



A Laconic Review of Ebola Virus Disease: Symptoms and Preventive Measures

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ABSTRACT

From the past several years West Africa is experiencing the largest, often calamitous, most severe, most complex outbreaks of Ebola virus disease (EVD) caused by the Ebola virus, a Filoviridae family virus. This virus was first recognized in the Democratic Republic of the Congo (formerly Zaire) in Africa. The Ebola virus outbreaks in 2014 are the most severe outbreak of Ebola in terms of the number of human deaths since the discovery of the virus in 1976. This disease has been classified among the highest priority for bioterrorism agents. The Ebola virus is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of the infected non-human primate. Currently, there is no specific vaccine or antiviral agent available to treat Ebola virus infection. Considering the current situation of EVD, the World Health Organization (WHO) suggested its member countries to remain alert for the possible introduction of the virus, to raise the awareness of health care professional precautions for infection prevention. Due to the large number Ebola virus disease outbreaks, WHO implemented ethical guidelines for clinical use of some unregistered drugs that have not yet been evaluated for safety and efficacy in humans.

1. Introduction

Ebola Virus Disease (EVD) or Ebola Hemorrhagic Fever (EHF) is a rare, highly infectious and deadly disease, caused by a negative-stranded RNA virus known as Ebola virus. Ebola virus is classified as a biological class 4 pathogen. Ebola virus looks like noosed ropes under the electron microscope (Fig. 1). By attacking the body's first responders, the Ebola virus cripples the immune system before it can mount an effective defense. It hijacks the functions of dendritic cells. The primary function of dendritic cells is to alert the immune system to the incoming threat. Other targets include monocytes and macrophages, types of white blood cells whose job is to absorb and clear away foreign organisms. It releases large amounts of secreted glycoprotein (sGP) into the bloodstreams of its victims. The diseased condition presents with high fever and an ensuing bleeding diathesis. Ebola Virus Disease (EVD) was first recognized in 1976 when two unrelated epidemics occurred in northern Zaire (Democratic Republic of the Congo) and southern Sudan, with subsequent outbreaks in Guinea, Liberia, Sierra Leone, Republic of the Congo (ROC), Ivory Coast, Gabon, Uganda, and South Africa (imported) [1]. In 1989-1991, another Ebola subtype was discovered in Reston, Virginia, among dying cynomolgus monkeys imported from the Philippines that infected four animal caretakers who remained clinically well. The episodes with the Reston strain occurred in Italy in 1992 and in the US in 1996. The Ebola was named after a river in the Democratic Republic of the Congo (formerly Zaire) in Africa, where it was first recognized. The natural habitat of Ebola virus is unknown; this is normally found in an animal host that is native to the African continent. This virus belongs to the Filoviridae family (filovirus) and Ebolavirus genus, which also includes Marburg virus having a similar morphology. Fruit bats of the Pteropodidae family are considered to be a likely natural host of the Ebola virus, with outbreaks amongst other species such as chimpanzees, gorillas, monkeys, forest antelope from time to time. Five species of Ebola virus have been identified, namely Zaire Ebola virus, Sudan Ebola virus, Reston Ebola virus, Tai Forest Ebola virus, and Bundibugyo Ebola virus, from samples

collected during humans and non-human primates outbreaks since the first outbreak in the Democratic Republic of the Congo [2-5].

The genome of Ebola virus is a linear, negative-sense, non-segmented RNA (~18,900 kb in length) and contains nucleoprotein NP (104 K), glycoprotein GP (125 K), L protein (180 K) and four proteins VP40 (40 K), VP30 (30 K) and VP24 (24 K) [6-9]. The Ebola virus proteins are encoded by monocistronic mRNA transcripts complementary to virion RNA. GP is the major protein of the surface spikes and only this 125K viral protein is glycosylated.

