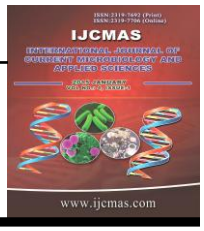
Int.J.Curr.Microbiol.App.Sci (2015) 4(1): 731-747

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 4 Number 1 (2015) pp. 731-747**
http://www.ijcmas.com



Review Article

The Ebola menace: Epidemic, evidence and expectations

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Keywords

Ebola virus, Disease, Transmission, Treatment, Vaccine

A B S T R A C T

Ebola virus, formerly designated Zaire ebolavirus, is one of the five known viruses within the genus Ebolavirus which cause disease in humans. Ebola Virus Disease (EVD) has become a public health emergency of international concern. The World Health Organization and Centers for Disease Control and Prevention have developed guidance to educate and inform healthcare workers and travelers worldwide. The natural reservoir of Ebola virus is believed to be bats, particularly fruit bats, and it is primarily transmitted between humans and from animals to humans through body fluids. Symptoms of EVD include abrupt onset of fever, myalgias, and headache in the early phase, followed by vomiting, diarrhea and possible progression to hemorrhagic rash, life-threatening bleeding, and multi-organ failure in the later phase. The disease is not transmitted via airborne spread like influenza, but rather from person-to-person, or animal to person, via direct contact with bodily fluids or blood. It is crucial that emergency physicians be educated on disease presentation and how to generate a timely and accurate differential diagnosis that includes exotic diseases in the appropriate patient population. There are experimental therapies for treatment of EVD virus; however the mainstay of therapy is supportive care. A major research thrust continues to develop an effective vaccine.

Introduction

Ebola virus was first discovered in 1976 when an outbreak of Ebola hemorrhagic fever occurred in Zaire and another later that year in Sudan. Each outbreak had about 300 victims, but did not spread much larger than that because of the remoteness of the areas in which they occurred. The Zaire Ebola virus has one of the highest fatality rates of any pathogenic virus affecting humans. This outbreak was caused by EBOV, formerly designated Zaire ebolavirus, which is a different member of the genus Ebolavirus than in the first Sudan outbreak. The first person infected with the disease was village school headmaster Mabalo Lokela, who began displaying symptoms on 26 August 1976. Ivory Coast Ebola virus was first discovered in 1994 when a scientist conducting autopsies on chimpanzees

contracted Ebola hemorrhagic fever. This strain found was different than the Zaire or Sudan strains. However, this has been the only case of Ivory Coast Ebola known to have occurred in humans (No author, 1978). The second major outbreak occurred in Zaire (now the Democratic Republic of the Congo) in 1995, affecting 315 and killing 254 (WHO, 2014a).

Most Ebola virus outbreaks have originated in Africa and have traveled only to other countries through shipment of non human primates or through accidental contamination in testing facilities. Crab eating macaque that was imported from the Philippines to Reston, Virginia in 1989 was found to have a virus similar to Ebola. Over 150 animal handlers were all tested for Ebola and only 6 were found to have developed antibodies to it, none of which actually developed Ebola hemorrhagic fever. The Center for Disease Control concluded that this strain had a low infection rate for humans and it was later classified as its own strain named Reston Ebola virus. In the outbreak of 1995 81% killed, in 1976, it killed 88% of patients, 73 % in 1996, 80 % in 2001-2002, and 90% in 2003, although none of these outbreaks were as large as the original. Sudan Ebola virus has a lower, yet still very dangerous, fatality rate of 53 percent in 1976, 65 percent in 1979, 53 percent in the over 400 patients infected in 2000, and 41 percent in 2004 (No author, 1978).

In 2000, Uganda had an outbreak affecting 425 and killing 224; in this case the Sudan virus was found to be the Ebola species responsible for the outbreak (WHO, 2014a). In 2003 there was an outbreak in the Republic of the Congo that affected 143 and killed 128, a death rate of 90 percent, the highest death rate of a genus Ebolavirus outbreak to date (CBC/Radio-Canada, 2007).

In 2004 a Russian scientist died from Ebola after sticking herself with an infected needle (The New York Times, 2014). Between April and August 2007, a fever epidemic in a four village region of the Democratic Republic of the Congo was confirmed in September to have cases of Ebola. Many people who attended the recent funeral of a local village chief died (NewScientist.com, 2007).

The 2007 outbreak eventually affected 264 individuals and resulted in 187 deaths (No author, 1978). 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 genus Ebolavirus, which was tentatively named Bundibugyo (WHO, 2012a). 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 (WHO, 2014a).

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 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 ((No author, 1978; WHO, 2012b; Castillo, 2012; CDC, 2014a; Baize *et al.*, 2014).

