REVIEW

Transmission of Ebola Virus Disease: An Overview

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ABSTRACT

Ebola is a viral illness of which the initial symptoms can include a sudden fever, intense weakness, muscle pain and a sore throat, according to the World Health Organization (WHO). Airborne transmission of Ebola virus has been hypothesized but not demonstrated in humans. Ebola is not spread through the air or by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bushmeat (wild animals hunted for food) and contact with infected bats. The disease infects humans through close contact with infected animals, including chimpanzees, fruit bats, and forest antelope. Ebola virus can be transmitted by direct contact with blood, bodily fluids, or skin of patients with or who died of Ebola virus disease. As of late October 2014, the World Health Organization reported 13,567 suspected cases and 4922 deaths, although the agency believes that this substantially understates the magnitude of the outbreak. Experimental vaccines and treatments for Ebola are under development, but they have not yet been fully tested for safety or effectiveness.

Key Words: EVD (Ebola virus disease), etiology, clinical features, control measures, transmission

INTRODUCTION

The largest Ebola virus disease (EVD) outbreak to date is ongoing in West Africa, particularly in Guinea, Sierra Leone, and Liberia, with 7178 reported cases including 3338 deaths as of October 1, 2014.[1] Twenty EVD cases (19 laboratory confirmed, 1 probable) have been reported in Nigeria, with no new cases reported since early September 2014. All 20 cases stemmed from a single importation from a traveler returning from Liberia in July 2014.[2]

Ebola virus causes severe viral hemorrhagic fever with a high fatality rate. Five Ebola virus species within the genus Ebola virus are known, including four that cause EVD in humans (a fifth species has only caused disease in nonhuman primates [NHPs]).[3] The 2014 outbreak of EVD in West Africa, caused by Ebola virus (*Zaire ebolavirus* species), is the largest outbreak of EVD in history.[4]

Ebola virus can be transmitted by direct contact with blood, bodily fluids, or skin of EVD patients or individuals who have died of the disease.[5] As of October 23, 2014, 450 health care personnel are known to have become infected with Ebola. Of these, 244 have died.[4,6]

Several US health care personnel working in West Africa also became infected with EVD and returned to the United States for evaluation and treatment.[7] Additionally, people in several US states who recently traveled to West Africa and have fever and other symptoms have been evaluated at US hospitals for possible EVD. As of late October 2014, there were two imported cases, including one death, and two locally acquired cases in health care workers reported in the United States. Ebola hemorrhagic fever (EHF) is an acute viral syndrome that presents with fever and an ensuing bleeding diathesis that is marked by high mortality in human and NHPs. It is caused by Ebola virus, a lipid-enveloped, negatively stranded RNA virus that belongs to the viral family *Filoviridae*.[8]

Infections with Ebola viruses originating from Africa cause a severe disease in humans called Ebola virus disease. There are five species of the genus Ebola virus (*Filoviridae* family): *Zaire ebolavirus* (ZEBOV), *Sudan ebolavirus* (SEBOV), *Cote d'Ivoire ebolavirus* (CEBOV), *Bundibugyo ebolavirus* (BEBOV), and *Reston ebolavirus* (REBOV). CEBOV has been associated with only one human case.[9-11] REBOV has only caused disease in NHPs and was found in swine suffering from porcine reproductive and respiratory disease syndrome.[12] ZEBOV,

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SEBOV, and BEBOV are responsible for most of the EHF outbreaks[13,14] but ZEBOV constitutes a particularly serious threat to both human and NHPs in sub-Saharan Africa. EHF has been associated with large human outbreaks, with case fatality rates (CFRs) for ZEBOV as high as 90%. The CFR of EBOV in NHP is unknown but some ecological data suggest that EBOV has contributed to declines of up to 98% of local great ape populations in Gabon and the Republic of Congo.[15]

In 1976, the first reported cases of Ebola fever surfaced during two simultaneous outbreaks in southern Sudan and the Democratic Republic of Congo (DRC; formerly Zaire). Fatality rates reached 53% and 88%, respectively.[16,17] From then until January 2003, 10 significant Ebola fever outbreaks occurred in Africa involving more than 1600 cases of infection and 1100 fatalities. Additionally, there have been a small number of subclinical infections in the United States and the Philippines from the Reston strain of the virus, which is harmless to humans but lethal for monkeys.[18]

