



**MATHEMATICAL MODELLING OF EBOLA VIRUS DISEASE IN SERENJE
DISTRICT WITH A LUSAKA DISTRICT OVERSPILL, ZAMBIA**

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**A dissertation submitted to the University of Zambia in partial fulfillment of the
requirements for the award of the degree of Master of Science in
One Health Analytical Epidemiology**

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DECLARATION

I, VELU MILOMBA RACHEL, do hereby declare that the content of this dissertation is my own work and has not been submitted to another University or institution for any award or degree.

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CERTIFICATE OF APPROVAL

This dissertation submitted by VELU MILOMBA RACHEL is approved as partial fulfillment of the requirements for the award of the degree of Masters of Science in One Health Analytical Epidemiology at the University of Zambia.

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MEMORIAM

In loving memory of my mother Josephine Gunumana, may her soul rests in peace.

DEDICATION

This dissertation is dedicated to my loving father Narcisse Velu, my brothers and sisters Dodo Velu, Taty Velu, Lucienne Magazini Velu, Doris Velu, Dady Velu, Frieda Frozone Velu, Joel Velu, Dr. Francis Mpipa, Dr. Anne Lepina, Mrs Scolatique Manika, for their endless love, support and encouragement.

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ABSTRACT

The Ebola virus causes an acute, serious illness, which is often fatal. Despite improved control measures, Ebola Virus Disease (EVD) remains a public health concern in endemic areas as well as in unaffected areas. Ecological niche-mapping places Zambia within the ecological niche of filovirus infections. Furthermore, the annual migration of the straw-coloured fruit bats (*Eidolon helvum*) to Kasanka National Park in Serenje District puts Zambia at high risk of exposure to an outbreak of EVD. Thus, a mathematical transmission model using the Susceptible-Exposed-Infectious-Recovered (SEIR) epidemic model was developed to predict spread patterns of a potential EVD outbreak in Serenje and Lusaka districts as well as to determine the influence of intervention measures in disease spread. Following the introduction of one infected person into the rural district of Serenje, the model predicted that without any interventions an epidemic would reach its peak by day 46 and, should the disease spread to the urban district of Lusaka, it would reach its peak by day 40. The epidemic would have a devastating impact in the community, mostly in Lusaka District than in Serenje District with 42.4 percent and 34.4 percent of the population affected, respectively. The model further predicted that with implementation of control measures (community education and reduction of the burial time) the peak days would be delayed by 25 days and 22 days, and the number of EVD cases would be reduced by 10.5 % and seven percent in Serenje and Lusaka districts, respectively. Nevertheless, the intervention would extend the length of the outbreak by almost twice in Lusaka District compared to Serenje District. The overall effect of interventions would be more optimal in Serenje District than Lusaka District. Our model also predicted that community education would have the largest effect on the reduction in the number of cases during the outbreak compared to the effect of reducing the burial time of the deceased person. Preventive measures based mostly on community education should always be implemented to avoid such an outbreak. Furthermore, a good EVD preparedness plan should always be in place for effective risk management and control.

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LIST OF ABBREVIATIONS

BDBV	: <i>Bundibugyo ebolavirus</i>
CDC	: Centers for Disease Control and Prevention
CMV	: Cytomegalovirus
CSO	: Central Statistical Office
CTC	: Clinical Trial Center
CVD	: Center for Vaccine Development
DRC	: Democratic Republic of Congo
EBOV	: <i>Zaire ebolavirus</i>
EVD	: Ebola Virus Disease
FX06	: Fibrin-derived peptide
GMP	: Good Manufacturing Practice
GSK	: GlaxoSmithKline
HAT	: Human African Trypanosoma
Hep C	: Hepatitis C
Hep B	: Hepatitis B
IFA	: Indirect Immunofluorescence Antibody
IFN	: Interferon
IgG	: Immunoglobulin G

IgM	: Immunoglobulin M
IHC	: Immunohistochemistry
IL-10	: Interleukin-10
IL-2	: Interleukin-2
KEMRI	: Kenya Medical Research Institute
MOH	: Ministry of Health
mRNA	: Messenger Ribonucleic Acid
NIAID	: National Institute of Allergy and Infectious Diseases
NIH	: National Institutes of Health
ODES	: Systems of Ordinary Differential Equations
PCR	: Polymerase Chain Reaction
PHAC	: Public Health Agency of Canada
PHEIC	: Public Health Emergency of International Concern
R_0	: Basic Reproductive Number
RNA	: Ribonucleic Acid
RSTV	: <i>Reston ebolavirus</i>
RSV	: Respiratory Syncytial Virus
RT-PCR	: Reverse Transcriptase - Polymerase Chain Reaction
SEIR	: Susceptible-Exposed-Infectious-Recovered

SIR : Susceptible-Infectious-Recovered

SIRS : Susceptible-Infectious-Recovered-Susceptible

SUDV : *Sudan ebolavirus*

TAFV : *Tai forest ebolavirus*

TNF- α : Tumor Necrosis Factor Alpha

TSA : Trend-Surface Analysis

UK : United Kingdom

USA : United States of America

WHO : World Health Organization

WRAIR : Walter Reed Army Institute of Research

CHAPTER ONE

1.0 INTRODUCTION

Ebola virus disease (EVD) is a severe, often-fatal zoonotic disease associated with high morbidity and mortality in humans and nonhuman primates (Muyembe *et al.*, 2012). It is caused by a single-stranded RNA virus of negative polarity, belonging to the order *Mononegalevirales*, family *Filoviridae* and genus *Ebolavirus* (Bukreyev *et al.*, 2014). Since the first case of Ebola virus was discovered in 1976, the virus has re-emerged several times in central Africa, a region considered to be endemic for *ebolavirus* (Feldmann *et al.*, 2011). Approximately 27,750 cases of EVD, including 11,279 deaths were reported during December, 2013 and July, 2015 in West African countries (WHO, 2015).

Despite considerable effort made, determination of the natural reservoir host species and the transmission pattern from the reservoir to humans or other primates remain a challenge (Feldmann *et al.*, 2011).

The natural reservoir host species of *ebolavirus* have not been determined (Feldman, 2014). However bats have been suspected as reservoir hosts due to molecular and serological evidence of Ebola virus infection (Leroy *et al.*, 2005; Pourrut *et al.*, 2007; Hayman *et al.*, 2010; Olival *et al.*, 2013).

Africa is the most affected continent by the disease, with at least 25 documented outbreaks since the disease was first reported in 1976 (Changula *et al.*, 2014), including the massive outbreak in West Africa in 2014, which resulted into a humanitarian crisis (Farrar and Piot, 2014). The disease has been reported in Sudan, Democratic Republic of Congo (DRC), Gabon, Republic of Congo, Uganda, Ivory Coast, Guinea, Sierra Leone, Nigeria, Mali, Senegal and Liberia (WHO, 2014).

Despite improved control measures, the disease remains a serious public health risk in African regions where recurrent outbreaks have been observed, as well as in previously uninfected areas (Changula *et al.*, 2014). This is the case of the Republic of Zambia, where the disease has not been reported. The annual migration of straw-coloured fruit bats (*Eidolon helvum*) to Kasanka National Park in Serenje District puts Zambia at high risk of exposure to *ebolavirus* or an outbreak of EVD (Changula *et al.*, 2014). The *Eidolon helvum* are migratory fruit bats with annual migration from equatorial Africa to central Zambia, between October and January, with an estimated colony size of five – ten million bats (Richter and Cumming, 2006).

Seroepidemiological studies have shown that these bats are regularly exposed to ebolaviruses; even though no ebolavirus has ever been isolated (Hayman *et al.*, 2010, Ogawa *et al.*, 2015). There have also been at least six outbreaks (CDC, 2014) of the disease in the neighboring DRC; increasing the risk of the disease spreading over into Zambia.

Furthermore, ecological and zoonotic niche modeling shows filoviruses are predicted to be found in Zambia, making the possibility of spread of the disease a real risk (Peterson *et al.*, 2004; Pigott *et al.*, 2014). Given this perceived risk of the disease entering Zambia, it is imperative that the country prepares plans for prevention of entry of the disease and management if such an outbreak was to occur. Mathematical models depicting such a scenario must be developed (Keeling *et al.*, 2009) using known data about the disease. Such a model would also assist authorities in the estimation of the amount of resources that could be required in case of an occurrence of any EVD epidemic. This study therefore aims at using a hypothetical situation to model the spread of the disease in Serenje and Lusaka districts.

1.1 Statement of the problem and study justification

Ebola virus disease has emerged in different countries in Africa including DRC, Gabon, South Sudan, Ivory Coast, Uganda, Republic of Congo and South Africa (imported) and recently Sierra Leone, Nigeria, Guinea, Mali, Senegal and Liberia.

This disease has never been reported in Zambia. However, Serenje District in Central province of Zambia, which shares borders with DRC, each year, receives millions of migratory fruit bats, which have been shown to be regularly exposed to *ebolavirus* and also ecological niche-mapping placed Zambia within the ecological niche of filovirus infection.

Given the above information, there is a likelihood and greater probability that if conditions of disease occurrence tip favorably for a possible outbreak, there is a real threat that Ebola Virus Disease can actually occur in this area of Zambia.

Therefore, there is a real need for Zambia and other countries or areas at risk to have an idea of the magnitude of public health emergency that can result from such an epidemic and make emergency preparedness plans.