2013 to 2014 West African outbreak

In March 2014, WHO reported a major Ebola outbreak in Guinea, a western African nation (WHO, 2014b). Researchers traced the outbreak to a two year old child who died December 2013 (WHO, 2014c; Common Dreams, 2014). 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.

Aside from the human cost, the outbreak has severely eroded the economies of the affected countries. A Financial Times report suggested that the economic impact of the outbreak could kill more people than the virus itself. As of 23 September 2014, in the three hardest hit countries, Liberia, Sierra Leone and Guinea, only 893 treatment beds were available even though the current need was 2122 beds. More than 216 health care workers were among the dead, partly due to the lack of equipment and long hours. On 23 October 2014, the Malian government confirmed its first case. The largest outbreak to date is the ongoing 2014 West Africa Ebola virus outbreak, which is affecting Guinea, Sierra Leone, Liberia, Mali, and Nigeria. As of 21 December 2014, 19,465 suspected cases and 7,580 deaths had been reported (The ministry of health and public health, 2014; UN Ebola Crisis Desk, 2014; WHO, 2014d). However, the WHO has said that these numbers may be vastly underestimated (WHO, 2014a).

Classification and taxonomy

Filoviruses (Ebola, Fig 1) are helical, non-segmented, negative, single-stranded RNA viruses, polymorphic, noninfectious, and have variable lengths. Infectious Ebola virions are usually 920 nm in length, 80 nm in diameter, and have a membrane stolen from the host cell by budding. The virus encodes for a nucleoprotein, a glycoprotein, 7 polypeptides, a polymerase, and 4 other undesignated proteins. These proteins are made from polyadenylated mRNA transcribed in the host cell from the virus RNA (Takada *et al.*, 1997).

The family Filoviridae consists of two genera, the Ebola and Marburg viruses, which are among the most virulent pathogens in humans. Ebola virus is a nonsegmented, negative sense, singlestranded RNA virus that resembles rhabdoviruses and paramyxoviruses in its genome organization and replication mechanisms. It is a member of the family Filoviridae, taken from the Latin "filum," meaning thread like, based upon their filamentous structure. In the past, Ebola and Marburg viruses were classified as "hemorrhagic fever viruses", based upon their clinical manifestations, which include coagulation defects, bleeding, and shock. The genus Ebola virus is divided into five species (Zaire, Sudan, Ivory Coast, Bundibugyo, and Reston). The following four species cause disease in humans (Kuhn, 2010).

●The Zaire virus, since it was first recognized in 1976, has caused multiple large outbreaks in Central Africa, with mortality rates of 55 to 88 percent. It is the causative agent of the 2014 West African epidemic.

●The Sudan virus has been associated with a case fatality rate of approximately 50 percent in four epidemics: two in Sudan in the 1970s, one in Uganda in 2000, and another in Sudan in 2004.

●The Ivory Coast virus has only been identified as the cause of illness in one person, and that individual survived. The exposure occurred when an ethologist

performed a necropsy on a chimpanzee found dead in the Tai Forest, where marked reductions in the great ape population had been observed.

●The Bundibugyo virus emerged in Uganda in 2007, causing an outbreak of Ebola virus disease with a lower case fatality rate (approximately 30 %) than is typical for the Zaire and Sudan viruses. Sequencing has shown that the agent is most closely related to the Ivory Coast species. The fifth Ebola species, the Reston virus, differs markedly from the others, because it is apparently maintained in an animal reservoir in the Philippines and has not been found in Africa.

The Ebola Reston virus was discovered when it caused an outbreak of lethal infection in macaques imported into the United States in 1989. This episode brought the filoviruses to worldwide attention through the publication of Richard Preston's book, The Hot Zone. Three more outbreaks occurred among nonhuman primates in quarantine facilities in the United States and Europe before the Philippine animal supplier ceased operations. None of the personnel who were exposed to sick animals without protective equipment became ill, but several animal caretakers showed evidence of seroconversion.

Nothing further was heard of Reston virus until 2008, when the investigation of an outbreak of disease in pigs in the Philippines unexpectedly revealed that some of the sick animals were infected both by an arterivirus (porcine reproductive and respiratory disease virus) and by Ebola

Reston virus. Serologic studies have shown that a small percentage of Philippine pig farmers have IgG antibodies against the agent without ever developing severe symptoms, providing additional evidence that Ebola Reston virus is able to cause mild or asymptomatic infection in humans. Whether or not the virus recovered from Philippine pigs and Philippine macaques is the same is unknown (Kuhn *et al.*, 2013).

