Review Article

Ebola: too far or so close?

Paul Torpiano, David Pace

Abstract

The year 2014 has witnessed the escalation of the largest ever Ebola outbreak which started in Guinea, and later spread to other countries in West Africa. The associated disease burden has already exceeded the total number of cases in all the sporadic outbreaks that occurred since the first description of Ebola in 1976. The threat of further spread across Africa, and possibly beyond through international travel, is of concern and has led several countries around the world to implement preparedness measures against Ebola. In an attempt to contain the spread of Ebola, WHO and other non-governmental humanitarian organisations have pooled their resources to fuel efforts at improving patient care, isolation facilities, healthcare worker training, and availability of personal protective equipment in the affected countries. The outbreak has brought to light the lack of past investment in research into treatment or potential vaccine development against the Ebola virus, with the only hope of expediting a cure that can be used in the current outbreak being through the launch of clinical trials investigating experimental drugs in the affected countries.

Paul Torpiano, MD*
Foundation Programme Year II
Department of Paediatrics
Mater Dei Hospital
Malta
paul.torpiano@gov.mt

David Pace, MD, PgDip PID (Oxf), FRCPCH
Consultant Infectious Disease Paediatrician
Department of Paediatrics
Mater Dei Hospital
Malta

**Corresponding Author*

Key words

Ebola virus, Ebola Virus Disease, West African outbreak, Ebola treatment and prevention

Introduction

The Ebola virus (EBOV) is one of the aetiologies of Viral Haemorrhagic Fever (VHF), a syndrome complex characterised by fever, capillary leak, bleeding and shock. This zoonotic RNA virus was first discovered in 1976, following the first documented outbreak near the Ebola River in Zaire (now the Democratic Republic of Congo) which occurred simultaneously with another outbreak in Sudan.[1] Several outbreaks have occurred since its discovery, almost all of which have occurred in sub-Saharan Africa.[2] The current ongoing outbreak in West Africa is the largest ever to be reported and the associated high mortality as well as its potential for international spread are a real concern. The statement on the Ebola virus disease (EVD) released on the 31st of July, 2014 by Margaret Chan, the Director General of the World Health Organization (WHO): "If the situation continues to deteriorate, the consequences can be catastrophic in terms of lost lives but also severe socioeconomic disruption and increased risk of spread to other countries"[3] has led several countries to implement public health preparedness measures to immediately contain imported cases of EVD.

Ebola virus

The most likely vector of the EBOV is the fruit bat, specifically *Hypsignathus monstrosus* (the hammer-headed fruit bat), *Epomops franqueti* (Franquet's epaulettes fruit bat), and *Myonycteris torquata* (the little-collared bat).[4] The means of transmission within bat populations remains unknown.[5] Little is known of the life cycle of the EBOV, and why it only appears during intermittent outbreaks. Human disease is thought to result from consumption of poorly-cooked infected animals, such as bats or chimpanzees (which are known to feed on bats).[4, 6] However unlike other zoonoses Ebola has the potential of spreading from human to human from exposure of mucous membranes or broken skin to infected body fluids including large aerosol droplets that can be produced during coughing. There are 5 known strains of the EBOV as described in table 1.[7]

Table 1: The 5 known strains of the Ebola virus[7]

Strain	Acronym	Description
Bundibugyo	BDBV	First discovered in 2007 during an outbreak in Uganda
Zaire	EBOV	Causative strain in the current outbreak. Commonest cause of human disease
Reston	RESTV	Cause of outbreaks in monkeys and pigs. Not known to cause clinically apparent human illness or death
Sudan	SUDV	Associated with large outbreaks, mostly centred in Sudan and Uganda
Taï Forest	TAFV	Emerged in Taï Forest, Ivory Coast in 1994, causing infection in a single individual