Despite concerted investigative efforts, the natural reservoir of the virus is unknown. As a result, little is understood about how Ebola virus is transmitted or how it replicates in its host. However, based on evidence from similar viruses, it is theorized that the virus is zoonotic and therefore is maintained by an unidentified animal host.[18-20] The fact that outbreaks of EHF have coincided with the end of the African rainy season may provide a clue as to the natural ecology of Ebola virus and to the host, which may be influenced by this weather cycle.[21]

Ebola Hemorrhagic Fever in Sudan 2004

The epicenter of this small outbreak of 17 cases and 7 deaths (CFR 41.2%) was the town of Yambio, near to the two previous Ebola sites (Nzara and Maridi).[22] During the 2008 Ebola outbreak, Kaluamba was affected again, with 37 cases and 16 deaths (CFR 43.8%). The index case was believed to be an 18-year-old girl who died from a post-abortion hemorrhage. However, the source of her exposure remains unknown. This outbreak was reported to the national and provincial health authorities 21 days after disease onset, compared with a period of 4 months in the 2007 epidemic.

Ebola Hemorrhagic Fever in the DRC (2007-2008, 2008-2009)

A further outbreak of EHF occurred in 2007, in the Mweka health zone, West Kasai Province, involving 264 cases and 187 deaths with a CFR of 71%. Kampungu city was the epicenter of the outbreak with 47% of cases, followed by the city of Kaluamba (42% of cases). The index case was the chief of the village and a hunter. The outbreak was apparently associated with a massive fruit bat migration through this region.[23] During this outbreak, there were fewer fatalities among health care workers. However, several human-to-human transmissions occurred in churches where patients had been taken for prayers and nursing.

Ebola Hemorrhagic Fever in Uganda (2011, 2007, 2000)

An outbreak of SEBOV occurred in Gulu in 2000 and spread to the cities of Mbarara and Masindi, with 425 cases and 224 deaths (CFR 52%).[24] This was the largest epidemic caused by SEBOV. The outbreak was recognized from a cluster of human cases and was amplified by nosocomial transmission. Uganda was again affected in 2007 when BEBOV killed 30 people out of 116 cases (CFR 26%).[14] An isolated case of EHF caused by SEBOV was reported from Uganda in 2011.[25]

EPIDEMIOLOGIC UPDATE

Situation in West Africa

Since December 2013 and as of late October 2014, the World Health Organization (WHO) has reported 13,567 suspected cases and 4,922 deaths.[26]

The distribution of EVD cases by affected countries (Fig. 1) is as follows:[27]

- Guinea: 1472 cases and 843 deaths as of October 12, 2014;
- Liberia: 4249 cases and 2458 deaths as of October 11, 2014;
- Sierra Leone: 3252 cases and 1183 deaths as of October 12, 2014;
- Nigeria: 20 cases and 8 deaths, with last confirmed case in Lagos on September 5, 2014 (37 days as of October 12, 2014) and in Rivers State on September 1, 2014 (41 days as of October 12);
- Senegal: 1 case, no deaths, confirmed on August 28, 2014 (45 days as of October 12, 2014). All contacts have completed 21 days of follow-up (Fig. 2).

ETIOLOGY

Ebola virus belongs to the family *Filoviridae*, in the order *Mononegavirales,* which includes *Rhabdoviridae* and *Paramyxoviridae*. Structurally, filovirus virions (complete viral particles) may appear in several shapes, biologic features called pleomorphism (Fig. 3). These shapes include long, sometimes branched filaments, as well as shorter filaments shaped like a "6," a "U," or a circle. Viral filaments may measure up to 14,000 nm in length, have a uniform diameter of 80 nm, and are enveloped in a lipid (fatty) membrane. Each virion contains one molecule of single-stranded, negative-sense RNA. New viral particles are created by budding from the surface of their hosts' cells; however, filovirus replication strategies are not completely understood.

