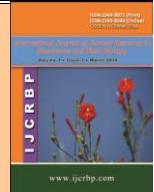
Int. J. Curr. Res. Biosci. Plant Biol. 2016, 3(3): 12-20

International Journal of Current Research in Biosciences and Plant Biology

ISSN: 2349-8080 (Online) • Volume 3 • Number 3 (March-2016)

Journal homepage: www.ijcrbp.com



Review Article

doi: http://dx.doi.org/10.20546/ijcrbp.2016.303.003

Ebola Virus, Its Manifestations and Reported Therapeutic Strategies

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Abstract

All five species of *Ebolavirus* discovered to date are known to cause a deadly disease known as Ebola hemorrhagic fever. This viral hemorrhagic fever is associated with severe manifestations and high case-fatality rate. It has caused several periodic outbreaks since its discovery in 1976, but the recent one in 2014 has affected a number of people than never before. It is endemic in the Philippines and Central Africa, showing that it has a strange geographic distribution. The Ebola virus (EBOV) comprises negative sense RNA which encodes seven viral proteins of which VP40 is of paramount importance in viral assemble, budding and egress. Its pathogenicity is multifactorial owing to which no licensed vaccines and approved treatments are currently available. However, several promising candidates have been produced by research in non-human primates. Here, we review the virology, manifestations, reported proposed therapeutic intervention strategies and the recent outbreak.

Article Info

Accepted: 10 February 2016
Available Online: 06 March 2016

Keywords

Ebolavirus
Filoviridae
Fruit bats
Hemorrhagic fever
VP40

Introduction

Belonging to the *Filoviridae* family (discovered in 1967), Ebola virus (EBOV) is one of the most virulent pathogens which infect humans (Adu-Gyamfi et al., 2014). The genus *Ebolavirus* was discovered by Peter Piot in 1976 while he was working at the Institute of Tropical Medicine in Antwerp, Belgium. Blood sample of a Belgian woman then working at the Democratic Republic of Congo was sent to the institute from where it was found that this woman had been working with a school headmaster, the first recorded victim of Ebola virus, near Yambuko, approximately 96 km away from the Ebola River, hence the name of this genus (Brizendine, 2014; Moshirfar and Fenzl, 2014). International Committee on Taxonomy classified this genus as negative-sense single-stranded RNA viruses which cause severe hemorrhagic fever (Brizendine, 2014). It is notorious for its variegated constellation of serious signs and symptoms (Moshirfar and Fenzl, 2014).

The genus comprises five species each of which is associated with a well-defined endemic area (Table 1) (de Wit et al., 2011; Bausch and Schwarz, 2014) and specific case-fatality rate (Brizendine, 2014):

a. ***Zaire ebolavirus*** (ZEBOV) caused one of the two concurrent outbreaks in 1976 after which EBOV was discovered. The one caused by ZEBOV occurred in the Democratic Republic of Congo (Zaire) (Report of an International Commission, 1978). It has caused multiple outbreaks between 1994 and 2008 in the Democratic Republic of Congo, Republic of Congo and Gabon, and has a high case-fatality rate ranging between 60% and 90% (Brizendine, 2014; de Wit et al., 2011). This species is greatly associated with the decline in the populations of great ape in the Congo basin (Leroy et al., 2004).

Table 1. Chronology of Ebola virus outbreaks in humans (de Wit et al., 2011; Martiez, 2014).

Year	Location	Ebola Virus	Affected species
1976	Democratic Republic of Congo	ZEBOV	Humans
1976	Sudan	SEBOV	Humans
1977	Democratic Republic of Congo	ZEBOV	Humans
1979	Sudan	SEBOV	Humans
1989	USA	REBOV	Cynomolgus macaques
1992	Italy	REBOV	Cynomolgus macaques
1994	Gabon	ZEBOV	Humans
1994	Ivory Coast (Taï Forest)	CIEBOV	Chimpanzees, Humans
1995	Democratic Republic of Congo	ZEBOV	Humans
1996	Gabon	ZEBOV	Humans
1996	Gabon	ZEBOV	Humans
1996	USA	REBOV	Cynomolgus macaques
1996	South Africa (ex-Gabon)	ZEBOV	Humans
2000	Uganda	SEBOV	Humans
2001	Gabon	ZEBOV	Humans, gorillas, duikers
2001	Republic of Congo	ZEBOV	Humans, gorillas, chimpanzees, duikers
2003	Republic of Congo	ZEBOV	Humans
2003	Republic of Congo	ZEBOV	Humans
2004	Sudan	SEBOV	Humans
2005	Republic of Congo	ZEBOV	Humans
2007	Democratic Republic of Congo	ZEBOV	Humans
2007	Uganda	BEBOV	Humans
2008	Democratic Republic of Congo	ZEBOV	Humans
2008	The Philippines	REBOV	Swine
2011	Uganda	SEBOV	Humans
2012	Uganda	SEBOV	Humans
2012	Uganda	SEBOV	Humans
2012	Democratic Republic of Congo	BEBOV	Humans
2014	Guinea	ZEBOV	Humans
2014	Sierra Leone	ZEBOV	Humans
2014	Liberia	ZEBOV	Humans
2014	Nigeria	ZEBOV	Humans
2014	Senegal	ZEBOV	Humans
2014	USA	ZEBOV	Humans
2014	Spain	ZEBOV	Humans
2014	Mali	ZEBOV	Humans
2014	Democratic Republic of Congo	ZEBOV	Humans

b. ***Sudan ebolavirus*** (SEBOV) caused an unrelated outbreak in Sudan in 1970s. It reemerged in the Sudan in 1979 and 2004 and in Uganda between 2000 and 2001. It has a high case-fatality rate of 40% to 60% (Sachez et al., 2007).