Clinical manifestations

EVD is a severe acute viral illness characterised by the sudden onset of fever, intense weakness, muscle pain, headache and sore throat followed by vomiting, diarrhoea, rash and impaired renal and liver function. Disease progression may lead to disseminated intravascular coagulation, causing the characteristic terminal haemorrhagic phase that manifests as internal and external bleeding[7] including epistaxis, haematemesis, melaena, petechiae, ecchymosis and bleeding at venepuncture sites.[8] These signs are manifest in around 50% of patients.[9] The incubation period is estimated to be between 2 and 21 days, with patients remaining infectious as long as their blood and secretions (including semen) contain the virus, which can persist in semen for up to 61 days after the onset of illness.[7] Patients do not transmit Ebola during the incubation period but become infectious once they develop clinical features of EVD.[7] A diagnosis of EVD can be confirmed by means of several laboratory methods such as an antibody-capture enzyme-linked immunosorbent assay, antigen detection tests, a serum neutralisation test, reverse transcriptase polymerase chain reaction (RT-PCR) assay, electron microscopy, or virus isolation by cell culture.[7] During the current outbreak, RT-PCR kits have proven the most useful, accurate, and popular diagnostic investigation.[7]

Ebola outbreaks

Since the first outbreak in 1976, several Ebola outbreaks have been reported in humans and livestock within Africa over the last four decades (Table 2). The only unrelated handful of isolated cases occurring in Europe, Russia and the USA were in research laboratory workers. The Ebola subtype which is responsible for the current outbreak is the EBOV (or Zaire) virus, a 19.0kb non-segmented genome encoding 8 proteins, which last appeared in DRC in 2008.[2] The total estimated case fatality rate from 1976 to 2008 is estimated at 79%.[2]

Spread of the current Ebola strain: 2014

West Africa

Ebola is spread in the community through human-to-human transmission, with infection resulting from direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other body fluids of infected people, and indirect contact through contaminated fomites. Burial ceremonies in which mourners have direct contact with the body of the deceased person have been reported to play a role in the transmission of Ebola.[7]

The onset of the latest outbreak which began in Guinea, on the West African coast (Figure 1) has been traced back to late 2013. Contact tracing has successfully identified the index case for the 2014 outbreak to be a 2-year old child inhabiting the Meliandou village in the Gueckedou prefecture of Guinea. This child died on the 6th December, 2013. By February 2014, it had been transmitted to two other locations in Guinea: Macenta and Kissidougou, and by March it had spread to 5 other locations in Gueckedou.[11] The first death in Guinea's capital, Conakry, occurred on 18th March 2014. The patient was a businessman who travelled from Dabola, in central Guinea, having allegedly contracted the virus there through contact with a visitor from Gueckedou (who later also died from the disease). The body of the businessman was taken to Watagala, his village of origin, and following this, 4 of his siblings, along with 4 mourners at his funeral have tested positive for EBOV.[12]

Since then, the virus has spread to involve three other West African countries: Liberia, Sierra Leone and Nigeria. Several suspected cases from Mali all tested negative for EBOV. Four foci for infection have emerged in Liberia, only 1 of which has been explained by contact tracing: a woman arriving from Guinea gave the disease to her sister in Foya, 24km from the outbreak's main focus in Gueckedou). Her sister then travelled to Monrovia, Liberia's capital city, and onwards to visit her husband at the Firestone Rubber Plantation Camp northeast of the city. She died on the 2nd April, 2014.[13, 14]

Table 2: All outbreak and isolated cases of Ebola Viral Disease (1976 to date)[10]

Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
1976	Zaire (DRC)	Ebola	318	280 (88%)	Disease spread by close personal contact and use of contaminated needles and syringes in hospitals/clinics.
1976	Sudan	Sudan	284	151 (53%)	Occurred simultaneously with outbreak in Zaire. Disease spread mainly through close personal contact within hospitals. Many medical care personnel infected.
1976	England	Sudan	1	0	Laboratory infection by accidental injury from a contaminated needle.
1977	Zaire (DRC)	Ebola	1	1 (100%)	Noted retrospectively in village of Tandala.
1979	Sudan	Sudan	34	22 (65%)	Recurrent outbreak at the same site as the 1976 Sudan epidemic.
1989	USA	Reston	0	0	Introduced into quarantine facilities by monkeys imported from the Philippines.
1990	USA	Reston	4 (asymptomatic)	0	Introduced into quarantine facilities by monkeys imported from the Philippines. Four humans seroconverted from asymptomatic infection.
1989-1990	Philippines	Reston	3 (asymptomatic)	0	High mortality among macaques in a primate facility responsible for exporting animals in the USA. Three workers seroconverted without evidence of disease.
1992	Italy	Reston	0	0	Introduced by monkeys imported from the Philippines. No humans infected.
1994	Gabon	Ebola	52	31 (60%)	Occurred in gold-mining camps deep in the rain forest.
1994	Ivory Coast	Tai Forest	1	0	Scientist became ill after autopsy on a wild chimpanzee in the Tai Forest. Patient treated in Switzerland.
1995	DRC	Ebola	315	250 (81%)	Epidemic spread through families and hospitals.

Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
1996	Gabon	Ebola	37	21 (57%)	Chimpanzee found dead in the forest eaten by people hunting for food. Nineteen of these became ill, and subsequently infected other family members.
1996-1997	Gabon	Ebola	60	45 (75%)	Index case was a hunter who lived in a forest camp. A dead chimpanzee found in the same forest at the time was also infected.
1996	South Africa	Ebola	2	1 (50%)	Index case was a medical professional who travelled from Gabon to South Africa after having treated EVD-infected patients. A nurse who took care of him became infected and died.
1996	USA	Reston	0	0	Introduced by imported monkeys from the Philippines.
1996	Philippines	Reston	0	0	Identified in monkey export facility. No human infections.
1996	Russia	Ebola	1	1 (100%)	Laboratory contamination.
2000-2001	Uganda	Sudan	425	224 (53%)	Spread associated with attending funerals of EVD patients, being in contact with patients within a family, and providing medical care to Ebola patients without using adequate PPE.
2001-2002	Gabon	Ebola	65	53 (82%)	Occurred over the border of Gabon and the Republic of the Congo.
2001-2002	Republic of Congo	Ebola	57	43 (75%)	Outbreak occurred over the border between Gabon and the Republic of the Congo. This was the first time that Ebola haemorrhagic fever was reported in the Republic of Congo.
2002-2003	Republic of Congo	Ebola	143	128 (89%)	Outbreak occurred in the districts of Mbomo and Kéllé in Cuvette Ouest Département.
2003	Republic of Congo	Ebola	35	29 (83%)	Outbreak occurred in Mbomo and Mbandza villages located in Mbomo district.
2004	Sudan	Sudan	17	7 (41%)	Concurrent with an outbreak of measles in the same area

