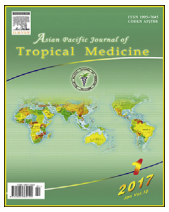
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm



Review http://dx.doi.org/10.1016/j.apjtm.2016.12.008

An update on the 2014 Ebola outbreak in Western Africa

Haaris A. Shiwani[1], Rebabonye B. Pharithi[2], Barkat Khan[2], Christian Binoun-A Egom[3], Peter Kruzliak[4], Vincent Maher[2], Emmanuel Eroume-A Egom[1,2,5]✉

[1]*Department of Clinical Medicine, Education Division, Trinity College Dublin, The University of Dublin, Dublin, Ireland*

[2]*Department of Cardiology, The Adelaide and Meath Hospital Dublin, Incorporating the National Children Hospital, Tallaght, Dublin, 24, Ireland*

[3]*University of Ndjamena, Faculty of Medicine, Ndjamena, Chad*

[4]*International Clinical Research Center, St. Anne's University Hospital and Masaryk University, Brno, Czech Republic*

[5]*Egom Clinical and Translational Research Services, Dartmouth, NS, Canada*

ARTICLE INFO

Article history:
Received 1 Nov 2016
Received in revised form 20 Nov 2016
Accepted 2 Dec 2016
Available online 27 Dec 2016

Keywords:
Ebola virus disease
Western Africa
Ebola virus vaccination
EBOV

ABSTRACT

The recent Ebola outbreak in Western Africa was the most devastating outbreak witnessed in recent times. There have been remarkable local and international efforts to control the crisis. Ebola Virus Disease is the focus of immense research activity. The progression of events in the region has been evolving swiftly and it is of paramount importance to the medical community to be acquainted with the situation. Over 28 000 people were inflicted with the condition, over 11 000 have died. Novel data has emerged regarding modes of transmission, providing rationale for recent flare-ups. Similarly, studies on survivors are elucidating the later stages of the disease recovery process. Novel techniques for diagnosis are also discussed. Finally, the current research regarding treatment and vaccine development is reviewed, particularly the implementation of rVSV-ZEBOV vaccination programs.

1. Introduction

The recent Ebola outbreak in Western Africa was the most devastating outbreak witnessed in recent times. The declaration of an international health emergency took place on the 8th of August 2014 [1]. In March of 2014, the first case of Ebola was confirmed in Guinea, Africa. By May, Liberia and Sierra Leone had cases of the condition, and by July the virus had spread to Nigeria and Senegal. In October, the disease touched Mali [2]. The outbreaks in Nigeria, Liberia, Sierra Leone and Guinea were officially declared over on 19th October 2014, 9th May 2015, 7th November 2015 and 29th December 2015, respectively [1,2]. On the 29th of March 2016, the WHO Director-General declared, during the 9th Emergency Committee meeting, that the outbreak was no longer a Public Health Emergency of International Concern [3]. In June 2016, Guinea and Liberia were declared to be free of transmission [4,5].

In the aftermath of the crisis which unfolded in Western Africa, it is now of interest to the medical community to assess where we stand today. What has happened since the media attention has dissipated? Can we forget about Ebola? What has been done to prevent future disasters of such catastrophic proportions? This review intends to update the reader on one of the worst medical emergencies of the modern era, particularly elaborating on (1) the latest epidemiological data, (2) recent studies (on survivors) which explicate the modes of viral transmission as well as the effects of the disease after recovery, (3) advances in treatment and prevention, and (iv) the future outlook of Ebola.

2. Epidemiology

Since its first occurrence in 1976, five different subtypes of Ebola virus have been identified across several areas of Africa. Evidence suggests that the Ebola virus tends to break out in

First author: Haaris A. Shiwani, Department of Clinical Medicine, Education Division, Trinity College Dublin, The University of Dublin, Dublin, Ireland.
✉Corresponding author: Emmanuel Eroume-A Egom, MD, Ph.D, M.Sc, MRCP, Egom Clinical and Translational Research Services, Dartmouth, NS, Canada.
Tel: +1 353(0)14142112
Fax: +1 353(0)14143052
E-mail: egomemmanuel@gmail.com
Peer review under responsibility of Hainan Medical University.

small villages that are in close proximity to or are perhaps located in tropical rainforests [6]. As it was the case for all previous Ebola outbreaks, which all began in Africa, the most recent epidemic started in the West African nation of Guinea in late 2013 and was confirmed by the World Health Organization in March 2014 [6].