Normal host

Tadarida (mops) trevori were found in the roof of the Nzara Cotton Factory during the 1976 outbreak of Ebola Sudan. The index case and the 2 other primary cases worked in the Nzara Cotton Factory. Since these three men did not live close to each other and did not have any social contact outside of the Nzara Cotton Factory, the Nzara Cotton Factory is considered to be the point of infection for these three men. The index case of the 1979 Ebola Sudan outbreak also worked at the Nzara Cotton Factory. A study done at the National Institute of Virology, South Africa has shown that Ebola can replicate in fruit bats and other bats in the Tadarida genus, inoculated with Ebola and can then pass through their stool. Infectious Ebola virions have been found in the stool of bats ("guano"). The infectious guano could have transmitted Ebola to humans or to another intermediate vector. Bats in Mount Elgon have been implicated in the transmission of Marburg (a filovirus closely related to Ebola) on two separate occasions. However, bats and guano collected from Mount Elgon have not tested positive for Ebola (Calisher *et al.*, 2006).

Reservoir and transmission

Ebola is transmitted through bodily fluids and/or direct contact with infected individuals. It is believed to spread to human populations through contact with infected primates, as opposed to directly from natural reservoirs. The suspected natural sources of the virus are certain species of fruit bats. They have been found to carry the virus, but they themselves are asymptomatic, making

them good candidates for natural reservoirs. Outbreaks of Ebola virus are often traced to an individual that has handled a gorilla or chimpanzee carcass. It is common for the virus to then spread to family members or hospital workers because of their close proximity to the victim. The virus spreads to people that come into contact with these patients' blood or contaminated medical equipment. Because Ebola kills its victims so quickly and the outbreaks usually occur in isolated areas, the disease does not typically spread very far. Also, Ebola has an incubation period of up to 21 days, but is normally closer to 10 days, so infected persons do not have time to carry the disease very far. It is highly unlikely that Ebola could turn into a large epidemic. Often Ebola outbreaks are mistakenly classified initially as outbreaks of malaria, dysentery, influenza, typhoid fever or other bacterial infections because the early symptoms are similar and these infections are common in the same areas of Africa. This misinterpretation of symptoms can lead to the spread of Ebola within medical centers because necessary precautions are not taken (Bausch *et al.*, 2007).

Transmission of Ebola virus among non human animals is a little different. It is proposed that fruit bats drop partially eaten fruits that carry viruses in the bat saliva. Gorillas or other monkeys then eat the fruit, and therefore the virus as well. Gorilla carcasses have been found to contain multiple strains of Ebola virus. Decomposing bodies only remain infectious for three to four days after death, and gorillas do not typically interact among different groups, which mean the victims were probably infected by several animal host reservoirs. The greatest mysteries regarding the filoviruses are the identity of their natural reservoir(s) and the mode of transmission to wild apes and humans. While Marburg virus has been isolated directly from bats captured in Uganda, only Ebola virus sequences, not infectious virus, have been detected in samples collected from bats in Central Africa. However, data suggest that bats are at least one of the reservoir hosts of Ebola viruses in Africa. The transmission pathway from bats to humans and the possible role of bats in the initiation of the 2014 West African outbreak have not been defined (CDC, 2014b).

It is thought that fruit bats of the Pteropodidae family are natural Ebola virus hosts. Ebola is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals such as chimpanzees, gorillas, fruit bats, monkeys, forest antelope and porcupines found ill or dead or in the rainforest. Ebola then spreads through human-to-human transmission via direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people (alive or death), and with surfaces and materials (e.g. bedding, clothing) contaminated with these fluids. The likelihood of infection depends, in part, upon the type of body fluid to which an individual is exposed and the amount of virus it contains. Health care workers have frequently been infected while treating patients with suspected or confirmed Ebola virus disease. This has occurred through close contact with patients when infection control precautions are not strictly practiced. 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. People remain infectious as long as their blood and body fluids, including semen and breast milk, contain the virus. Men who have recovered from the disease can still transmit the virus through their semen for up to 7 weeks after recovery from illness (WHO, 2014a).

Epidemics of Ebola virus disease are generally thought to begin when an individual becomes infected through contact with the meat or body fluids of an infected animal. Once the patient becomes ill or dies, the virus then spreads to others who come into direct contact with the infected individual's blood, skin, or other body fluids. Studies in laboratory primates have found that animals can be infected with Ebola virus through droplet inoculation of virus into the mouth or eyes, suggesting that human infection can result from the inadvertent transfer of virus to these sites from contaminated hands (Blaine, 2008).

Prior to the 2014 epidemic in West Africa, outbreaks of Ebola virus disease were typically controlled within a period of weeks to a few months. This outcome was generally attributed to the fact that most outbreaks occurred in remote regions with low population density, where residents rarely traveled far from home. However, the 2014 West African epidemic has shown that Ebola virus disease can spread rapidly and widely as a result of the extensive movement of infected individuals (including undetected travel across national borders), the spread of the disease to densely populated urban areas, and the avoidance and/or lack of adequate personal protective equipment and medical isolation centers. As examples:

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

●During the early phase of the 2014 West African epidemic, several hundred African doctors and nurses became infected while caring for patients with Ebola virus disease, showing that healthcare workers are at high risk of infection if they do not use appropriate protective measures (Liberia Ebola SitRep, 2014).