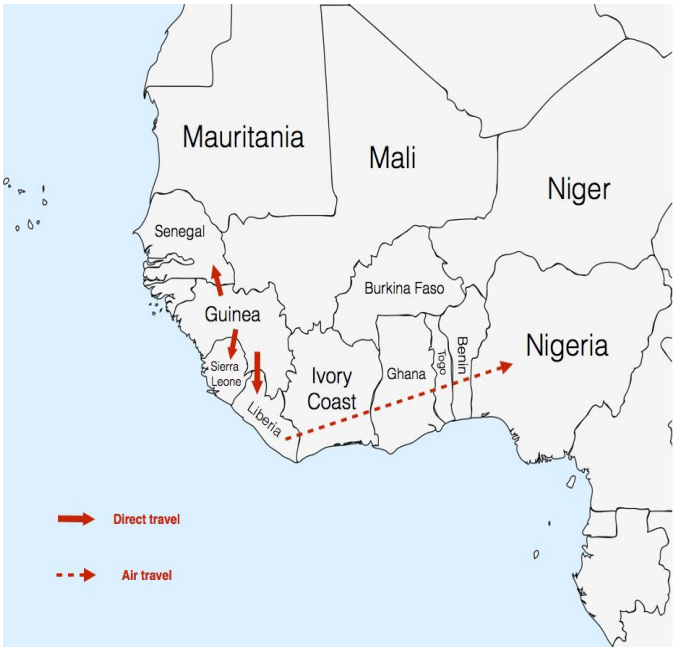
Year(s)	Country	Ebola Subtype	Reported No. of human cases	Reported number (%) of deaths among cases	Description
2004	Russia	Ebola	1	1 (100%)	Laboratory contamination
2007	DRC	Ebola	264	187 (71%)	Outbreak occurred in Kasai Occidental Province
2007-2008	Uganda	Bundibugyo	149	37 (25%)	First reported occurrence of a new strain
2008	Philippines	Reston	6 (asymptomatic)	0	First known occurrence in pigs. Six workers from the pig farm and slaughterhouse seroconverted
2008-2009	DRC	Ebola	32	15 (47%)	Outbreak occurred in the Mweka and Luebo health zones of the Kasai Occidental Province
2011	Uganda	Sudan	1	1 (100%)	The Ugandan Ministry of Health informed the public that a patient with suspected EVD died on May 6th, 2011 in the Luwero dietrict, Uganda.
2012	Uganda	Sudan	11	4 (36.4%)	Outbreak in the Kibaale district of Uganda
2012	DRC	Bundibugyo	36	13 (36.1%)	Outbreak in DRC's Province Orientale: had no epidemiological link with the near contemporaneous Ebola outbreak in Uganda.
2012	Uganda	Sudan	6	3 (50%)	Outbreak in the Luwero district. The CDC assisted the Ministry of Health in the epidemiological and diagnostic aspects of the outbreak.
2014	Guinea, Liberia, Sierra Leone, Nigeria, Senegal	Ebola	-	-	Ongoing outbreak. Suspected/confirmed case count = 3707; Suspected/confirmed deaths = 1848; Lab-confirmed cases = 2106.

Sierra Leone registered its first case on the 25th May 2014, while in Nigeria 1 patient died of probable EVD on the 27th July. This case was never confirmed as the courier refused to transport the serological sample for testing at WHO Collaborating Centre at the Institut Pasteur in Dakar, Senegal. Twenty other cases have been reported in Nigeria, with seven subsequent deaths. Sixteen cases were confirmed EBOV positive by laboratory testing.[5]

On the 25th July, Sierra Leone's top Ebola doctor, Sheikh Umar Khan, succumbed to the disease, highlighting the risk of healthcare workers acquiring EVD through contact with Ebola patients. More than 100 medical workers are estimated to be amongst the victims of this outbreak.[15] Healthcare workers are at an increased risk of contracting EVD, because of prolonged contact with infected patients and the associated risk of contact with body fluids or infected needles.[16] The proper use of PPE during contact with such patients is essential, and ensuring availability of PPE, as well as

training in its use, has been one of the priorities listed by WHO in response to the current Ebola outbreak.[17]

***Figure 1**: Spread of the 2013-2014 West African Ebola* Outbreak



On the 29th of August, reports emerged of the first case of EVD in Senegal, another West African country which borders Guinea. The case is that of a 21-year old male from Guinea who arrived in Dakar, Senegal by road on the 20th August, and stayed with relatives in the outskirts of the city. He developed fever, diarrhoea and vomiting and was later diagnosed with EVD.[17]

Characteristics of the current Ebola outbreak

Previous Ebola outbreaks tended to occur in rural areas, such as remote parts of Uganda and DRC, and thus were for the most part self-contained due to geographic isolation of cases. The EVD outbreak that is ongoing this year, however, marks the first outbreak in a densely populated urban area within Conakry's large shanty towns.[18] The scale of this outbreak has raised a concern on the potential of a pandemic, with epidemiological modelling based on the data from previous Ebola outbreaks producing a basic reproduction number (R_0) of 2.7 (95% confidence interval: 1.9-4.1)[19] meaning that every case of EVD leads to infection in another 2.7 individuals, a figure that is comparable to the R_0 of influenza.[20]

The extent of the current Ebola outbreak is also unprecedented. The previous total death toll since 1976 was estimated to be 1590,[15] while, since December 2013, EVD has already caused at least 1427 deaths.[5] Spread between non-neighbouring African countries by travellers, as occurred between Liberia and Nigeria demonstrates the ease of spread of Ebola, raising fears of its potential for uncontrolled escalation of this outbreak.[15]