The Centres for Disease Control and Prevention has reported extensive data regarding the scale of the crisis [7]. Among the most heavily inflicted countries within Africa–Sierra Leone, Liberia and Guinea – there have been a total of 28616 cases reported (14124, 10678 and 3814 cases, respectively), resulting in 11310 deaths (3956, 4810 and 2544, respectively). As of the 13th of April 2016, 7 other countries have also reported cases of the disease. Nigeria, Mali, the United States, Senegal, Spain, the United Kingdom and Italy have encountered a total of 36 cases (20, 8, 4, 1, 1, 1 and 1 cases, respectively). Of the 36 cases, there were 8 deaths in Nigeria, 6 in Mali and 1 in the United States. Eight hundred and eighty one healthcare workers were infected during this tragedy and 513 died due to the disease. The healthcare workforce in Liberia, Sierra Leone and Guinea was reduced by 8%, 7% and 1%, respectively [8]. In Sierra Leone, consequently, there was a drastic 23% reduction in the delivery of health care services [8].

After the end of the initial outbreak, there have been a relatively low number of new cases that have re-emerged, all of which were rapidly and efficiently controlled [9]. Initially, in March 2015, 1 case was reported in Liberia, where 192 contacts were identified and sexual transmission was suspected. In June 2015, Liberia encountered 7 cases, with 126 identified contacts. August 2015 saw 6 cases emerge in Sierra Leone, with 840 contacts and sexual transmission suspected. Additionally, 1 case was reported in Sierra Leone in September 2015, with 780 identified contacts. In November, Liberia once again had 3 new cases of the condition being reported, with 165 contacts. In January 2016, Sierra Leone was challenged with a further 2 cases with over 150 contacts. Finally, March 2016 saw both Liberia and Guinea affected with 13 new cases and over 1200 contacts identified with a suspicion of sexual transmission.

In the most severely affected countries, services have been established in order to accommodate survivors of the disease, e.g. MSF survivor clinics [10]. From August to November 2014, an EBOV outbreak unrelated to that in the West of Africa emerged in the Democratic Republic of Congo, with 66 cases reported, resulting in 49 deaths (74%). The initial case was reported on August 24th in a pregnant woman involved in the dissection of a bush animal [11].

3. Pathogenesis and transmission

Epidemics of Ebola virus disease are generally thought to begin when an individual becomes infected through contact with the meat or body fluids of an infected animal [6]. Once the individual becomes ill or dies, the virus then spreads to others who come into direct contact with the infected individual's blood, skin, or other body fluids [6]. However, it should be noted that for any large-scale human transmittance to occur, there must be a direct contact of mucous membranes, or broken skin with bloody or bodily fluids of an infected person [6]. Such transmission can involve any contact by the form of blood or bodily fluids including but not limited to urine, saliva, sweat, faeces, vomitus, breast milk, and semen, as well as via contaminated objects like needles and syringes [6]. It has become evident, by the repeated re-emergence of the Ebola virus disease, that periods of transmission persist even when there are no active cases of the disease present. This phenomenon can be attributed to human to human transmission, rather than the animal to human transmission that led to the initial appearance of the disease in humans. After a patient recovers from Ebola virus disease, the virus can survive in organs where there is relative protection from the immune system – sites of immune privilege [12]. Infectious Ebola virus has been identified in the following survivors' body fluids or tissue: cerebrospinal fluid, breast milk, seminal fluid, vaginal fluids, gastrointestinal (rectal swab, faeces, saliva, vomitus), urine, lower respiratory tract (alveoli), eye (aqueous humour, tears, conjunctivae), and other (skin, sweat, placenta, cord blood and amniotic fluid) for extended periods of time after onset of the illness, as highlighted in Figure 1 [13]. Survivors facing neurological or ocular symptoms after recovery from Ebola may still harbour replicating EBOV [13]. This persistence may explain the re-emergences of the disease that have occurred, particularly in settings of sexual transmission. One case of a survivor of EVD showed the presence of EBOV RNA in a semen sample by RT-PCR assay at 175 days after there was a negative serum EBOV [14]. A contact of this survivor contracted the disease and subsequently died following unprotected intercourse in a period after the survivor had recovered from the acute illness [14]. Data from the PREVAIL III trial demonstrated that in 97 (male) survivors of Ebola virus disease, viral RNA was detected in 37% of patients, with 18 months being the longest gap between active disease and detection [15]. It has been elucidated that although there have been no cases to indicate airborne transmission of the virus, studies have shown that small-particle viral aerosols can be a route of infection in rodents [16]. Thus, extensive exposure to aerosolised virus by healthcare workers may pose a risk.

