Chapter 8

Ebola Virus Disease: Progress So Far in the Management of the Disease

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Additional information is available at the end of the chapter

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Abstract

Ebola virus disease is one of the most deadly emerging infectious diseases in the world which causes severe haemorrhagic fever, with a mortality rate of 50–90%. Following the largest outbreak in West Africa in 2014 which was the most deadly of all time challenging global health, so much concern has been tilted towards the management of the disease. Some of the major global challenges that prolonged and escalated the gravity of the 2014 outbreak were the lack of prompt, reliable and affordable diagnostic tools, but most importantly no specific treatment and vaccines were available to manage the infection. Though certain non-licensed experimental drugs as well as vaccines were introduced during the 2014 outbreak that contributed towards the control of the epidemic, their efficacy was yet to be confirmed in randomized trials. Presently, a few rapid diagnostic test kits have been approved by FDA and WHO. Also, several experimental drugs and vaccines are undergoing randomized clinical trials with a few currently at phase III. Thus, it is our hope that most of these drugs and vaccines will be available in future to better manage re-emerging Ebola infections or outbreaks.

Keywords: Ebola virus disease, haemorrhagic fever, rapid diagnostic test, specific treatment, vaccine, outbreak

1. Introduction

Ebola haemorrhagic fever is very deadly viral disease which originated in the Democratic Republic of Congo (DRC), a formerly known as Zaire with the first outbreak in 1976 [1]. Since then this virus has spread across the globe but more prominent in the African continent. This virus causes fatal haemorrhagic fever to humans as well as non-humans including monkeys, gorillas, chimpanzees, etc. [2]. Though a definitive host is yet to be confirmed, this virus is

believed to be transmitted by bats being the primary reservoir mostly through body fluid or contact to humans and other primates. The virus can penetrate mucosal membrane to infect various cells in the body including macrophages, monocytes, dendritic cells, etc. and spread into the circulatory and lymphatic systems damaging blood vessels leading to haemorrhage. Though no approved standard treatment is available for the disease, it has been managed with certain antiretrovirals and supportive treatments such as rehydrating solutions for maintaining fluid and electrolyte balance as well as treatments against secondary infections. Thus, the availability of a standard approved drug is one of main concern in recent time following the 2014 fatal outbreak. More so, since this disease is sporadic and usually emerges as an outbreak, effective control is usually difficult as diagnosing viraemia is usually challenging. Also, no existing vaccine is available against the disease. Following the introduction of experimental drugs and vaccines during the 2014 West-Africa Ebola outbreak which contributed to its control [3], it has been of interest to know the progress so far and efforts that are been laid to ensure that these drugs and vaccines are licensed in future. Hence, this chapter will focus on the progress towards the provision of diagnostic tools, and availability of specific treatments and vaccines. However, an understanding of the aetiology and pathogenesis of Ebola virus disease is necessary so as to expose possible drug targets as well as various vaccine candidates for a better management of the disease.

2. The origin and epidemiology of Ebola virus disease

This viral disease emerged around 1976 with the first outbreak in the northern part of DRC, formerly known as Zaire which affected about 318 individuals with a mortality rate of 88% [1]. Almost at the same period and year, another outbreak emerged in southern Sudan with 284 cases killing about 150 individuals (53%) [4]. In 1976, a case of the infection of the Sudan virus was identified in England but there was no casualty [5]. The following year in 1977, a case was reported in DRC which the individual died. By 1979, there was reoccurrence of an outbreak in Southern Sudan which affected 34 individual with a 65% mortality rate. The disease was absent for about 2 decades before re-emerging in Gabon and Ivory Coast in 1994, with a mortality rate of 60% in Gabon [6]. The disease reoccurred in Gabon in 1996 and 1997 [6], and again in DRC in 1995 [7]. In 2000, an outbreak was reported in Uganda with over 80% mortality while the following year, another outbreak was reported in Gabon with 53% and 82% mortality rate respectively [8]. Since then, there has been reoccurrence of outbreaks in DRC between 2001 and 2008 [9] and in Uganda between 2007 and 2012 [10]. In 2012, there was another outbreak in DRC with a fatality rate of about 40% [11]. In 2014, the largest outbreak was recorded in DRC [12] and West Africa [13] that spanned across various countries including United State, Spain, Mali, Senegal and Nigeria [14].

It should also be noted that some non-human primate infections have also occurred. The first to be observed was in the United States between 1989 and 1990 [15] followed by another outbreak in Italy in 1992 which were related to the importation of monkeys from the Philippines [16]. In 2008, cases of respiratory and porcine reproductive syndrome in sows and piglets caused by the Ebola virus were observed in China and Philippines with high mortality. Animal farmer workers who were in contact with the virus became infected but the infection was asymptomatic and no casualties were recorded [17].