Mortality Rate

In contrast to previous outbreaks, this outbreak has an estimated mean case mortality rate of 56%, a sharp drop compared to the 90% observed previously.[15] This discrepancy is most probably due to the smaller scale of previous outbreaks with the deaths occurring in the few that were infected resulting in a high case fatality rate. Data on the number of cases, deaths and lab-confirmed cases in the 4 affected countries, as of the 22nd August, 2014 are shown in table 3.[5]

Public health measures

WHO has been following this outbreak since late 2013, and is continually providing updated infection control recommendations as well as aiding their implementations in an effort to control this epidemic. It has been suggested that the scale of this EVD outbreak, as well as the speed with which it has escalated, places other countries in West Africa at a significant risk of being affected. Kenya and Togo in particular, where healthcare infrastructure is poor and appropriate facilities for early identification, isolation and treatment of cases are lacking, have been identified as being at a high-risk.[17] WHO recommendations have largely focused on the need for the availability and correct use of personal protective equipment (PPE), in addition to the appropriate management of suspected cases through the use of guidelines on diagnosis, isolation of cases and contact tracing.[15] WHO has also explicitly expressed the need for more funds and resources, emphasising that this outbreak and its subsequent spread is a result of the poor infrastructure and quality of healthcare in the countries affected.[15] On the 31st July, WHO pledged $100 million for this purpose, while the World Bank has added a further $200 million. Médecins Sans Frontièrs and the International Committee of the Red Cross have both shown hope that with more resources and investment, the disease can realistically be contained by the end of this year.[15]

***Table 3**: Number of cases and deaths from suspected and laboratory-confirmed EVD until 15th September, 2014.[5] Continuous updates to these figures are available at http://www.afro.who.int*

	Guinea	Sierra Leone	Liberia	Nigeria	Senegal	Total
Suspected/ confirmed cases	771	1216	1698	21	1	3707
Suspected/ confirmed deaths	494	476	871	7	0	1848
Lab-confirmed cases	579	1107	403	16	1	2106

WHO has provided Interim Infection Control Recommendations, published in March 2008 and updated in August 2014, for those exposed to cases of suspected EVD with a focus on thorough washing of contaminated surfaces, detailed medical evaluation and follow-up, isolation pending exclusion of Ebola infection, and contact tracing.[21] A more recent document, updated in August 2014, has also been published by the UK Department of Health, and makes similar basic recommendations to those mentioned by WHO.[22] WHO also suggests preventive measures for avoiding spread of the virus, and recommends that if any HCW is within 1m of an affected patient, then a face-shield or medical mask with goggles, gloves, and a clean, non-sterile long-sleeved gown should be worn.[21] The affected countries have taken measures to ensure that the spread of the outbreak is controlled, placing patrols at the borders, while enforcing quarantine of suspected cases as well as proper burial of deceased patients.[5] Despite this, the increasing sense of panic has led to suspected patients escaping from medical facilities so as to avoid quarantine, while international news agencies have reported that families are leaving the bodies of deceased relatives in the street out of fear of contracting the disease or of being forced into quarantine, instead of waiting for doctors to visit their homes and dispose of the bodies appropriately.[15]

Countries outside of Africa are also making preparations and advising on precautionary measures to contain any inadvertently imported cases in order to prevent local spread of Ebola. The European Centre for Disease Prevention and Control (ECDC) has issued guidelines suggesting measures to prevent exportation of cases to other countries and spread within the European Union (EU).[23] These suggest that, in the event of the outbreak reaching a European country, local authorities should consider barring known EVD cases, as well as their contacts, from leaving the country, for a minimum of 21 days following exposure (the incubation period of the EBOV).[23] The ECDC also suggests that travellers from affected areas should be informed about the clinical presentation of EVD, the importance of revealing their travel history when seeking medical care, the need to indicate possible contact with sick individuals or wild animals, and the procedures for contacting public health authorities for support if infection is suspected.[23] Recommendations also extend to informing healthcare providers about the possibility of EVD among returning travellers from affected areas, the clinical presentation of the disease, the availability of protocols for the ascertainment of possible cases and procedures for referral to healthcare facilities, and the need for strict implementation of barrier management, use of PPE and disinfection procedures when providing care to suspected EVD cases.[23] The Department of Health in the UK has published guidelines on the assessment and management of suspected EVD in febrile travellers who visited affected countries within the prior 21 days.[22] The CDC has provided similar guidelines for hospital use in the USA, as well as advice on infection control procedures designed to prevent in-hospital spread of viral haemorrhagic fever.[5] Based on these guidelines, several governments have invested heavily in training of hospital staff to follow recommendations, as well as to ensure availability of all necessary PPE, diagnostic kits, isolation and contact-tracing facilities, and treatment requisites.[22]

