Word Count: 2993 (Not including references, figures and headings)

"World Health - it's in our hands. Can we beat Ebola?"

Introduction

Ebola is a viral pathogen responsible for the Ebola virus disease characterised by haemorrhagic fever and high case fatality rates. Ebola virus was first identified in 1976 in Zaire (Now the Democratic Republic of Congo (DRC), Africa (World Health Organisation (WHO), 2015). The Ebola virus belongs to the virus family *filoviridae* and is closely associated with two other viruses in this family: *Marburgvirus* and *Cuevavirus.* There are five different species of Ebola virus that have been identified: *Zaire, Bundibugyo, Sudan, Reston* and *Taï Forest* (WHO, 2015). The most virulent strain is the Ebola Zaire variant accountable for over a dozen outbreaks between 1976-2008, with a case fatality rate of 79% (Centre for Disease Control and Prevention (CDC), 2014 cited in Camacho, 2014). The virus is zoonotic in nature, transmission occurs from wild animals to humans and spreads further by human-to-human transmission. The main animal reservoir is thought to be in fruit bats (Peacock *et al*., 2014). The Ebola virus is considered an important public health pathogen due to high fatality rates and the lack of any effective treatments or vaccines (Feldmann and Geisbert, 2011). As a result, the focus is on control strategies to prevent the spread of the virus and vaccination work is underway to treat the Ebola Virus Disease (EVD). Recently an outbreak of Ebola Zaire virus was detected in West Africa with the first case reported from Guinea in March 2014 (Baize *et al*., 2014). Guinea, Liberia and Sierra Leone were the most affected areas in this outbreak. Almost all human cases are due to the emergence or re-emergence of Zaire Ebola virus (Schanez, 2006 cited in Feldmann and Geisbert, 2011). On 8th August 2014, the WHO Director-General declared 'the West Africa outbreak a Public Health Emergency of International Concern under the International Health Regulations (2005)' (WHO, 2015). The Ebola virus disease continues to remain a plague for the population in Western Africa, with the total deaths, for the three countries calculated at 10,824 people to date (CDC, 2015). This is therefore the greatest and most complex Ebola outbreak since the discovery of the Ebola virus in 1976 (WHO, 2015). Raising awareness of the virus and community engagement in the use of control strategies is effective in preventing the spread of the outbreak. This essay will discuss give an overview of the Ebola virus disease and importantly the control strategies that agencies should ensure are in place to combat the virus. With the Ebola outbreak on '*our hands*' there is no question that World Health can beat it.

Ebola Virus

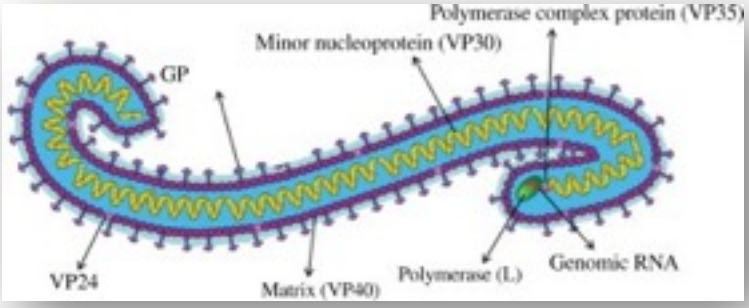

Figure 1: Illustration of structure of Ebola virus (VP: viron protein, GP: glycoprotein). This image shows the lengthy rod shaped virus and the structural components (Rajak *et al*., 2015)

The Ebola virus the causative agent in the Ebola outbreaks belongs to the virus family *filoviridae*. The Filovirusses are enveloped, non-segmented, negative-stranded RNA viruses (Figure 1). The virus is constructed of a uniform diameter of 80nm but can greatly vary in length with lengths of up to 14000nm. (Feldmann and Geisbert, 2011). The virus contains a lipid envelope with a lipid bilayer coat that provides protection to the virion (Ansari, 2014). Glycoproteins (GP) are the only viral proteins found on the envelope of the virus with the likely functions of viral attachment and entry into the host cell (Feldmann *et al*., 1999 cited in Kobinger *et al*., 2006). The Ebola virus contains a matrix layer beneath the viral membrane. This layer contains VP40 protein to maintain the structural integrity of the virus and is assumed to initiate viral budding (Klenk and Feldmann, 2004). The nucleocapsid complex is located in the centre of the virus, formed mostly by the Nucleoproteins (NP). NPs are responsible for the viral replication cycle (Konstantinov *et al*., 2012). The VP24 function is not well understood but it is known to act as an interferon antagonist (Konstantinov *et al*., 2012).The Ebola virus also possesses RNA-dependent RNA polymerase and minor proteins VP30 and VP35. The L protein is the largest viral protein in Ebola with the function of replicating the viral genome.