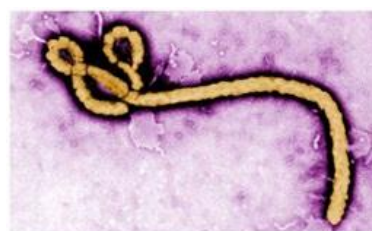


Fig. 1 Structure of Ebola virus

Morphologically this virion is enveloped, helical, cross-striated nucleocapsid, filamentous or pleomorphic virion that is flexible with extensive branching (80 nm diameter and 970-1200 nm length). The Ebola-Reston species (found in the Philippines and the People's Republic of China), has caused disease only in nonhuman primates. This species is lethal in primates only. The Zaire Ebola virus is highly lethal with case death rate of up to 90%. The incubation period of Ebola virus varies from 2 to 21 days [2]. The EVD has been reported in Africa such as the Democratic Republic of the Congo, Gabon, Ghana, Guinea, Liberia, Nigeria, the Ivory Coast, Sierra Leone, Sudan, Uganda, etc., (Fig. 2). As of November 4, 2014, the World Health Organization (WHO) and the Center for Disease Control (CDC) reported a total of 13268 cases and 4960 human deaths due to the Ebola virus infection (Table 1). The most recent outbreak of Ebola virus infection was reported on 26 August 2014 in Republic of Congo.

The 2014 Ebola virus outbreak is the largest Ebola virus outbreak in history till date and the first in West Africa. The Ministry of Health, Democratic Republic of Congo (DRC) notified to the World Health Organization (WHO) of a most recent outbreaks of Ebola virus disease (EVD) on 26 August 2014 in Equateur Province. The 2014 Ebola virus

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outbreak started with the death of a 2-year-old boy who died 6 December 2013 in the village of Meliandou, Gueckedou Prefecture, Guinea. His mother, 3-year-old sister and grandmother then became ill with symptoms similar to Ebola infection and died. First travel-associated case of Ebola in the United States was confirmed by Center for Disease Control on September 30, 2014. The patient passed away on October 8, 2014. Mali reported its first confirmed case of Ebola on October 23, 2014. The child passed away on October 24, 2014. On October 24, 2014 the New York City Department of Health and Mental Hygiene confirmed a travel-associated case of Ebola in a medical aid worker who travelled from Guinea. Nigeria and Senegal declared as free of Ebola virus transmission by WHO on October 20 and 17th 2014, respectively. According to the WHO updates, in late August 2015, a woman in Sella Kafta village from Sierra Leone died from Ebola virus disease, bitterly disappointing the hope to see an end of Ebola transmission.

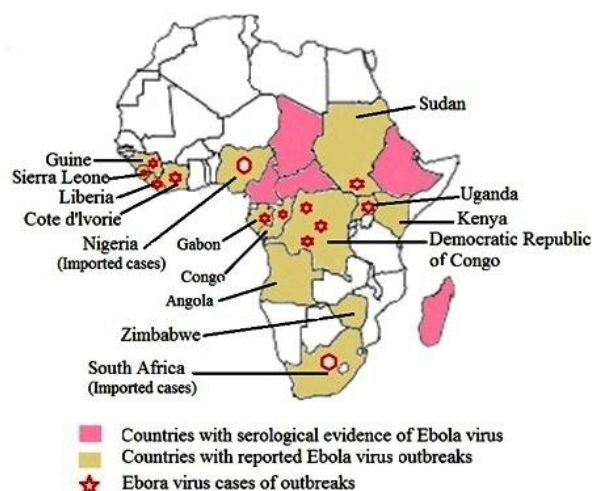


Fig. 2 Geographical distributions of Ebola outbreaks in Africa (1967-2014)

Table 1 Known cases and outbreaks of Ebola virus disease in November 2014.

Year(s)	Country	Ebola subtype	Reported number of human cases	Reported number of deaths	Ref.
August 2014-Present	Democratic Republic of the Congo	Zaire virus	66	49	[10]
March 2014-Present	Guinea, Liberia, Sierra Leone, Mali, Spain, United States	Zaire virus	13241	4950	[11]
November 2012-January 2013	Uganda	Sudan virus	6	3	[12]
June-November 2012	Democratic Republic of the Congo	Bundibugyo virus	36	13	[12]
June-October 2012	Uganda	Sudan virus	11	4	[12]
May 2011	Uganda	Sudan virus	1	1	[13]
December 2008-February 2009	Democratic Republic of the Congo	Ebola virus	32	15	[14]
December 2007-January 2008	Uganda	Bundibugyo virus	149	37	[15]
2007	Democratic Republic of Congo	Ebola virus	264	187	[16]
2004	Russia	Ebola virus	1	1	[17]
2004	South Sudan	Sudan virus	17	7	[18]
November-December 2003	Republic of Congo	Ebola virus	35	29	[19]