The virus was first recognized in 1976 when two unrelated EHF outbreaks occurred 800 km apart in northern Zaire (Yambuku) and southern Sudan (Nzara

or Maridi).[28,29] It was given the name "Ebola" after the small river near the catholic mission of Yambuku, the epicenter of the 1976 EHF outbreak. Ebola virus is not restricted to Africa. A new species, REBOV, was described in cynomolgus monkeys (*Macaca fascicularis*) imported from the Philippines (Manila) to a quarantine facility in Reston, Virginia in 1989. Subsequently, REBOV has been reisolated from cynomolgus monkeys and domestic pigs in the Philippines.[12]

PATHOGENESIS AND TRANSMISSION

Ebola viruses are biosafety level-4 pathogens and require special containment measures and barrier protection, particularly for health care workers. The viruses can survive in liquid or dried material for many days.[30] They are inactivated by gamma irradiation, heating for 60 minutes at 60°C or boiling for 5 minutes, and are sensitive to sodium hypochlorite (bleach) and other disinfectants.[31,32] Freezing or refrigeration will not inactivate Ebola viruses.[33]

The incubation period (the period between infection and first symptoms) is usually 4 to 10 days but can be as short as 2 days and as long as 21 days. The CFR for ZEBOV infections is estimated to be between 44% and 90%.[34] Ebola viruses are highly transmissible by direct contact with infected blood, secretions, tissues, organs, and other bodily fluids from dead or living infected persons.[35] Transmission via inanimate objects contaminated with infected bodily fluids (fomites) is possible.[36] The principal mode of transmission in human outbreaks is person-to-person transmission through direct contact with a symptomatic or dead EVD case (Table 1). Airborne transmission has not been documented.[37]

Table 1. Levels of Risk for Transmission of Ebola Viruses

Level of Risk	Type of Contact
Low	Casual contact with a feverish but ambulant and self-caring patient (e.g., sharing a seating area or public transportation; receptionist tasks).
High	Direct contact with any material soiled by bodily fluids from a probable or confirmed case.
	Percutaneous injury (e.g., with needle) or mucosal exposure to bodily fluids, tissues, or laboratory specimens of a probable or confirmed case.
	Participation in funeral rites with direct exposure to human remains in or from an affected area without appropriate personal protective equipment.
	Direct contact with bushmeat or bats, rodents, primates, living or dead in or from affected areas.

Due to its lethal nature, this filovirus is classified as a biologic class-4 pathogen. Three subtypes of the virus have been identified as pathogenic for humans: Ebola Zaire, Ebola Sudan, and Ebola (Cote d'Ivoire) Tai.[8] The infection generally involves necrosis of the liver, spleen, kidney, lymph nodes, testes, and ovaries due to viral replication within parenchymal cells.[16,38-41] More significant effects are microvascular damage, changes in vascular permeability, and activation of the clotting cascade.[13,42] Damage to platelets and endothelial cells results in the disruption of fluid balance and homeostasis.[16,39,41,43] Additionally, the virus is believed to compromise and suppress immunologic function.[13,38,40,42,44-47]

Although the natural reservoir host of Ebola viruses has not yet been identified, the way in which the virus first appears in a human at the start of an outbreak is unknown. However, scientists believe that the first patient becomes infected through contact with an infected animal, such as a fruit bat or primate (apes and monkeys), which is called a *spillover event*. Person-to-person transmission follows and can lead to large numbers of affected people. In some past Ebola outbreaks, primates were also affected by Ebola and multiple spillover events occurred when people touched or ate infected primates. When an infection does occur in humans, the virus can be spread in several ways. Ebola is spread through direct contact (through broken skin or mucous membranes in, e.g., the eyes, nose, or mouth) by the following:

- Blood or bodily fluids (including but not limited to urine, saliva, sweat, feces, vomit, breast milk, and semen) of a person who is sick with Ebola;
- Objects (like needles and syringes) that have been contaminated with the virus; or
- Infected fruit bats or primates (apes and monkeys).