3. The 2014 West African Ebola outbreak

The first trace of the infection was in Guinea in December 2013 which subsequently spread to Liberia and Sierra Leone. In 2014, the world recorded the largest Ebola virus outbreak in West Africa particularly in Sierra Leone, Guinea, and Liberia, with over 7178 infected cases 3338 deaths amounting to a mortality rate of 51% as of 1st October, 2014 [18]. Also, the disease spread to other countries including Nigeria and USA. [18]. In August 2014, the epidemic was declared by the World Health Organization (WHO) as a public health emergency of international concern [19]. By September 2014, the fatality rate of infected individuals was about 70.8% in Liberia, Guinea, and Sierra Leone. About 20 cases were report in Nigeria which originated from a traveller from Liberia in July 2014 with a fatality rate of 45.5%. As of 23rd October, 2014, about 450 health care personnel were known to be infected with Ebola virus of which 244 died [20]. In October 2014, two imported cases with one death, as well as two locally acquired cases from health care workers were identified in the United States. By November 2014, a cumulative total of 20,000 Ebola cases were reported in the West Africa outbreak including 5740 cases from Guinea, 9890 from Liberia and 5000 from Sierra Leone [20] killing over 11,300 individuals within the course of 2 years.

4. The 2018 Ebola outbreak in DRC

Recently, an Ebola outbreak has emerged in DRC with the first cases detected on May 8, 2018 at the Bikoro zone, a remote rural region and the virus has spread to Mbandaka, an urban area which inhabits more than 1 million people. Mbandaka is about an hour's flight from Congo's capital Kinshasa, thus, there is more concern about the possibility of the virus to spread to other larger populations. As of May 21, 2018, about 46 cases of haemorrhagic fever had been recorded. Among these cases, 21 have been confirmed as Ebola infected, 21 are probable cases of the virus while 4 are only suspected to be related to the epidemic. Twenty-six deaths have already been reported [21].

5. Ebola virus species

Ebola haemorrhagic disease is caused by Ebola virus which is an RNA virus in nature. It is a virus that belongs to mononegavirales order, Filoviridae and the genus *Ebola*. There exist five species of this virus which include the following [22, 23].

i. Zaire Ebola virus (EBOV): Previously known as the Zaire virus (ZEBOV) was the first to be identified following the first outbreak in DRC in 1976. It has recorded the highest mortality rate of approximately 83% over 27 years.

ii. Sudan Ebola virus (SUDV): This virus emerged in 1976 in Southern Sudan as the second outbreak almost simultaneously with the Zaire outbreak. It presents an average fatality rate of 53% since 1976 to 2001.

iii. Reston Ebola virus (RESTV): It was discovered in 1989 during an outbreak of simian haemorrhagic fever virus (SHFV) in Reston USA which infected non-human primates. It has also been identified in Pennsylvania, Texas and Siena, Italy.

iv. Côte d'Ivoire Ebola virus: Also referred to as Taï Forest Ebola virus (TAFV), it was first discovered in chimpanzees from the Taï Forest in Ivory Coast in 1994

v. Bundibugyo Ebola virus (BDBV): This virus species was discovered in 2007 in Uganda following the outbreak in Bundibugyo District which recorded 39 deaths with a mortality rate of 34%.

6. Ebola virus morphology

The genus Ebola are negative-sense, single stranded RNA viruses which are non-segmented belonging to the Filoviridae family. The negative-sense RNA genome is approximately 19 kb in size but varies among the various Ebola species and it is encapsulated in a lipid membrane used for the formation of new particles on the surfaces of their host cells [24, 25]. The core of the virus constitutes the genomic RNA surrounded by nucleoproteins (NP). The Ebola genome consists of seven genes that codes viral proteins (VPs) each of which differs in function [26]. Among these proteins, VP24 which constitutes the main matrix protein is the most abundant virion protein. VP30 is involved in the activation of RNA transcription while VP35 is involved in viral RNA synthesis. VP35 is also attributed to be responsible for varying degrees of virulence among different strains of Ebola virus. VP40 is also a matrix protein of the negative stranded RNA and its roles is to assemble the lipid envelop of the virus by linking the nucleocapsid to the surrounding membrane. The virus also contains a transmembrane glycoprotein (GP) which is responsible for the formation of virion spikes which facilitates viral entry into cells. A section of this glycoprotein (GP1 and GP2) are responsible for immunosuppression