c. ***Côte d'Ivoire ebolavirus*** (CIEBOV), also known as *Taï Forest ebolavirus*, was discovered in 1994 during an epizootic in chimpanzees kept in the Taï National Park in Côte d'Ivoire. This was the first reported EBOV infection in a great ape population (Le Guenno et al., 1995). So far, CIEBOV has been found in only one person, i.e. has caused a single, non-fatal human case. The affected was an ethologist working with deceased chimpanzees (Brizendine, 2014). This, along with ZEBOV, is associated for the fatal outbreaks in the populations of the African great ape (Leroy et al., 2004; Formenty et al., 1999).

d. ***Bundibugyo ebolavirus*** (BEBOV) emerged in 2007 when a large outbreak of viral hemorrhagic fever occurred in humans in Uganda with a case-fatality rate between 25% and 30%. The causative agent was identified as a new species of EBOV (Towner et al., 2008).

Reston ebolavirus (REBOV) is sustained in animal reservoir in the Philippines and was discovered in 1989 during a lethal outbreak in cynomolgus macaques imported from the Philippines to the United States (Jahrling et al., 1990). The outbreaks reoccurred in 1990, 1992 and 1996 in the same animal and in 2008 in domestic pigs in the Philippines (Barrette et al., 2009). The caretakers of macaques and farmers working with the infected pigs did not fall ill, but both were seroconverted which shows that REBOV can cause symptomless infection in humans (MMWR, 1990).

Non-human primates were initially thought to be the cause of animal-to-human transmission of EBOV. Later, studies proved that monkeys simply cannot serve as the host for persistent viral infection as they are themselves vulnerable to lethal filoviral disease. It is most likely that one or many species of small animals, especially fruit bats, sustain EBOV. It is worth noting that fruit bats are consumed in soup in West Africa; hence, consumption of or exposure to these bats probably serve as the source of infection for primates and humans (Bausch and Schwarz, 2014).

Human-to-human transmission occurs through exposure to body fluids such as blood, sweat, breast milk, barf, urine, semen, and vaginal fluids (Kash, 2009; Bausch et al., 2007). The virus can be transmitted by patients while febrile and during the later stages of the disease as well as during postmortem. It has been reported to be isolated from semen even after 61 days of the onset of the illness. The transmission can also be nosocomial as was seen in 1976 when a 44-year old, being treated at the Yambuku Mission Hospital, had undiagnosed Ebola virus and infected a 100 more people owing to inappropriate washing and reuse of syringes, resulting in the death of all. Same reason resulted in an outbreak in 2005 in Angola which resulted in 329 deaths (Brizendine, 2014; Roddy et al., 2010). There is no evidence for the transmission of filoviruses by biting arthropods like mosquitos. However, one primary human case has a potential of generating 1-3 secondary cases on average despite the low risk of transmission via inanimate objects (towel, money, clothing, dishes, etc.) (Bausch et al., 2007).

Virology and pathogenicity of EBOV

The family of *Filoviridae* got its name from the Latin word *filum*, meaning thread-like structure. Ebola virus makes a filamentous particle of unvarying diameter but non-uniform shape and length (Fig. 1). Its genome, comprising RNA, encodes seven proteins (Adu-Gyamfi et al., 2014). Glycoprotein (GP) is expressed and exposed on the surface of the EBOV envelope, derived from the host cell membrane, and mediates entry of the virions into the host cell (Lee et al., 2008) via an interaction with Niemann-Pick C1 receptor in the latter (Carette et al., 2011; Cote et al., 2011).The primary product of the gene encoding GP is soluble glycoprotein (sGP); GP is actually produced after translational editing (Wahl-Jensen et al., 2005).

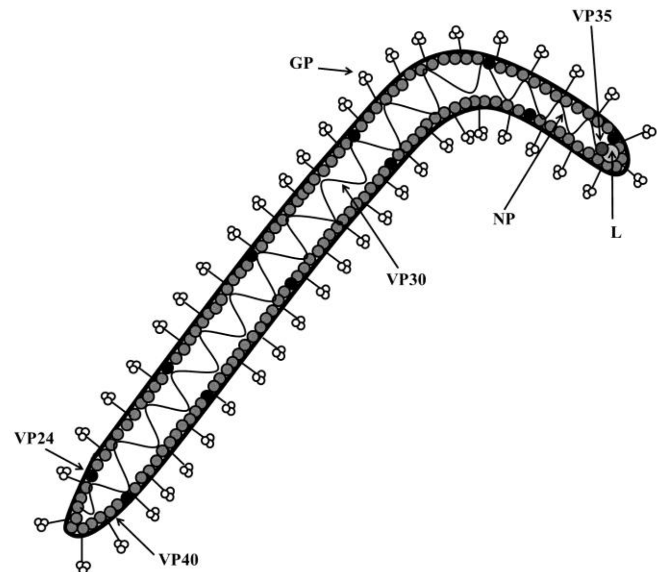

Fig. 1: Schematic representation of an EBOV particle.

The genome of EBOV is encapsidated by the nucleoprotein (NP). This nucleocapsid (NC), made up of nucleoprotein (NP), minor matrix protein (VP24), minor nucleoprotein (VP30), polymerase cofactor (VP35), the viral polymerase (L protein) and other viral proteins, is crucially required for transcription and replication of viral RNA (Sachez et al., 2007; Olejnik et al., 2001). In addition to the aforementioned function, VP24 also facilitates viral budding (Sachez et al., 2007).