1.2 Research question

Can mathematical models be used to predict spread patterns of EVD in Serenje and Lusaka districts of Zambia?

1.3 Objectives

1.3.1 Main objective

This study was aimed at developing a mathematical simulation of EVD spread in Serenje and Lusaka districts that could inform disease control planning in the development of strategies for prevention, management and control of the disease in the event of an outbreak.

1.3.2 Specific objectives

- (a) To predict possible spread patterns of EVD using the Susceptible-Exposed-Infectious-Recovered (SEIR) epidemic model in Serenje and Lusaka districts.
- (b) To determine the influence of intervention measures in disease spread.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Description of Ebola virus

Ebola virus, named after a river in DRC (formerly Zaire), where it was first recognized, is the causative agent of Ebola virus disease (EVD), a severe and fatal disease of humans and non-humans primates (Muyembe *et al.*, 2012). The virus is one of three genera of RNA-viruses of the family *Filoviridae*, namely *Ebolavirus*, *Marburgvirus* and *Cuevavirus* (Bukreyev *et al.*, 2014).

Ebola virus is divided into five species namely: *Zaire ebolavirus* (EBOV), *Sudan ebolavirus* (SUDV), *Tai forest ebolavirus* (TAFV), *Bundibugyo ebolavirus* (BDBV), all of which cause human disease and the *Reston ebolavirus* (RSTV) that has never been reported in Africa and causes disease in non-human primates as well as pigs, in America (Barette *et al.*, 2009; Morikawa *et al.*, 2007; Bray, 2003; Jahrling *et al.*, 1990).

EBOV is the most virulent with case fatality ranging between 70 percent and 90 percent, followed by SUDV (50-55 percent) and BDBV (40-48 percent) (Lefebvre *et al.*, 2014). TAFV caused deaths of chimpanzees and a single human case of an acute non-lethal infection has been reported in Ivory Coast in 1994 (Legueno *et al.*, 1995).

The virions of filoviruses have particular bacilliform morphology with filamentous particles of 800 nm to 1,000 nm in length and a uniform diameter of 80 nm, hence the name of the family *Filoviridae* (Figure 2. 1).

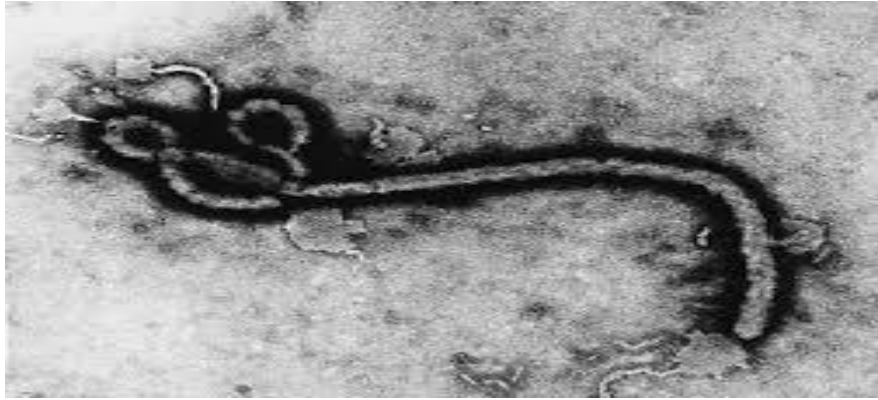


Figure 2.1 Filovirus virion (Source: CDC, 2005)

The virus possesses a helicoidal capsid, an envelope and seven major structural proteins. The genome is composed of a single negative strand of linear RNA which requires a polymerase for transcription before replication (Feldman *et al.*, 1996).

2.2 Epidemiology

2.2.1 Geographical distribution

The geographical distribution of filovirus disease-spread seems to be generally across the humid Afro-tropics where the disease appears to be endemic with EVD being reported in the humid central and western rain forests and Marburg virus disease in the more open dry areas of eastern and south central Africa (Groseth *et al.*, 2007; Peterson *et al.*, 2004). However, one species of *Ebolavirus*, RSTV has been reported outside Africa, in the Philippines and China (Negredo *et al.*, 2011; Towner *et al.*, 2008).

African countries that have reported the disease to-date are Sudan, DRC, Uganda, Ivory Coast, Gabon, Republic of Congo, Liberia, Nigeria, Sierra Leone and Guinea (Figure 2.2) (WHO, 2014). The virus has been imported out of Africa into the United States of America, Europe and Asia (WHO, 2014). From an observational standpoint, Peterson *et al.* (2004) noted that viruses and subtypes from particular geographic areas cluster together

phylogenetically, even when occurrences from different years were studied. This is the case of outbreak sites for EBOV and TAFV which are the same ecologically, and from the point of view of phylogenetic, there are sister taxa. SUDV is distinct genetically and ecologically from other species (Peterson *et al.*, 2004).

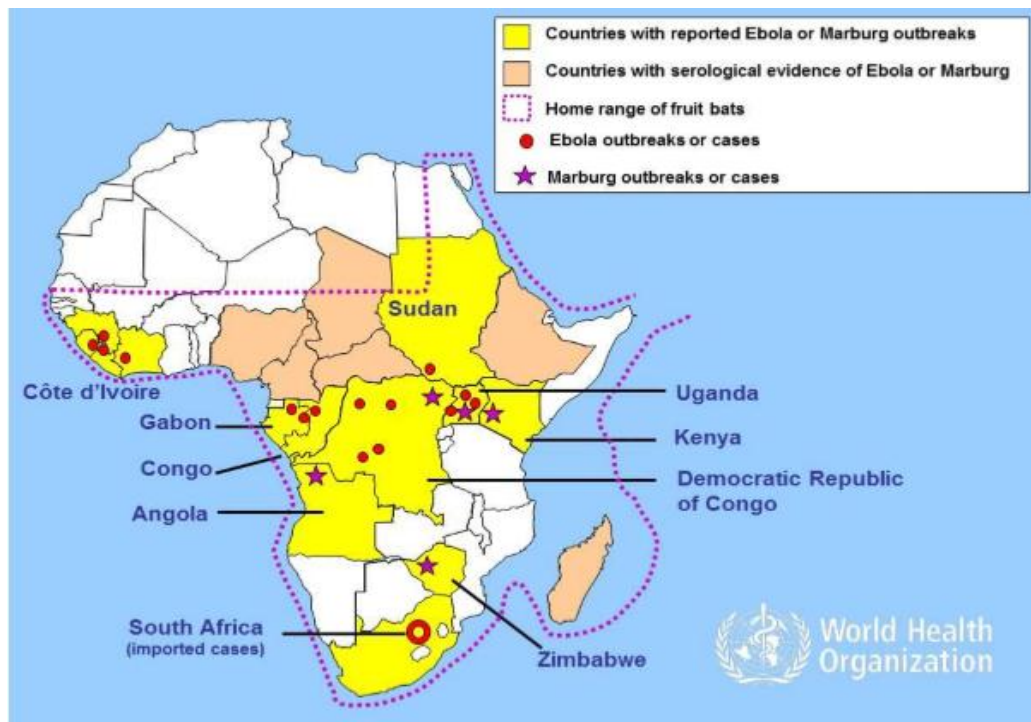


Figure 2.2: Geographical distribution of EVD and Marburg virus disease outbreaks in Africa 1967-2014 (Source: WHO, 2014).

2.2.2 Current and past outbreaks

(a) 2014-2015 West Africa outbreak

In March 2014, the World Health Organization (WHO) reported a major EVD outbreak in Guinea (Baize *et al.*, 2014). The outbreak later spread to the neighboring countries of Sierra Leone, Nigeria, Senegal and Mali. It is the largest Ebola outbreak ever documented, and the first recorded in the region for which the WHO Director General declared a Public Health Emergency of International Concern (PHEIC) and also grade 3 emergency under the WHO

emergency response framework. At the time of writing this thesis, the outbreak was still going on with some reported cases in Liberia (WHO, 2015).

(b) 2014 Ebola virus imported to outside of West Africa

As of 15 October 2014, at least 14 EVD cases were treated outside of Africa in the 2014 West Africa outbreak. Most of these cases involved health and aid workers who contracted Ebola in West Africa and were transported back to their home countries for medical care (Bogoch *et al.*, 2014). Countries involved in this importation included the United States of America, Spain and the United Kingdom (Bogoch *et al.*, 2014).

(c) 1994 to 2014

The first outbreak of EVD was reported simultaneously in DRC (formerly Zaire) and Sudan in 1976. After a long period of silence, the virus reappeared in 1994 in Gabon. Since 1994, the frequency of outbreaks has increased in Africa (Changula *et al.*, 2014). As of now, the second major outbreak of EVD due to EBOV infections occurred in DRC in 1995, affecting and killing 315 persons, most of whom were health workers (Pigott *et al.*, 2014). Uganda, an East African country had an outbreak of EVD involving SUDV, which affected 425 people and killed 224 in 2012 (Mbonye *et al.*, 2012).

The Republic of Congo notified of an outbreak of EVD in 2003, affecting 143 people and killed 128 (Formenty *et al.*, 2003).

Between May and November, 2007, an outbreak of EVD occurred in Luebo district, in the Occidental Kasai Province of DRC. This outbreak is reported to have resulted from a direct exposure to fruit bats (Leroy *et al.*, 2009).

In November, 2007, the Ministry of Health of Uganda confirmed an outbreak of EVD in the district of Bundibugyo during which a new strain of *Ebolavirus*, named Bundibugyo virus

(BDBV) was discovered (Towner *et al.*, 2008). This new strain affected 149 people of which 37 died (Mbonye *et al.*, 2012).