According to the World Health Organization, the most infectious body fluids are blood, feces, and vomit (WHO, 2014a). Infectious virus has also been detected in urine, semen, saliva, and breast milk. Reverse-transcription-polymerase chain reaction (RT-PCR) testing has also identified viral RNA in tears and sweat, suggesting that infectious virus may be present. Infectious virus or viral RNA can persist in some of these fluids even after it is no longer detected in blood; however, the risk of transmission from persistent virus at these sites is not well established. As examples:

●Follow-up studies of approximately 40 survivors in the 1995 Kikwit, Democratic Republic of Congo outbreak found that viral RNA sequences could be detected by RT-PCR in the semen of male patients for up to three months, and infectious virus was recovered from the semen of one individual 82 days after disease onset.

●A study of patient samples collected during the outbreak of Ebola Sudan virus disease in Gulu, Uganda in 2000 detected virus in the breast milk of a patient, even after virus was no longer detectable in the bloodstream. Two children who were breastfed by infected mothers died of the disease.

●During the 2014 outbreak in West Africa, virus was cultured from a patient's urine 12 days after the last positive culture was identified in plasma (http://www.virology.ws/2014/09/27/transmission of ebola virus, Retrieved 2014).

Ebola virus may be transmitted though contact with contaminated surfaces and objects. The Centers for Disease Control and Prevention (CDC) indicates that virus on

surfaces may remain infectious from hours to days. There are no high-quality data to confirm transmission through exposure to contaminated surfaces, but it is clear that the potential risk can be greatly reduced or eliminated by proper environmental cleaning.

Risk of airborne transmission -There is no evidence that Ebola virus can spread from person to person by the respiratory route. However, laboratory experiments have shown that Ebola virus released as a small-particle aerosol is highly infectious for rodents and nonhuman primates Healthcare workers may therefore be at risk of Ebola virus disease if exposed to aerosols generated during medical procedures.

Nosocomial transmission -Transmission to healthcare workers may occur when appropriate personal protective equipment is not available or is not properly used, especially when caring for a severely ill patient who is not recognized as having Ebola virus disease.

During the 2014 outbreak in West Africa, a large number of doctors and nurses have become infected with Ebola virus In Sierra Leone, the incidence of confirmed cases over a seven month period was approximately 100 fold higher in healthcare workers than in the general population. Several factors have accounted for these infections, including incorrect triage and/or failure to recognize patients and corpses with Ebola virus disease; delayed laboratory diagnosis; limited availability of appropriate personal protective equipment and hand washing facilities; and inadequate training about safe management of contaminated waste and burial of corpses.

Medical procedures played a major role in some past Ebola epidemics by amplifying the spread of infection (http://www.virology.ws/2014/09/27/transmission of ebola virus, Retrieved 2014).

●A tragic example of an iatrogenic point-source outbreak occurred in 1976, when an individual infected with Ebola virus was among the patients treated in a small missionary hospital in Yambuku, Zaire. At this hospital, the medical staff routinely injected all febrile patients with antimalarial medications, employing syringes that were rinsed in the same pan of water, and then re-used. Virus from the index case was transmitted simultaneously to nearly 100 people, all of whom developed fulminant Ebola virus disease and died. Infection then spread to family caregivers, hospital staff, and those who prepared bodies for burial.

●A different type of iatrogenic amplification occurred in 1995 in Kikwit, Democratic Republic of the Congo when a patient was hospitalized with abdominal pain and underwent exploratory laparotomy. The entire surgical team became infected, probably through unprotected respiratory exposure to aerosolized blood. Once those persons were hospitalized, the disease spread to hospital staff, patients, and family members through direct physical contact.

Despite these dramatic episodes of nosocomial transmission, other hospital-based experiences have demonstrated a much lower incidence of secondary spread. As an example, when a patient with unrecognized Ebola virus disease was treated in a South African hospital in 1998, only one person became infected among 300 potentially exposed healthcare workers. A similar observation was made when a patient with an unrecognized infection with Marburg virus, a closely related filovirus, was treated in a South African hospital in 1975, resulting in the spread of infection to only two people with close physical contact.

Assistance from the international medical community has played an important role in controlling large epidemics in Africa. In the past, intervention strategies focused largely on helping local healthcare workers to identify Ebola patients, transfer them to isolation facilities, provide basic supportive care, monitor all persons who had been in direct contact with cases, and rigorously enforce infection control practices. During the 2014 West African epidemic, the massive international response is making it possible to supplement isolation procedures with more effective supportive care.