Ebola is not spread through the air or by water, or in general, by food. However, in Africa, Ebola may be spread as a result of handling bushmeat (wild animals hunted for food) and contact with infected bats. There is no evidence that mosquitos or other insects can transmit Ebola virus. Only a few species of mammals (e.g., humans, bats, monkeys, and apes) have shown the ability to become infected with and spread Ebola virus.[5,8,18,42,47-49] The main routes of infection are through mucous membranes, the conjunctiva, and small skin breaks.[19,50] Case reports of hospital personnel acquiring the disease that are not attributable to the percutaneous route suggest that rubbing one's eye after caring for a patient with acute illness transmits enough inoculum to produce clinical infection. Aerosol dissemination of Ebola virus has not been established as a mode of transmission in humans. However, in NHPs, this mode of transmission has been associated with disease.[8,18,19,49,50]

There is no evidence of communicability during the viral incubation period with nonfebrile, asymptomatic individuals.[8] Isolated cases of transmission between individuals convalescing from EHF and close household

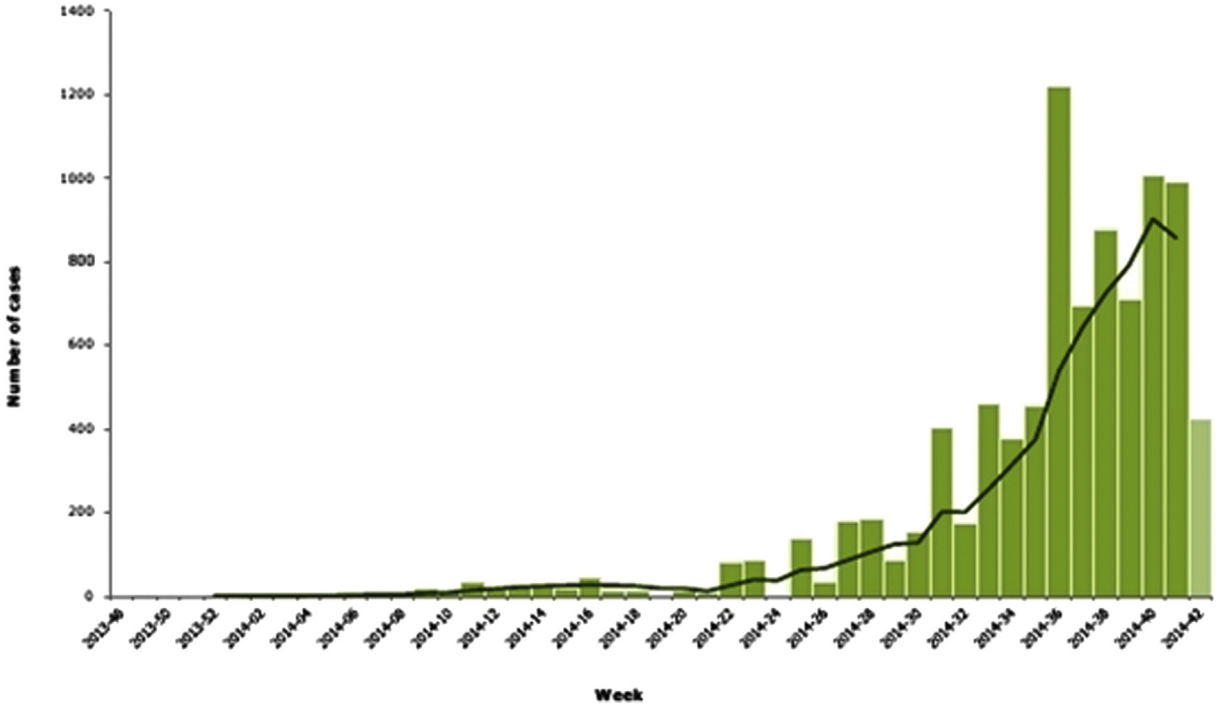

Figure 1. Distribution of cases of EVD by week of reporting in Guinea, Sierra Leone, Liberia, Nigeria, and Senegal, weeks 48/2013 to 42/2014* (N = 8994). EBV, Ebola virus disease. *The bar for week 42/2014 does not represent a complete week. The solid green line represents the trends based on a 5-week moving average plotted on the fifth week of the moving average window. The figure includes one imported case from Senegal.

contacts have been found and are primarily attributed to sexual contact. A cohort prospective study described a case involving a male convalescent who had Ebola viral antigen still present in seminal fluid almost 3 months after the initial diagnosis.[47] Transmission risk does increase significantly with direct patient contact during the acute disease phase.[5]

A more recent experiment that was specifically designed to further evaluate the possibility of naturally occurring airborne transmission of Ebola virus among NHPs showed no transmission of Ebola virus from infected to control primates placed 0.3 m apart in separate open-barred cages and ambient air conditions, but with a plexiglass divider that prevented direct contact between the animals.