December 2002-April 2003	Republic of Congo	Ebola virus	143	128	[20]
October 2001-March 2002	Republic of Congo	Ebola virus	57	43	[21]
October 2001-March 2002	Gabon	Ebola virus	65	53	[12]
2000-2001	Uganda	Sudan virus	425	224	[22]
1996	Russia	Ebola virus	1	1	[23]
1996	South Africa	Ebola virus	2	1	[24]
1996-1997 (July-January)	Gabon	Ebola virus	60	45	[25]
1996 (January-April)	Gabon	Ebola virus	37	21	[25]
1995	Democratic Republic of the Congo (formerly Zaire)	Ebola virus	315	250	[26]
1994	Gabon	Ebola virus	52	31	[25]
1979	South Sudan	Sudan virus	34	22	[27]
1977	Zaire	Ebola virus	1	1	[28]
1976	South Sudan	Sudan virus	284	151	[1, 29]
1976	Zaire (Democratic Republic of the Congo - DRC)	Ebola virus	318	280	[29]

2. Transmission of Ebola Virus Infection

There is no transmission mode for first case patient has been reported. However, it has been hypothesized that the first patient becomes infected through contact with an infected non-human primates, such as monkeys, forest antelopes, rodents and bats, (dead or alive). After the first case-patient, this virus is transmitted through direct contact with the blood or other bodily fluids of the infected person (dead or alive) when the family members, friends or health care professional come in close contact with infected persons when caring for them. The spread of a disease through person-to-person during healthcare settings is known as Nosocomial transmission. Thus, once a person comes into contact with an infected human or non-human primate, it can spread from human to human. Infection can spread from the direct contact (through broken skin or mucous membranes) with the blood [30, 31], or other bodily fluids or secretions (stool, urine, saliva) of infected human or non-human primates. Semen can contain virus for seven weeks after apparent recovery from the illness. Thus, the unprotected sexual contact with patient up to seven weeks after they have recovered could also a disease transmission mode. The disease can also occur if the broken skin or mucous membrane (e.g. in the mouth, under eyelids) of a healthy person comes into contact with environments that have become contaminated with an Ebola patient's infectious fluids. This virus could also spread through contact with contaminated medical equipment such as needles, reuse of unsterilized needles in hospitals, eating or handling of the carcass of infected animals, use of infected non-human primate as a food source. There is no risk of virus transmission during its incubation period. In Africa, fruit bats of the genera *Epomops franqueti*, *Hypsignathus monstrosus*, and *Myonycteris torquata* are believed as possible natural hosts for the Ebola virus [32, 33]. Ebola virus does not transmit through the air as occurs for measles or smallpox and influenza. Simple physical contact with a sick person appears not to be sufficient for Ebola virus transmission. Mosquitoes also do not transmit the Ebola virus. Traditional burial ceremonies in affected areas of Africa are also known as high risk activity for transmission of disease.

3. Symptoms of Ebola Virus Disease

The symptoms Ebola virus disease includes sudden onset of high fever ($> 40^{\circ}\text{C}$) with intense weakness, muscles and joint pain, stomach and chest pain, cold and cough, fever, headache, nausea and sore throat. This is followed by vomiting, diarrhoea, breathing difficulties and hiccup, depression and confusion, shock and impaired consciousness, impaired kidney and liver function, skin rash, redness in the eyes and in some cases, both internal and external bleeding. Laboratory findings frequently include low white blood cell and platelet counts and elevated liver enzymes. Some cases present with profuse internal and external bleeding and progress shock and with multi-organ failure. During the current outbreak in West Africa, haemorrhagic symptoms have been reported less frequently than fever, vomiting and diarrhoea [34].

