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Review

Recent advances in the development of vaccines for Ebola virus disease

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ABSTRACT

Ebola virus is one of the most dangerous microorganisms in the world causing hemorrhagic fevers in humans and non-human primates. Ebola virus (EBOV) is a zoonotic infection, which emerges and re-emerges in human populations. The 2014 outbreak was caused by the Zaire strain, which has a kill rate of up to 90%, though 40% was recorded in the current outbreak. The 2014 outbreak is larger than all 20 outbreaks that have occurred since 1976, when the virus was first discovered. It is the first time that the virus was sustained in urban centers and spread beyond Africa into Europe and USA. Thus far, over 22,000 cases have been reported with about 50% mortality in one year. There are currently no approved therapeutics and preventive vaccines against Ebola virus disease (EVD). Responding to the devastating effe1cts of the 2014 outbreak and the potential risk of global spread, has spurred research for the development of therapeutics and vaccines. This review is therefore aimed at presenting the progress of vaccine development. Results showed that conventional inactivated vaccines produced from EBOV by heat, formalin or gamma irradiation appear to be ineffective. However, novel vaccines production techniques have emerged leading to the production of candidate vaccines that have been demonstrated to be effective in preclinical trials using small animal and non-human primates (NHP) models. Some of the promising vaccines have undergone phase 1 clinical trials, which demonstrated their safety and immunogenicity. Many of the candidate vaccines are vector based such as Vesicular Stomatitis Virus (VSV), Rabies Virus (RABV), Adenovirus (Ad), Modified Vaccinia Ankara (MVA), Cytomegalovirus (CMV), human parainfluenza virus type 3 (HPIV3) and Venezuelan Equine Encephalitis Virus (VEEV). Other platforms include virus like particle (VLP), DNA and subunit vaccines.

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1. Introduction

Ebola virus disease (EVD) formerly called Ebola hemorrhagic fever (EHF) is caused by Ebola virus of the family *Filoviridae*. Ebola virus was discovered in 1976 with simultaneous outbreaks in Democratic Republic of Congo (DRC) and Sudan (Feldmann and Geisbert, 2011). Since its discovery 40 years ago, the virus has caused over 20 sporadic outbreaks mostly confined to rural areas in East and Central Africa (Patel et al., 2007). Hence the disease did not attract much global attention. But the 2014 outbreak, which emerged in West Africa, took a new and unprecedented pattern. The disease was first noticed in a 2 years old child on 6 December 2013 in a rural village in Guinea (Onwuakor, 2014) close to the borders of Liberia and Sierra Leone. From there, it appears that the virus spread within these three countries unnoticed. But officially, the World Health Organization (WHO) declared an outbreak of EVD on 22 March 2014 in Guinea, 31 March 2014 in Liberia, 26 May 2014 in Sierra Leone, 20 July in Nigeria and 29 August in Senegal. Due to increased travel mostly through air, the disease was reported in other parts of the World including US (25 October 2014), Spain (6 October 2014) and Mali (25 October 2014). Other cases were also reported in the UK. Hence what started as a West African problem soon became a global threat. Hence, on 8 August 2014, the WHO declared the epidemic as a global public health emergency, while on 18 September 2014, the United Nations Security Council (UNSC) adopted resolutions 2177, declaring the disease a threat to international peace and security. The world responded, though a little late, by sending medical personnel, equipment, supportive drugs and finance. International NGOs particularly Doctors Without Borders (MSF) and other charity organization sent their staff to combat EVD even at a time when West Africa was practically isolated. Some of these NGO staff got infected and returned home to seek medical attention, which was partially how the disease spread to Western Countries. As there were no cure, they were given experimental therapies, while some survived, a few unfortunately died. Notably among the countries that assisted West Africa against EVD was USA, UK, France, Germany, China, Japan, and Cuba. The World Bank, Africa Development Bank and Bill and Melinda Gates Foundation supported financially. By the time most of this assistance came, the disease has caused major catastrophic disaster in West Africa. As of 14 September 2014, a total of 4507 EVD cases have been reported in Liberia, Sierra Leone, Guinea, Nigeria and Senegal with 2296 deaths (WHO Ebola Response Team, 2014). The spread of Ebola virus was successfully curtailed in Senegal and Nigeria, with the WHO official declaring them free of EVD after 42 days i.e., twice the incubation period of the virus on 17 October 2014 and 20 October 2014 respectively. Current statistics from WHO show that as of 19 August 2015 a total of 27,988 persons have been infected worldwide with the following breakdown in the three main countries; Guinea (3766 infected, 2524 dead), Liberia (10,672 infected, 4808 dead) and Sierra Leone (13,494 infected, 3952 dead) (WHO, 2015). The published data might have been under reported (Choi et al., 2015; The Economist, 2015). Through international/global concerted efforts, the rate of infection is now declining. Apart from deaths, and the burden of disease, EVD has caused social challenges (Tayo et al., 2015; Chigbu and Ntiador, 2014) and economic problems (Adegun, 2014; Cheto, 2014). The infection rate may not abate in the next decade. The World Bank (2014) estimated the short-term fiscal impacts of EVD based on sector component methods. They found out that the impact was large, being $93 million (4.7% of GDP) for Liberia, $79 million in (1.8% of GDP) of Sierra Leone and $120 million (1.2% of GDP) for Guinea.