Treatment

Currently there is no licensed treatment for EVD. Management of affected patients is supportive and includes the administration of intravenous resuscitative

fluids, maintenance of electrolyte balance, and intensive care measures.[1] The allegedly successful treatment of two US nationals with ZMAPP, an experimental treatment consisting of a mixture of three humanised monoclonal antibodies against Ebola that is being developed by Mapp Biopharmaceuticals, San Diego, California and which has not yet been studied in humans,[24] has fuelled speculation on the effectiveness and the need for availability of such treatment. The rarity of EVD and VHF in general meant that little investment was made to develop preventive or therapeutic medicinals. This has led to calls for experimental drugs to be opportunistically distributed during the current outbreak in the form of a clinical trial, in the interest of developing better therapeutic agents.[15] However, there are several issues that need to be carefully considered with such a clinical trial, apart from the huge associated expense. Traditionally, West African populations are suspicious of Western European doctors,[15] an attitude that will complicate attempts in contact tracing, correct burial of deceased cases, and isolation of suspected cases and which will hinder the use of experimental drugs against Ebola. Questions have also been raised over the ethics of testing populations within poverty-stricken demographic areas.[15]

The FDA however, has previously brought forward a 2-animal rule on drug testing, suggesting that, in an emergency, a drug that has shown efficacy in two different animal models, and that has been proven not to have serious side effects in healthy humans can be made available on compassionate grounds.[25]

Published reports on experimental approaches to treat Ebola are limited. Jahrling et al, in separate publications in 1996 and 1999, suggested that the use of hyperimmune horse anti-Ebola serum is protective in animal models.[26,27] Maruyama et al, also in 1999, reported success with human monoclonal antibodies acting against the EBOV surface protein (derived from mRNA extracted from bone marrow of survivors of EVD).[28] A novel approach for extracting immunoglobulins from survivors of EVD has reportedly been highly successful in animal trials, with results expected to be published in the upcoming months.[15] Tekmira Pharmaceuticals in Canada are developing an experimental drug called TKM-Ebola which consists of small interfering RNAs that target the EBOV and halts viral replication by blocking DNA synthesising proteins.[29] TKM-Ebola had entered Phase I human safety clinical trials in January 2014.[24] However, the FDA halted the trials on the 3rd July, and is requesting more information on the proposed mechanism of action of TKM-Ebola which is administered according to a complicated dosage regimen.[15,24] BioCryst Pharmaceuticals in North Carolina have adopted a similar approach to develop an experimental drug called BCX4430, which has allegedly been proven to be effective in preventing death from Marburg virus, the other member of the Filoviridae family of viruses causing VHF, in animal trials.[24]

Furthermore, the potential of favipiravir, an antiviral agent against Ebola is being investigated with Ostereich et al reporting promising results with its use in a murine model.[30] This drug selectively inhibits the RNA-dependent RNA polymerase of the virus, and was initially developed and promoted for its role in treating influenza.[31]

Vaccine Prevention

The development of a vaccine against Ebola has been hindered by the lack of interest and investment by pharmaceutical companies in researching an infection with a previously very low disease burden confined to poor developing countries. Dr Anthony Fauci, director of America's National Institute of Allergy and Infectious Diseases (NIAID) recently announced that phase I clinical trials of a promising Ebola vaccine are to be initiated in September, hoping for favourable results by January and very optimistically to have this vaccine manufactured and available for distribution by late 2015. The precise components of this proposed vaccine have not been published, though a study in 2005 by Geisbert et al showed promising results with a vaccine made from the Vesicular Stomatitis Virus.[32] In this study recombinant Vesicular Stomatitis Virus vectors expressing homologous filoviral glycoproteins were found to partially protect 4 of 5 macaques challenged with the Zaire Ebolavirus.[32]