4. Prevention of Ebola Virus Infection

The infection generally does not occur through routine, social contact (such as shaking hands) with asymptomatic individuals. Patient care without the use of a mask, protective gown, gloves, eye glasses or a face shield leads to the exposure to the virus. In addition, when needles or syringes are used, they may not be of the disposable type, or may not have been sterilized, but only rinsed before reinsertion into multi-use vials of medicine. If needles or syringes become contaminated with virus and are then reused, numerous people can become infected. The risk for infection transmission during healthcare settings can be significantly reduced through the appropriate use of infection control precautions and adequate barrier procedures. The Ebola virus is stable at room temperature. Ebola virus can be inactivated by soap, lipid solvents, machine washing at higher temperatures, ultraviolet radiation (including sunlight), gamma irradiation, heating for 60 min at 60 °C or boiling for five min, formaldehyde, sodium hypochlorite (bleach) and phenolic disinfectants. Freezing or refrigeration cannot inactivate Ebola virus. Various standard precautions have been recommended in the care and treatment of Ebola virus infected patients, such as, avoid contact with the blood, or other bodily fluids or secretions (stool, urine, saliva, semen etc.) of Ebola infected animals and humans (dead or alive) by maintaining good hygienic and sanitation conditions; isolation of Ebola infected patients; dispose of Ebola infected dead bodies in a safe manner and avoid local traditional burial rituals such as embalming for the Ebola infected dead body. Healthcare workers caring for Ebola patients should wear proper personal protective equipment such as N-95 masks, gloves, eye glasses or a face shield preferably with an anti-fog visor, gown, and use of disposable needles and avoid reuse of inadequately sterilized needles. Because Ebola virus is transmitted through breastfeeding, it is recommended that women symptomatic for the disease pending confirmation and those who have been confirmed for the disease not breastfeed. Any persons having some disease symptoms reported on flights from Guinea, Liberia, Sierra Leone or Mali and neighbouring countries need to be evaluated by the relevant health officials. Ebola virus disease test in South Africa is only available at the National Institute for Communicable Diseases [35, 36].

5. Primary laboratory diagnosis and treatment of Ebola virus disease

A sample from the ill person having similar symptoms of Ebola virus infections must be collected (whole blood and / or serum) for the diagnosis purpose by trained healthcare personnel with extreme biosecurity measures. Ebola virus infections can be diagnosed through enzyme-linked immunosorbent assay (ELISA) [37], antigen detection tests, serum neutralization test, reverse transcriptase polymerase chain reaction (RT-PCR) assay, and virus isolation by cell culture test. In 1995, the Center for Disease Control and Prevention developed a colorimetric test that can identify Ebola virus in formalin-preserved skin biopsies from infected humans [38]. The confirmation of Ebola virus infection can only be performed in patients who have already developed symptoms as the confirmation of infection is not possible during the incubation period. If the patient has died and had symptoms similar to the Ebola virus disease, collecting an oral swab sample is suggested. This virus is classified as a Risk Group 4 pathogen, and therefore requires being handled in an equivalent level of biosafety. Since, the persons returning from affected areas with fever may have other causes for their illness, particularly because of malaria. So, the final confirmation of Ebola virus infection should be performed by a WHO Collaborating Center only.

Shortly after the discovery of Ebola virus in 1976, attempts for vaccine development were initiated using inactivated virus. Although inactivated *Zaire ebolavirus* was efficacious in guinea pigs infected with *Zaire ebolavirus* [39]. Currently, there is no approved vaccine or treatment available for the treatment of Ebola virus infections. The World Health Organization (WHO) and other regulatory agencies are currently working to identify potential vaccine or drug to control the disease. According to U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) report by Pettitt et al., 100 percent and 43 percent of infected non-human primates recovered after receiving the MB-003 (ZMapp) treatment intravenously one hour and 104 to 120 h after Ebola exposure. According to the report, ZMapp is a "cocktail" of monoclonal antibodies that bind to the virus cell and inactivate them. The ZMapp identifies infected cells and triggers the immune system to kill them. ZMapp is considered as a promising candidate for the treatment of Ebola virus infections. ZMapp is manufactured by Kentucky BioProcessing in Owensboro, Kentucky. The next goal of USAMRIID is to conduct more safety tests in human volunteers to obtain Food and Drug Administration (FDA) license for the ZMapp [40]. Two U.S. health workers, who contracted Ebola virus in Liberia, were successfully treated using this vaccine. A Spanish priest was also treated using ZMapp, but later died. Three infected African doctors, one of whom

died in Monrovia on 24 August, also received this experimental vaccine [41]. Pyrazinecarboxamide derivative T-705 (Favipiravir), already licensed in Japan for the treatment of influenza, also shows positive response in disease infected animal models (mouse) [42, 43]. The chimpanzee adenovirus vaccine containing a surface Ebola protein (ChAd3), has been developed by the US National Institute of Allergy and Infectious Diseases and drug giant GlaxoSmithKline (GSK). It is being tested in the United States, the United Kingdom and Mali. Recombinant vesicular stomatitis virus (rVSV) vaccine has been developed by the Public Health Agency of Canada and licensed to NewLink Genetics in Ames, Iowa. It is being tested in the United States, with plans to start trials soon in Europe and Africa. Recently, progress on nonreplicating vaccine vectors such as alphavirus and flavivirus replicons, DNA vaccines, and replication-competent vaccine vectors, such as recombinant vaccinia virus-based vaccine vectors, recombinant cytomegalovirus-based vaccine vectors, recombinant paramyxovirus-based vectors, recombinant vesicular stomatitis virus-based vectors, and recombinant rabies virus-based vectors, has been reviewed by Marzi and Feldmann (2014) [44].