In 2012, the BDBV species caused an outbreak in the Oriental Province of DRC, affecting 15 people with nine mortalities (CDC, 2012).

More recently, in 2014 an outbreak of EVD occurred in the Equateur Province of the DRC, with a total of 69 cases and 49 deaths. The viral strain isolated from this outbreak was different from the strain isolated in the 2014 West Africa EVD outbreak (Maganga *et al.*, 2014).

(d) 1976 and 1979 Outbreaks

The first outbreaks of EVD occurred simultaneously in DRC and Sudan in 1976. The case fatality rates were 88 percent and five percent, respectively. The two outbreaks were caused by two different strains, EBOV for the DRC outbreak and SUDV for the Sudan outbreak (Muyembe *et al.*, 2012). In 1979, another outbreak of EVD occurred in South Sudan with 34 cases and 22 deaths. The viral strain was SUDV (Baron *et al.*, 1983).

2.3 Host range and susceptibility

Fruit bats are considered to be the natural host of the Ebola virus, as a result, the geographical distribution of Ebola virus may overlap with the range of the fruit bats (Leroy *et al.*, 2005). Ebola virus can infect human and several other species of animals including various monkey (*Macaca Fascicularis*) species, chimpanzees (*Pan troglodytes*), gorillas, baboons (*Papio*), dogs (*Canis lupus familiaris*), pigs (*Sus Scrofa Scrofa*) and duikers (*Sylvicapra grimmia*) (Allela *et al.*, 2005). The Ebola virus genome was detected in two species of rodents and one species of shrews living in forest border areas, raising the possibility that these animals may be intermediary hosts (Morvan *et al.*, 2000). A survey of small vertebrates captured during the

2001 and 2003 outbreaks in Gabon found evidence of asymptomatic infection in three species of fruit bats (*Hypsignathus monstrosus*, *Epomops franqueti*, and *Myonycteris torquata*) (Leroy *et al.*, 2005).

There have been various studies, focusing on the evidence that fruit bats are probably the reservoir of the virus (Pigott *et al.*, 2014; Ogawa *et al.*, 2015).

2.4 Mode of transmission

The Ebola virus is introduced into the human population through close contact with the blood, secretions, organs or other bodily fluids of infected animals. In Africa, contraction of infection has been often documented through the handling of infected monkeys found ill or dead in the rain forest (Leroy *et al.*, 2004). The virus then spreads in the community through human-to-human transmission (Figure 3), with infection resulting from direct contact (through broken skin or mucous membranes) with the blood, secretions, organs or other bodily fluids of infected people, and indirect contact with environments contaminated with such fluids (Bausch *et al.*, 2007).

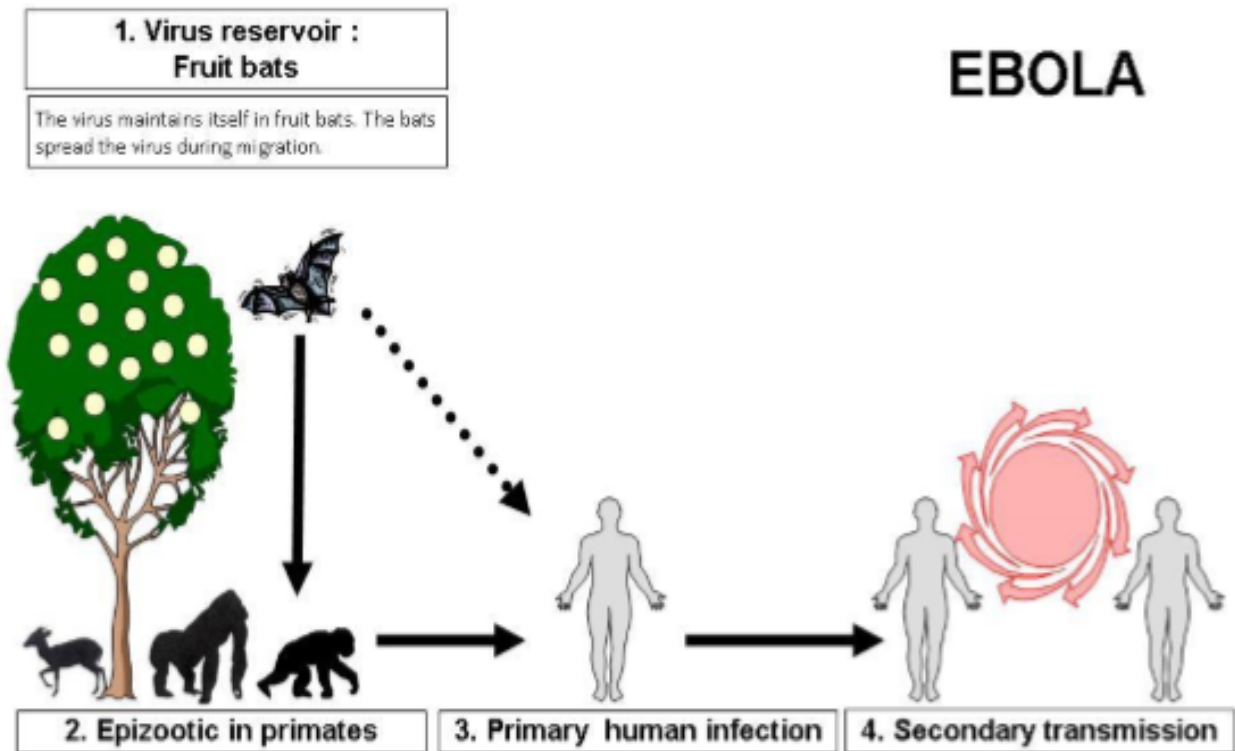


Figure 2.3: Hypothesis of Ebola virus transmission at the human-animal interface. Source: WHO, 2014

2.5 Pathogenesis

Most of what is known about *Filovirus* pathogenesis comes from experiments in laboratory animals, principally non-human primates, which develop a rapidly lethal illness believed to closely resemble the human disease (Bray *et al.*, 2002). The severe disease caused by Ebola virus infection can be attributed to three main factors: (1) rapid viral replication, (2) host immune suppression induced by the virus, and (3) vascular dysfunction. Recent data suggests that the central player in the pathogenesis of filovirus infections may be the infected macrophage (Geisbert *et al.*, 2003; Hartman *et al.*, 2010).

According to Sullivan *et al.* (2003), during infection, there is evidence that both host and viral proteins contribute to the pathogenesis of EVD. Increases in the levels of inflammatory cytokines, IFN, interleukin-2 (IL-2), IL-10 and tumor necrosis factor alpha (TNF- α) have

been associated with fatality from EVD. Moreover, in-vitro experiments demonstrated that TNF- α released from filovirus-infected monocytes and macrophages increased the permeability of cultured human endothelial cell monolayers (Feldmann *et al.*, 1996). However, other reports have observed an association between elevated levels of IFN-mRNA and protection from infection, and a protective effect of IFN. Whether the effects of cytokines are protective or damaging may depend not only on the cytokine profile but also may represent a delicate balance influenced by the route and titer of incoming virus as well as factors specific to the individual host immune response (Sullivan *et al.*, 2003).

It has been shown that survivors of EVD develop immunoglobulin G (IgG) antibodies mainly against viral nucleoprotein early in the course of illness, thereafter; the cytotoxic T cells are activated (Sullivan *et al.*, 2003). In contrast, terminally ill patients never develop IgG antibodies, and only one-third of these patients mount a weak IgM antibody response (Paessler *et al.*, 2013).

2.6 Disease manifestation

The incubation period for Ebola virus infection is usually five to seven days, but may exceed two weeks. Illness is abrupt in onset, with fever and chills, headache, muscle pain, arthralgias, myalgia, hiccups, nausea, vomiting, abdominal pain and diarrhea, in the second phase of the illness (Table 2.1). Respiratory symptoms, such as cough, are rare (Chertow *et al.*, 2014).

All victims display some degree of impairment of blood coagulation. The signs usually consist of conjunctival hemorrhages, easy bruising, failure of venipuncture sites to clot, and the presence of blood in the urine or feces; usually occur in the last phase of the illness (Table 1). Massive bleeding is much rarer than popular accounts suggest (Kortepeter *et al.*, 2011; Baize *et al.*, 2014). It is generally limited to the gastrointestinal tract. The onset of shock is heralded by severe nausea and vomiting, prostration, tachypnea, anuria and a fall in body

temperature. Death usually occurs six to nine days after the onset of illness (Bray *et al.*, 2003).

Table 2.1 Clinical features of EVD

Phase of illness	Time since symptoms onset	Clinical features
Early febrile	0-3 days	Fever, malaise, fatigue, body aches. Primary: epigastric pain, nausea, vomiting, diarrhea.
Gastrointestinal	3-10 days	Associated: persistent fever, asthenia, headache, conjunctival injection, chest pain, abdominal pain, arthralgia, myalgia, hiccups, and delirium.
Shock or recovery	7-12 days	Shock: diminished consciousness or coma, rapid thread pulse, oliguria, anuria, tachypnea. Recovery: resolution of gastrointestinal symptoms, increased oral intake, increased energy.
Late complications	≥ 10 days	Gastrointestinal hemorrhage, secondary infections, meningoencephalitis, persistent neurocognitive abnormalities.