Symptoms

The Ebola virus disease may be asymptomatic for a period of three weeks (Williams, 2014). The incubation period is the time interval from viral infection to the onset of symptoms and is usually 2 to 21 days (WHO, 2015). People infected with the Ebola virus are not infectious until they become symptomatic. The initial symptoms present themselves in a non-specific, flu-like manner with fever, headache, fatigue, sore throat and intense muscle weakness (CDC, 2014). The symptoms begin to progress causing the person to vomit and to have diarrhoea. A macropapular rash becomes evident on the trunk and shoulders in almost half of infected individuals. The symptoms evolve into a multi-systematic disease comprising the gastrointestinal, respiratory, vascular and neurological systems. In some cases, infected individuals may experience excessive bleeding internally or externally (bleeding gums, blood in faeces, etc.) (Williams, 2014). Often leading to a fatal outcome, infected individuals show disseminated intravascular coagulation, multiple organ failure and symptoms associated with hypotensive shock ending in death.

Transmission

The reservoir for the Zaire Ebola virus is thought to be infected fruit bats of the family Pteropodidae (WHO, 2015). Leroy (2005) states that this was documented by the identification of viral RNA and antibodies in three species of fruit bats: *Hypsignathus*

monstrosus, Epomops franqueti and *Myonycteris torquataa.* The zoonotic nature of the virus allows the virus to transfer from infected animals to humans as a result of close contact with the infected animal (chimpanzees, gorillas, fruitbats, forest antelope and porcupines) or its bodily secretions (WHO, 2015) (Figure 2). The hunting culture in Africa means consumption of wildlife is the norm and this is considered a possible route of transmission for the virus into the human population. Handling and ingestion of freshly killed infected fruit bats caused an outbreak of the Zaire Ebola virus in the Democratic Republic of Congo in 2009. (Leroy *et al*., 2009). Once the Ebola virus crosses the species barrier it can then spread quickly amongst humans though unprotected direct contact with an infected person, the virus can enter through breaks and microabrasions on the skin surface. Transmission can also occur through contact with blood and other body fluids (faces, saliva, urine and vomit) as well as contaminated objects that have been associated with infected bodily secretions (Peacock *et al*., 2014). Sexual transmission of the virus has not been ruled out as viral particles can be isolated in seminal fluids of convalescent men 82 days after the onset of symptoms (WHO, 2015).