During the past decades, considerable research has been carried out to develop vaccines and therapeutic agents to treat Ebola virus disease. These vaccines or drugs have shown promising results in the preliminary laboratory tests in animal models. The safety and efficacy tests for a new medicine involves a series of trials in humans to make sure the developed drug or vaccine is safe to use in humans. Safety and efficacy tests of these vaccines or drugs in humans have not yet been assessed. Due to the large number of deaths from the Ebola virus outbreak and the high case-fatality rate (50 - 90%), on August 11, 2014 WHO implemented ethical guidelines for clinical use of such unregistered drugs that have not yet been evaluated for safety and efficacy in humans. These implications in ethical guidelines are based on the promising results in the preliminary laboratory tests in animal models and based on the results of recent treatment of two health workers from Samaritan's Purse. WHO suggested certain parameters during the use of such interventions, such as, transparency about all aspects of care (so that maximum information is obtained about the effects of the interventions), fair distribution in the face of scarcity, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity and involvement of the community.

6. Conclusion

Since its first reported case in 1976, Ebola virus disease has emerged as one of the deadliest known disease caused by the Ebola virus, a class 4 pathogen belonging to Filoviridae family. The literature with sufficient data and information on Ebola virus and its outbreaks was searched in PubMed, SCOPUS Database and Google Scholar and was selected to reach a valid conclusion. Currently, there is no approved specific treatment for this deadliest disease. Transmission of this virus occurs through the exchange of blood and body secretions. The infection transmission can be controlled through proper health measures, including proper infection control, isolation of the infected person, and use of proper protective measures by the healthcare workers. To control the current death rate due to the Ebola virus, there is an urgent need to develop an effective and safe Ebola vaccine. However, recently WHO has implemented the ethical guidelines on use of unregistered drugs on human patients. Soon the initial human testing of an investigational vaccine is going to start by the National Institute of Allergy and Infectious Disease (NIAID) and GlaxoSmithKline at NIH Clinical Center in Bethesda, Maryland. The future awaits the successful development of an effective and registered Ebola virus vaccine.

References

- [1] Ebola hemorrhagic fever in Sudan, 1976, Report of a WHO/international study team, Bull. World Health Organ. 56 (1978) 247-270.
- [2] World Health Organization, WHO recommended guidelines for epidemic preparedness and response: Ebola haemorrhagic fever (EHF), Geneva, 1997.
- [3] H. Feldmann, T.W. Geisbert, Ebola haemorrhagic fever, Lancet. 377 (2011) 849-862.
- [4] J.H. Kuhn, S. Becker, H. Ebihara, T.W. Geisbert, K.M. Johnson, Y. Kawaoka, et al., Proposal for a revised taxonomy of the family Filoviridae: classification, names of taxa and viruses, and virus abbreviations, Arch. Virol. 155 (2010) 2083-2103.
- [5] H. Feldmann, S. Jones, H.D. Klenk, H.J. Schnittler, Ebola virus: from discovery to vaccine, Nat. Rev. Immunol. 3 (2003) 677-685.
- [6] A. Sanchez, T.W. Geisbert, H. Feldmann, Filoviridae Marburg and Ebola viruses. In: D.M. Knipe, P.M. Howley (Eds.), Fields virology, Lippincott Williams and Wilkins, Philadelphia, 2006, pp.1409-1448.
- [7] H. Feldmann, T.W. Geisbert, P.B. Jahrling, H.D. Klenk, S.V. Netesov, C.J. Peters, et al., In: C. Fauquet, M.A. Mayo, J. Maniloff, U. Desselberger, L.A. Ball (Eds.), Virus

