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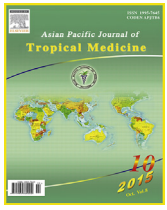

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Is there a way out for the 2014 Ebola outbreak in Western Africa?

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ABSTRACT

The 2014 Ebola outbreak in West Africa, primarily affecting Guinea, Sierra Leone, and Liberia, has exceeded all previous Ebola outbreaks in the number of cases and in international response. Although infections only occur frequently in Western Africa, the virus has the potential to spread globally and is classified as a category A pathogen that could be misused as a bioterrorism agent. This review aims (i) to discuss the latest data to aid our current recommendations for the prevention and control of the Ebola virus infection, (ii) to review its pathophysiology as well as offering insights on the most current data available about Ebola vaccine progress and potential use.

1. Introduction

In today's world, it is important that we take careful consideration of relevant issues that can pose a threat to our overall well-being. Thus, as humans and caretakers of this world, we must carefully examine and research health issues; particularly viruses, as they can be quite deadly. Researching about viruses can allow us to gain a better understanding of how viruses function so that better treatment options and preventative measures can be undertaken. This paper will examine one such virus that has developed over the course of the past year causing several fatalities: the Ebola virus. In December of 2013, the first case of the Ebola virus was identified. On December 26, 2013, a 2-year-old child in the remote Guinean village of Meliandou presented to the hospital complaining of fever, black stools, and vomiting [1]. Two days after presentation, the patient passed away and within the next few months thousands of people living in the surrounding areas also started to experience similar symptoms within Guinea, Liberia, and Sierra Leone [1]. The mysterious illness, as described by the local populations, was soon after identified as the Ebola virus infection, which was prevalent 30 years ago. In 1976, a new filovirus was identified in Zaire (now the Democratic Republic of Congo), and was named Ebola after the River Ebola in the Democratic Republic of Congo. The mortality rate caused by the virus was around 90% [1]. In this article, we will review the virology and epidemiology behind the Ebola virus along with topics such as the diagnostic procedures, as well as ways in which the virus is transmitted and the potential treatment options.

2. Classification of Ebola virus disease

Ebola virus is a nonsegmented, negative-sense, single-stranded 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

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structure. Within the Filoviridae family there are five different Ebola genuses including Zaire (EBOV), Sudan, Bundibugyo, Tai Forest and Reston [2]. Out of the five different species of the Ebola virus, only the Bundibugyo, Zaire, and Sudan species have been responsible for the recent Ebola outbreaks over the course of the past year [3]. The Bundibugyo virus emerged in Uganda in 2007, causing an outbreak of Ebola virus disease with a lower case-fatality rate (approximately 30%) that is typical for the Zaire and Sudan viruses. Sequencing has shown that the agent is most closely related to the Ivory Coast species [4]. The Zaire virus, since it was first recognized in 1976, has caused multiple large outbreaks in Central Africa, with mortality rates ranging from 55% to 88% [5]. It is the main causative agent of the West African epidemic [5]. The Sudan virus has been associated with a case-fatality rate of approximately 50% in four epidemics: two in Sudan in the 1970s, one in Uganda in 2000, and another in Sudan in 2004 [6]. The Tai Forest Virus, was initially identified from a patient and a chimpanzee in 1994 in the Ivory Coast [1]. 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 [7]. This type was first identified within the United States during the time of 1989 and 1990 and was followed by a similar outbreak in Italy [1].