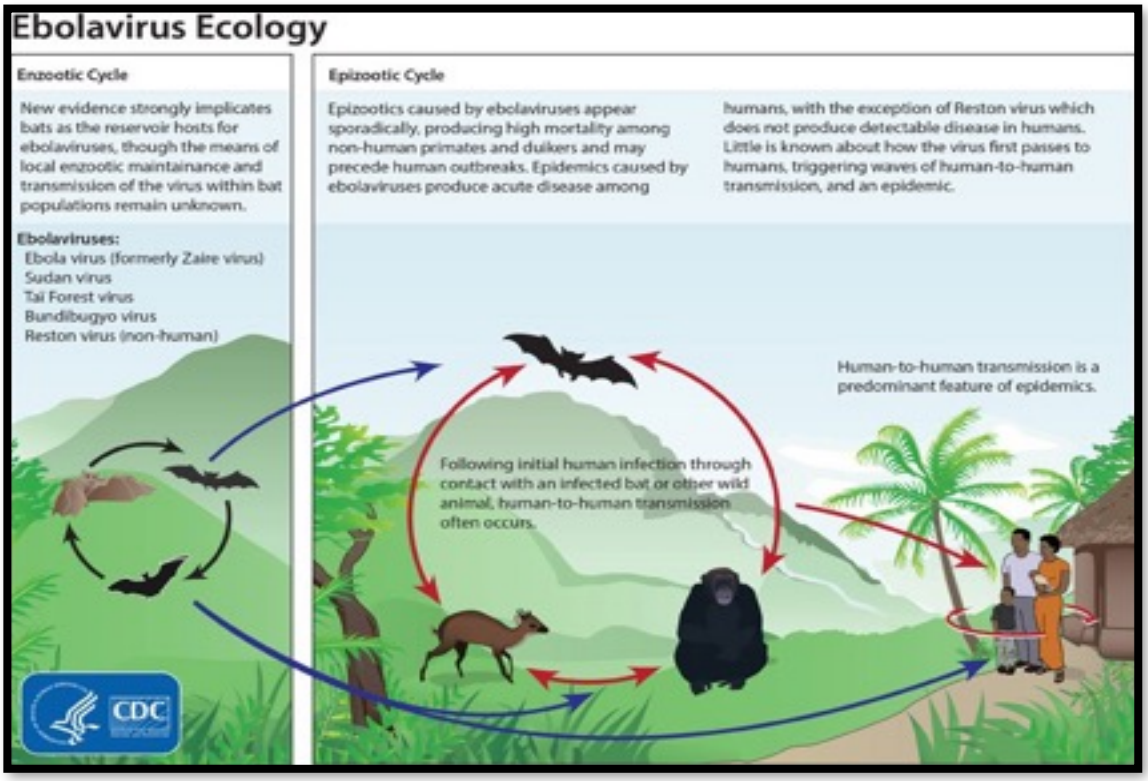

Figure 2: The diagram above illustrates the transmission cycle of the zoonotic Ebola disease depicting the transmission in wildlife and the cross of the virus from animals to humans (CDC, 2014).

Research has highlighted the profound effect hospital-based infections can play in the role of transmission (Camacho *et al*., 2014). It has not been unheard of for health care workers becoming infected with the Ebola virus whilst treating patients with suspected and confirmed Ebola virus infections. The transmission has occurred as a result of health care workers coming into close contact with the patient and not following the strict protocol (WHO, 2015). Camacho *et al*. (2014) reviewed data regarding the first Zaire Ebola outbreak in 1976, described a trend whereby the outbreak was localised around Yambuka Mission Hospital. The transmission of Ebola virus was aided through the use of contaminated syringes because only five syringes were issued each day for health care staff use. It has become

apparent that contact with deceased people infected with the Ebola virus is also an exposure route. People are infectious as long as their blood carries the virus (WHO, 2015).

Diagnosis

The diagnosis of Ebola virus relies on samples collected from patients. These samples are tested under maximum biological containment conditions as samples that potentially contain Ebola virus are a severe biohazard risk (WHO, 2015). During the first Zaire Ebola Outbreak (1976) many patients were getting misdiagnosed as the symptomology of this virus reflected that of other diseases (malaria, typhoid fever and meningitis) that were known to be common to this country. Samples were taken from infected individuals and sent to the Centre for Disease Control (CDC), where it was confirmed that these were cases of the Zaire Ebola virus. An attempt at setting up a field laboratory in the epidemic setting, during this outbreak, relied upon immunofluorescence assay (IFA) for the identification of virus but the results of this were largely unsuccessful (Towner *et al*., 2003). When the Uganda outbreak occurred diagnosis was carried out using an antigen-capture diagnostic assay along with the newly developed nested reverse transcription-PCR assay (RT-PCR). These methods proved to be a successful field diagnostic tool in the detection of viral antigens and nucleic acid in patient samples (Towner *et al*., 2003). Diagnosis of Ebola virus cannot be based on a single diagnostic method alone (Saijo *et al*., 2006) as there are inadequacies in using RT-PCR assay as in some cases readings can appear as false positive or false negatives. Both readings can be detrimental: with a false positive putting an individual in an isolation ward surrounded by others with the virus and a false negative placing a contagious individual back into the community with the potential to infect other people. Diagnosis by detection of the viral antigens is also only suitable during the early stages of illness as when a fever arises the virus circulates the blood. RT-PCR and antigen capturing techniques will be unable to confirm a diagnosis prior to the onset of symptoms. RT-PCR and antigen detection ELISA remain the primary techniques used in diagnosis of Ebola virus (Feldmann and Geisbert, 2011). Serological techniques by identifying specific IgM and IgG antibodies are generally used in the screening of patients in the late stages of the illness (Saijo *et al*., 2006).