- taxonomy: VIIIth report of the international committee on taxonomy of viruses, Elsevier/Academic Press, London, 2004, pp.645-653.
- [8] E. Muhlberger, M. Weik, V.E. Volchkov, H.D. Klenk, S. Becker, Comparison of the transcription and replication strategies of Marburg virus and Ebola virus by using artificial replication systems, *J. Virol.* 73 (1999) 2333-2342.
- [9] C.F. Basler, X. Wang, E. Muhlberger, V. Volchkov, J. Paragas, H.D. Klenk, et al., The Ebola virus VP35 protein functions as a type I IFN antagonist, *Proc. Natl. Acad. Sci. USA.* 97 (2000) 12289-12294.
- [10] Centers for Disease Control and Prevention, Chronology of Ebola hemorrhagic fever outbreaks [internet], Atlanta: CDC, 2014.
- [11] World Health Organization, Ebola - Disease Outbreak News, WHO, Africa, 2014.
- [12] C.G. Albarino, T. Shoemaker, M.L. Khristova, J.F. Wamala, J.J. Muyembe, S. Balinandi, et al., Genomic analysis of filoviruses associated with four viral hemorrhagic fever outbreaks in Uganda and the Democratic Republic of the Congo in 2012, *Virology* 442 (2013) 97-100.
- [13] T. Shoemaker, A. MacNeil, S. Balinandi, S. Campbell, J.F. Wamala, L.K. McMullan, et al., Re-emerging Sudan Ebola Virus disease in Uganda 2011, *Emerg. Infect. Dis.* 18 (2012) 1480-1483.
- [14] World Health Organization, End of the Ebola outbreak in the Democratic Republic of the Congo, Global Alert and Response, WHO, Congo, 2009.
- [15] A. MacNeil, E.C. Farnon, O.W. Morgan, P. Gould, T.K. Boehmer, D.D. Blaney, et al., Filovirus outbreak detection and Surveillance: Lessons from Bundibugyo, *J. Infect. Dis.* 204 (2011) S761-S767.
- [16] G. Grard, R. Biek, J.J.M. Tamfum, J. Fair, N. Wolfe, P. Formenty, et al., Emergence of divergent Zaire Ebola virus strains in Democratic Republic of the Congo in 2007 and 2008, *J. Infect. Dis.* 204 (2011) S776-S784.
- [17] L.A. Akinfeyeva, O.I. Aksyonova, I.V. Vasilyevich, Z.I. Ginko, K.A. Zarkov, N.M. Zubavichene, et al., A case of Ebola hemorrhagic fever, *Infektsionnye Bolezni Moscow* 3 (2005) 85-88.
- [18] World Health Organization, Outbreak of Ebola haemorrhagic fever in Yambio, South Sudan, April-June 2004, *Weekly Epidemiological Record.* 80 (2005) 370-375.
- [19] World Health Organization, Ebola haemorrhagic fever in the Republic of the Congo - Update 6 Weekly Epidemiological Record, WHO, Geneva, 2004.
- [20] P. Formenty, F. Libama, A. Epelboin, Y. Allarangar, E. Leroy, H. Moudzeo, et al., Outbreak of Ebola hemorrhagic fever in the Republic of the Congo, 2003: A new strategy?, *Med. Trop. Mars.* 63 (2003) 291-295.
- [21] World Health Organization, Outbreak(s) of Ebola haemorrhagic fever, Congo and Gabon, October 2001- July 2002, *Weekly Epidemiological Report* 78 (2003) 223-225.
- [22] S.I. Okware, F.G. Omaswa, S. Zaramba, A. Opio, J.J. Lutwama, J. Kamugisha, et al., An outbreak of Ebola in Uganda, *Trop. Med. Int. Health.* 7 (2002) 1068-1075.
- [23] I.V. Borisevich, V.A. Markin, I.V. Firsova, A.A. Evseev, R.A. Khamitov, V.A. Maksimov, Hemorrhagic (Marburg, Ebola, Lassa, and Bolivian) fevers: epidemiology, clinical pictures, and treatment, *Vopr. Virusol.* 51 (2006) 8-16.
- [24] World Health Organization, Ebola haemorrhagic fever - South Africa, *Weekly Epidemiological Record* 71 (1996) 359.
- [25] A.J. Georges, E.M. Leroy, A.A. Renaut, C.T. Benissan, R.J. Nabias, M.T. Ngoc, et al., Ebola hemorrhagic fever outbreaks in Gabon, 1994-1997: epidemiologic and health control issues, *J. Infect. Dis.* 179 (1999) S65-S75.