Perhaps the greatest mysteries regarding the filoviruses are the identity of their natural reservoir(s) and the mode of transmission to wild apes and humans [8]. The exact location, origin and natural reservoir of the Ebola virus remains uncertain, however it is believed that the virus is zoonotic and fruit bats may be the cause of its dissemination [1]. In accordance to the above, Tosh and Sampathkumar also agree that the exact origins, locations and natural reservoirs are not explicitly known but do seem likely to be linked to a zoonotic disease [3]. Furthermore, it has also been examined that members of the primate family, such as monkeys and apes, can also get infected with the Ebola virus and more importantly act as intermediate hosts of the virus [1,3]. As such in certain cases if people are in contact with or have perhaps eaten the infected reservoir of an infected animal, they could be infected in turn. However, with that being said and as summarized later in this article, in order for Ebola to be transmitted in any large-scale person–person transmission, the virus would have to be spread through blood or other bodily fluids including urine, saliva, sweat, feces, vomitus, breast milk, and semen as well as contaminated objects such as needles and syringes [1]. Moreover, the Ebola virus is not transmitted through air or water or food in general [1]. In addition to this, the infectivity only occurs once there is an onset of the symptoms [1]. Thus, transmission of the Ebola virus is relatively low in the early stages of the virus. In contrast with the early stages of the virus, the later stages can cause much of a strain because the amount of viral particles originating from the patient in question is extremely high and will most easily effect a person who is not taking the proper preventative measures [1].

3. Epidemiology

Since its first occurrence in 1976, the Ebola virus has thus manifested itself into five different subtypes and thus has spread into several areas of Africa. It has been mentioned, through historical evidence and recent studies, that the Ebola virus tends to break out in small villages that are in close proximity to or are perhaps located in tropical rainforests [3]. This can be further supported by the fact that certain types of Ebola viruses, including EBOV and Sudan virus, can be carried in members of the primate family that tend to reside in rainforests.

Although all previous Ebola outbreaks occurred in Africa, the epidemic began in the West African nation of Guinea in late 2013 and was confirmed by the World Health Organization in March 2014 [9]. As mentioned above, the initial case was a two-year-old child who developed fever, vomiting, and black stools, without other evidence of hemorrhage [9]. The outbreak subsequently spread to Liberia, Sierra Leone, Nigeria, Senegal, and Mali [10]. Areas that have been drastically hit by the Ebola virus are Guinea, Sierra Leone, Nigeria, and Liberia [3]. In less than one year, the Ebola outbreak managed to develop into 9216 cases from an initial amount of 86 cases and 4555 deaths from an initial amount of 60 deaths [3]. The magnitude of the outbreak, especially in Liberia and Sierra Leone, has probably been underestimated, due in part to individuals with Ebola virus disease being cared for outside the hospital setting [11]. As of January 21, 2015, the cumulative number of probable, suspected, and laboratory-confirmed cases attributed to Ebola virus is 21724, including 8641 deaths [12]. In Guinea, Liberia, and Sierra Leone, the number of new cases has decreased as appropriate resources to isolate and treat patients have become increasingly available [12]. In the parts of West Africa where transmission was limited (Senegal, Nigeria, and Mali), the disease appears to have been eliminated [12–14].

4. Pathogenesis and transmission

The Ebola virus enters the host in question through mucosal surfaces, a skin defect, or perhaps by a parental introduction [1]. After entering the body through mucous membranes, breaks in the skin, or parenterally, Ebola virus infects many different cell types. Macrophages and dendritic cells are probably the first to be infected; filoviruses replicate readily within these cells, causing their necrosis and releasing large numbers of new viral particles into extracellular fluid [15]. It has also been studied that the virus has the capability of disseminating to regional lymph nodes through the lymphatic system along with the liver and spleen via blood [1]. The detailed pathogenesis of Ebola virus disease is illustrated in Figure 1 [16].

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 individual 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. However, it should be noted that for any large-scale human transmittance to occur there must be a direct contact of mucous membranes, or broken skin with bloody or bodily fluids of an infected person [1]. Such transmission can involve any contact by the form of blood or bodily fluids including but not limited to urine, saliva, sweat, feces, vomitus, breast milk, and semen, as well as via contaminated objects like needles and syringes [1]. There are no reported cases of Ebola virus being spread from person to person by the respiratory route [17]. However, laboratory experiments have shown that Ebola virus released as a small-particle aerosol is highly infectious for rodents and nonhuman primates [18]. Healthcare workers may therefore be at risk of Ebola virus disease if exposed to aerosols generated during