The matrix protein viral protein (VP40) associates with the viral lipid coat and is required for the budding of the Ebola virus particle from the plasma membrane (Timmins et al., 2001). It is also important for the structure and stability of the virus (Jasenosky et al., 2001). Virus particles fail to form in the absence of VP40 as nucleocapsid is inefficaciously transported to the plasma membrane (Noda et al., 2006). In the absence of the rest of the six proteins, VP40 has been reported to be capable of forming virus like particles (VLPs) on being expressed in human cells (Noda et al., 2002) which resemble bona fide Ebola virions (Licata et al., 2004). VP40 possesses C- and N-terminal domains; the former

one is reported to mediate membrane binding and oligomerization, while the latter one modulates dimerization (Timmins et al., 2003; Bornholdt et al., 2013). Inhibition of oligomerization halts budding in an effective manner. Therefore, VP40 serves to be a representative model of budding and has been used to study lipid-protein and protein-protein interactions (Rulgrok et al., 2000).

GP, NP, VP24 and VP35 are important determinants of *Ebolavirus* pathogenicity (Figure 1). EBOV replicates at an exceptionally high rate and its main targets are hepatocytes, mononuclear phagocytes and endothelial cells. In short, it is an immunodeficiency virus for which dendritic cells serve as a major site of replication. Infected cells are unable to present antigens to naïve lymphocytes (as discussed later). Thus patients dying of Ebola are unable to develop antibodies to the virus. Though lymphocytes remain unaffected, they do undergo bystander (chance spectator) apoptosis induced by inflammatory mediators (Brizendine, 2014).

While experimenting in cynomolgus macaques, a decrease in endothelial barrier function and upregulation of cell adhesion indicate endothelial cell activation caused by GP *in vitro*, leading to shock and edema (Wahl-Jensen et al., 2005). The mucin domain of GP shields both epitopes on GP and major histocompatibility complex I molecules which could otherwise be recognized by antibodies and lead to antigen presentation by the host cell, respectively (Francica et al., 2010). GP also induces pro-inflammatory cytokines and suppressor of cytokine signaling 1 (SOCS1) via interaction with Toll-like receptor 4, which in turn affect the innate immune system (Okumura et al., 2010).

In vivo, VP24 and NP play vital roles in the virulence of *Ebolavirus*. Mutations in these two proteins made them capable to counteract the type 1interferon (IFN)-induced innate immune response which resulted in adaptation of ZEBOV to guinea pigs and mice (Feldmann and Kawaoka, 2006). Residues 42 and 142-146 of VP24 are involved in this mechanism, as proven *in vitro*. These residues inhibit the expression of gene induced by IFN-α/β via their interaction with karyopherin-α1 (another name of which is importin-α) which results in nuclear accumulation of phosphorylated signal transducer and activator of transcription 1 (STAT1), hence inhibiting type 1 interferon-induced cell signaling (Reid et al., 2006). Any such mechanism has not been reported for NP to date (Feldmann and Kawaoka, 2006).

VP35 works in the favor of pathogenesis by blocking IFN-α/β production as proven *in vitro* (Basler et al., 2000). Through its residues 309 and 312, VP35 binds to double-stranded RNA thus preventing the activation of retinoic acid-inducible gene 1 (RIG1), which is a dsRNA-mediated process (Cardenas et al., 2006). The activation of RIG1 would have otherwise resulted in phosphorylation and nuclear translocation of interferon regulatory factor 3 (IRF3) and consequently in the expression of IFN-α/β genes (Cardenas et al., 2006). Also, amino-terminal domain of VP35 affects maturation of dendritic cells. VP35 suppresses upregulation of pro-inflammatory cytokines and co-stimulatory molecules in dendritic cells and, subsequently, weakens their ability to activate $CD4^+$ T cells (Jin et al., 2010).

Clinical manifestations

Symptoms of Ebola virus disease begin abruptly after an initial incubation period ranging from 2-28 days with fever, chills, headache, extreme asthenia, general malaise, myalgia and progress to include nausea, vomiting, diarrhea, loss of appetite (anorexia), chest and abdominal pain, coughing, breathlessness and a maculopapular rash (a rash characterized by flat, red area covered with small raised spots) (Le Guenno et al., 1995; Bwaka et al., 1999). Fever occurs early and in 94.1% of patients owing to which it is the most prevalent sign of disease (Lamunu et al., 2004). On the occurrence of symptoms, patients have high levels of the virus in the body fluids and are infectious. Hemorrhagic manifestations develop at the peak of the illness, though not in all cases. These include subconjuctival hemorrhage along with excessive lacrimation (Kibadi et al., 1999), "unexplained bleeding" from conjunctiva, nose, gums and venipuncture sites (WHO Ebola Response Team, 2014) internal and subcutaneous bleeding (petechiae) (Brizendine, 2014), and blood in the vomits (hematemesis) and stools (melena) (de Wit et al., 2011). Fatal cases eventually progress to soma, shock and death (Bwaka et al., 1999).

Fatal outcomes result owing to the loss of peripheral $CD4^+$ and $CD8^+$ T lymphocytes, hefty production of pro-inflammatory cytokines, and cessation of antibody induction and type I interferon (IFN) production (Baize et al., 1999). Thrombocytopenia, lymphocytopenia, disseminated intravascular coagulation, low total protein (because of capillary leakage), and increased levels of aminotransferase are some of the laboratory findings. The survivors begin to show improvement in the second

week. This is due to the resolving of the viremia by virus-specific antibodies (WHO Ebola Response Team, 2014).