Treatment

Unfortunately, there is currently no licenced treatment or vaccine available for Ebola virus disease. Treatment involves a myriad of supportive care consisting of rehydration with oral or intravenous fluids; maintenance of blood pressure and oxygen levels; nutritional support and treatment of specific symptoms. A range of probable treatments including blood products, immune therapies and drug therapies are at present being evaluated (WHO, 2015). An anti-viral drug, favipiravir is a pyrazine carboxamide derivative that acts on the virus inhibiting the process of viral replication. This drug has been effectively tested on laboratory infected mice (Oesterich *et al*., 2014). At present, favipiravir still remains in phase

II trials. JK-05 is a drug containing the viral RNA polymerase which acts by inhibiting viral replication. This drug therapy has passed pre-clinical and clinical safety trials but is generally only used in acute emergency situations (Gebre *et al*., 2014). Plans for distributing this drug in West Africa have not yet been announced (Kilgore *et al*., 2008). In addition, BCX44430 an adenosine analogue antiviral has received attention in the hope that it may become a treatment in the fight against Ebola virus. This drug functions by inhibiting RNA polymerase through the insertion of new viral RNA which causes chain termination. This drug was tested on mice and gunniea pig models and it showed clinical protection following viral exposure (Kilgore *et al*., 2008). Zmapp is a drug combination consisting of three humanised monoclonal antibodies that have originated from Ebola virus infected mice, and have subsequently been expressed in transgenic tobacco plants. Zmapp has completed phase I trials and phase II trials began in February 2015. The use of antibodies from individuals who have survived the Ebola virus disease, are passed onto infected individuals. Human convalescent blood or serum containing high levels of effective antibodies are considered to give passive immunisation but there remain controversies about the success of using convalescent therapies.

In addition to the above, a prolonged treatment to cure Ebola virus is currently under investigation. Previous attempts to develop a vaccine for Ebola virus was hindered due to pharmacological companies showing little interest in the disease which was considered rare (Gebre *et al*., 2014). Since March 2014 various companies have ventured on the journey to develop a vaccine to combat the largest outbreak of Ebola. To date there are currently two vaccine candidate's cAd3-EBOV (cAd3) and rVSVG-EBOV-GP (rVSV) both under evaluation. The Sierra Leone Ministry of Health and Sanitation and the CDC are uniting in the task of introducing the candidate Ebola vaccine rVSV for testing in infected individuals (CDC, 2015). It is hoped that a safe and effective vaccine will be available by the end of 2015 (WHO, 2015).

Prevention and Control Strategies

Control strategies for an Ebola outbreak involve numerous interventions such as case management surveillance, contact tracing, rapid laboratory diagnosis, disease surveillance community awareness and individual prevention techniques that are used to minimise the risk of infection (WHO, 2015). The US Centres for Disease Control and Prevention claim that 60% of Ebola infections in West Africa remain undiagnosed in the community increasing the potential for thousands of cases (Dhillon *et al*., 2014). Therefore, it is crucial for control measures to be created and agencies to ensure that these procedures are adhered too.

The virus being a zoonosis means that people in the epidemic area must reduce contact with wildlife to prevent transmission of the virus. Matua *et al.* (2015) argues that primary prevention of the Ebola outbreak is often impacted due to the unknown reservoir for the

virus. La Torre *et al.* (2014) claims mapping spread among the population and Ebola in wild animals could be effective in controlling the infection. Research has shown that fruit bats are the potential reservoir and the monkey and apes can carry the virus. Wild animals that have been hunted should be handled with gloves and protective clothing (WHO, 2015). The bush meat should be cooked thoroughly to avoid consumption of contaminated meat.

The exposure route is primarily human-to-human transmission, therefore reducing contact with infected persons can minimise the spread of the virus. Gloves should be used to avoid direct contact with a person or contact with infected bodily fluids. Good hygiene is fundamental especially when in an epidemic area, effective hand washing should be carried out regularly (WHO, 2015). Sexual transmission of the virus is not known, but the presence of the virus in seminal fluid means that this transmission route should not be overlooked. Persons recovering form Ebola should refrain from all types of sexual intercourse for at least three months after the onset of symptoms (WHO, 2015).