4. Complications of Ebola virus infection

After the outbreak, many researchers have extensively followed-up survivors of the disease. Numerous complications have been identified in survivors including but not limited to arthralgia, myalgia, depression and anxiety, uveitis, vision loss, hearing Loss, paraesthesia, and concentration, mood and memory disturbances [17–19].

5. Diagnosis

Although there are no approved specific therapies for Ebola virus disease, it is essential to make the diagnosis as early as possible, in order to initiate supportive measures before the development of irreversible shock and to institute infection control procedures [6]. The methods of diagnosis used in the recent outbreak include Antigen-capture ELISA (Enzyme Linked ImmunoSorbent Assay) testing, Immunoglobulin (Ig) M ELISA, PCR, Virus Isolation, Serum IgM, IgG, and Immunohistochemistry [20]. These methods were effective; however, there is relative room for improvement, particularly in optimising speed, sensitivity and cost effectiveness. Several novel techniques are in the process of development, and recent evidence suggests that they may provide some advantages over existing methods. Optofluidic nanoplasmonic biosensor,

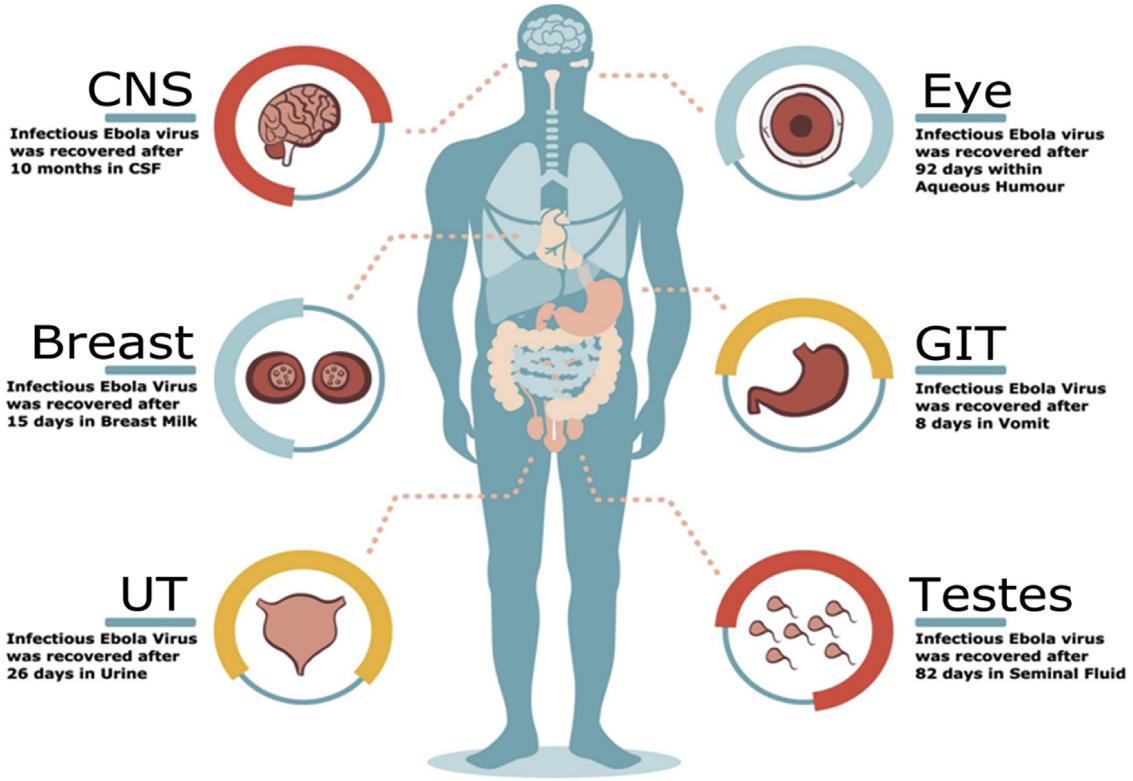


Figure 1. Ebola virus persistence data in different body fluid or tissue after the illness onset. Infectious Ebola virus has been identified in the following survivors' body fluids or tissue: cerebrospinal fluid, breast milk, seminal fluid, vaginal fluids, gastrointestinal (rectal swabs, faeces, saliva, vomitus), urine, lower respiratory tract (alveoli), eye (aqueous humour, tears, conjunctivae), and other (skin, sweat, placenta, cord blood and amniotic fluid) for extended periods of time after onset of the illness.

developed by Yanik and colleagues, may be able to directly detect active viruses in low ranges (106–109 PFU/mL) [21]. SP-IRIS – Single Particle Interferometric Reflectance Imaging Sensor, developed by Daaboul and colleagues, specifically and sensitively detects low levels of viral particles in blood (5×10^{-3} pfu/mL) [22]. Experts