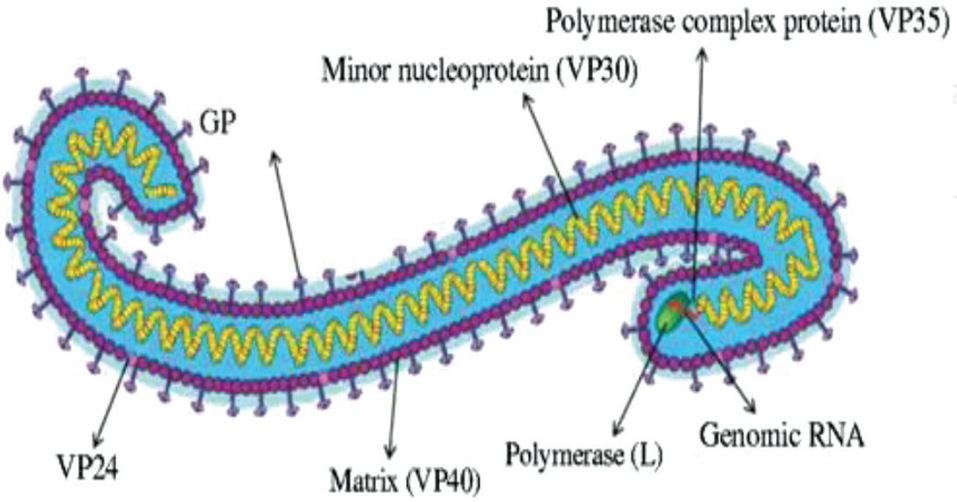

Figure 1. Morphological representation of the Ebola virus showing the various proteins: VP, virion protein; and GP, glycoprotein [28].

permitting the virus to evade the immune system as they show very high homology with immunosuppressive protein found in oncogenic retroviruses [27]. There is also an RNA-dependent RNA polymerase known as the L protein which catalyzes transcription. The morphology of Ebola virus is shown in **Figure 1**.

7. Transmission and transmission dynamics

Ebola haemorrhagic fever is a zoonotic borne disease believed to be transmitted from rodents and bats as primary reservoirs. It has been noticed that bats are usually present at the sites of several outbreaks in large numbers and Ebola virus antibodies have been found in fruit bats [29] though the virus has not been isolated from these animals. It is believed that this infection is asymptomatic in bats and can be transmitted to chimpanzees, gorillas, monkeys, other mammals and humans. These transmissions may be due to direct contact with the reservoir species (**Figure 2**). In humans, transmission from infected persons to health humans is through direct contact with body fluids or secretions such as saliva, stool, urine, semen, and blood [30]. The virus has been shown to persist for up to 7 weeks in semen after recovery of infected individuals from the illness suggesting sexual intercourse as probable means of transmission. Also, contact of broken skin or mucous membranes with items such as clothing, bed linen, or used needles are possible means of transmission [30].

Health workers are another category of persons exposed to the infection following their care for Ebola infected patients as contact with used equipment, gloves and other clinical materials can promote transmission. Health workers or other individuals can become infected if they get in contact with dead bodies of infected subjects. In all, it has been concluded that Ebola transmission is only by means of contact as there has been no evidence of transmission from

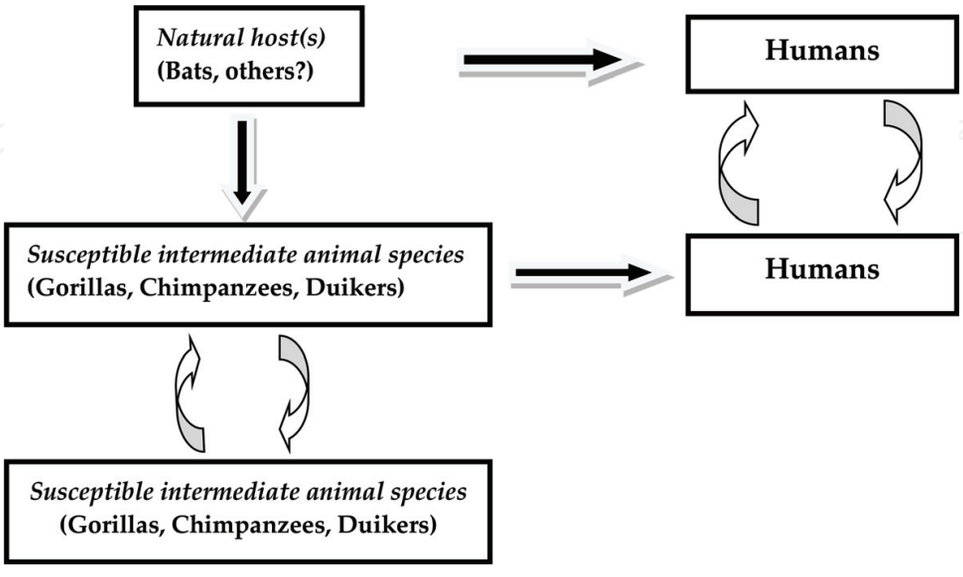

Figure 2. Transmission of Ebola virus. Source: http://www.cdc.gov/vhf/ebolaresources/virus-ecology/.html.

Levels of risk of transmission	Type of contact
Very low or no recognized risk	Casual contact with a feverish, ambulant, self-caring patient. Examples: sharing a sitting area or public transportation; receptionist tasks.
Low risk	Close face-to-face contact with a feverish and ambulant patient. Example: physical examination, measuring temperature and blood pressures.
Moderate risk	Close face-to-face contact without appropriate personal protective equipment (including eye protection) with a patient who is coughing or vomiting, has nose bleeds or who has diarrhoea.
High risk	Percutaneous, needle stick or mucosal exposure to virus-contaminated blood, bodily fluids, tissues or laboratory specimens in severely ill or known positive patients.