Viral antigens or RNA sequences can be detected in blood and body fluids of the symptomatic patients by enzyme-linked immunosorbent assay or reverse transcriptase polymerase chain reaction, respectively, in order to diagnose Ebola virus infection. Electron microscopy showing characteristic viral particles confirms the diagnosis by using cell culture carried out in BSL-4 containment laboratory (WHO Ebola Response Team, 2014).

Therapeutic approaches

A myriad of vaccines, antibodies, anti-viral agents and small-molecule agents are undergoing repeated testing in animal models. The only treatment available to date is supportive which is used to rectify coagulopathy, and maintains blood pressure and circulatory function (Ribner, 2014).

Vaccines

Vaccination is among the primary control strategies employed to counter infection diseases in humans. Withal, no licensed vaccines for treating Ebola virus are available to date. Initial attempts to make vaccines in this regard included formulating inactivated/attenuated virus with different ancillaries, such as lipid A-containing liposomes and Ribi adjuvants (Geisbert et al., 2002). Also, protective immunity was tested in some rodent models, but futile. When these therapeutic stratagems were tested in non-human primates after successfully generating protection in mouse and guinea pig models, they showed limited predictive value for efficaciousness of vaccines. Nonetheless, these rodent models serve to be worthful for pre-screening the vaccines (Bente et al., 2009). Thus classical vaccines failed to give the desired results owing to which novel vaccine approaches are being researched on.

Employing recombinant viral vector vaccines is one such approach. These may comprise either replication-deficient or replication-competent vectors. Adenoviral vector is an example of vaccine vector incapable of replication that has broad cellular tropism because of which it is being used in various gene therapy studies (Hensley et al., 2010). Incorporation of ZEBOV and SEBOV glycoprotein in a single adenoviral vector rendered absolute protection against ZEBOV and SEBOV in non-human primates (Pratt et al., 2010). Lately, phase I clinical trial has proven the safety of using recombinant adenovirus serotype 5 expressing ZEBOV and SEBOV glycoprotein in humans (Ledgerwood et al., 2010). Using viral vectors capable of replication have proven to be vital in the development of veterinary vaccines. One such replication-competent viral vector is ZEBOV-glycoprotein-expressing human parainfluenza virus type 3 (HPIV3) which has been reported to be extremely immunogenic subsequently protecting non-human primates after administering two intranasal medications (Bukreyey et al., 2007).

Another approach of paramount importance is the use of DNA vaccines. These are preparations containing purified plasmids with one or more DNA sequences of pathogen of interest incorporated which get expressed in the recipient once delivered. A ZEBOV-glycoprotein-expressing DNA vaccine has called forth a protective immune response from a potential state by stimulation in mice and has also partly protected guinea pigs (Xu et al., 1998). Despite the clearance of a three-plasmid DNA vaccine coding for SEBOV glycoprotein, ZEBOV glycoprotein and NP in enkindling cellular and humoral responses in humans from phase I clinical trial, currently there are no licensed DNA vaccines available for human use (Martin et al., 2006).

Virus-like particles (VLPs), as discussed before, are generated by expressing one or many viral proteins which mimic the natural virion but do not contain the viral genome. VLPs for EBOV are made by expressing GP, NP and VP240 of ZEBOV at 293T cells at the same time. Combined with Ribi adjuvant, these were administered thrice to non-human primates; this resulted in protection against homologous ZEBOV (Warfield et al., 2007). Another prospect is the VLP generated by eliminating VP30 gene. Mice and guinea pigs have been protected from ZEBOV challenge by using two such vaccinations (Halfmann et al., 2009). Despite all these advancements, no licensed VLP vaccines are available for human use.

Other supportive treatments

In 2002, Toyama Chemicals developed a pyrazinecarboxamide derivative as an antiviral agent called T-705 (alias favipiravir). It was originally developed to inhibit influenza virus replication on account of its ability to act as a nucleotide analog which causes fatal mutagenesis upon incorporation into the viral RNA, or selectively inhibits the viral RNA-

dependent RNA polymerase. Mice were dosed with 1000 focus-forming units of EBOV diluted in phosphate-buffered saline. Initially, all mice in the favipiravir group lost weight and developed viremia. But within 4 days of treatment with this antiviral agent, blood was found to be free from virus. Furthermore, surviving mice had developed viral NP-specific $CD8^+$ T cells along with virus-specific antibodies. Hence it was concluded that T-705 suppresses the replication of Ebola virus by 4 $\log_{10}$ units in cell culture (Oestereich et al., 2014).

Another potential candidate is ZMapp, a potpourri of monoclonal antibodies – one being c13C6 and two from ZMab (2G4 and 4G7). Experiments were carried out in rhesus monkeys in which six animals were infected with Ebola of which three were dosed thrice with ZMapp at various times. All 18 animals survived on treatment with ZMapp. An American health care worker infected with Ebola virus in Liberia has received this medication (Qui et al., 2014).