Transmission from animals

Contact with infected animals - Human infection with Ebola virus can occur through contact with wild animals (examples, hunting, butchering, and preparing meat from infected animals). In Mayibou, Gabon in 1996, for example, a dead chimpanzee found in the forest was butchered and eaten by 19 people, all of whom became severely ill over a short interval. Since that time, several similar episodes have resulted from human contact with infected gorillas or chimpanzees through hunting.

Exposure to bats - Direct transmission of Ebola virus infection from bats to wild primates or humans has not been proven. However, Ebola RNA sequences and antibodies to Ebola virus have been detected in bats captured in Central Africa. Bats have been identified as a direct source of human infection with Marburg virus (Drazen *et al.*, 2014).

Other routes - Other potential routes of transmission include accidental infection of workers in any Biosafety-Level-4 (BSL-4) facility where filoviruses are being studied (WHO, 2014a).

Incubation period

Art 28 The incubation period of Ebola virus disease (EVD) varies from 2 to 21 days, with an observed average of 8 to 10 days. Following the introduction of Ebola virus in the human population through animal-to-human transmission, person-to-person transmission by direct contact body fluids/secretions of infected persons is considered the principal mode of transmission. Indirect contact with environment and fomites soiled with contaminated bodily fluids (e.g. needles) may also occur. Airborne transmission has not been documented during previous EVD outbreaks.

The quarantine period for Ebola virus

The quarantine period for an infectious disease is based on the incubation period, the time before symptoms of an infection appear. For Ebola virus, the incubation period is 2-21 days after infection. During this time it is believed that individuals infected with the virus are not contagious, but they could produce small amounts of virus. Whether or not a patient is contagious during the incubation period depends on the virus.

It is clearly important to determine the correct quarantine period for Ebola virus to prevent chains of infection. The longer the quarantine period imposed the less risk of infecting others. However the cost of enforcing quarantine must be balanced with the cost of releasing exposed individuals (Fig. 2). According to Haas, the optimal quarantine time should be at the intersection of the two curves.

To determine how the Ebola virus quarantine period was set at 21 days, Haas examined the incubation periods calculated

for previous outbreaks. In a study of the 1976 Zaire outbreak, the mean time between exposure and disease for 109 cases of person-to-person spread was calculated at 6.3 days with a range of 1 to 21 days. Mean incubation times for the 1995 Congo outbreak (315 cases) and the 2000 Uganda outbreak (425 cases) were 5.3 and 3.35 days, respectively. Two other analyses of the 1995 Congo outbreak gave mean incubation times of 10.11 and 12.7 days. WHO has estimated a mean incubation period for the first 9 months of the current West African outbreak as 11.4 days, with an upper limit (95% confidence) of 21 days. Haas concludes that the 21 day quarantine value is derived from a 'reasonable interpretation' of outbreak data, but it might not be long enough. He estimates that there is a risk of between 0.2% and 12% of developing Ebola virus infection after 21 days. The current outbreak should allow collection of data for revising and updating the 21 day quarantine period for Ebola virus infection (Drazen *et al.*, 2014).

Diagnosis

It can be difficult to distinguish EVD from other infectious diseases such as malaria, typhoid fever and meningitis. Confirmation that symptoms are caused by Ebola virus infection are made using the following investigations:

- Antibody-capture enzyme-linked immunosorbent assay (ELISA)
- Antigen-capture 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; laboratory testing on non-inactivated samples should be conducted under maximum biological containment conditions (WHO, 2014a).

Principles of management

Prevention and control

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 mobilisation. Community engagement is key to successfully controlling outbreaks. Raising awareness of risk factors for Ebola infection and protective measures that individuals can take is an effective way to reduce human transmission. Risk reduction messaging should focus on several factors:

- Reducing the risk of wild life-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 from direct or close contact with people with Ebola symptoms, particularly with their bodily fluids. 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.

- Outbreak containment measures including prompt and safe burial of the dead, identifying people who may have been in contact with someone infected with Ebola, monitoring the health of contacts for 21 days, the importance of separating the healthy from the sick to prevent further spread, the importance of good hygiene and maintaining a clean environment. Fact sheet who

- To help prevent infection, food products should be properly cooked since the Ebola virus is inactivated through cooking. In addition, basic hygiene measures (eg, hand washing, and changing clothes and boots after touching the animals) should be followed (WHO, 2014).

Treatment

There is currently no treatment for Ebola hemorrhagic fever. Infected individuals are treated for the symptoms they have, but the body must fight off the virus on its own. To help patients deal with symptoms better, supportive care is usually given (Table 1) (CDC, 2014c).