Table 1. Risk of Ebola virus transmission and its association with the level of contact.

human to human via the respiratory route [31]. The type of contact among individuals can influence the risk of transmission of Ebola virus disease as shown in **Table 1** [32].

8. Pathogenesis of the disease

Though the natural reservoir of Ebola virus is unknown, bats are the main primary reservoirs along with some non-human primates such as monkeys, baboons, chimpanzees and gorillas known to transmit the virus to humans through contact with the animals or their body fluids such as sweat, blood, urine, and other secretions or other infectious objects. Ebola virus can persist on objects in a dried state for several hours and can persist in body fluids for several days [28, 33]. Once humans get in contact with the virus, it enters the body through mucous membranes following abrasions or cuts and adheres to cell membranes. Following attachment on cell membrane, it penetrates, uncoating its membrane and replicates it RNA which then expresses its constituent proteins and reassembled to a matured virus that is release from the cell. It gets into the circulatory system infecting monocytes, dendritic cells and macrophages and subsequently spread in the lymphatic system infecting lymphocytes and other organs such as the spleen, liver, kidney, etc. [34]. This has been confirmed in *in vitro* studies where macrophages largely infected by Ebola virus produce high amounts of viral particles which are delivered to various organs such as the lymph nodes, liver, spleen, endothelium, adrenal gland, kidney and pancreas [35, 36].

The infected cells as well as lymphocytes becomes destroyed releasing inflammatory substances such as interleukins (interleukin-2 and -10), interferons (interferons-alpha and -gamma), tumour necrosis factor etc. which destroys the vascular and endothelial system increasing vascular permeability. Peripheral smears of infected persons have shown atypical or death lymphocytes which are suggested to result from apoptosis triggered by inflammatory mediators released from viral infected target cells and/or from viral glycoprotein secretions [36].

The destruction of the microvascular tissues changes vascular permeability, cause cellular necrosis and activate clotting factors thereby leading to coagulopathy, hypotensive shock and possibly death [37]. Also, impairment of endothelial and platelet cells alter fluid and electrolyte balance disrupting the body's homeostasis [38]. Virus induced shock is due to elevated

increase in nitric oxide production which leads to damage of the vascular system altering the blood pressure [39]. Also, these hypotensive shock may also result from platelet-derived agents such as thrombin following the damaged of endothelial cells. Theses clotting factors can disseminate into various organs causing intravascular coagulation [40].

One of the possible mechanisms the virus is able to persist in the body is through its ability to evade the immune system by destroying immune cells such as lymphocytes, natural killer cells, phagocytes as well as impairment of the action of dendritic cells [41].

9. Clinical manifestation

Once an individual gets infected with Ebola virus, it can persist in the body for a few days with no clinical manifestation. Thus, the incubation period ranges from 2 to 21 days with an average between 4 and 10 days. After this incubation period, an acute infection emerges which starts to portray clinical manifestations. The illness commences with symptoms of flu-like syndrome which includes a sudden onset of high fever, chills and myalgia. This early infection can affect the gastrointestinal system causing anorexia, vomiting, nausea, diarrhoea, abdominal pain, as well as the respiratory system causing cough, chest pain and dyspnea. Also, the vascular system can be affected leading to hypotension, oedema as well as neurologic system causing headache and coma [42, 43]. Though the periodical manifestation of Ebola virus varies among individuals, generally, these clinical features can be categorized into four phases as suggested by Suresh and Dashrath [44].

Phase 1 - Influenza-like syndrome: The onset of the infection commences with non-specific signs or symptoms such as high fever, nausea, headache, sore throat, arthralgia, and myalgia.

Phase 2 - Acute phase: A persistent acute fever emerges along with headache and intense fatigue within 1–6 days which is not responsive to antibiotics or antimalarial drugs. This is usually followed by gastrointestinal obstructions such as abdominal pain, diarrhoea, vomiting, etc.

Phase 3 - Pseudo-remission: After the acute phase, a false recovery phase emerges by days 7–8 where the patient feels better showing some signs of recovery such as gain of appetite. In some patients, this phase may eventually lead to total recovery and survival of the disease.

Phase 4 - Aggravation phase: By day 9, the health status gets worsen in most individuals presenting respiratory disorders such as cough, dyspnea, hiccups, throat and chest pain as well as cardiovascular distress and hypovolemic shock. Also, rask may develop on the skin as well as petechiae.

During the infection, laboratory investigations show high levels of aminotransferase, and marked lymphocytopenia, and thrombocytopenia in patients' blood [45]. More so, bleeding usually occurs in the gastrointestinal tract and may be expressed as petechiae, melena, conjunctival haemorrhage, easy bruising, haematuria, or intraperitoneal bleeding. Also, mucous membrane bleeding as well as excessive clot formation and failure of venipuncture sites are evident during infection. Progression of these symptoms over a period of time may lead to dehydration, confusion, stupor, hypotension and failure of multiple organs culminating to

fulminant shock and eventually death which occurs between the 6 and 16 days of illness [46, 47]. However, a few patients may survive and recovery from the infection gradually presenting arthralgia and fatigue.