Conclusion

The magnitude of this year's EVD outbreak is already much larger than any previous Ebola outbreaks, partly due to the very poor infrastructure of healthcare systems in affected countries, failure to follow adequate barrier precautions, and unavailability of PPE. Cultural attitudes such as fear of quarantine, as well as mistrust in advice provided by developed countries have hindered containment of the current outbreak. Fear and panic have resulted in an increased scattering of contacts, making contact tracing difficult.

Still, WHO is optimistic that with proper funding and investment, the current outbreak can be controlled effectively through the use of simple infection control measures, aided by emerging drug therapies and possibly vaccination.

References

1. Peters CJ, LeDuc JW. An Introduction to Ebola: the Virus and the Disease. J Infect Dis. 1999 Feb;179(Suppl1):ix-xvi.
2. Gatherer D. The 2014 Ebola virus disease outbreak in West Africa. J Gen Virol. 2014 Aug;95:1619-24.

3. Chan M. WHO director general assesses the Ebola outbreak with 3 West African presidents [Internet]. United Nations Information Centre, Canberra. 2014 Aug [cited 2014 Aug 29]. Available from: http://un.org.au/2014/08/04/who-director-general-assesses-the-ebola-outbreak-with-three-west-african-presidents/.
4. Leroy EM, Kumulungui B, Pourrut X, Rouquet P, Hassain A, Yaba P, et al. Fruit bats as reservoirs of Ebola virus. Nature. 2005 Dec 1;438:575-6.
5. CDC. 2014 Ebola outbreak in West Africa [Internet]. 2014 Aug 3 [updated 2014 Aug 22; cited 2014 Aug 24]. Available from: http://www.cdc.gov/vhf/ebola/outbreaks/guinea/index.html.
6. Biek R, Walsh PD, Leroy EM, Real LA. Recent common ancestry of Ebola Zaire virus found in a bat reservoir. PLoS Pathog. 2006 Oct 27;2(10):e90.
7. WHO. Ebola Virus Disease. Fact Sheet No 103. Disease Fact Sheets [Internet]. 2014 Apr [cited 2014 Aug 29]. Available from: http://www.who.int/mediacentre/factsheets/fs103/en/.
8. Coleblunders R, Borchert M. Ebola haemorrhagic fever - a review. J Infect. 2000 Jan;40(1):16-20.
9. Bwaka MA, Bonnet MJ, Calain P, Coleblunders R, De Roo A, Guimard Y, et al. Ebola haemorrhagic fever in Kikwit, Democratic Republic of Congo: clinical observations in 103 patients. J Infect Dis. 1999 Feb;179(Suppl1):S1-7.
10. CDC. Outbreaks Chronology: Ebola Haemorrhagic Fever [Internet]. 2014 Aug [updated 2014 Aug 22; cited 2014 Aug 24]. Available from: http://www.cdc.gov/vhf/ebola/resources/outbreak-table.html.
11. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. Emergence of Zaire Ebola Virus Disease in Guinea - preliminary report. N Engl J Med [Internet]. 2014 Apr 16. Available from: http://www.nejm.org/doi/full/10.1056/NEJMoa1404505.
12. Guineenews.org [Internet]. Ebola a Conakry: la contamination limitee aux membres d'une seule famille et a ceux qui les ont approches. Guineenews: Dernieres Nouvelles de la Guinee par les Guineens. 2014 Mar 29. Available from; http;//guineenews.org/2014/03/ebola-a-conakry-la-contamination-limitee-aux-membres-dune-seule-famille-et-a-ceux-qui-les-ont-approches/.
13. FrontPageAfrica [Internet]. Liberia: Ebola manhunt - biker likely carrying virus on the run. FrontPageAfrica. 2014 Apr 7. Available from: http://frontpageafricaonline.com/index.php/health-sci/1260-ebola-manhunt-biker-likely-carrying-virus-on-the-run.