Adapted from Chertow *et al.*, 2014

2.7 Diagnosis

2.7.1 Clinical and differential diagnosis

Diagnosing EVD in an individual who has been infected for only a few days is a challenge. This is due to the fact that the early symptoms, such as red eyes and a skin rash are not exclusively specific to Ebola virus infection, but is also seen often in patients with other more commonly occurring diseases (Khan *et al.*, 1999).

Ebola virus is easily transmitted from person-to-person, particularly to medical and nursing staff and to those caring for patients. Therefore, early diagnosis and isolation of the patient are essential to prevent spread of the disease. The EVD must be suspected in all febrile patients in or travelling from areas in Africa where the virus is known or suspected to be endemic (Simpson, 1977).

The sudden onset of fever, headache and malaise, chest pain, diarrhoea and vomiting soon followed by rapid cachexia, should alert physicians to the possibility of Ebola virus infection (CDC, 2010). All information about natural history of the disease, physical examination of the patient and epidemiological background should then be carefully assessed (Bray *et al.*, 2015).

Diseases such as malaria, typhoid fever, shigellosis, cholera, leptospirosis, plague, rickettsiosis, relapsing fever, meningitis, hepatitis and other viral hemorrhagic fevers like Lassa fever, Crimean-Congo hemorrhagic fever, Rift Valley fever and Marburg hemorrhagic fever should be ruled out before a diagnosis of EVD is made (Chia *et al.*, 2015).

2.7.2 Laboratory diagnosis

Early laboratory confirmation of suspected clinical of EVD cases is essential for the timely implementation of appropriate control measures.

The following laboratory tests are used for the definitive diagnosis of Ebola virus infection:

- (a) **Enzyme-linked immunosorbent assay (ELISA)**: It is a commonly used method for the detection of any *Ebolavirus*-antigen in serum or plasma in early stage of onset (Table 2.2). It is currently the reference test because of its high specificity (Niikura *et al.*, 2001; Nakayama *et al.*, 2010);
- (b) **Reverse transcriptase - polymerase chain reaction (RT-PCR) assay**: It consists of amplifying viral RNA genome using suitable specific primers. It has high sensitivity

and specificity (Ogawa *et al.*, 2011). There is both conventional and real time RT-PCR.

- **Conventional RT-PCR:** old method including a separate cDNA synthesis step prior to PCR, agarose gel analysis of PCR products and finally either a second round of nested amplification or a southern hybridization (Sanchez *et al.*, 1999, Ogawa, 2011).
- **Real time RT-PCR:** Is a fast single-tube method consisting of a 30-min RT step which is linked to a 45-cycle PCR at 95 and 60 degrees centigrade that generates a fluorogenic signal in positive samples (Allahan *et al.*, 2001; Towner *et al.*, 2006). It requires expensive, sophisticated equipment; not practical for routine use (Ogawa *et al.*, 2011).

(c) **Virus isolation by cell culture:** Is a sensitive method for diagnosis of EVD using Vero cells (Saijo *et al.*, 2006). Detection of virus in cell culture is not as fast as antibody and RT-PCR test. Culture is less used now because of the new generation of genome sequencing methods; however it's remains the gold standard for virus detection (Bannister *et al.*, 2010).

(d) **Electron microscopy:** It works on the basis of visualization of the virus particles in specimens by providing ultrastructural details of morphology of the virus (Geisbert *et al.*, 1995; Wang *et al.*, 2011).

Table 2.2: Diagnosis of EVD according to the stage of infection

Timeline of infection	Diagnostic test available
Within a few days after symptoms begin	a. Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing b. IgM ELISA c. Polymerase Chain reaction (PCR) d. Virus isolation.
Later in disease course or after recovery	IgM and IgG antibodies ELISA
Retrospectively in deceased patients	Immuno-histochemistry testing RT-PCR, virus isolation.

Source: CDC, 2010.

Samples from patients are an extreme biohazard risk. Testing should be conducted under maximum biological containment conditions (WHO, 2015).

2.8 Treatment

2.8.1 Post exposure therapy

Standard treatment for EVD is still limited to supportive therapy that involves balancing the patient's fluids and electrolytes, maintenance of their oxygen status and blood pressure as well as management of any complicating infections (Koenig *et al.*, 2014).

Currently, available therapeutics to treat the infected patients or vaccines to prevent people from infection are under- development.

There are also several well-recognized EVD therapeutic candidates under development (Table 2.3) (Choi *et al.*, 2015).

Table 2.3: Drug clinical trials

Product / Company	Phase	Trial	Location Description
Favipiravir Fujifilm/Toyama, Japan	Phase II	By INSERM in Guinea: Conakry, Guéckedou, Macenta, Nzérékoré	Used to treat influenza. Clinical trials began in December, 2014. Preliminary data presented in February, 2015 does not permit a firm conclusion regarding efficacy and more data is required; trial continues
Brincidofovir Chimerix, USA	Phase II	By Oxford University at the ELWA 3 Clinic, Monrovia, Liberia	An antiviral used to treat CMV. Clinical trial halted and abandoned; the drug has been deprioritized for use in Ebola treatment
Zmapp MappBio USA	Phase II	By NIAID in Monrovia, Liberia	Cocktail of three monoclonal antibodies with excellent activity against Ebola virus in animal models. Phase I trials completed and Phase II efficacy trial was initiated in early February, 2015.
TKM-100802 (siRNA) Tekmira, Canada	Phase II	By Oxford University in Kerry Town, Sierra Leone	siRNA clinical trials have been scheduled to commence
BCX-4430 Biocryst, USA	Phase I	By Quotient Clinic in the UK	Broad-spectrum direct-acting nucleoside analogue. Phase I safety trial is underway. No efficacy trial is planned until safety data have been analyzed.
Interferons		By Guinea MOH in Coyah, Guinea	Approved for treatment of HepB and C and multiple sclerosis. Guinean authorities, in collaboration with Canadian scientists are launching a clinical study of an interferon in Ebola-infected patients. Details of this study are not yet available.

Amiodarone	At the Lakka and Goderich ETU in Sierra Leone	Used to treat cardiac dysrhythmia. Has been used compassionately in patients in Sierra Leone and reportedly reduced case fatality rates when compared with local historical norms. The statistical significance of this result is not known at this stage.
Atorvastatin + Irbesartan +/- Clomiphene	Sierra Leone	Approved for cholesterol control /hypertension / infertility, respectively. Used alone or in combination to treat some patients in Sierra Leone. No clinical data are available and therefore no conclusion on efficacy is possible.
FX06		Peptide for use in treating vascular leakage. Administered compassionately to two patients. No conclusions can be drawn yet.
Zmab		Non-good manufacturing practice (GMP) experimental monoclonal antibody product with no plans for GMP production. Also administered on a compassionate basis.

Source: WHO, 2015

2.8.2 Vaccination

Two potential vaccine candidates are undergoing efficacy trials in humans: ChAd3-ZEBOV developed by GlaxoSmithKline (GSK), in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID) and rVSV-ZEBOV, developed by NewLink Genetics and Merck Vaccines USA, in collaboration with the Public Health Agency of Canada.

Both of these have been shown to be safe and well tolerated in humans in Phase I clinical trials (WHO, 2015). Moreover, several other vaccine candidates have been investigated for their efficacy in animal models (Table 2.4) (WHO, 2015).

Table 2.4: Vaccine clinical trials

Product / Company	Phase	Trial Location	Dates
ChAd3-ZEBOV		By VRC at NIH, USA	September, 2014
		By Oxford University in the UK	
GlaxoSmithKline and PHAC	Phase I	By CVD in Mali	October, 2014
		At the University of Lausanne, Lausanne, Switzerland	
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase I	By WRAIR in the US	October, 2014
		By NIAID in the US	
		By CTC North GmbH in Hamburg, Germany	November, 2014
		At Albert Schweitzer Hospital in Lambarene, Gabon	
		At the University of Geneva, Geneva, Switzerland	
By KEMRI Wellcome Trust in Kilifi, Kenya	December, 2014		
At the IWK Health Center, Halifax, Canada			
Ad26-EBOV and MVAEBOV Johnson & Johnson and Bavarian Nordic	Phase I	By Janssen Institute in the UK	January, 2015
		TBD, US	
		TBD, Ghana	1Q2015
		TBD, Kenya	
		TBD, Uganda	
TBD, United Republic of Tanzania			
Recombinant protein Ebola vaccine candidate Novavax	Phase I	Australia	February, 2015

		TBD, Cameroon	
ChAd3-ZEBOV		TBD, Ghana	
GlaxoSmithKline and PHAC	Phase II	TBD, Mali	1Q2015
		TBD, Nigeria	
		TBD, Senegal	
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase III	By WHO and MOH Guinea in Conakry, Guinea	March, 2015 – Ring vaccination trial Design
ChAd3-ZEBOV GlaxoSmithKline and PHAC	Phase III	By US NIH and MOH Liberia in Monrovia, Liberia	March, 2015 – Randomized control trial design
rVSV-ZEBOV NewLink Genetics and Merck Vaccines USA	Phase III	By US CDC and MOH Sierra Leone in Freetown, Sierra Leone	March, 2015 – Stepped wedge trial Design

Adapted from Ebola QAs, WHO, 2015

2.9 Control

Currently, there are no vaccines and specific drugs for the control and management of EVD. The control of epidemics is by isolation of cases, implementation and compliance to biosafety measures in hospitals and early recognition of the epidemic (CDC, 2010). Muyembe *et al.* (2012) also stated that the cornerstone for controlling an outbreak of EVD is to interrupt the viral transmission chain. By raising awareness of risk factors for Ebola infection which include the reduction of the exposure risk to suspected wildlife animals (fruit bats, monkeys, apes, donkeys, duikers, chimpanzees), the reduction of human-to-human transmission through direct or close contact with people with Ebola symptoms, particularly with their bodily fluids

and application of outbreaks containment measures: prompt and safe burial of the dead, control tracing and quarantine system to separate the healthy from the sick.