at the College of Medicine and College of Engineering at Florida International University have proposed that development of a point-of-care diagnostic approach involving the production of electrochemical Ebola immuno-sensors with specific monoclonal antibodies would be able to provide significantly faster detection (approx. 40 mins vs 3 days) at lower levels (pM levels vs nM levels) than ELISA testing [20]. This would enable swift screening.

6. Treatment and prevention

Currently, there are no FDA approved treatment or vaccination options for Ebola Virus Disease. However, there are numerous products in development.

A recent single arm phase II clinical trial involving the treatment of 14 EVD confirmed patients with 0.3 mg/kg/d of TKM-130803 (a small interfering RNA lipid nanoparticle product, or siRNA), showed no survival benefit when compared to controls of previous experiments [23]. Although TKM-130803 previously showed potential for EVD treatment, this latest result indicates that TKM-130803 may not be one of the candidates to cure EVD.

Similarly, a nonrandomised comparative study treated 99 EVD confirmed patients in Guinea with convalescent plasma. A total of up to 500 mL was transfused. The level of neutralising antibody was unknown in the blood samples. 84 patients were suitable for primary analysis. The study found no significant survival benefit in this treatment regimen. This exemplifies another case of a previously promising solution not surviving robust experimentation [24].

The single arm, proof-of-concept, JIKI trial [25] investigated the use of Favipiravir in the treatment of EVD in Guinea. The trial included 126 patients. The authors concluded that Favipiravir in patients with high viral load was unlikely to be effective, and in those with loads that were intermediate to high, this drug would require further investigation.

Relatively new data regarding ZMapp, the monoclonal antibody cocktail previously used experimentally for the treatment of EVD, is lacking. Robust research and evidence proving its efficacy is not available as of yet in the literature.