14. Nah V, Johnson O. Liberia: Ebola kills woman at Duside Hospital in Firestone [Internet]. allAfrica. 2014 Apr 4. Available from: http;//allafrica.com/stories/201404040742.html.
15. Arie S. Ebola: an opportunity for a clinical trial? BMJ. 2014 Aug 6;349:g4997.
16. McCartney M. Courage is treating patients with Ebola. BMJ. 2014 Aug 4;349:g4987.
17. WHO. WHO Disease Outbreak Update: Ebola Outbreak Response in West Africa [Internet]. 2014 Jul 28. Available from: http://www.who.int/csr/disease/ebola/evd-outbreak-response-plan-west-africa-2014.pdf?ua=1.
18. Diallo B. Ebola en Guinée: l'ONG Plan-Guinée craint une aggravation de l'épidémie. Africaguinée.com [Internet]. 2014. Available from: http://africaguinee.com/articles/2014/03/30/ebola-en-guinee-l-ong-plan-guinee-craint-une-aggravation-de-l-epidemie.
19. Legrand J, Grais R, Boelle PY, Valleron AJ, Flahaut A. Understanding the dynamics of Ebola epidemics. Epidemiol Infect. 2007 May;135(4):610-21.
20. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. Nature. 2004 Dec 16;432(7019):904-6.
21. WHO. Interim infection control recommendations for care of patients with suspected or confirmed Filovirus Haemorrhagic Fever, in health-care settings, with focus on Ebola [Internet]. 2014 Aug. Available from: http://www.who.int/csr/bioriskreduction/filovirus_infection_control/en/.
22. United Kingdom Department of Health. Advisory committee of dangerous pathogens. Management of Hazard Group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence [Internet]. 2014 Aug. Available from: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1194947382005.
23. European Centre for Disease Prevention and Control. Rapid risk assessment: Outbreak of Ebola Virus Disease in West Africa [Internet]. 2014 Aug 1. Available from: http://www.ecdc.europa.eu/en/publications/Publications/ebola-outbreak-west-africa-1-august-2014.pdf.
24. Reardon S. Ebola treatment caught in limbo. Nature. 2014 Jul 29;511(7511):520.
25. US Food and Drug Administration. Guidance for industry: product development under the animal rule [Internet]. 2014 May. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf.
26. Jahrling PB, Geisbert J, Swearengen JR, Jaax GP, Lewis T, Huggins JW, et al. Passive immunisation of Ebola virus-infected cynomologus monkeys with immunoglobulin from hyperimmune horses. Arch Virol Suppl. 1996;11:135-40.
27. Jahrling PB, Geisbert TW, Geisbert JB, Swearengen JR, Cray M, Jaax NK, et al. Evaulation of immunoglobulin and recombinant interferon-a2b for treatment of experimental Ebola virus infections. J Infect Dis. 1999 Feb;179(Suppl1):S224-34.
28. Maruyama T, Parren PW, Sanchez A, Rensink I, Rodriguez LL, Khan AS, et al. Recombinant human monoclonal antibodies to Ebola virus. J Infect Dis. 1999 Feb;179(Suppl1):S235-9.
29. Geisbert TW, Bausch DG, Feldmann H. Prospects for immunisation against Marburg and Ebola viruses. Rev Med Virol. 2010 Nov;20(6):344-57.
30. Ostereich L, Ludtke A, Wurr S, Rieger T, Munoz-Fontela C, Gunther S. Successful treatment of advances Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res. 2014;105:17-21.
31. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favirpiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res. 2013 Nov;100(2):446-54.
32. Geisbert TW, Daddario-Dicaprio KM, Lewis MG, Geisbert JB, Leung A, Paragas J, et al. Vesicular stomatitis virus-based ebola vaccine is well-tolerated and protects immunocompromised nonhuman primates. PLoS Pathog. 2008 Nov;4(11):e1000225.