggested as a potential treatment for Ebola based on promising *in vitro* results. Mapp is a monoclonal antibody vaccine. The limited supply of the drug has been used to treat a small number of individuals infected with the Ebola virus. Although some individuals have recovered, the outcome is not considered statistically significant.

Blood Products

The WHO has stated that transfusion of whole blood or purified serum from Ebola survivors is the therapy with the greatest potential to be implemented immediately, although there is little information as to its efficacy. September 2014, WHO issued an interim guideline for this therapy. The blood serum from those who have survived an infection is currently being studied to see if it is an effective treatment. During a meeting arranged by WHO, this research was deemed to be a top priority. Seven of eight people with Ebola survived after receiving a transfusion of blood donated by individuals who had previously survived the infection in 1999 outbreak in the Democratic Republic of the Congo. This treatment, however, was started late in the disease meaning they may have already been recovering on their own and the rest of their care was better than usual.] Thus this potential treatment remains controversial. Intravenous appear to be protective in non-human primates who have been exposed to large doses of Ebola. The World Health Organisation has approved the use of convalescent serum and whole blood products to treat people with Ebola.

Vaccine

As of September 2014, no vaccine was approved by the United States Food and Drug Administration (FDA) for clinical use in humans. It was hoped that one would be initially available by November 2014. The most promising candidates are DNA vaccinesur vaccines

derived from adenoviruses, vesicular stomatitis Indiana virus (VSIV) or filovirus-like particles (VLPs) because these candidates could protect nonhuman primates from ebolavirus-induced disease. DNA vaccines, adenovirus-based vaccines, and VSIV-based vaccines have entered clinical trials. 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. 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, opening clinical trials in humans. Over a three month human trial, three vaccinations safely induced 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. An experimental vaccine made by researchers at Canada's national laboratory in Winnipeg was used, in 2009, to pre-emptively treat a German scientist who might have been infected during a lab accident. However, actual EBOV infection was never demonstrated beyond doubt. Experimentally, recombinant vesicular stomatitis Indiana virus (VSIV) expressing the glycoprotein of EBOV or SUDV has been used successfully in nonhuman primate models as post-exposure prophylaxis. The CDC's recommendations are currently under review. Simultaneous phase 1 trials of an experimental vaccine known as the NIAID/GSK vaccine commenced in September 2014. GlaxoSmithKline and the NIH jointly developed the vaccine, based on a modified chimpanzee adenovirus, and contains parts of the Zaire and Sudan ebola strains. If this phase is completed successfully, the vaccine will be fast tracked for use in West Africa. In preparation for this, GSK is preparing a stockpile of 10,000 doses.

Availability in the most affected regions

The unavailability of experimental treatments in the most affected regions during the 2014 outbreak spurred controversy, with some calling for experimental drugs to be made more widely available in Africa on a humanitarian basis, and others warning that making unproven

experimental drugs widely available would be unethical, especially in light of past experimentation conducted in developing countries by Western drug companies[8].

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