2.10 Mathematical models

Over the past Century, various mathematical models have been used for the modeling of different diseases and their spread. This has sparked-off great interest from scientists and public health professionals (Quantum leap innovations, 2007). The modeling of infectious diseases dates back to the year 1760 when Daniel Bernoulli developed a model for the transmission dynamics of small pox (Caldwell and Douglas, 2004).

In these initial models, deterministic equations were used to model the transition rate between disease compartments. Then after, the probabilistic aspects were included to represent disease spread, which lead to a stochastic aspect of disease modeling (Abbas *et al.*, 2004).

A mathematical model is a representation in mathematical terms of the behavior of real devices and objects of life.

Mathematical models can be divided into two components, stochastic and deterministic, based on the probabilistic aspect included in the model.

2.10.1 Stochastic model

It allows the number of individuals who move between compartments to vary through chance. It is a tool for estimating probability distributions of potential outcomes by allowing for random variation in one or more inputs over time. In stochastic models, factors such as disease dynamics, the environment or demographics to the variability that exists in the system for which the disease spread is being modeled (Allen, 2008).

2.10.2 Deterministic model

In the deterministic model, individuals in the population are assigned to different subgroups or compartments, each representing a specific stage of the epidemic. Deterministic models describe what happens on average in a population. The input parameters are fixed such that the model's predictions are predetermined (Vynnycky *et al.*, 2010).

Different mathematical models have been used to model different diseases such as those caused by respiratory syncytial virus (RSV) (Stuart *et al.*, 2014), Ebola virus, bubonic plague and Rhodesian human African Trypanosomiasis (HAT). These methods include a susceptible, infectious, and recovered (SIR) model of RSV, a simple deterministic SEIR model of Ebola, the susceptible infective resistant susceptible (SIRS) models and the trend-surface analysis (TSA) models of various diseases. Others include a full deterministic model of bubonic plague (Laudisoit *et al.*, 2007), a one-step and two step logistic regression model together with a generalized linear model in case of Rhodesian HAT. Most of these models fall under the broad category of stochastic or deterministic models.

Mathematical modeling is an important tool for gaining understanding of the dynamics of the spread of infectious diseases (Lekone *et al.*, 2006). They outline the role the different parameters play in the extrapolation of the occurrence, state and progress of an outbreak, allowing prediction of future outbreaks.

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Study areas

The study used a hypothetical situation to depict the initial spread of an EVD epidemic in Serenje District (rural area) in the Central Province of Zambia, with subsequent spread of the disease to Lusaka District (urban area) in Lusaka Province of Zambia. Serenje District was purposively selected due to migration of fruit bats to the Kasanka National Park located in the district and its proximity to DRC where the disease has been previously reported (WHO, 2015).

Serenje District (Figure 3.4) lies between Longitude 30° and 31° East and Latitude 13° and 14° South in Central Province of Zambia. The human population is estimated at 166, 741 ≈170,000 (CSO, 2012). The livelihood of the majority of the population in the district is based on subsistence agriculture. The major crops grown include maize, finger millet, cassava and beans. Other sources of income include handicrafts, brewing of illicit beers and fishing.

Lusaka District (Figure 3.4) lies between Latitude 15⁰ 25' 00'' South and Longitude 29⁰ 17' 0'' East in Lusaka Province of Zambia. The total population is estimated at 1,750,000 (CSO, 2012). The majority of the population depends on non-agriculture activities for livelihoods.

The two districts are approximately 412 Kilometers apart and are connected by the great north road which facilitates the transport.

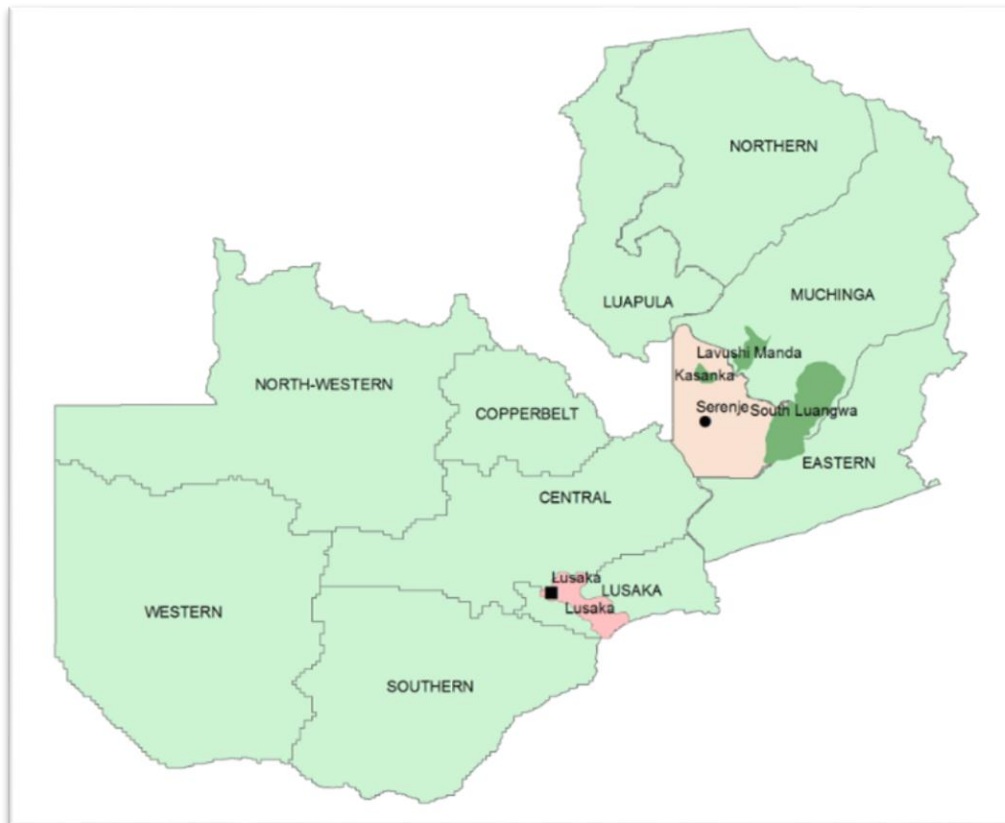


Figure 3.4: The map of Zambia showing the study areas

3.2 Study design

This relied on desk top review of information regarding migratory pathways of fruit bats that come to Serenje annually, and other related sources of information. Other available metadata and analysis has been used to fit in the final model.

To simulate disease transmission, an SEIR compartmental epidemiological model was used to describe the rate of change of transitional disease states in the human population (Figure 3.5). The SEIR has been chosen because the natural history of EVD has a short latent period of one week (Nakayama and Masayuki, 2013) and an incubation period of 2-21 days (Hartman *et al.*, 2010).

The model was set up using differential equations with a discrete time step of one day to describe the transitional states.

Using known epidemiological data about the disease, from published literature, the transitional states in the population following the introduction of one infected human was modeled. The introduction of one infected human was assumed because the direct contact with infected bats is a rare event. The disease was then assumed to spread through contact between the infected and the susceptible group. At a time t , the number of susceptible individuals depended on the number already susceptible, the number of individual already infected and the amount of contact between susceptible and infected.

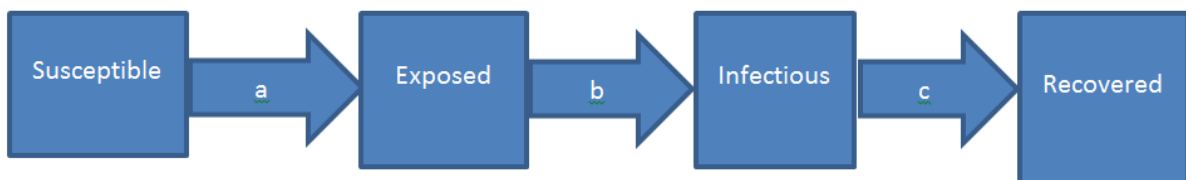


Figure 3.5 Flow diagram of a SEIR epidemic model.

Where: a = the rate of exposed, b = the rate of infection, c = the rate of recovery

3.2.1 Definition of terms used in the model

- (a) Susceptibility period: time period within which an individual has not yet been infected and but is at risk of infection.
- (b) Pre-infectious period: time period between infection and onset of infectiousness (also called “latent period”).
- (c) Infectious period: the time period during which individuals are infectious.
- (d) Recovery period: the time period during which individuals get immunity from the disease (Vynnycky and White, 2010).

- (e) Incubation period: time period between infection and onset of clinical symptoms (Vynnycky and White, 2010)
- (f) Basic Reproductive number (R_0): Average number of secondary infectious persons resulting from one infectious person following their introduction into a totally susceptible population (Vynnycky and White, 2010).
- (g) Case: Person with overt clinical signs of EVD
- (h) Study population: Total population of Serenje and Lusaka districts.