The genus *Ebolavirus* consist of 5 distinct species in decreasing order of virulence; Zaire Ebola virus (ZAIV), Sudan ebolavirus (SUDV), Bundibugyo ebolavirus (BDBV or BEBOV), Tai Forest ebolavirus (TAFV) and Reston ebolavirus (RESTV) (Bukreyev et al., 2014), which do not infect human but mostly non-human primates (NHPs). Fruit bats are regarded as the primary host of the virus, from where it spreads to human directly or indirectly through intermediate reservoirs such as NHPs particularly monkeys, gorilla and baboons and other wildlife including duikers, pigs and arthropods. Among humans, Ebola virus can spread via direct contact through exchange of body fluids and secretions such as sweat, semen, blood, urine, catarrh, saliva, sputum, and vomitus. Ebola virus is spread by direct contact with infected persons or corpse during funerals. Ebola virus is also commonly spread via nosocomial infections (Shuaib et al., 2014). Though, the incubation period of the virus is 2–21 days, death usually occurs within 4–10 days.

Ebola virus disease is characterized by sudden onset of fever, weakness, headache, muscle pain, sore throat, hiccups, conjunctivitis and red eyes, rash, diarrhea and vomiting, internal and external bleeding. Like HIV/AIDs, Ebola virus evade and damage the host immune system (Qiu et al., 2012, 2013; Watanabe et al., 2007; Smith et al., 2013) leading to coagulopathy resulting in multi-organ destruction including the liver and kidneys (Beeching et al., 2014; Bente et al., 2009; Martin et al., 2006). The ability of Ebola virus to interfere with the innate immunity system of the host, especially the interferon response is caused by virus matrix proteins VP24 and VP35 (Bente et al., 2009; Watanabe et al., 2007; Qiu et al., 2012, 2013).

Ebola virus disease, which started as a localized problem in Africa has grown to become a global threat. Ebola virus disease is now a threat to global peace and security for several reasons. The virus is a zoonotic pathogen with outbreak occurring sporadically in Africa, emerging and re-emerging (Peters et al., 1994; Marston et al., 2014; Sarwar et al., 2015). There have been over 20 outbreaks since, the disease was first reported in 1976 (Kortepeter et al., 2011; Mire et al., 2013). According to Richardson et al. (2009) EVD has drawn increasing interest in the past few years due to increasing number of natural outbreaks especially in Africa. Zaire Ebola virus is the most aggressive/virulent species (Richardson et al., 2011; Bausch, 2014), its fatality rates have been reported to be up to 90% (Basler and Amerasinghe, 2009; Gunther et al., 2011; Marzi et al., 2011; Mire et al., 2014; Sullivan et al., 2006; Tsuda et al., 2011). Zaire Ebola virus is the cause of the 2014 EVD outbreak in West Africa (Kanapathipillai et al., 2014; Sarwar et al., 2015; Bishop, 2015) though with less fatality rate 40–87% (Ohimain, 2015). The current outbreak, which is caused by Makona outbreak strain of EBOV, is larger than all previous epidemics combined (Bishop, 2015). This is the first time that EVD is localized primarily in urban areas with a global spread (Sarwar et al., 2015).

The World Health Organization classified Ebola virus as a biosafety level 4 pathogens (Bente et al., 2009; Enterlein et al., 2006; Gunther et al., 2011) though there are limited level 4 facilities in Africa, where the outbreaks occur frequently. The Center for Disease Control and prevention (CDC) classified Ebola virus as a category A pathogen that can be used as a biological weapon for bioterrorism (Richardson et al., 2009; Feldmann et al., 2007; Swenson et al.,