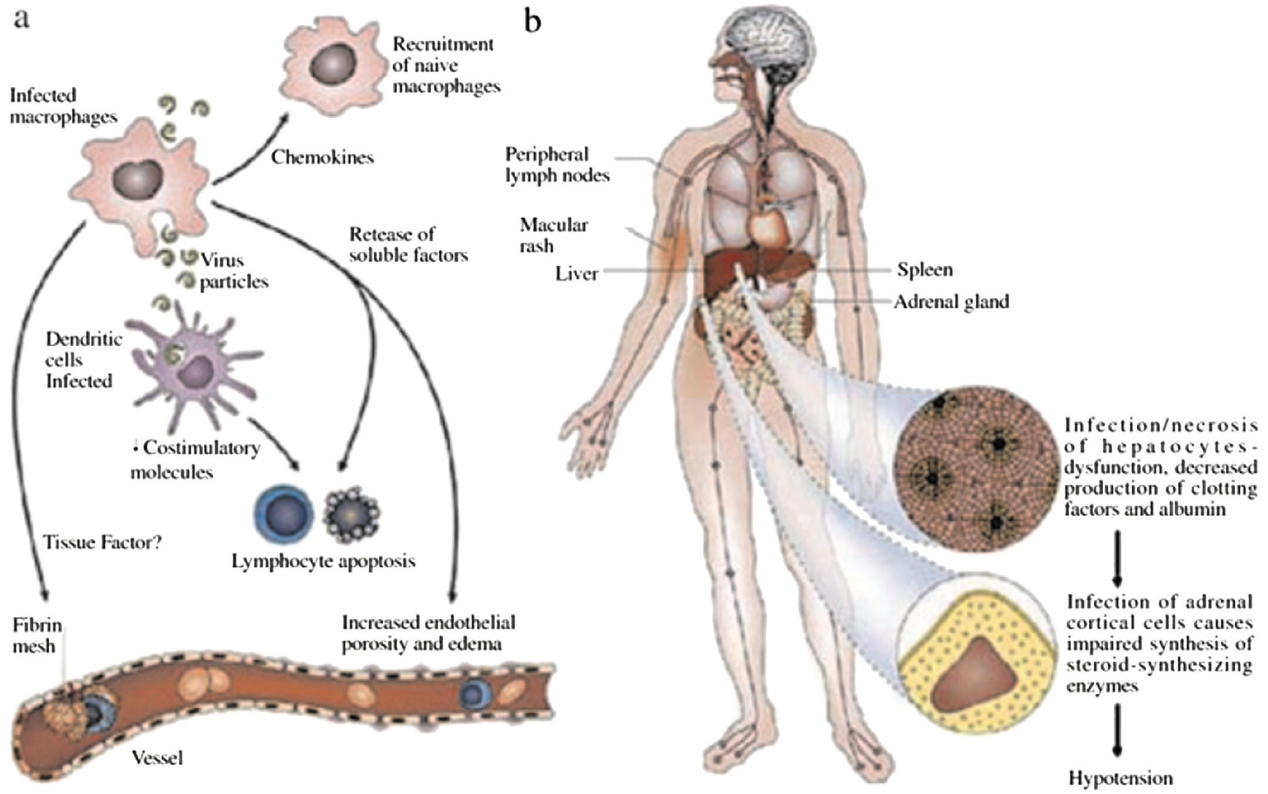

Figure 1. Model of Ebola virus pathogenesis in primates [16].
(a) Virus spreads from the initial infection site to regional lymph nodes, liver and spleen. At these sites, the virus infects tissue macrophages (including Kupffer cells) and dendritic cells. Soluble factors released from virus-infected monocytes and macrophages act locally and systemically. Release of chemokines from these virus-infected cells recruits additional macrophages to sites of infection, making more target cells available for viral exploitation and further amplifying the dysregulated host response. Although none of these viruses infects lymphocytes, their rapid loss by apoptosis is a prominent feature of disease. The direct interaction of lymphocytes with viral proteins cannot be discounted as having a role in their destruction, but the marked loss of lymphocytes is likely to result from a combination of factors including virus infection of dendritic cells and release of soluble factors from virus-infected monocytes and macrophages. For example, virus infection of dendritic cells impairs their function by interfering with the up-regulation of costimulatory molecules, which are important in providing rescue signals to T lymphocytes. Additionally, release of soluble factors from infected monocytes and macrophages results in deletion of lymphocytes, both directly by release of mediators such as nitric oxide and indirectly by contributing to up-regulation of proapoptotic proteins such as Fas and TRAIL. The coagulation abnormalities vary in nature and magnitude among the VHFs. For example, Ebola virus induces the overexpression of tissue factor, which results in activation of the clotting pathway and the formation of fibrin in the vasculature. In contrast, coagulation disorders are less marked in Lassa fever, and impairment of endothelial function contributes to edema, which seems to be a more prominent finding in Lassa fever than in other VHFs. (b) The hemodynamic and coagulation disorders common among all of the VHFs are exacerbated by infection of hepatocytes and adrenal cortical cells. Infection of hepatocytes impairs synthesis of important clotting factors. At the same time, reduced synthesis of albumin by hepatocytes results in a reduced plasma osmotic pressure and contributes to edema. Impaired secretion of steroid-synthesizing enzymes by hemorrhagic fever virus-infected adrenal cortical cells leads to hypotension and sodium loss with hypovolemia. Macular rashes are often seen in VHFs.