Forthcoming prospects

Death of a 2-year-old in Guinea on December 6, 2013 marked the onset of the recent outbreak. 4,477 deaths have been reported till October 14, 2014 which brought this hemorrhagic fever in limelight once again (Chamary, 2014). Effective therapeutic treatments are being actively sought for the EBOV disease. There has been a limited success as in the case of KZ52, a neutralizing antibody, which did not work. Also, ribavirin (used for treating hepatitis B and C) and IFN-α2b are in the list (Huggins, 1989; Jahrling et al., 1999). However, limited therapeutic efficacy has been reported with various prospects. Recombinant human activated protein C (rhAPC) saved two out eleven non-human primates in a lethal ZEBOV challenge (Hensley et al., 2007). Similar results were obtained by using nematode anticoagulant protein c2 (rNAPc2) which protected three out of nine non-human primates (Geisbert et al., 2003).

Understanding of replication and virulency of Ebola virus has been greatly elucidated in the past ten years owing to the increased availability of BSL4 facilities and advancement in molecular tools. RNA interference, high-throughput and 454 sequencing, and mRNA expression profiling technologies are a few examples which have applications in development of antivirals, vaccines and diagnostics, epidemiology, host response, viral pathogenesis, and various other fields of virology. Nonetheless, all these technological advancements have proven less fruitful in the case of Ebola as compared to other viral pathogens, such as HIV and influenza virus A (Quinn et al., 2009).

Undoubtedly, panoptic genomic and post-genomic research is required to get benefit from the aforementioned strategies and approaches. Reverse vaccinology is a novel vaccine approach which relies on the insight of genomic sequences of Ebola virus (Rappuoli, 2001). A good information is that despite mutations occurring in the genome of EBOV at a high rate, no change in size of the outbreak has been observed. Hence, no serious changes have emerged in this mutating RNA virus (Kash, 2009). Therefore, future research in this regard should be focused on understanding the cellular processes mired in replication and pathogenesis of Ebola virus by using *in vitro* and *in vivo* experimental data, and broad approaches of genomics and proteomics.

Conflict of interest statement

Authors declare that they have no conflict of interest.

Acknowledgement

I would like to thank GC University Lahore and respected Vice Chancellor, Prof. Dr. Hassan Amir Shah, for providing me with this platform. This piece of writing would have never been written without the continuous backing and counselling of my instructor, Dr. Zahid Hussain (IIB, GC University Lahore). Doubtlessly, I cannot forget the invariant and ceaseless encouragement and support of my grandfather, parents and sister. I apologise to all whose works could not be cited due to space constraints.

References

Adu-Gyamfi, E., Soni, S.P., Jee, C.S., Digman, M.A., Gratton, E., Stahelin, R.V. 2014. A loop region in the N-terminal domain of Ebola virus VP40 is important in viral assembly, budding, and egress. Viruses. 6(10), 3837-3854.

Baize, S., Leroy, E.M., Georges-Courbot, M.C., Capron, M., Lansoud-Soukate, J., Debre, P., Fisher-Hoch, S.P., McCormick, J.B., Georges, A.J. 1999. Defective humoral responses and extensive intravascular apoptosis are associated with fatal outcome in Ebola virus-infected patients. Nat. Med. 5(4), 423-426.

Barrette, R.W., Metwally, S.A., Rowland, J.M., Xu, L., Zaki, S.R., Nichol, S.T., Rollin, P.E., Towner, J.S., Shieh, W.J., Batten, B., Sealy, T.K., Carrillo, C., Moran, K.E., Bracht, A.J., Mayr, G.A., Sirios-Cruz, M., Catbagan, D.P., Lautner, E.A., Ksiazek, T.G., White, W.R., McIntosh, M.T. 2009. Discovery of swine as a host for the Reston ebolavirus. Science. 325(5937), 204-206.

Basler, C.F., Wang, X., Muhlberger, E., Volchkov, V., Paragas, J., Klenk, H.D., Garcia-Sastre, A., Palese, P. 2000. The Ebola virus VP35 protein functions as a type 1 IFN antagonist. Proc. Natl. Acad. Sci. USA. 97(22), 12289-12294.

Bausch, D.G., Schwarz, L. 2014. Outbreak of Ebola virus disease in Guinea: where ecology meets economy. PloS Negl. Trop. Dis. 8(7), e3056.

Bausch, D.G., Towner, J.S., Dowell, S.F., Kaducu, F., Lukwiya, M., Sanchez, A., Nichol, S.T., Ksiazek, T.G., Rollin, P.E. 2007. Assessment of the risk of Ebola virus transmission from bodily fluids and fomites. J. Infect. Dis. 196(Suppl 2), S142-S147.

Bente, D., Gren, J., Strong, J.E., Feldmann, H. 2009. Disease modeling for Ebola and Marburg viruses. Dis. Model. Mech. 2(1-2), 12-17.

Bornholdt, Z.A., Noda, T., Abelson, D.M., Halfmann, P., Wood, M.R., Kawaoke, Y., Saphire, E.O. 2013. Structural rearrangement of Ebola virus vp40 begets multiple functions in the virus life cycle. Cell. 154(4), 763-774.

Brizendine, K.D. 2014. Ebola virus: questions, answers and more questions. Cleveland Clinic Journal of Medicine.81(12), 729-735.

Bukreyev, A., Rollin, P.E., Tate, M.K., Yang, L., Zaki, S.R., Shieh, W.J., Murphy, B.R., Collins, P.L., Sanchez, A. 2007. Successful topical respiratory tract immunization of primates against Ebola virus. J. Virol. 81(12), 6379-6388.

Bwaka, M.A., Bonnet, M.J., Calain, P., Colebunders, R., De Roo, A., Guimard, Y., Katwiki, K.R., Kibadi, K., Kipasa, M.A., Kuvula, K.J., Mapanda, B.B., Massamba, M., Mupapa, K.D., Muyembe-Tamfum, J.J., Ndaberey, E., Peters, C.J., Rollin, P.E., den Enden, E.V. 1999. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. J. Infect. Dis. 179(Suppl. 1), S1-S7.