Development of ebola vaccine

Many Ebola vaccine candidates had been developed in the decade prior to 2014, (Richardson *et al.,* 2010) but as of November 2014, none had yet been approved by the United States Food and Drug Administration (FDA) for clinical use in humans (WHO, 2014e; CDC, 2014d; Galvani *et al.,* 2014). Several promising vaccine candidates have been shown to protect non-human primates (usually macaques) against lethal infection (Hoenen*et al.,* 2012; Peterson *et al.,* 2004; Fausther-Bovendo *et al.,* 2012), These include replication-deficient adenovirus vectors, replication-competent vesicular stomatitis (VSV) and human parainfluenza (HPIV-3) vectors, and virus-like particle preparations. Conventional trials to study efficacy by exposure of humans to the pathogen after immunization are obviously not feasible in this case. For such situations, the FDA has established the "animal rule" allowing licensure to be approved on the basis of animal model studies that replicate human disease, combined with evidence of safety and a potentially potent immune response (antibodies in the blood) from humans given the vaccine. Phase I clinical trials involve the administration of the vaccine to healthy human subjects to evaluate the immune response, identify any side effects and determine the appropriate dosage.

1. cAd3-EBOZ

In September 2014, two Phase I clinical trials began for the vaccine cAd3-EBO Z, which is based on an attenuated version of a chimpanzee adenovirus (cAd3) that has been genetically altered so that it is unable to replicate in humans (Vaccine Research Center, NIAID, 2014a). It was developed by NIAID in collaboration with Okairos, now a division of Glaxo Smith Kline. For the trial designated VRC20, 20volunteerswererecruited by the NIAID in Bethesda, Maryland, while three dose-specific groups of 20 volunteers each were recruited for trial EBL01 by University of Oxford, U.K. Initial results released in November 2014 were promising, with the vaccine appearing to be both safe and effective, with all 20 volunteers developing antibodies against Ebola (Ledgerwood *et al.,* 2014; Stanley *et al.,* 2014).

In December 2014, University of Oxford expanded the trial to include a booster

vaccine based on MVA-BN, a strain of Modified vaccinia Ankara, developed by Bavarian Nordic, to investigate whether it can help increase immune responses further (University of Oxford, News and Events, 2014). The trial which has enrolled a total of 60 volunteers will see 30 volunteers vaccinated with the booster vaccine.

2. VSV-EBOV

A replication-competent vaccine based on the vesicular Stomatitis virus, called VSV-EBOV, was developed by the Canadian National Microbiology Laboratory and licensed to the small company New Link Genetics. With the strong support of the U.S. Defense Threat Reduction Agency, it started Phase I clinical trials on healthy human subjects on 13 October 2014 at the Walter Reed Army Institute of Research in Silver Spring, Md (Globe and Mail, 2014; CBC News, 2014; Canadian Press, 2014). Also in October 2014, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) were recruiting healthy human volunteers for a "Phase 1 Randomized, Double- Blind, Placebo Controlled, Dose-Escalation Study to Evaluate the Safety and Immunogenicity of Prime Boost VSV Ebola Vaccine in Healthy Adults (U.S. NIAID, 2014b). On 20 October, the Public Health Agency of Canada began air shipment of 800 doses of the VSV-EBOV vaccine to the WHO in Geneva (Hannah Thibedeau, 2014). This vaccine is intended to be used in Phase I clinical trials, to start in late October or early November.

The WHO has recruited 250 volunteers ready to begin Phase I clinical trials in four locations: Switzerland, Germany, Gabon and Kenya. If the results of this and following trials show that the earlier results in non human primates are replicable in humans, this vaccine could be deployed in areas such as West Africa and would be expected to require only a single dose. Also, its efficacy in protecting nonhuman primates when administered even after viral exposure has occurred may help protect health care workers after a suspected exposure. In early November 2014, the Swiss government approved a clinical trial of an EVD vaccine called VSV-ZEBOV, which was created by Canada's Public Health Agency. The University Hospitals of Geneva will run the clinical trials (Ashley, 2014).

3. Triazoverin

The Health Ministry of Russia also claims to have developed a vaccine called Triazoverin, which is said to be effective against both Ebola and Marburg filoviruses, and might be available for clinical trials in West Africa as soon as the start of 2015 (BBC News, 2014; RT Question Time, 2014; The Moscow Times, 2014). EBOVGP At the 8th Vaccine and ISV Conference in Philadelphia on 27-28 October 2014, Novavax Inc. reported the development in a "few weeks" of a Glycoprotein (GP) nanoparticles Ebolavirus (EBOVGP) vaccine using their proprietary Recombinant technology (Novavax, 2014).