medical procedures. 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. Infected patients are not typically contagious during the incubation period, and become so only when they are actually ill. During severe illness with Ebola, blood, sweat, feces, and vomit are highly infectious [19]. Therefore, it is also thought that healthcare workers who do not follow proper preventative measures are at the highest risk for secondary infection [3]. Moreover, it has also been studied that the route of transmission has an effect on the outcome of the virus [19]. In the early EBOV outbreak in 1976, case fatality rates after transmission by injection was 100% versus 80% in contact exposure cases [19]. This has also been confirmed in non-human primate models, which show a faster progression of the Ebola virus through injection versus those received by other transmission methods [19].

5. Clinical manifestation

Patients with Ebola virus disease have an incubation period of 2–21 d with a mean ranging from 4 to 10 d [1,3,19]. Most cases of Ebola virus disease begin with the abrupt onset of flu-like symptoms including fever, chills, and myalgia [1,3,19]. Once further developed, the flu-like symptoms may progress into vomiting and diarrhea [19]. In addition to this further progression, the Ebola virus continues to transpire thereby effecting multiple systems within the body including gastrointestinal, respiratory, vascular, and neurological systems [1]. Such symptoms involved with the above mentioned systems can include nausea, vomiting, abdominal pain, diarrhea, chest pains, coughing, postural hypertension, edema, as well as headache, confusion, and possibly coma [1,19]. Approximately 5–7 d after the initial symptoms have transpired, a diffuse erythematous, nonpruritic maculopapular rash begins to develop along with severe abdominal pains, severe watery diarrhea, nausea and vomiting

[1,19]. Hemorrhagic manifestations arise during the peak of the illness and include petechiae, ecchymoses, uncontrolled oozing from venepuncture sites, mucosal hemorrhages, and post-mortem evidence of visceral hemorrhagic effusions [1]. The hemorrhages can be quite severe but affect only half of the patients infected by Ebola [1]. Patients that present severe clinical signs early on during the course of the infection tend to die typically within 6–16 d with hypovolemic shock and multi-organ failure [1]. Those who do not possess fatal symptoms such as a fever for several days, tend to recover within 6–11 d with a prolonged period of weakness, fatigue, poor appetite, and failure to regain weight that was lost during the illness [3]. As suggested by Goeijenbier *et al.*, there has not been much scientific evidence to support the long-term complications of the Ebola virus for those who have successfully recovered; however, available literature suggests that recovered patients of Ebola could potentially develop disorders such as recurrent hepatitis, myelitis, prolonged hair loss, psychosis and uveitis [19].