3.2.2 Model parameter inputs

The following were the model inputs parameters as obtained from literature:

- (a) Incubation period for Ebola virus disease: 2-21 days (average 14 days) (Hartman *et al.*, 2010).
- (b) Latent period: 5-7 days, average 6 days (Nakayama and Masayuki, 2013).
- (c) Infectious period: 6-16 days, average 10 days (Nakayama and Masayuki, 2013; Kortepeter *et al.*, 2011; Legrand *et al.*, 2007).
- (d) Basic reproductive number (R_0): 1.5-5 (Legrand *et al.*, 2007; Camacho *et al.*, 2014).
- (e) Life expectancy: 52 years (Zambia demographic 2014)
- (f) Age at which Ebola is contracted in a given population: average 26 years (Lu *et al.*, 2015)
- (g) Estimated basic reproductive number: $1 + \text{Life expectancy} / \text{Age at which the disease is contracted in a given population}$ (Vynnycky and White, 2010).

$$\text{Estimated } R_0 = 1 + 52/26 = 3.00$$

(h) Average rate of progression to infectious state = $\frac{1}{\text{latent period}}$ (Vynnycky and White, 2010).

(i) Average rate of recovery = $\frac{1}{\text{infectious period}}$ (Vynnycky and White, 2010).

(j) Case fatality rate (CFR) = 81% (Legrand *et al.*, 2007)

(k) Total population of Serenje District \approx 170,000 (CSO, 2010).

(l) Total population of Lusaka District \approx 1,750,000 (CSO, 2010)

3.2.3 Assumptions

The simulation was carried out with the following assumptions:

- (a) The entire population is susceptible at the start in both districts and one infectious person come in contact with the total population.
- (b) The contact parameters remained unchanged over time.
- (c) All cases which were reported experienced the disease.
- (d) No other current ongoing interventions other than those specified in the model.
- (e) Same risk of infection for all ages.
- (f) The recovered group is immune to re-infection for life.
- (g) Country population input/output (i.e. birth, immigration, emigration, natural deaths) were negligible (fixed population).
- (h) We assume the outbreak to spread from Serenje (rural area) to Lusaka (urban area) by introduction of one infectious person.

(i) Case detection rate is equal to 1.0

3.2.4 Equations used in the model

Below is a summary of equations used in the model:

$$\frac{dS(t)}{dt} = -\beta(t)S(t) \quad (1)$$

$$\frac{dE(t)}{dt} = +\beta(t)S(t) - f(t)E(t) \quad (2)$$

$$\frac{dI(t)}{dt} = +f(t)E(t) - r(t)I(t) \quad (3)$$

$$\frac{dR(t)}{dt} = +rI(t) \quad (4)$$

Where t = time unit

S = Number of susceptible persons in population

β = The rate at which two specific persons come into effective contact per unit time

E = Number of exposed or preinfectious persons in population

f = Rate of onset of infectiousness

I = Number of infectious persons in population

r = Rate at which individuals recover from being infectious

R = Number of recovered persons in population

N = Total number of individuals, $N = S + E + I + R$

Description of the above mathematical equations:

- (1) Explains the differential equation of susceptible (S) at time $t = -$ New infections. This describes the population of the susceptible group with respect to time. Susceptible individuals become exposed (preinfectious) at rate β . This means that the change in susceptible population is equal to the negative product of β , $S(t)$.
- (2) Explains the differential equation of Exposed (E) = + New infections – New infectious. The population of pre-infectious individuals begins with adding what had just been removed from the susceptible population, $\beta S(t) E(t)$. The Exposed population is reduced by becoming infectious at rate f .
- (3) Explains that the differential equation of infectious (I) = + New infectious – New removed. The population of the infected group is reduced by individuals who recover at a rate r .
- (4) Explains the differential equation of recovered (R) = + New recovered. The recovered group is increased by those that recover from the disease at a rate r .

3.3 Data analysis

The model was run in Berkeley Madonna version 8.1.18 which is a program that numerically solves systems of ordinary differential equations (ODES) and difference equations. Two models were derived, without intervention and with intervention for each district.

CHAPTER FOUR

4.0 RESULTS

4.1 Model without interventions

The model assumed the introduction of one infectious person into a total susceptible population of Serenje District (rural area = r) (Figure 4.6A) initially, with subsequent disease spreads to Lusaka District (urban area = u) (Figure 4.6B). Note that the arrows indicate the possible transitions, and the parameters that govern them. Further detailed information is provided in Appendix.

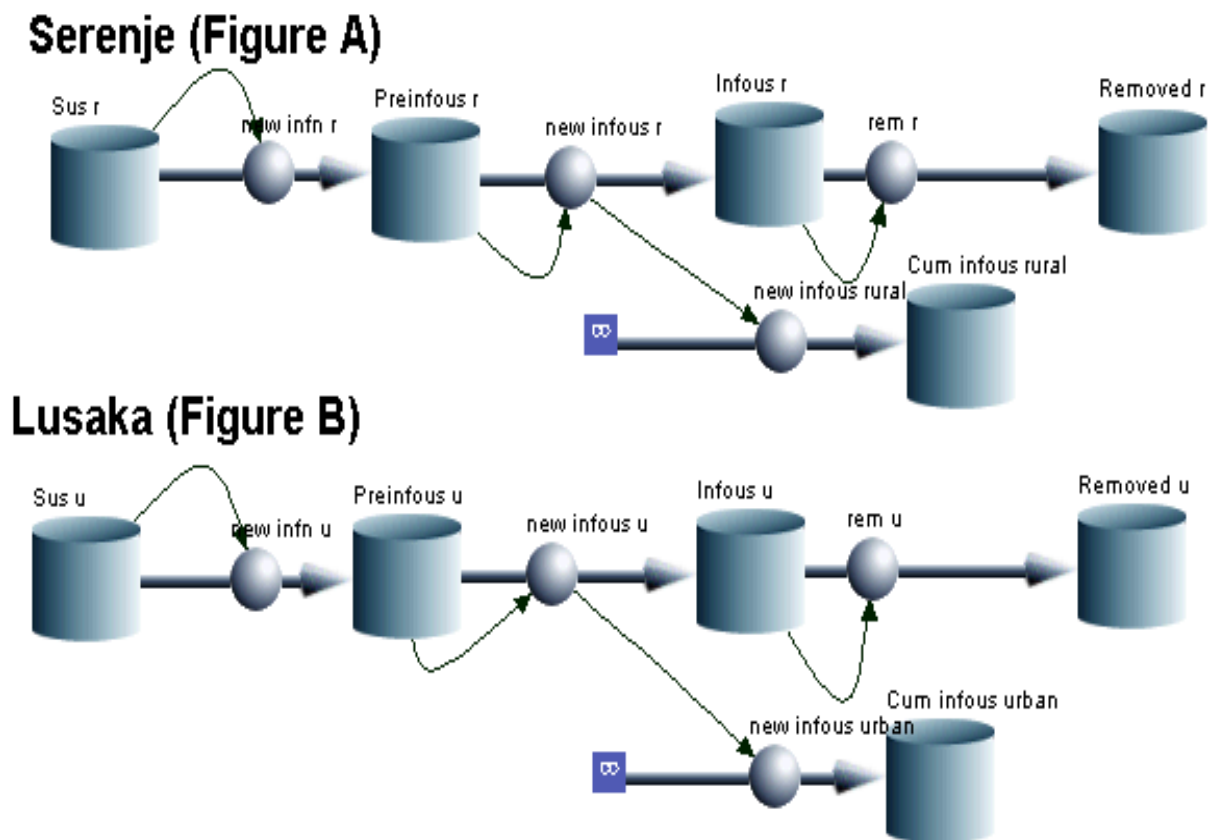


Figure 4.6: Representation of the SEIR disease transmission model without interventions. (A) In Serenje District; (B) In Lusaka District. Adapted from Legrand *et al.*, 2007

When the basic reproduction number is three ($R_0 = 3$) and without any intervention, the model predicted that the epidemic would reach its peak at day 46 with 58,529 cases being reported. The epidemic would then die down by day 148 in Serenje District. From the onset of the outbreak up to the peak day, 114,308 individuals (67.2%) would have been infected (Figure 4.7).