A recombinant protein is a protein whose code is carried by recombinant DNA. The vaccine is based on the newly published genetic sequence (Gire *et al.,* 2014) of the 2014 Guinea Ebola strain that is responsible for the current Ebola disease epidemic in West Africa. In "preclinical models", a useful immune response was induced, and was found to be enhanced ten to a hundred fold by the company's "Matrix-M" immunologic adjuvant. A study of the response of non-human primate to the vaccine had been initiated. Attractive features of such a vaccine could be no need for frozen storage, and the possibility of rapid scaling to manufacture of large dose

quantities. Novavax has initiated a primate study and expects to initiate a Phase 1 clinical trial in December 2014. Nasal vaccines On November 5, 2014, the Houston Chronicle reported that a research team at the University of Texas-Austin developed a nasal spray EVD vaccine, which the team had been working on for seven years. In a test, 100 percent of monkeys given the vaccine were saved from the virus. When researchers tested an injected version of the same vaccine on monkeys, half of the monkeys were saved. The team's research conclusion was accepted the Journal of Molecular Pharmaceutics. However, as of early November 2014, the team was running out of money. Without further funding, it will not be able to conduct human trials, which is then extstepin the research process (Todd, 2014; Dan, 2014).

Current research

The National Institute of Allergies and Infectious Diseases, collects records of all new and emerging research on Ebola virus. In 2005, a study was performed in collaboration with the United States Army Medical Research Institute for Infectious Diseases to test the efficiency and effects of a new, longer-lasting immunization for non-human primates against Ebola virus that required only the boost dose in lieu of the previous vaccination followed by the boost. The results showed that the boost was just as effective on its own.

Due to these results, a fast-acting, single dose vaccination was developed and tested in humans. The purpose of such a vaccine is to allow health workers the ability to contain Ebola virus outbreaks through ring vaccinations. In a ring vaccination, vaccines are given to all people not yet infected in the region of Ebola cases. A fast acting vaccine is the best for this strategy and protects the entire community from a devastating outbreak. This study was completed in 2008 and is still being followed to see if the immunity is long lasting. Before this single dose vaccine was created, there was another vaccine developed for humans that was tested in 2005. This vaccine entailed three doses of vaccine but proved to be safe, without serious side effects and appeared to create good immune responses in trial participants. However, with the discovery of the new, fast-acting vaccine this three-dose vaccine may no longer be relevant (NIAID, 2014a). In 2009, a study is currently underway that includes collaborations from the United States Military as well as international groups that tests new DNA vaccines for Ebola and Marburg viruses. This new type of vaccine is still being experimented with and the results are unknown (Associated Press, 2009). A major concern in formulating an Ebola vaccine is that in the regions where the virus is most commonly observed, many of the patients are immunocompromised due to HIV. A vaccine could therefore be more harmful than helpful in preventing Ebola hemorrhagic fever because it could actually cause the disease. A study done in 2008 on rhesus macaque monkeys who were infected with simian immunodeficiency virus (SIV) showed that the monkeys did not contract Ebola from the vaccine. The vaccine is therefore thought to be safe for immunocompromsied human patients (Choi *et al.*, 2008). A study was published in the Journal of Infectious Diseases in 2004 that brought to light interesting new information on the natural reservoirs of Ebola virus. It was recorded that approximately 13 percent of wild-born chimpanzees had Ebola antibodies in their blood. This finding showed researchers that Ebola virus is and was in circulation in the forests of countries where no human cases have been reported or before it infected humans. It also showed

that chimps can be in contact with Ebola and survive, telling also that they have probably been exposed multiple times. An aspect of this research that is very relevant to global health is the possibly that is now known that Ebola can exist in places where it has not been before and could cause human outbreaks in unexpected countries. Subsequent research is being conducted and will hopefully lead to an Ebola vaccine in the near future (Monath, 1999).

Conclusions and future perspectives

Main goals currently being addressed with Ebola virus are finding ways of treatment for Ebola hemorrhagic fever and finding safe and effective vaccines for the virus that can be applied to humans. If an approved vaccine could be developed for Ebola virus, it would save many people from the painful effects of Ebola hemorrhagic fever. Although it is not a problem right now for most populations outside of Africa, Ebola virus has the potential to be dangerous from the point of view of global health in the future. With more research and a greater understanding of the virus, Ebola will hopefully become a less pressing matter in global health.