6. Diagnosis

Although there are no approved specific therapies for Ebola virus disease, it is essential to make the diagnosis as early as possible, in order to initiate supportive measures before the development of irreversible shock and to institute infection control procedures. From what has been gathered about the previously mentioned symptoms of Ebola, it can be surmised that its early symptoms have the power to mimic other diseases; the Ebola virus usually presents as an acute viral prodrome and many differential diagnoses should be considered, such as malaria, typhoid fever, yellow fever and meningococcal meningitis, which are also endemic diseases in Africa [1]. The approach to evaluate patients with possible Ebola virus disease depends upon whether or not the individual displays appropriate signs and symptoms, how likely it is that the exposure will result in disease, and when the exposure occurred. According to Chan and Tseng, laboratory diagnosis of Ebola should be performed in a well-equipped laboratory with up to a level 4 biosafety for bio-contaminant facilities for viral culturing [1]. Furthermore, key symptoms that should be a definite sign of the presence of the Ebola virus include the following: (1) acute febrile illness (38 °C) (2) headache, myalgia, nausea, vomiting, diarrhea and abdominal pain, (3) bleeding with unknown reason, and (4) sudden death with unknown reason [1]. In addition to these symptoms, laboratory conditions should be reflective of the following: (1) clinical specimen (throat swab or skin biopsy) that were isolated and identified as Ebola virus, (2) clinical specimen that show positive by reverse transcription polymerase chain reaction, and (3) serology (enzyme link immunosorbent assays, IgM and IgG) positive [1]. Lastly, epidemiologic conditions, with any of the following 21 d before onset of symptoms: (1) history of travel from or living in the endemic area of EVD, (2) exposure of blood, body fluids or discharge pollutants from possible or defined cases, (3) history of contact with bats, rodents, or primates in endemic area of EVD, and (4) operate the specimen of EVD in a laboratory [1].

7. Treatment

According to Chan and Tseng, there is no standard treatment present for the Ebola virus [1]. However, wherever outbreak is identified, similar strategies and treatment methods are undertaken. Whenever possible, patients with Ebola virus disease should receive care in designated treatment centers and by clinicians trained to care for such patients [20]. Treating patients with Ebola requires a multidisciplinary approach [21]. All healthcare workers involved in the care of infected or potentially infected patients should use infection control precautions, including the proper use of personal protective equipment. Currently, main strategies to deal and treat with the Ebola virus are symptomatic and supportive care which include fluid and electrolyte preservation, maintaining oxygen saturation and blood pressure, and treating complication such as secondary infections [1,22]. Once identified that the patient is in fact infected, then they must be isolated and treated promptly according to the symptoms exhibited [19,22]. If identified early on, the best treatment option which can result in a higher rate of survival is to replace lost fluid [3]. Additional supportive measures may include symptomatic management of fever, pain (abdominal, joint, muscle), nausea, vomiting, and diarrhea. The use of anti-diarrheal agents may also decrease fluid and electrolyte losses [23]. Patients with coagulopathy and bleeding may require blood. Renal replacement therapy may be needed to manage severe acute kidney injury in the setting of shock [24]. In some case series, empiric antimicrobial therapy was used for all patients at the time of initial presentation, or for patients who had evidence of gastrointestinal dysfunction, even if clinical evidence of bacterial sepsis was absent [25]. However, data are currently lacking to justify this approach.