Bwaka, M.A., Bonnet, M.J., Calain, P., Colebunders, R., De Roo, A., Guimard, Y., Katwiki, K.R., Kibadi, K., Kipasa, M.A., Kuvula, K.J., Mapanda, B.B., Massamba, M., Mupapa, K.D., Muyembe-Tamfum, J.J., Ndaberey, E., Peters, C.J., Rollin, P.E., Van den Enden, E. 1999. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. J. Infect. Dis. 179(Suppl. 1), S1-S7.

Cardenas, W.B., Loo, Y.M., Gale, M. Jr., Hartman, A.L., Kimberlin, C.R., Martinez-Sobrido, L., Saphire, E.O., Basler, C.F. 2006. Ebola virus VP35 protein binds double-stranded RNA and inhibits alpha/beta interferon production induced by RIG-1 signaling. J. Virol. 80(11), 5168-5178.

Carette, J.E., Raaben, M., Wong, A.C., Herbert, A.S., Obernosterer, G., Mulherkar, N., Kuehne, A.I., Kranzusch, P.J., Griffin, A.M., Ruthel, G.,Dal Cin, P., Dye, J.M., Whelan, S.P., Chandran, K., Brummelkamp, T.R. 2011. Ebola virus entry requires the cholesterol transporter niemann-pick c1. Nature.477(7364), 340-343.

Chamary, J.V. 2014. 4000 deaths and counting: the Ebola epidemic in 4 charts. Forbes. Accessed November 5, 2014. Available at: http://www.forbes.com/sites/jvchamary/ 2014/10 /13/ ebola-trends.

Cote, M., Misasi, J., Ren, T., Bruchez, A., Lee, K., Filone, C.M., Hensley, L., Li, Q., Ory, D., Chandran, K., Cunnigham, J. 2011. Small molecule inhibitors reveal niemann-pick c1 is essential for Ebola virus infection. Nature. 477(7364), 344-348.

de Wit, E., Feldmann, H., Munster, V.J. 2011. Tackling Ebola: new insights into prophylactic and therapeutic intervention strategies. Genome Medicine.3(1), 5.

Feldmann, H., Kawaoka, Y. 2006. Molecular determinants of Ebola virus virulence in mice. PLoS Pathog. 2(7), e73.

Formenty, P., Boesch, C., Wyers, M., Steiner, C., Donati, F., Dind, F., Walker, F., Le Guenno, B. 1999. Ebola virus outbreak among wild chimpanzees living in a rain forest of Cote d'Ivoire. J. Infect. Dis. 179(Suppl 1), S120-S126.

Francica, J.R., Varela-Rohena, A., Medvec, A., Plesa, G., Riley, J.L., Bates, P. 2010. Steric shielding of surface epitopes and impaired immune recognition induced by the ebola virus glycoprotein. PLoS Pathog. 6(9), e1001098.

Geisbert, T.W., Hensley, L.E., Jahrling, P.B., Larsen, T., Geisbert, J.B., Paragas, J., Young, H.A., Fredeking, T.M., Rote, W.E., Vlasuk, G.P. 2003. Treatment of Ebola virus infection with a recombinant inhibitor of factor Vlla/tissue factor: a study in rhesus monkeys. Lancet. 362(9400), 1953-1958.

Geisbert, T.W., Pushko, P., Anderson, K., Smith, J., Davis, K.J., Jahrling, P.B. 2002. Evaluation in nonhuman primates of vaccines against Ebola virus. Emerg. Infect. Dis. 8(5), 503-507.

Halfmann, P., Ebihara, H., Marzi, A., Hatta, Y., Watanabe, S., Suresh, M., Neumann, G., Feldmann, H., Kawaoka, Y. 2009. Replication-deficient ebolavirus as a vaccine candidate. J. Virol. 83(8), 3810-3815.

Hensley, L.E., Mulangu, S., Asiedu, C., Johnson, J., Honko, A.N., Stanley, D., Fabozzi, G., Nichol, S.T., Ksiazek, T.G., Rollin, P.E., Wahl-Jensen, V., Bailey, M., Jahrling, P.B., Roederer, M., Koup, R.A., Sullivan, N.J. 2010. Demonstration of cross-protective vaccine immunity against an emerging pathogenic Ebolavirus species. PLoS Pathog.6(5), e1000904.

Hensley, L.E., Stevens, E.L., Yan, S.B., Geisbert, J.B., Macias, W.L., Larsen, T., Daddario-DiCaprio, K.M., Cassell, G.H., Jahrling, P.B., Geisbert, T.W. 2007. Recombinant human activated protein C for the postexposure treatment of Ebola hemorrhagic fever. J. Infect. Dis. 196(Suppl 2), S390-S399.

Huggins, J.W. 1989. Prospects for treatment of viral hemorrhagic fevers with ribavirin, a broad-spectrum antiviral drug. Rev. Infect. Dis. 11(Suppl 4), S750-S761.

Jahrling, P.B., Geisbert, T.W., Dalgard, D.W., Johnson, E.D., Ksiazek, T.G., Hall, W.C., Peters, C.J. 1990. Preliminary report: isolation of Ebola virus from monkeys imported to USA. Lancet. 335(8688), 502-505.