- [26] A.S. Khan, F.K. Tshioko, D.L. Heymann, B. LeGuerno, P. Nabeth, B. Kerstiens, et al., The Reemergence of Ebola Hemorrhagic Fever, Democratic Republic of the Congo, 1995, Commission de Lutte contre les Epidemies a Kikwit, *J. Infect. Dis.* 179 (1999) S76-S86.
- [27] R.C. Baron, J.B. McCormick, O.A. Zubeir, Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread, *Bull. World Health Organ.* 61 (1983) 997-1003.
- [28] D.L. Heymann, J.S. Weisfeld, P.A. Webb, K.M. Johnson, T. Cairns, H. Berquist, Ebola hemorrhagic fever: Tandala, Zaire, 1977-1978, *J. Infect. Dis.* 142 (1980) 372-376.
- [29] World Health Organization, Ebola haemorrhagic fever in Zaire, 1976, Report of an International Convention, *Bull. World Health Organ.* 56 (1978) 271-293.
- [30] C.J. Peters, P.B. Jahrling, A.S. Khan, Patients infected with high-hazard viruses: scientific basis for infection control, *Arch. Virol. Suppl.* 11 (1996) 141-168.
- [31] C.J. Peters, J.W. LeDuc, An introduction to Ebola: the virus and the disease, *J. Infect. Dis.* 179 (1999) 9-16.
- [32] E.M. Leroy, B. Kumulungui, X. Pourrut, P. Rouquet, A. Hassanin, P. Yaba, et al., Fruit bats as reservoirs of Ebola virus, *Nature* 438 (2005) 575-576.
- [33] X. Pourrut, A. Delicat, P.E. Rollin, T.G. Ksiazek, J.P. Gonzalez, E.M. Leroy, Spatial and temporal patterns of Zaire ebolavirus antibody prevalence in the possible reservoir bat species, *J. Infect. Dis.* 196 (2007) S176-S183.
- [34] C. Comoro, J. Sivalon, Ebola: Fear of the unknown, *Azania Health Res. Bull.* 3 (2001) 1-4.
- [35] CDC, Management of patients with suspected viral hemorrhagic fever, Morbidity and Mortality Weekly Report 37 (1988) 1-16.
- [36] World Health Organization, Ebola haemorrhagic fever - fact sheet, WHO Media centre, Geneva, 2012.
- [37] P.B. Jahrling, T.W. Geisbert, D.W. Dalgard, E.D. Johnson, T.G. Ksiazek, W.C. Hall, C.J. Peters, Preliminary report: isolation of Ebola virus from monkeys imported to USA, *Lancet.* 335 (1990) 502-505.
- [38] S.R. Zaki, W.J. Shieh, P.W. Greer, C.S. Goldsmith, T. Ferebee, J. Katshitshi, et al., A novel immune histochemical assay for the detection of Ebola virus in skin: implications for diagnosis, spread, and surveillance of Ebola hemorrhagic fever, *J. Infect. Dis.* 179 (1999) S36-S47.
- [39] H.W. Lupton, R.D. Lambert, D.L. Bumgardner, J.B. Moe, G.A. Eddy, Inactivated vaccine for Ebola virus efficacious in guineapig model, *Lancet.* 2 (1980) 1294-1295.
- [40] J. Pettitt, L. Zeitlin, D.H. Kim, C. Working, J.C. Johnson, O. Bohorov, et al., Therapeutic intervention of Ebola virus infection in rhesus macaques with the MB-003 monoclonal antibody cocktail, *Sci. Transl. Med.* 5 (2013) 99-113.
- [41] UPDATE 1-Liberian doctor who received rare Ebola drug ZMapp dies, <http://af.reuters.com/article/guineaNews/idAFL5N0QV2AB20140825>, Reuters Africa, 25 August 2014. (Accessed on 25 August 2014).
- [42] Ebola outbreak: Japan offers anti-influenza drug for treatment, <http://www.cbc.ca/news/health/ebola-outbreak-japan-offers-antiinfluenza-drug-for-reatment-1.2745915>, CBC News Health. (Accessed on 25 August 2014).
- [43] M.A. Trad, D.A. Fisher, P.A. Tambyah, Ebola in West Africa, *The Lancet Infect. Dis.* 14 (2014) 1045.
- [44] A. Marzi, H. Feldmann, Ebola virus vaccines: an overview of current approaches, *Expert Rev. Vaccines* 13 (2014) 521-531.