Early detection of the virus is crucial as it allows effective isolation of individuals as well as contact tracing. Dhillion *et al*. (2014) argues the case for effective isolation in controlling the outbreak by estimating each Ebola patient transmits the virus onto 1 - 8 other people resulting in an exponential growth in the number of cases of the disease. Identifying people that have come into contact with those infected individuals should result in them having their health monitored for 21 days in order to identify early onset of the virus allowing prompt isolation and treatment (WHO, 2015). The process of contact tracing has proved a useful approach in controlling the Ebola virus in previous outbreaks (Dhillon *et al*., 2014).

It is important that health-care workers treat all patients with probable or suspected Ebola virus cautiously. Working in an epidemic setting it is crucial that health-care workers follow the strict protocols in place for the use and maintenance of personal protective equipment (PPE). The necessary PPE includes protective clothing and respirators (Feldman and Geisbert, 2011) (Image 1). Countless cases have occurred in Ebola outbreaks whereby health care workers have become infected e.g., a total of 861 cases to date (ECDPC, 2015). The use of PPE acts as a barrier in reducing contact with infected patients, blood and bodily fluids. Careful handling of materials and proper disinfection of surfaces are required in health care settings to minimise the spread of the virus. Failure to control Ebola outbreaks in Western Africa is often fundamentally due to the poor infrastructure that encompasses the health-care system. Hospital settings have often been perceived to infect rather than cure the virus due to their poor sanitation and lack of equipment (Baize *et al*., 2014). One basic requirement that is associated with outbreak prevention comprises the provision of sterile equipment (Feldman and Geisbert, 2011).

Image 1: Trained personnel wearing protective equipment in the removal of an Ebola patient (Cooper, 2014).

Human-to-human transmission of the virus still occurs even when the infected person is deceased. Approximately 20% of new Ebola infections occur during burials of deceased Ebola infected individuals (WHO, 2014). Establishing a safe burial practice involves no direct contact with the corpse and the burial being carried out by trained personnel wearing protective equipment (Matua *et al*., 2014). WHO have created a 'Safe and Dignified Burial Protocol' in order to comply with the religious beliefs and cultural traditions as well as ensuring that the transmission of the virus is minimised.

Knowledge is a powerful solution in controlling an outbreak by minimising the transmission of the infection. When an outbreak of a disease occurs, knowledge of the causative agent is not only useful to professionals that are handling the situation but it is important for those in the community to be aware of the disease symptomology and the preventative measures that individuals can take to minimise their chance in contracting the virus and passing it on to others. Matua *et al*. (2015) claims good understanding of public views about Ebola is a preventive strategy. Thus, it is important that governments, organisations and the health care workers are aware of the public perspective on the outbreak and aid further understanding as a means of support and encouragement for individual engagement in preventing the spread. La Torre *et al.* (2014) states that 'well informed communities can reduce the main ways of spreading infection'. In the absence of effective treatment and a vaccination, raising awareness is key in reducing the spread of the Ebola virus disease and its associated high levels of mortality.

Conclusion

The re-emergence of the Ebola virus and the height of the current outbreak has taken many people by surprise. It once was considered a rare disease but at present it continues to plague Western Africa. Vaccination programmes were previously disrupted due to the lack of interest in what was considered a ‘rare disease’. It has now turned into a race against time with several antiviral drugs and vaccine candidates undergoing clinical trials. It is ill-fated that such a large outbreak has struck a less developed continent. The unstable infrastructure along with the poverty makes it hard for a strong health care system to be established to cope with the burden of a large outbreak. The virus is only transmitted through direct contact with those infected (including the deceased), their bodily fluids and contaminated objects that have come into contact with patients. It is thought that the virus cannot be transmitted via water or air so restricting the spread of the virus should be more achievable when detected early and relevant control measures are taken. Ebola has become the forefront of World Health in the past year and a combination of control measures should be put in place. Controlling the disease involves early diagnosis, isolation, contact tracing and health surveillance within the local communities. Preventing the disease consists of a good practice of health and hygiene through protective clothing, avoiding contact with infected individuals and safe burials. Raising awareness in the community is a fundamental factor in preventing and controlling the outbreak. Individuals becoming knowledgeable of the disease and the protective measures that they can take can only prevent Ebola from being on ‘their hands’. It is hopeful that a vaccine may be approved by the end of 2015 but until a suitable vaccine candidate is approved control and preventative measures coinciding with community engagement in these efforts can help the fight against Ebola.

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