Several potential Ebola vaccines are currently under development and include Ad26.ZEBOV with MVA boosting [26,27], ChAd3-EBO-Z [28], and rVSV-ZEBOV [29,30]. The rVSV-ZEBOV vaccine in particular is taking centre stage in the STRIVE (Sierra Leone Trial to Introduce a Vaccine against Ebola) [31] Phase 2/3 clinical trial. Some of the most heavily affected regions of Sierra Leone have been chosen for the trial and over 8500 people have been enrolled. The design of the trial is relatively unconventional owing to the unique nature of the situation being addressed. STRIVE is an unblinded, individually randomised trial. The 2 arms of the study involve receiving immediate or deferred vaccination. Numerous sub-studies are being conducted with the patient cohort. No results are available as of yet.

Similarly, "Ebola ça suffit", a Phase 3 ring vaccination cluster randomised trial has proven to be highly successful in Guinea [32]. The 2 arms of the study involved immediate or deferred

vaccination. The interim results of 7651 patients demonstrated safety and 100% efficacy.

Randomisation stopped on the 26th of July 2015, at a similar time when approval was granted for continuation of the trial by the Ethics Committee of Guinea and the WHO Ethics Committee [33]. The vaccine has also found utility in flare-ups of EVD after the outbreaks in the region were declared over [34].

7. Summary and the way forward

Although the outbreak is over, the WHO has anticipated that flare-ups are likely [34]. Currently Guinea and Liberia are in a 90-day heightened state of surveillance after the suppression of the latest flare up. The WHO is currently in Phase 3 of its Ebola Response, which hopes to (1) "Accurately define and rapidly interrupt all remaining chains of transmission" [35] and (2) "Identify, manage and respond to any consequences of the remaining Ebola risks" [35]. The WHO and partner agencies have set up a host of services in the affected regions, such as providing households with food packages and hygiene kits, employing expert vaccinators, contact tracers, epidemiologists etc [34].

The outbreak has been one of the most valuable learning sources for the international medical community as a whole. The outbreak initially exposed numerous weaknesses [36] including deficiencies in the surveillance system, slow speed of response, inadequate protection of healthcare workers, movement across borders of infected individuals, deficiencies in communication with communities at large and contact tracing. However, it has become evident that these initial weaknesses were addressed, setting a precedent for a more advanced response if such an outbreak were to re-occur. Currently, vaccination programs are in place in the afflicted countries [37]. Furthermore, vaccine and drug development is ongoing, with the hope of new breakthroughs on the horizon.

In conclusion, the crisis that was witnessed in West Africa in 2014 was one of the greatest challenges of the modern era. The aggressive international response by a collaboration of charities, governments and individuals narrowly prevented a disaster of unprecedented proportions. It is with hope we look to the future with a recovering West Africa and a strengthened international medical community.

Conflict of interest statement

We declare that we have no conflict of interst.

References

[1] Passi D, Sharma S, Dutta SR, Dudeja P, Sharma V. Ebola virus disease (The killer virus): another threat to humans and bioterrorism: brief review and recent updates. *J Clin Diagn Res* 2015; **9**: LE01-LE8.

[2] Centers for Disease Control and Prevention. *Timeline: CDC's response to Ebola*. March 2014 July 2015 [Online]. Available at: http://www.cdc.gov/about/ebola/timeline.html [Accessed on 12 July 2016]

[3] World Health Organisation. WHO | Statement on the 9th meeting of the IHR Emergency Committee regarding the Ebola outbreak in West Africa. [Online]. Available from: http://apps.who.int/mediacentre/news/releases/2016/ebola-liberia/en/index.html. [Accessed on 12 July 2016].

[4] World Health Organisation. *WHO | end of ebola transmission in Guinea*. 2016 [Online]. Available from: http://apps.who.int/mediacentre/news/releases/2016/ebola-guinea/en/index.html [Accessed on 12th July 2016]

[5] World Health Organisation. *WHO | End of the most recent Ebola virus disease outbreak in Liberia*. 2016 [Online]. Available from: http://apps.who.int/mediacentre/news/releases/2016/ebola-liberia/en/index.html [Accessed on 12 July 2016]

[6] Andreas A, Binoun AEC, Kruzliak P, Egom EE. Is there a way out for the 2014 Ebola outbreak in Western Africa? *Asian Pac J Trop Med* 2015; **8**(10): 773-778.