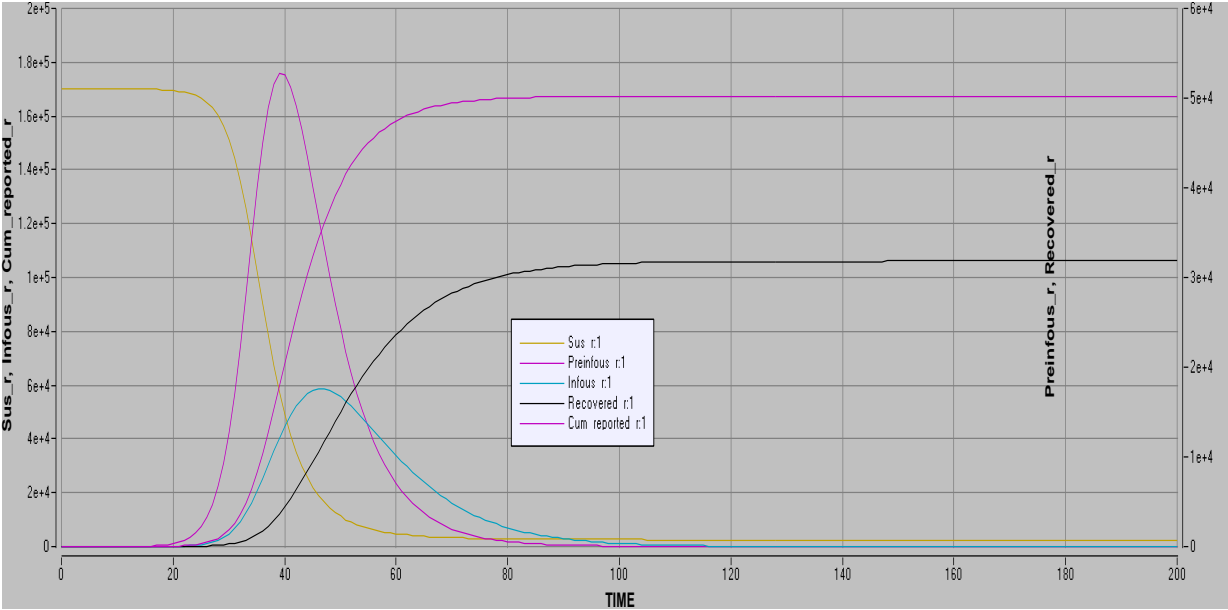


Figure 4.7: Rate of change from susceptible, Exposed, infectious and removed in Serenje District during the predicted outbreak of EVD when $R_0 = 3$.

In Lusaka District, the model without any interventions predicts that the epidemic would reach its peak by day 40 at which stage 741,400 cases would have been reported and would die down by day 67. From the onset of the outbreak up to the peak day, 1,320,000 persons (75.4%) would be infected (Figure 4.8).

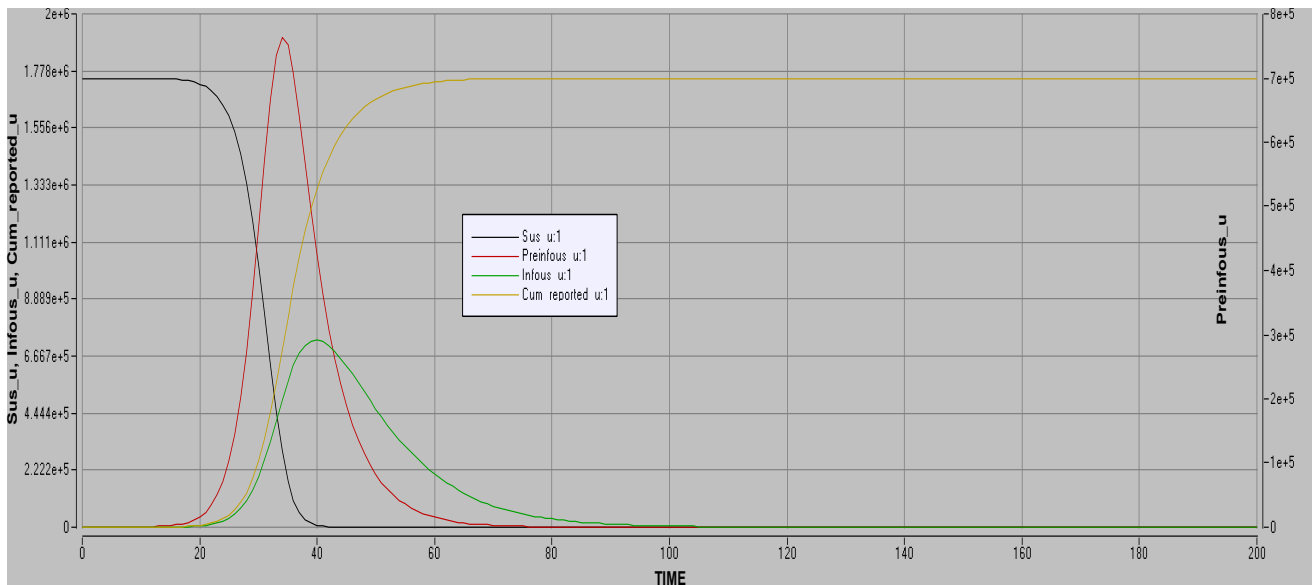


Figure 4.8: Rate of change from susceptible, Exposed, infectious and removed in Lusaka District during the predicted outbreak of EVD when $R_0 = 3$.

Furthermore, the model predicts that almost the entire population of Serenje and Lusaka districts (1,917,320) would be affected by the disease by day 100 (Figure 4.9).

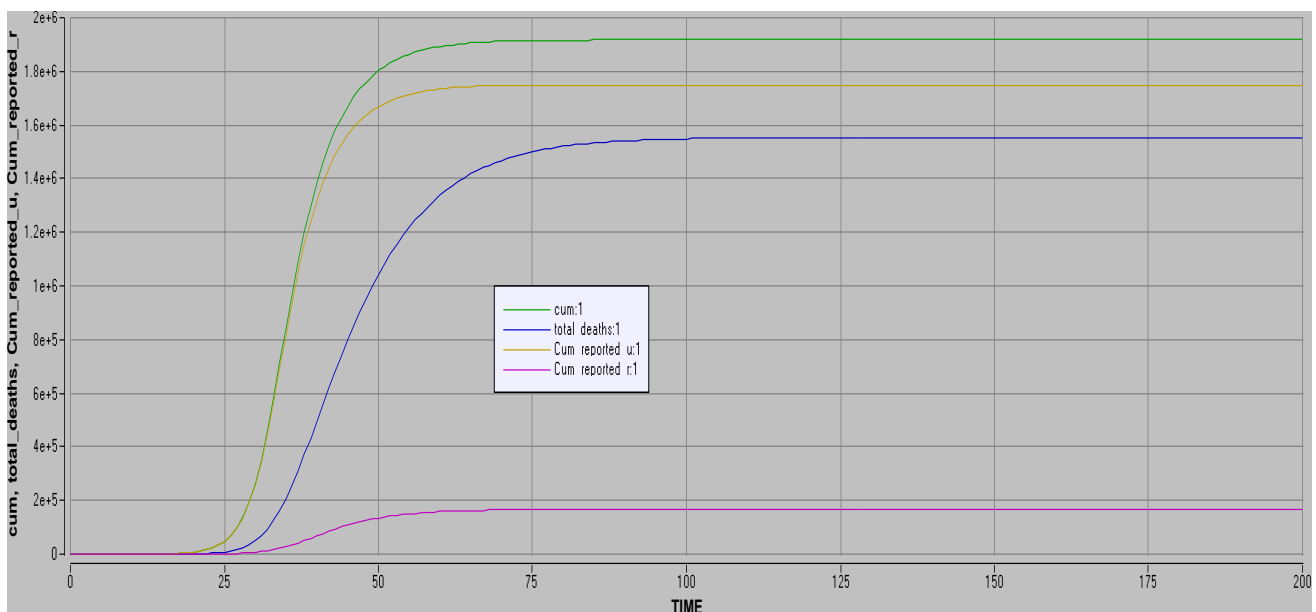


Figure 4.9: Predictive model of cumulative cases by day 100 for both Serenje and Lusaka districts without interventions.

4.2 Model with interventions

All other parameters were similar to the model without any intervention except for specified parameters of intervention.

The interventions that were assumed to be put in place are community education and reduced burial time. Through educating the community, it was assumed that infectivity from corpses would be reduced by 50 percent. This affected the parameters beta (the transmissibility rate) and also the duration of infection in the model (Figure 4.10). The model assumed further that there was an ability to reach and educate the entire susceptible population.

In Zambia, deceased individuals are normally buried after a period of three days (Tembo *et al.*, 2012). By reducing this period at two days (Figure 4.10), it was assumed that the transmissibility from the deceased person with EVD to relatives and friends coming to pay their respects would be reduced also by 50%.