Figure.1 General structure of Ebola virus

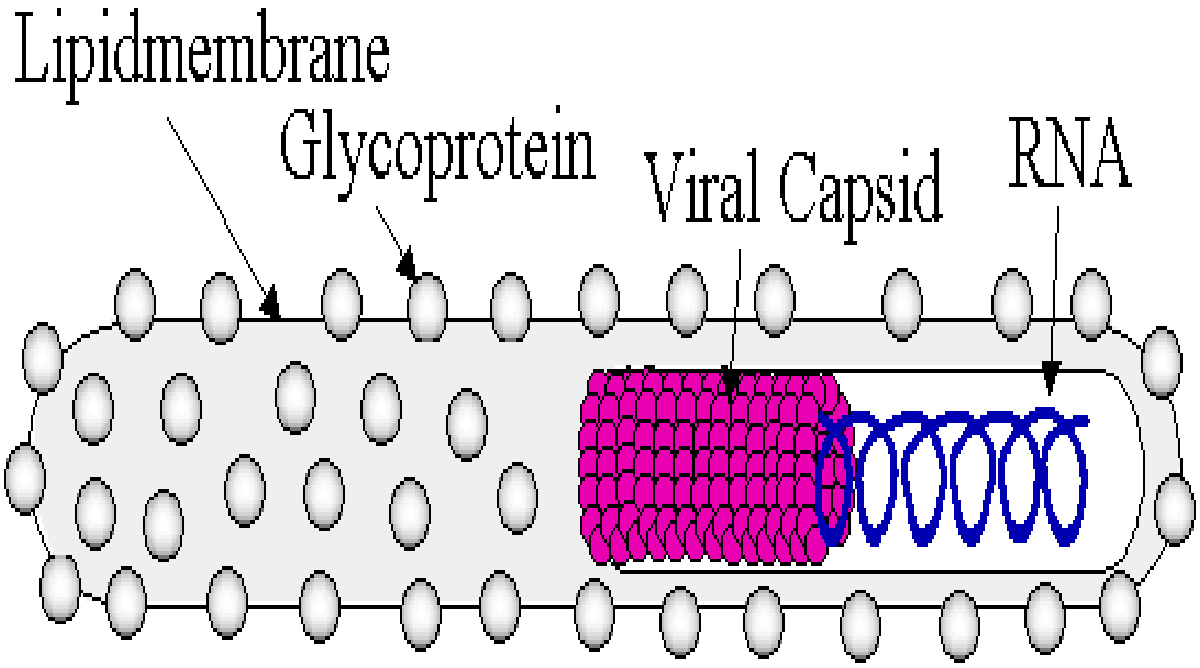

Figure.2 Quarantine for ebola virus (Haas, 2014)

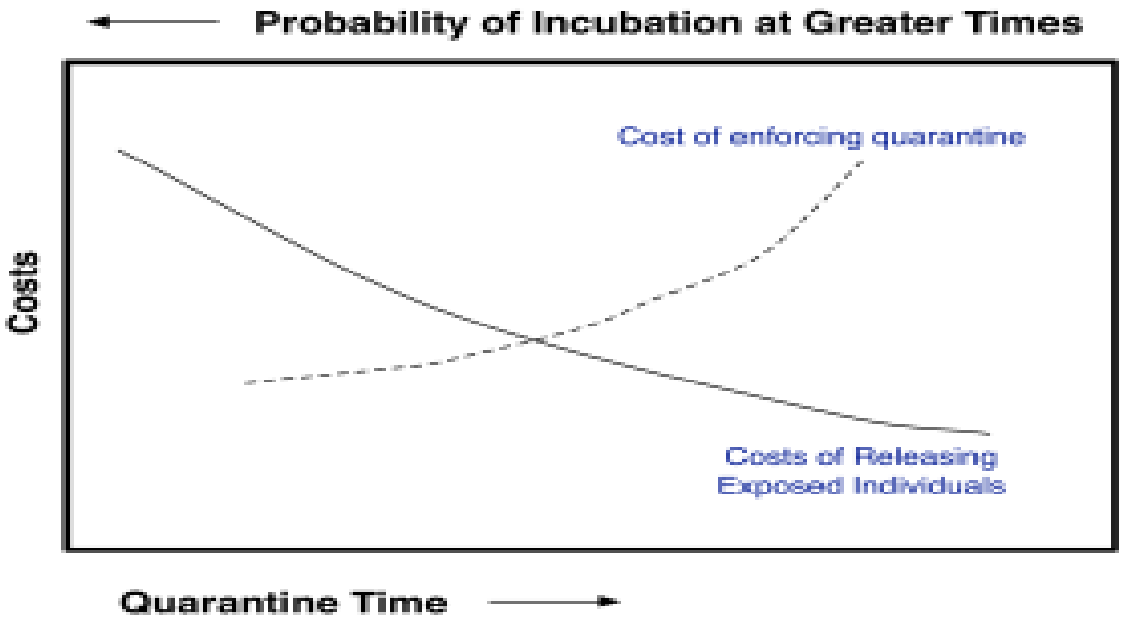

Table.1 Supportive care for ebola victims

1.	Administering intravenous fluids in order to keep normal levels of electrolytes.
2.	Using breathing devices to maintain oxygen levels and drugs to control fever.
3.	Maintaining blood pressure and trying to aid in blood clotting through medications.
4.	Preventing infections from bacteria through use of antibiotics.
5.	Relieving pain and keeping as clean of an environment as possible through good nursing care.

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