10. Ebola virus identification

One of the primary means of management of Ebola disease is to promptly diagnose the virus. Hence, early laboratory diagnosis for the confirmation of suspected individuals with haemorrhagic fever is paramount for the implementation of appropriate control measures. Reverse transcription-Polymerase chain reaction (RT-PCR) and viral isolation on Vero cells are definitive diagnostic methods for the detection of Ebola virus infections [48, 49]. Also, serological diagnosis based on enzyme-linked immunosorbent assays (ELISAs) to detect immunoglobulins such as IgG and IgM specific to Ebola virus antigens are effective diagnostic tools [50, 51]. Viral nucleic acid and antigen can be detected in blood as early as 3 days after symptoms starts to manifest and can be identified by the above diagnostic tools [52]. Prior to laboratory diagnosis, clinicians should examine patients for vital signs and symptoms such as high fever, severe headache, muscle pain, bleeding, bloody diarrhoea, blood in urine, vomiting, abdominal pain, diarrhoea, or unexplained haemorrhage, etc. in suspected individuals [53]. In addition to primary diagnosis of Ebola virus, secondary diagnosis, particularly in infected patients such as the presence of atypical lymphocytes, leucopenia (as low as 1000 cells/L), thrombocytopenia (50,000–100,000 cells/L), elevated aspartate aminotransferase and alanine aminotransferase level, prothrombin and partial thromboplastin time are necessary to manage related complications that may arise due to the infection [54]. The various diagnostic tests for Ebola are summarized in **Table 2**.

One of the major challenges in the diagnosis of Ebola virus is that the infection presents similar signs and symptoms to that of common diseases such as flu, malaria, yellow fever, typhoid, meningococcal meningitis and other bacterial and viral infections [24, 30]. As such, clinical diagnosis is usually not sufficient for routine screening especially during outbreaks where the infection rate is high. More so, definitive diagnosis by RT-PCR and viral culture are usually not

Time line of infection	Primary diagnostic tests	Secondary diagnostic tests
Within a few days after symptoms begin	Immunohistochemistry testing Rapid diagnostic test Antigen-capture ELISA testing IgM ELISA RT-PCR Virus isolation on Vero cells	Atypical lymphocytes Leucocytes Thrombocytes Aspartate aminotransferase, alanine aminotransferase prothrombin and thromboplastin
Later stage of disease course or after recovery	Rapid diagnostic test IgM and IgG antibodies	
Deceased patients	Rapid diagnostic test Immunohistochemistry testing RT-PCR Virus isolation on Vero cells	

Table 2. Ebola diagnostic test.

feasible in Africa as most local health settings lack or do not have sufficient or adequate laboratory facilities for such molecular techniques. Another major challenge is the high cost for the molecular diagnostic tests (RT-PCR, ELISA). The cost per sample may cost between $50 to $100 which may not be affordable by majority of individuals in developing countries especially in endemic areas including West Africa, Sub-Saharan Africa and central East Africa. More so, though these molecular diagnostic tools are very reliable, analyses take about 2–6 h, which is too long for such acute infection. As such, there is considerable need for rapid diagnostic tests which can take just a few minutes for detection. Also, cell culture on vero E6 African monkey kidney cells which is a traditional gold standard test requires biosafety level 4 (BSL-4) containment, thus, restricts its use for routine diagnosis. More so, the test can last for up to 5 days from the moment of viral inoculation to microscopic visualization [55].

An immunochromatographic assay may be suitable for such effective and prompt diagnosis. In 1995, a colorimetric assay was developed by Dr. Sherif Zaki of the CDC for the identification of Ebola virus in skin biopsies preserved in formalin [56]. However in recent years, this diagnostic tool is not readily available.

10.1. Rapid diagnostic test for Ebola virus disease

Following the 2014, outbreak in West Africa, several field trials on rapid diagnostic tests (RDTs) are ongoing and a few RDT kits have been approved by U.S. Food and drug Administration (FDA) and WHO on Emergency Use Authorization (EUA) status. These RDT kits are lateral flow immunoassays (LFIs) which basically detects viral protein antigens circulating in blood. Three of the recently approved RDTs include ReEBOV Antigen Rapid Test kit, OraQuick Ebola Rapid Antigen Test and SD Q Line Ebola Zaire Ag test [57].