According to the World Health Organization, since the severity and magnitude of the current outbreak of the Ebola virus is quite grand, it is ethical to use experimental drugs for treatment and prevention [19]. The urgent need for effective treatments has thus accelerated the evaluation of several experimental therapies that had been developed specifically to treat or prevent Ebola or Marburg virus infection, but have only been tested in laboratory animals. Several treatment options have been available and in most part such treatment options have transpired because initial symptoms tend to vary from patient to patient. One of the experimental drugs used for treatment is known as Zmapp, developed by Mapp Biopharmaceutical, Inc., is a combination of three humanized murine antibodies generated by Ebola virus infected mice, and subsequently produced in tobacco plants [1]. In a study carried out to experiment the viability of Zmapp, 43% of infected mice survived with the Zmapp treatment [1]. Other Ebola-specific agents in development include TKM-Ebola (a short interfering RNA molecule), phosphorodiamidate morpholino oligomers (a type of antisense oligonucleotide), and BCX4430 (a nucleoside analog). In addition, two antiviral agents with anti-Ebola virus activity in cell culture or laboratory animals (favipiravir and brincidofovir) that have been used in patients with Ebola virus disease, are also currently being evaluated [26,27]. Two other antiviral drugs that are used in the treatment of Ebola are ribavirin and lamivudine [1]. However, ribavirin has not been a recommended treatment option due to its adverse effects and with lamivudine there wasn't any significant survival rate [1,22].

Another treatment option is convalescent therapies. Convalescent therapies are treatment options that utilize plasma from recovered Ebola patients [1]. In 1976, the treatment had been used for a woman with EVD in Zaire. Initially, her symptoms were improved but she eventually passed [1]. Similar to the experimental drug Zmapp, convalescent therapies are a

working progress and as such other treatment methods have been implemented including antiviral drugs and vaccines.

Preventing the transmission remains the way of controlling the infection. Several concurrent strategies should be employed to prevent the spread of Ebola virus. Strict infection control measures and the proper use of personal protective equipment are essential to prevent transmission to healthcare workers. In addition, individuals who have been exposed to Ebola virus should be monitored, so that they can be identified quickly if signs and symptoms develop. Other preventive measures may eventually include vaccination. However, at present, there are no approved vaccines to prevent Ebola virus disease. Two vaccines have been in use as a treatment option for Ebola; cAd3-EBOV (cAd3) and rVSVDG-EBOV-GP (rVSV) [1]. Both of these vaccines are still under investigation for their viability.

8. Conclusions and the way forward

Overall, it can be surmised from the discussion presented above that the Ebola virus disease may be a deadly and extensive disease that requires our utmost attention. Over the course of the past year, the Ebola virus has spread like wildfire in Western Africa. In addition to this, it has also managed its way across to North America. As such it is very important that we carefully examine Ebola as it is a virus that is constantly changing and getting ever so stronger. Such an epidemic has most definitely shaken up the scientific world causing research in the field of medicine to heighten in order to not only learn more about the virus itself but also study preventative measures as well as treatment options. As mentioned in this review, the virus can reflect varying symptoms as it has the potential to affect multiple systems of the body including gastrointestinal, respiratory, vascular, and neurological systems. As such various treatment options are underway to deal with the virus in the best possible way so as to reduce the risk of fatality. Due to the virus's severity and magnitude, the World Health Organization has stated that experimental drugs are ethical and can be used as a form of treatment. Other options have been put into place including vaccines, antiviral drugs, and convalescent therapies; however, each of them seem to either have their own set of issues or are perhaps considered a relatively new treatment method and require further consideration and examination.

In conclusion, the world has been faced with quite a struggle and further research in the medical field must be carried out at a continuous pace. With such a deadly virus on the rise, it is pertinent that safety measures and health precautions be advised and followed for the sake of humanity. Next steps should involve not only research incentives to learn more about Ebola and how to deal with it but to raise awareness of it for the sake of the public. People should learn more about Ebola and its potential. Moreover, the public should be given access to ways in which they can learn more about Ebola and should be able to know what the signs and symptoms are so as to seek medical attention as needed. With that being said, much work has been done thus far in order for the public to gain more knowledge about Ebola. Furthermore, it is essential that we point out the admirable work that is being done in places in Western Africa to medically assist those who have been diagnosed with Ebola as they are risking their own health for the safety of others. We must adamantly continue to learn more the Ebola virus, carry out research studies to examine its roots and strive to develop treatment options. In addition to this, it should also be wise to point out that such areas that are affected by the Ebola virus and those areas where outbreaks tend to occur are in smaller impoverished area. As such it is extremely important that we identify these areas and provide adequate medical attention as swiftly as possible [1,19].

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

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