CLINICAL FEATURES

The onset of the disease is abrupt after an incubation period of 2 to 21 days. The clinical features can be divided into four main phases as follows:

Phase 1: Influenza-like syndrome: The onset is abrupt with nonspecific symptoms or signs such as high fever, headache, arthralgia, nausea, sore throat, and myalgia.

Phase 2: Acute (days 1-6): Persistent fever not responding to antimalarial drugs or to antibiotics, headache and intense fatigue followed by diarrhea and abdominal pain and vomiting.

Phase 3: Pseudo-remission (days 7-8): During this phase the patient feels better and seeks food. The health situation presents with some improvement. Some patients may recover during this phase and survive from the disease.

Phase 4: Aggravation (day 9): In many if not most cases, the health status gets worse. The following symptoms may be observed:

- Skin manifestations: petaechiae (not so obvious on black skin), purpura (morbiliform skin rash)
- Respiratory disorders: dyspnea, cough, hiccups, throat and chest pain,
- Cardiovascular distress and hypovolemic shock.

Based on these clinical manifestations, it is obvious that at the start of EHF, the disease can mimic many other tropical diseases such as malaria or typhoid fever. In most outbreaks, recognition of EHF is delayed because physicians are not accustomed to seeing this illness and its symptoms are generally nonspecific.[20]

DIAGNOSIS

Early laboratory confirmation of suspected clinical hemorrhagic fever cases is essential to implement appropriate control measures. Definitive diagnosis of suspected cases of EHF is usually made by polymerase chain reaction detection and virus isolation on Vero cells. As a class-4 pathogen, Ebola virus culture requires a maximum containment facility.

Additional laboratory diagnostic tests include enzyme-linked immunosorbent assays (ELISAs) for the