[7] Centers for Disease Control and Prevention. *Ebola outbreak in West Africa – case counts*. 2014 [Online]. Available from: http://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/case-counts.html [Accessed on 12 July 2016]

[8] Centers for Disease Control and Prevention. Cost of the Ebola Epidemic [Online]. Available from: https://www.cdc.gov/vhf/ebola/pdf/impact-ebola-healthcare.pdf. [Accessed on 12 July 2016].

[9] Centers for Disease Control and Prevention. CDC's Ongoing Work to contain Ebola in West Africa Flare-Ups of ebola since the control of the initial outbreak. [Online]. Available from: http://www.cdc.gov/vhf/ebola/pdf/cdcs-ongoing-work.pdf. [Accessed on 11 July 2016].

[10] Medecins Sans Frontieres. *Ebola activity update – March*. 2016 [Online]. Available from: http://www.msf.org/en/article/ebola-activity-update-march-2016 [Accessed on 12 July 2016]

[11] Centers for Disease Control and Prevention. Ebola outbreaks 2000–2014. [Online]. Available from: http://www.msf.org/en/article/ebola-activity-update-march-2016. [Accessed on 12 July 2016].

[12] Hong S, Van Kaer L. Immune privilege: keeping an eye on natural killer T cells. *J Exp Med* 1999; **190**(9): 1197-1200.

[13] Centers for Disease Control and Prevention. Interim guidance for management of survivors of Ebola virus disease in U.S. healthcare settings. [Online]. Available from: http://www.cdc.gov/vhf/ebola/healthcare-us/evaluating-patients/guidance-for-management-of-survivors-ebola.html. [Accessed on 14th July 2016].

[14] Mate SE, Kugelman JR, Nyenswah TG, Ladner JT, Wiley MR, Cordier-Lassalle T, et al. Molecular evidence of sexual transmission of ebola virus. *N Engl J Med* 2015; **373**: 2448-2454.

[15] Taylor BS, Olender SA, Tieu H-V, Wilkin TJCROI. Advances in antiretroviral therapy. *Top Antivir Med* 2016; **2016**(24): 59-81.

[16] Zumbrun E, Abdeltawab N, Bloomfield H, Chance T, Nichols D, Harrison P, et al. Development of a murine model for aerosolized ebolavirus infection using a panel of recombinant inbred mice. *Viruses* 2012; **4**(12): 3468-3493.

[17] Epstein L, Wong KK, Kallen AJ, Uyeki TM. Post-Ebola signs and symptoms in U.S. Survivors. *N Engl J Med* 2015; **373**(25): 2484-2486.

[18] Qureshi AI, Chughtai M, Loua TO, Pe Kolie J, Camara HFS, Ishfaq MF, et al. Study of ebola virus disease survivors in Guinea. *Clin Infect Dis* 2015; **61**(7): 1035-1042.

[19] Chancellor JR, Padmanabhan SP, Greenough TC, Sacra R, Ellison RT, Madoff LC, et al. Uveitis and systemic inflammatory markers in convalescent phase of ebola virus disease. *Emerg Infect Dis* 2016; **22**(2): 295-297.

[20] Kaushik A, Tiwari S, Dev Jayant R, Marty A, Nair M. Towards detection and diagnosis of Ebola virus disease at point-of-care. *Biosens Bioelectron* 2016; **75**: 254-272.

[21] Yanik AA, Huang M, Kamohara O, Artar A, Geisbert TW, Connor JH, et al. An optofluidic nanoplasmonic biosensor for direct detection of live viruses from biological media. *Nano Lett* 2010; **10**(12): 4962-4969.

[22] Daaboul GG, Lopez CA, Chinnala J, Goldberg BB, Connor JH, Unlü MS. Digital sensing and sizing of vesicular stomatitis virus pseudotypes in complex media: a model for Ebola and Marburg detection. *ACS Nano* 2014; **8**(6): 6047-6055.