The ReEBOV Antigen Rapid Test kit by Corgenix, Inc. was the first LFI for EVD to receive emergency use authorization (EUA) status from both FDA and WHO) [58, 59]. This chromatographic dipstick immunoassay kit is a RDT that detects the Ebola virus VP40 matrix protein of three species which includes EBOV, SUDV, and BDBV in whole blood, plasma or serum. Following a finger prick, a drop of blood is applied directly unto the nitrocellulose test strip. The nitrocellulose strip is then deepened into a tube containing reaction buffer which initiates the movement of the sample along the test strip by capillary action. The presence of VP40 in the sample leads to the formation of an immune complex between the VP40 matrix protein antigen and gold-labelled anti-antibodies against VP40 which is subsequently deposited along the strip boundary of anti-VP40 producing a pink-red line that is visible between 15 to 25 min after the analysis. Validation study for the performance of ReEBOV RDT conducted in Sierra Leone on venipuncture blood showed a 100% sensitivity and 92% specificity when compared with results obtained from RealStar Filovirus Screen RT-PCR kit by Altona Diagnostics [58].

The second RDT kit that has received approval from WHO and FDA on EUA status is the OraQuick Ebola Rapid Antigen Test manufactured by OraSure Technologies, Inc. [60, 61]. Just like the ReEBOV Antigen Rapid Test kit, this RDT kit detects VP40 matrix protein of EBOV, SUDV, and BDBV species with similar assay procedure. In addition to the use of whole blood, this kit also makes use of cadaveric oral fluid which is collected using an oral mucosa swab for the detection of Ebola virus. Similarly as ReEBOV RDT, the presence of Ebola virus antigens is

visibly detected following immune complex between viral proteins and gold-labelled antibodies bound along the test line in less than 30 minutes. Validation of the test performance of the OraQuick RDT based on a retrospective study in Sierra Leone as reported by WHO showed the OraQuick RDT with a 84% sensitivity and 98% specificity compared to clinical real-time RT-PCR testing [60].

SD Q Line Ebola Zaire Ag test by SD Biosensor, Inc. is the third and most recent RDT kit to be approved by WHO on EUA status [62]. Unlike ReEBOV and OraQuick RDTs which detects only VP40 in EBOV, SUDV, and BDBV species, SD Q Line Ebola Zaire Ag test is a chromatographic deep stick test that simultaneously detects GP, NP, and VP40 antigens of EBOV in whole blood, serum or plasma. In this test, the presence of the three antigens in the sample forms complex with their specific gold-labelled mouse monoclonal antibodies at three different test boundaries at which visible lines are seen. Thus, three drops of sample are added to a sample port on the assay device and visualized at 20–30 min. The presence of at least any of the three test lines is interpreted as positive result. A WHO validation study in Sierra Leone using a total of 446 specimens including 100 fresh venous whole blood and 346 frozen plasma showed SD Q Line Ebola Zaire Ag test with 84.9% sensitivity and 99.7% specificity when compared to the RealStar Filovirus Screen RT-PCR kit 1.0 as gold standard [62].

In a nutshell, these RDT kits are very effective in diagnosis Ebola virus and useful for field settings especially during outbreaks as results can be obtained within a very short time without the use of any electronic equipment and does not require refrigeration for storage. The approval of these RDTs is of major importance for public health management of the disease as prompt diagnosis especially in the field following Ebola outbreaks is key to effective treatment.

Recently, a new immunochromatographic strip and a smartphone reader based on Sudan virus (SUDV) glycoprotein monoplex which detects and semiquantifies Ebola-specific IgG antibodies in human survivors has been developed [63, 64]. When the point-of-care test was tested in freshly collected patient samples including 90 SUDV survivors and 31 non-infected controls in Uganda, it showed a sensitivity of 100% and a specificity of 98% compared to standard enzyme-linked immunosorbent assay (ELISA) of whole Ebola antigen [64]. More so, a multiplex test which simultaneous detects antibodies against three recombinant SUDV proteins has also been developed. A pilot study involving 15 survivors and 5 non-infected controls showed sensitivity and specificity of 100% compared to standard ELISA [64]. Also, another multiplex subtype assay for the identification of three Ebola species: BDBV, SUDV, and EBOV based on recombinant viral glycoproteins has been developed [64]. The advantage of this multiplex viral species test is that it could differentiate the host's immunity to specific viral species and also identify cross-reactive immunity in infected patients.

11. Therapeutic interventions

Till date, there is no precise treatment for Ebola virus disease which constitutes one of the major draw backs in its management. Treatments available for Ebola virus infection are basically supportive and symptomatic remedies for dehydration, maintenance of oxygen

saturation and blood pressure, replenishment of nutrients, antivirals as well as antibiotics for concomitant infections [65]. Administration of sufficient fluids by oral or intravenous route serve to maintain circulatory stability and replenish electrolytes and fluids lost during the infection. A broad-spectrum of antibiotics are used to manage potential concomitant bacterial infections; antimalarials are used for the treatment of malaria while antiretrovirals are used to inhibit viral replication. Antipyretics and analgesics are frequently used for the control of fever or body temperature and pain respectively. Also, specific drugs could be administered for the control of organ failure.