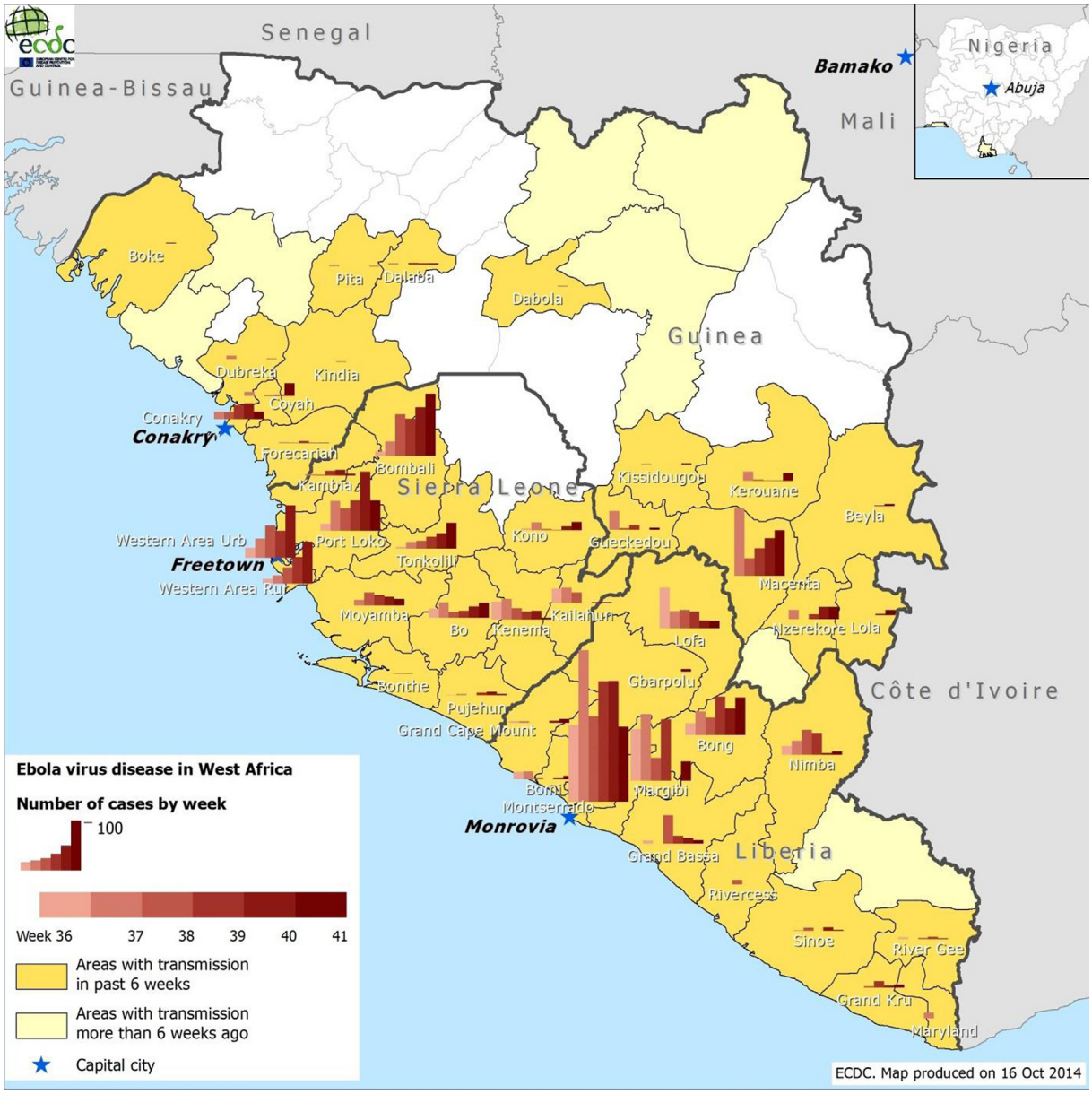

Figure 2. Distribution of cases of Ebola virus disease by week of reporting in Guinea, Sierra Leone, Liberia, and Nigeria (as of week 41/2014).

detection of Ebola immunoglobulin (Ig_G- and IgM-specific antibodies and virus antigens; more specialized molecular testing is also available but is not readily available in the usual clinical setting. In Africa, laboratory confirmation of Ebola cases has been challenging and early recognition of the first outbreaks was severely hampered as a result. Because the disease was poorly known or rare, laboratory investigations were oriented toward the more common, endemic pathogens in the area.

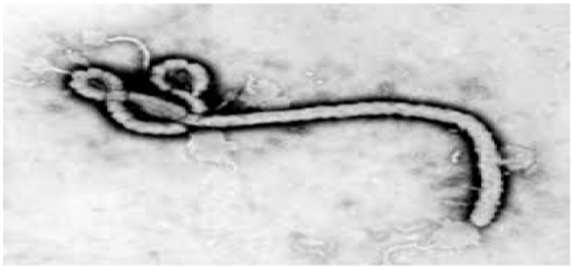

Figure 3. Ebola virus.

Since 1994, the incidence of Ebola outbreaks increased and, as a consequence, the awareness of the disease has improved and facilities capable of diagnosing EHV were established in Africa. National Public Health laboratories in endemic countries like Uganda (UVRI), Kenya (KEMRI), and Gabon (CIRMF) have already developed capacities to diagnose EHF by ELISA and reverse transcriptase (RT)-PCR. South Africa is the only African country with a maximum-containment, enclosed-suit laboratory where all class-4 viral

Table 2. Diagnostic Tests

Time Line of Infection	Diagnostic Tests Available
Within a few days after symptoms begin	• Antigen-capture ELISA testing • IgM ELISA • PCR • Virus isolation
Later in disease course or after recovery	• IgM and IgG antibodies
Retrospectively in deceased patients	• Immunohistochemistry testing • PCR • Virus solation

ELISA, enzyme-linked immunosorbent assay; IG, immunoglobulin, PCR, polymerase chain reaction.

pathogens can be handled safely. After the 2008-2009 Ebola outbreak in Kaluamba, DRC, the Ebola diagnostic technologies of ELISAs for the detection of antigens and IgM antibody, and RT-PCR have been transferred to the National Institute of Biomedical Research in Kinshasa (Table 2).