Jahrling, P.B., Geisbert, T.W., Geisbert, J.B., Swearengen, J.R., Bray, M., Jaax, N.K., Huggins, J.W., LeDuc, J.W., Peters, C.J. 1999. Evaluation of immune globulin and

recombinant interferon-alpha2b for treatment of experimental Ebola virus infections. J. Infect. Dis. 179(Suppl 1), S224-S234.

Jasenosky, L.D., Neumann, G., Lukashevich, I., Kawaoka, Y. 2001. Ebola virus vp40-induced particle formation and association with the lipid bilayer. J. Virol. 75(11), 5205-5214.

Jin, H., Yan, Z., Prabhakar, B.S., Feng, Z., Ma, Y., Verpoten, D., Ganesh, B., He, B. 2010. The VP35 protein of Ebola virus impairs dendritic cell maturation induced by virus and lipopolysaccharide. J. Gen. Virol. 91(Pt 2), 352-361.

Kash, J.C. 2009. Applications of high-throughput genomics to antiviral research: evasion of antiviral responses and activation of inflammation during fulminant RNA virus infection. Antiviral Res. 83, 10-20.

Kibadi, K., Mupapa, K., Kuvula, K., Massamba, M., Ndaberey, D., Myumbe-Tamfum, J.J., Bwaka, M.A., De Roo, A., Colebunders, R.1999. Late ophthalmologic manifestations in survivors of the 1995 Ebola virus epidemic in Kikwit, Democratic Republic of the Congo. J. Infect. Dis. 179(Suppl 1), S13-S14.

Lamunu, M., Lutwama, J.J., Kamugisha, J., Opio, A., Nambooze, J., Ndayimirjie, N., Okware, S.. 2004. Containing a haemorrhagic fever epidemic: the Ebola experience in Uganda (October 2000-January 2001). Int. J. Infect. Dis. 8(1), 27-37.

Le Guenno, B., Formenty, P., Wyers, M., Gounon, P., Walker, F., Boesch, C. 1995. Isolation and partial characterization of a new strain of Ebola virus. Lancet. 345(8960), 1271-1274.

Ledgerwood, J.E., Costner, P., Desai, N., Holman, L., Enama, M.E., Yamshchikov, G., Mulangu, S., Hu, Z., Andrews, C.A., Sheets, R.A., Koup, R.A., Roederer, M., Bailer, R., Mascola, J.R., Pau, M.G., Sullivan, N.G., Goudsmit, J., Nabel, G.J., Graham, B.S. 2010. A replication defective recombinant Ad5 vaccine expressing Ebola virus GP is safe and immunogenic in healthy adults. Vaccine. 29(2), 304-313.

Lee, J.E., Fusco, M.L., Hessell, A.J., Oswald, W.B., Burton, D.R., Saphire, E.O. 2008. Structure of the Ebola virus glycoprotein bound to an antibody from a human survivor. Nature. 454(7201), 177-182.

Leroy, E.M., Rouquet, P., Formenty, P., Souquiere, S., Kilbourne, A., Froment, J.M., Bermejo, M., Smit, S., Karesh, W., Swanepoel, R., Zaki, S.R., Rollin, P.E. 2004. Multiple Ebola virus transmission events and rapid decline of central African wildlife. Science. 303(5656), 387-390.

Licata, J.M., Johnson, R.F., Han, Z., Harty, R.N. 2004. Contribution of Ebola virus glycoprotein, nucleoprotein, and vp24 to budding of vp40 virus-like particles. J. Virol. 78(14), 7344-7351.

Martiez R. 2014. Global Alert and Response. World Health Organization (WHO).

Martin, J.E., Sullivan, N.J., Enama, M.E., Gordon, I.J., Roederer, M., Koup, R.A., Bailer, R.T., Chakrabarti, B.K., Bailey, M.A., Gomez, P.L., Andrews, C.A., Moodie, Z., Gu, L., Stein, J.A., Nabel, G.J., Graham, B.S. 2006. A DNA vaccine for Ebola virus is safe and immunogenic in a phase I clinical trial. Clin. Vaccine Immunol. 13(11), 1267-1277.

MMWR Morb. Mortal. Wkly. Rep. 1990. Update: filovirus infections among persons with occupational exposure to nonhuman primates. 39, 266-267,273.

Moshirfar, M., Fenzl, C.R., Li, Z. 2014. What we know about ocular manifestations of Ebola. Clinical Opthalmology. 8, 2355-2357.

Noda, T., Ebihara, H., Muramoto, Y., Fujii, K., Takada, A., Sagara, H., Kim, J.H., Kida, H., Feldmann, H., Kawaoka, Y. 2006. Assembly and budding of Ebolavirus. PLoS Pathog. 2(9), e99.

Noda, T., Sagara, H., Suzuki, E., Takada, A., Kida, H., Kawaoka, Y. 2002. Ebola virus vp40 drives the formation of virus-like filamentous particles along with gp. J. Virol. 76(10), 4855-4865.

Oestereich, L., Lüdtke, A., Wurr, S., Rieger, T., Muñoz-Fontela, C., Günther, S. 2014. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res. 105, 17-21.

Okumura, A., Pitha, P.M., Yoshimura, A., Harty, R.N. 2010. Interaction between Ebola virus glycoprotein and host toll-like receptor 4 leads to induction of proinflammatory cytokines and SOCS1. J. Virol. 84(1), 27-33.

Olejnik, J., Ryabchikova, E., Corley, R.B., Muhlberger, E. 2001. Intracellular events and cell fate in filovirus infection. Viruses. 3(8), 1501-1531.