With no specific treatment against the disease, considerable efforts in research have been ongoing for the identification of possible drug candidates for therapeutic interventions. One of such clinical investigation was conducted in 1995 during the Ebola epidemic in Kikwit where blood of improving patients was transfused to eight Ebola patients as a means of passive immunization. Among the eight patients, seven of them successfully survived the infection while only one patient died [66]. However, subsequent *in vitro* assays showed antibodies not to have neutralizing action against Ebola virus. As such, clinical investigation based on passive immunization has not been conducted in subsequent outbreaks. Furthermore, *in vitro* assays showed monoclonal antibodies against the GP of Ebola virus to exhibit defensive and healing properties in mice but were unable to protect non- human primates [67, 68]. Also, immunoglobulins which were raised in goat and had undergone pre-clinical test on laboratory animals were administered to infected scientists with Ebola haemorrhagic fever during an outbreak showed some degree of protection against the disease. Thus, these immunoglobulins were suggested to be beneficial as an emergency cure for individuals inadvertently infected with Ebola virus [69]. More so, a series of nucleoside analogue inhibitors for carbocyclic 3 deazaadenosine and S-adenosylhomocysteine hydrolase were shown to avert death in infected mice by inhibiting Ebola virus replication [70].

With such preliminary studies showing immunoglobulins to have protective effects against the infection, several researches have dueled on this aspect as well as other targets and several clinical trials have been ongoing to assess some potential drug candidates. The main classes of drugs which are being evaluated for potential therapeutic effect against Ebola virus infection include monoclonal antibodies such as ZMapp, nucleoside analogues, RNA inhibitor based (TKM-Ebola) agents, positively charged phosphorodiamidate morpholino oligomers as well as antisense-based (AVI-7537) drugs [71]. Among these drug candidates, ZMapp is one of the most promising therapeutic interventions against Ebola virus disease that affects viral replication inhibiting its expression.

ZMapp is an experimental drug by Mapp Biopharmaceutical, Inc., which comprises of a combination of 3 monoclonal humanized murine antibodies produced in mice infected with Ebola virus and subsequently generated in tobacco plants [71, 72]. *In vivo* pre-clinical animal study showed 43% of infected mice treated with Zmapp to survived infection [73]. Though pre-clinical studies had exhibited therapeutic effect of Zmapp against Ebola virus, the experimental drug came into the lamplight when two US citizens who were health workers in Liberia during the 2014 West-Africa outbreak became infected and were successfully treated with ZMapp in Atlanta USA. Following this success, the drug was then used as an experimental treatment in the 2014 West-Africa Ebola outbreak and several patients survived and recovered

from the infection [74]. Though this experimental drug was helpful during the outbreak, its therapeutic efficacy remained inconclusive since no randomized controlled clinical trial had been conducted as of 2014 [74, 75].

Another hopeful candidate drug that act by preventing viral replication is favipiravir (T-705), a pyrazinecarboxamide derivative which has shown to be effective against EBOV in *in vitro* and *in vivo* studies [76]. Also, a promising experimental drug for Ebola virus infection is BCX4430. This drug possesses antiviral activity for marburg, yellow and Ebola fever and it is also being tested for its ability to inhibit target enzymes in Ebola virus. BCX4430 has been shown to be effective in infected animals if the treatment was administered within 48 h after the infection [77]. Other therapeutic candidate drugs include RNA polymerase inhibitors as well as small interfering RNA nano particles that act as protein synthesis inhibitors. Studies in Ebola infected guinea pigs and non-human primate models showed small interfering RNAs agents and gene-silencing drugs to protect against Ebola infections [78].

One of the major challenges for the availability of treatment against Ebola virus disease is the inconsistency and sporadic nature of the virus which has limited clinical trials in humans. In as much as several drug candidates have emerged and have been effective in pre-clinical studies, without clinical trials in humans, there is no guarantee that these experimental drugs can effectively treat infected patients. It is relevant for such trials to be conducted even though it remains difficult as the disease usually emerges periodically as outbreaks. Even though these challenges are limiting, efforts in identifying other potential drugs targets should be encouraged with emphasis on the key viral surface proteins as well as nucleoproteins involved in viral replication and pathogenesis.

12. Vaccine candidates undergoing trials

Vaccines are one of the most effective means of managing viral infections especially for recurrent infections. This suggests that a vaccine for Ebola virus fever will be important for the management of the disease. Till date despite the several recurrent outbreaks of Ebola haemorrhagic fever, no licensed vaccine is available. However, several clinical trials are ongoing in Europe, United States, and West Africa, with preliminary findings on efficacy, and safety becoming available. These vaccine candidates are categorized as replication incompetent or non-replicative and replication competent vaccines [79]. Some of these vaccine candidates are summarized below.