TREATMENT

No proven Ebola virus—specific treatment presently exists; however, there are measures that can be taken that will improve a patient's chances of survival. Ebola symptoms may begin as early as 2 days or as long as 21 days after exposure to the virus. Symptoms usually begin with a sudden flulike stage characterized by fatigue, fever, and muscle and joint pain. No specific treatments or vaccines are presently available for EVD. However, early supportive treatment can improve the chances of recovery.[51] Potential new Ebola therapies and vaccines were reviewed during two WHO meetings in September 2014 and further assessed by scientific review.[52,53] Several of these potential drugs recently have been used in experimental treatment of individual EVD cases.

During the first WHO consultation meeting, there was consensus that the use of whole-blood therapies and convalescent blood serums needs to be considered as a matter of priority.[52]

ZMapp is a combination of monoclonal antibodies. The limited supply of the drug has been used to treat seven individuals infected with the Ebola virus.[54] Although some of them have recovered, the outcome is not considered to be statistically significant.[55] ZMapp has proved highly effective in a trial involving rhesus macaque monkeys.[56]

Symptoms of Ebola are treated as they appear. The following basic interventions, when used early, can significantly improve chances of survival:

- Provide intravenous fluids and balancing electrolytes (body salts).
- Maintain oxygen status and blood pressure levels.
- Treat other infections if they occur.

Experimental vaccines and treatments for Ebola are under development, but have not yet been fully tested for safety or effectiveness. Managing Ebola patients in the African setting is a major challenge because there is no specific vaccine available. Only supportive care can be administered to sustain cardiac and renal functions with prudent use of perfusion. Oral rehydration is recommended but sometimes not realistic because of throat pain and vomiting. The main objective is to provide optimal care to the patient with maximum protection of the medical and nursing staff.

In a clinical experiment conducted late during the 1995 Ebola outbreak in Kikwit, human convalescent blood was used for passive immunization to treat patients who had been infected naturally with ZEBOV; seven of the eight patients who received blood transfusion from convalescent Ebola patients survived.[57] Additionally, although monoclonal antibodies to the glycoprotein of Ebola virus showed protective and therapeutic properties in mice, they failed to protect NHPs.[58,59]

As Ebola virus is generally considered a potential biologic weapon, it is urgent to develop effective antiviral drugs and vaccines. The ideal is to develop a candidate vaccine able to confer interspecies cross-protection against SEBOV, BEBOV, ZEBOV, and other as-yet-unknown Ebola virus species.

CONTROL MEASURES

The cornerstone for controlling an outbreak of EHF is to interrupt the viral transmission chain. Reducing transmission requires several strict public health measures to be implemented as quickly as possible, including isolation of patients, barrier precautions, and identification and tracking of all contacts. Most of the time, outbreaks are managed by the WHO's International Committee on Scientific and Technical Coordination. This committee is in charge of implementing control measure activities on a daily basis and has the following working subgroups:

- The patient management team is involved in the isolation of clinical cases in a quarantine ward, training medical and relief personnel on the proper use of personal protective equipment (gloves, gowns, masks, etc.), and providing medical care based on symptomatic therapy to maintain vital respiratory, cardiovascular, and renal functions.
- The coordination committee is responsible for all epidemic response activities, chairs daily meetings, and writes reports for public health authorities and health partners.
- The epidemiologic surveillance team is in charge of active and passive case finding, contact tracing, and rumor verification of suspect cases or deaths in the community.

- The hygiene and sanitation team is in charge of disinfection and burial of all Ebola and non-Ebola dead bodies under safe conditions. Local Red Cross volunteers usually perform these activities.
- The laboratory and research team is in charge of collecting, storing, and shipping clinical samples for diagnostic confirmation.
- The logistic support team is in charge of providing any administrative, logistic, and technical support to the other teams, such as coordination of secretariat, transport, and communication.

CONCLUSION

EHF epidemics constitute a significant public health concern in Africa and an effective vaccine is needed urgently. Such a vaccine would primarily benefit doctors, nurses, and field epidemiologists working in endemic countries. The second target group would be the scientists working with Ebola virus as well as veterinarians and those involved in wildlife conservation in endemic areas. Since its discovery in 1976, much is known about Ebola virology, physiopathology, clinical features, and epidemiology, but the missing link certainly remains the virus reservoir in nature. The current research focused on bats as putative ZEBOV reservoirs has to be reinforced and extended to the reservoirs of other Ebola species. The early detection and isolation of a patient with EVD decreases the risk for transmission in the community.

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