Pratt, W.D., Wang, D., Nichols, D.K., Luo, M., Woraratanadharm, J., Dye, J.M., Holman, D.H., Dong, J.Y. 2010. Protection of nonhuman primates against two species of Ebola virus infection with a single complex adenovirus vector. Clin. Vaccine Immunol. 17(4), 572-581.

Qui, X., Wong, G., Audet, J., Bello, A., Fernando, L., Alimonti, J.B., Fausther-Bovendo, H., Wei, H., Aviles, J., Hiatt, E., Johnson, A., Morton, J., Swope, K., Bohoroy, O., Bohorova, N., Goodman, C., Kim, D., Pauly, M.H., Velasco, J., Pettitt, J., Olinger, G.G., Whaley, K., Xu, B., Strong, J.E., Zeitlin, L., Kobinger, G.P. 2014. Reversion of advanced Ebola virus disease in nonhuman primates with ZMapp. Nature. 514(7520), 47-53.

Quinn, K., Brindley, M.A., Weller, M.L., Kaludov, N., Kondratowicz, A., Hunt, C.L., Sinn, P.L., McCray, P.B. Jr., Stein, C.S., Davidson, B.L., Flick, R., Mandell, R., Staplin, W., Maury, W., Chiorini, J.A. 2009. Rho GTPases modulate entry of Ebola virus and vesicular stomatitis virus pseudotyped vectors. J. Virol. 83(19), 10176-10186.

Rappuoli, R. 2001. Reverse vaccinology, a genome-based approach to vaccine development. Vaccine. 19(17-19), 2688-2691.

Reid, S.P., Leung, L.W., Hartman, A.L., Martinez, O., Shaw, M.L., Carbonnelle, C., Volchkov, V.E., Nichol, S.T., Basler, C.F. 2006. Ebola virus VP24 binds karyopherin alpha 1 and blocks STAT1 nuclear accumulation. J. Virol. 80(11), 5156-5167.

Report of an International Commission, 1978. Ebola haemorrhagic fever in Zaire, 1976. Bull. World Health Organ. 56(2), 271–293.

Ribner, B.S.Treating patients with Ebola virus infections in the US: lessons learned. Presented at IDWeek, October 8, 2014. Philadelphia PA.

Roddy, P., Thomas, S.L., Jeffs, B., Folo, P.N., Palma, P.P., Henrique, B.N., Villa, L., Machado, F.P.D., Bernal, O., Jones, S.M., Strong, J.E., Feldmann, H., Borchert, M. 2010. Factors associated with Marburg hemorrhagic fever: analysis of patient data from Uige, Angola. J. Infect. Dis. 201(12), 1909-1918.

Ruigrok, R.W., Schoehn, G., Dessen, A., Forest, E., Volchkov, V., Dolnik, O., Klenk, H.D., Weissenhorn, W. 2000. Structural characterization and membrane binding properties of the matrix protein vp40 of Ebola virus. J. Mol. Biol. 300(1), 103-112.

Sachez, A., Geisbert, T.W., Feldmann, H., 2007. Filoviridae. Marburg and Ebola Viruses. In: Fields Virology. (Ed: Knipe, D.M., Howley, P.M.) 5thEdn. Lippincott Williams & Wilkins, Philadelphia. pp. 1409-1448.

Timmins, J., Schoehn, G., Kohlhaas, C., Klenk, H.D., Ruigrok, R.W., Weissenhorn, W. 2003. Oligomerization and polymerization of the filovirus matrix protein vp40. Virology. 312(2), 359-368.

Timmins, J., Scianimanico, S., Schoehn, G., Weissenhorn, W. 2001. Vesicular release of Ebola virus matrix protein vp40. Virology. 283(1), 1-6.

Towner, J.S., Sealey, T.K., Khristova, M.L., Albarino, C.G., Conlan, S., Reeder, S.A., Quan, P.L., Lipkin, W.I., Downing, R., Tappero, J.W., Okware, S., Lutwama, J., Bakamutumaho, B., Kayiwa, J., Comer, J.A., Rollin, P.E., Ksiazek, T.G., Nichol, S.T. 2008. Newly discovered ebola virus associated with hemorrhagic fever outbreak in Uganda. PLoS Pathog. 4(11), e1000212.

Wahl-Jensen, V.M., Afanasieva, T.A., Seebach, J., Stroher, U., Feldmann, H., Schnittler, H.J. 2005. Effects of Ebola virus glycoproteins on endothelial cell activation and barrier function. J. Virol. 79(16), 10442-10450.

Warfield, K.L., Swenson, D.L., Olinger, G.G., Kalina, W.V., Aman, M.J., Bavari, S. 2007. Ebola virus-like particle-based vaccine protects nonhuman primates against lethal Ebola virus challenge. J. Infect. Dis. 196(Suppl 2), S430-S437.

WHO Ebola Response Team. 2014. Ebola virus disease in West Africa – the first 9 months of the epidemic and forward projections. N. Engl. J. Med. 371(16),1481-1495.

Xu, L., Sanchez, A., Yang, Z., Zaki, S.R., Nabel, E.G., Nichol, S.T., Nabel, G.J. 1998. Immunization for Ebola virus infection. Nat. Med. 4(1), 37-42.

How to cite this article:
Qureshi, A.S., Hussain, Z., 2016. Ebola virus, its manifestations and reported therapeutic strategies. Int. J. Curr. Res. Biosci. Plant Biol. 3(3), 12-20.
doi: http://dx.doi.org/10.20546/ijcrbp.2016.303.003