12.1. Recombinant adenovirus based vaccines

Adenoviruses are generally non-enveloped, double-stranded DNA viruses isolated from mammalian species. Following the deletion of the E1 region in their genome which renders the virus non-replicative, this property makes them suitable as recombinant vectors [80, 81]. Several Ebola vaccines that have been developed make use of a variety of recombinant Adenovirus serotypes which includes the human serotypes such as Ad26 and Ad35 and the

chimpanzee Adenovirus serotypes; Ad3, Ad7 and Ad62 [82]. Recombinant Adenovirus 5 (rAd5) was the first recombinant Ebola vaccine to show protection to Non-human primates against the EBOV virus but required a period of over 6 months to attain complete immunization [83]. A double-blinded, placebo-controlled phase I clinical trial in 2010 showed rAd5 vaccine encoding the envelope GP from EBOV and SEBOV 1976 strain to be safe and immunogenic [84]. Following the 2014 West Africa outbreak, another phase 1 clinical trial was conducted with another rAd5 vaccine which encoded the envelope GP of EBOV 2014 strain. The findings showed that the vaccine was immunogenic and safe at high dose of immunization [85]. Studies with other recombinant adenovirus vaccines such as rAd26 and rAd35 have them to be immunogenic by stimulating T-cell responses of CD4+ and CD8+ as well as increase cytokine (TNF/IFN-γ) secretion. Recently, rAd26 vaccine expressing the full-length GP of EBOV is currently undergoing phase III trials [86].

ChAd3-EBOV defined as chimpanzee adenovirus serotype 3 encoding the monovalent Zaire strain of Ebola virus glycoprotein is a genetically modified non-replicative vaccine candidate produced by GlaxoSmithKline in collaboration with the National Institutes of Health, USA. In 2014, five phase 1 trials of ChAd3 conducted in Europe, North America, and Africa confirmed the vaccine to be immunogenic and safe [87]. As a result, Phase II and III trials were initiated in Sierra Leone, Liberia, and Guinea in 2015 [88, 89].

12.2. Recombinant Vesicular Stomatitis Virus

A recombinant Vesicular Stomatitis Virus (rVSV**)** was the first replicating Ebola virus vaccine developed in 2005. This vaccine was shown to provide 100% protection in non-human primates eliciting both humoral and cellular immune responses against lethal EBOV challenged animals [90]. Since then, eight human phase I trials of rVSV-EBOV vaccine has been conducted across Europe, North America and Africa. A phase III trial involving 7651 individuals to evaluate the efficacy of rVSV-ZEBOV showed a 100% vaccine efficacy after 6 days of vaccination [91]. These findings have shown that rVSV confers protection against Ebola between 6 and 21 days after vaccination [92].

Other potential vaccine candidates [35] which have initiated phase I clinical trials in 2015 include; EBOV GP Vaccine which is a recombinant nanoparticle vaccine using adjuvant Matrix-M. It is the first Ebola vaccine candidate based on the 2014 Guinea Ebola strain genetic sequence. DNA-EBOV is a multiagent filovirus DNA vaccine delivered into the body through intramuscular electroporation. Recombinant rabies EBOV is a chemically killed inactivated rabies virus virions containing EBOV glycoprotein.

Other forms of vaccine candidates include virus-like particle vaccines (VLPs). VLPs are produced by expressing certain viral proteins that mimics the conformation of natural Ebola virus in cells without any viral genetic material. EBOV VLPs have been produced by simultaneously expressing NP, GP, and VP40 proteins of EBOV in 293T cells. These particles when administered three times to NHPs in combination with Ribi adjuvant protected against EBOV [93, 94].

Following the recent Ebola outbreak in DRC, an experimental Ebola vaccine (rVSV-ZEBOV) developed by Merck, a German pharmaceutical company which is not yet licensed but was

effective during the catastrophic Ebola epidemic of 2014 has been approved by WHO for vaccination. According to Peter Salama, WHO's deputy director-general for emergency, preparedness and response, 8000 individuals are expected to be vaccinated, thus, about 8000 dose are required with 4000 doses already deployed to DRC [95].

13. Conclusion

Following the devastating 2014 West Africa Ebola outbreak, more concerted efforts have been put in place to improve on the management of the disease. More especially, three rapid diagnostic kits which includes ReEBOV, OraQuick and SD Q Line Ebola Zaire Ag RDTs have been approved by FDA and WHO on EUA status to overcome the urgency of prompt diagnosis during outbreaks and make routine screening cost-effective and available in the field as well as in local health settings. More so, several experimental drugs such as ZMapp, favipiravir, BCX4430, etc. and vaccines such as rAd5, rAd26, rAd35, ChAd3, rVSV, etc. are undergoing randomized clinical trials across the world with a few currently at phase III. Recently, an experimental rVSV-ZEBOV Ebola vaccine which was effective at the 2014 West Africa outbreak is been deployed for the present 2018 Ebola outbreak in DRC. Concerted effort is therefore needed from regularly bodies such as FDA, international organization such as WHO, UN, etc., pharmaceutical companies, as well as stakeholders to make available funds for research to improve on the existing experimental drugs and vaccine candidates as well as rapid diagnostic tools. Thus, it is our hope that most of these experimental drugs and vaccines will be available in future to help control the disease and better manage re-emerging Ebola infections or outbreaks across the world.

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