[23] Dunning J, Sahr F, Rojek A, Gannon F, Carson G, Idriss B, et al. Experimental treatment of ebola virus disease with TKM-130803: a single-arm phase 2 clinical trial. *PLoS Med* 2016; **13**(4): e1001997.

[24] van Griensven J, Edwards T, de Lamballerie X, Semple MG, Gallian P, Baize S, et al. Evaluation of convalescent plasma for ebola virus disease in Guinea. *N Engl J Med* 2016; **374**(1): 33-42.
[25] Sissoko D, Laouenan C, Folkesson E, M'Lebing A-B, Beavogui A-H, Baize S, et al. Experimental treatment with Favipiravir for ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med* 2016; **13**(3): e1001967.
[26] Milligan ID, Gibani MM, Sewell R, Clutterbuck EA, Campbell D, Plested E, et al. Safety and immunogenicity of novel adenovirus type 26- and modified vaccinia ankara-vectored ebola vaccines: a randomized clinical trial. *JAMA* 2016; **315**(15): 1610-1623.
[27] Ewer K, Rampling T, Venkatraman N, Bowyer G, Wright D, Lambe T, et al. A monovalent chimpanzee adenovirus ebola vaccine boosted with MVA. *N Engl J Med* 2016; **374**(17): 1635-1646.
[28] De Santis O, Audran R, Pothin E, Warpelin-Decrausaz L, Vallotton L, Wuerzner G, et al. Safety and immunogenicity of a chimpanzee adenovirus-vectored Ebola vaccine in healthy adults: a randomised, double-blind, placebo-controlled, dose-finding, phase 1/2a study. *Lancet Infect Dis* 2016; **16**(3): 311-320.
[29] Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 trials of rVSV ebola vaccine in Africa and Europe. *N Engl J Med* 2016; **374**(17): 1647-1660.
[30] Huttner A, Dayer J-A, Yerly S, Combescure C, Auderset F, Desmeules J, et al. The effect of dose on the safety and immunogenicity of the VSV Ebola candidate vaccine: a randomised double-blind, placebo-controlled phase 1/2 trial. *Lancet Infect Dis* 2015; **15**(10): 1156-1166.
[31] Centers for Disease Control and Prevention. Sierra Leone Trial to Introduce a Vaccine against Ebola (STRIVE) Q&A. [Online]. Available from: http://www.cdc.gov/vhf/ebola/strive/qa.html. [Accessed on 14th July 2016].
[32] World Health Organisation. *WHO | Guinea: ebola vaccine trial*. 2015 [Online]. Available from: http://www.who.int/features/2015/guinea-ebola-vaccine/en/ [Accessed on 14th July 2016]
[33] World Health Organisation. *WHO | ebola vaccine phase III clinical trial, Guinea next steps*. 2015 [Online]. Available from: http://www.who.int/medicines/ebola-treatment/vax_phase3_next-steps/en/ [Accessed on 14th July 2016]
[34] World Health Organisation. WHO | WHO coordinating vaccination of contacts to contain Ebola flare-up in Guinea. [Online]. Available from: http://apps.who.int/features/2016/ebola-contacts-vaccination/en/index.html. [Accessed on 14th July 2016].
[35] World Health Organisation. *Ebola response phase 3 framework for achieving and sustaining a resilient zero*. 2015 [Online]. Available from: http://apps.who.int/iris/bitstream/10665/184693/1/ebola_resilientzero_eng.pdf?ua=1 [Accessed on 14th July 2016]
[36] Kouadio KI, Clement P, Bolongei J, Tamba A, Gasasira AN, Warsame A, et al. Epidemiological and surveillance response to ebola virus disease outbreak in lofa county, Liberia (March-September, 2014): lessons learned. *PLoS Curr* 2015; **7**; http://dx.doi.org/10.1371/currents.outbreaks.9681514e450dc8d19d47e1724d2553a5.
[37] World Health Organisation. *WHO | Looking, hopefully, towards an Ebola-free future*. 2016 [Online]. Available from: http://apps.who.int/features/2016/ebola-vaccine/en/index.html [Accessed on 14th July 2016]