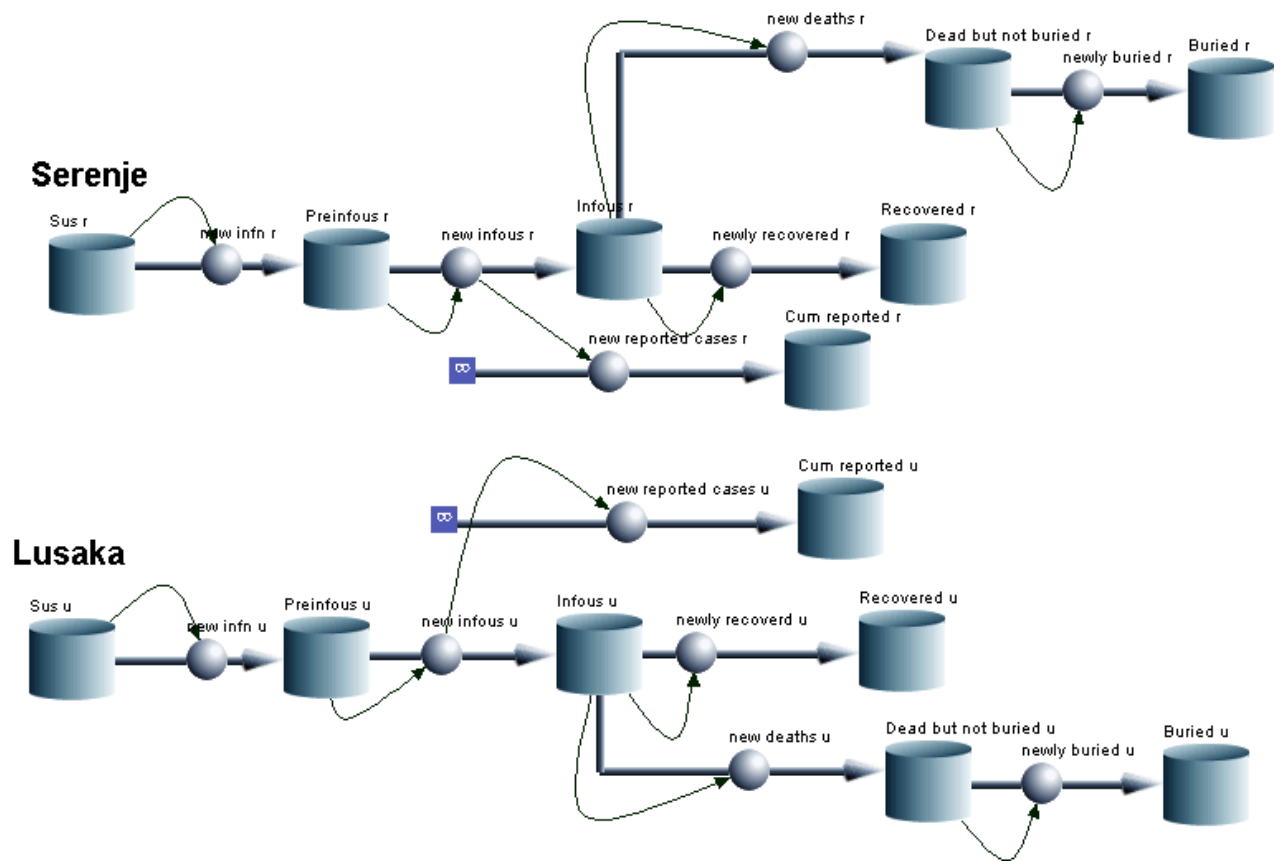


Figure 4.10: Representation of the SEIR disease transmission model for Serenje and Lusaka districts with interventions. Adapted from Legrand *et al.*, 2007

When the reproductive number is taken as three ($R_0=3$), and interventions applied (community education and reducing burial time) the model predicted that an epidemic would reach its peak by day 71 (40,650 cases) and would die down by day 183 in Serenje District (Figure 4.11). However, in Lusaka District the epidemic would reach its peak by day 62 (619,573 cases) and would die down by day 139 (Figure 4.11).

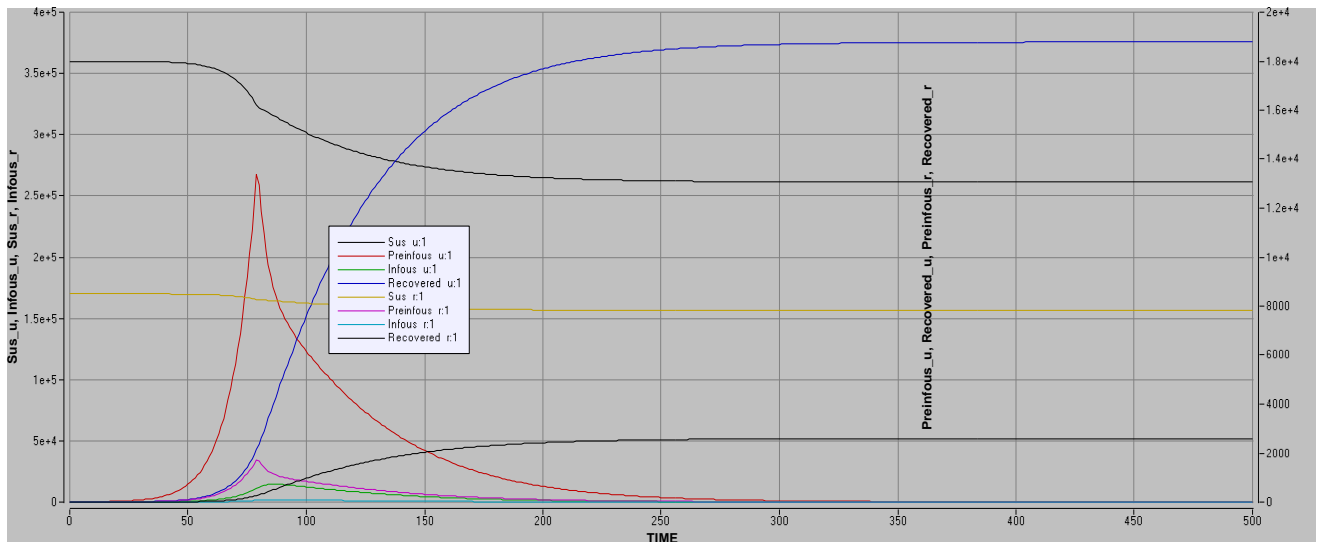


Figure 4.11: Rate of change from susceptible, pre-infectious, infectious and removed in Serenje and Lusaka districts during the predicted outbreak of EVD ($R_0 = 3$) after implementing of intervention measures. (Legend: sus_u:1, preinfous_u:1, infous_u:1, recovered_u:1, sus_r:1, preinfous_r: 1, infous_r:1, recovered_r:1).

A comparative table generated from the predictive models without and with intervention indicates that the number of cases would decrease by 10.5% and 7% in Serenje and Lusaka districts, respectively if interventions (community education and reducing burial time were implemented (Table 4.5). The effect of interventions would be more optimal in Serenje District than Lusaka District (Figure 4.12).

Table 4.5: Overall effect of intervention on the epidemic size

	Without intervention		With intervention		Total cases prevented (%)
	Day at peak	Cases (%)	Day at peak	Cases (%)	
Serenje District	46	58,529 (34.4)	71	40,650 (23.9)	17,879 (10.5)
Lusaka District	40	741,400 (42.4)	62	619,573 (35.4)	121,827 (7.0)

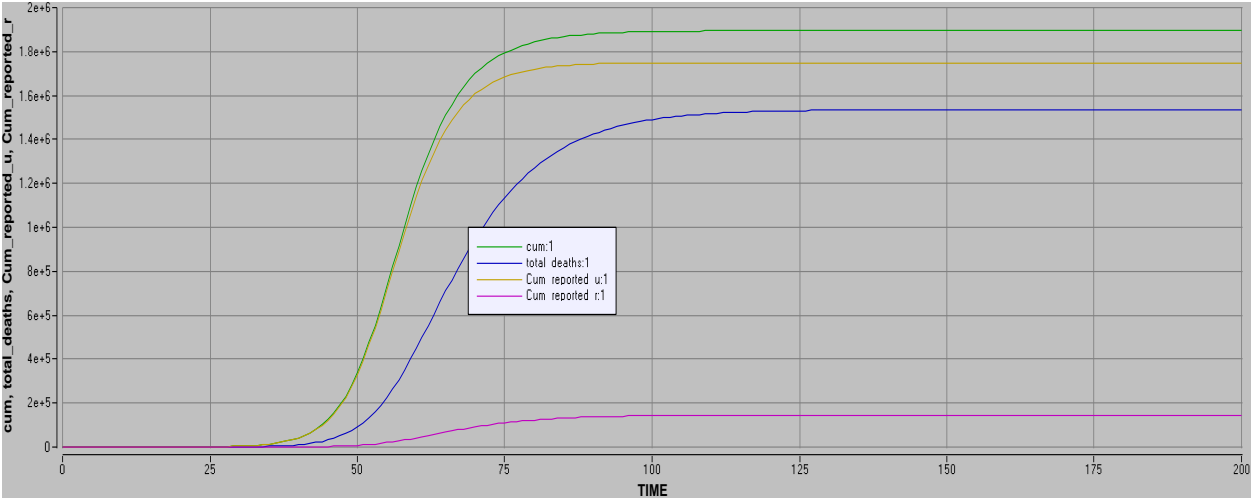


Figure 4.12: Predictive model of EVD outbreak with all intervention measures in Serenje and Lusaka districts. (Legend: cum:1, total_deaths:1, cum_reported_u:1, cum_reported_r:1).

Considering each intervention separately, the model predicted that, in both Serenje and Lusaka districts, introducing community education would have the largest effect in reducing the number of cases during the outbreak as compared to the effect of reducing the burial time of person deceased from EVD (Table 4.6 and 7). However, the community education would

have greater effect in Serenje District where ten percent of the total cases would be prevented, while only 6.7% would be prevented in Lusaka District (Table 4.6 and 7).

Table 4.6: Impact of each intervention on the epidemic size in Serenje District

Intervention	Day at peak of outbreak	Total cases (%)	Total cases prevented (%)
Burial practice (3 days < 2 days)	44	55,540 (32.6)	2,989 (1.8)
Community education	69	41,524 (24.4)	17,005 (10.0)

Table 4.7: Impact of each intervention on the epidemic size in Lusaka District

Intervention	Day at peak of outbreak	Total cases (%)	Total cases prevented (%)
Burial practice (3 days -> 2 days)	40	727,690 (41.6)	13,710 (0.8)
Community education	61	624,975 (35.7)	116,425 (6.7)

4.3 Sensitivity analysis

This analysis was done in Berkeley Madonna to explore the sensitivity of model predictions to the size of a given parameter (single) or combinations of parameters (multiple).

The sensitivity analysis for the basic reproductive number in the model revealed that as R_0 increases, the number of infected cases increases (Figure 4.13). As the number of day to burial is increasing (>2 day), the proportion of infected in both Serenje and Lusaka districts is also increasing (Figure 4.14). The sensitivity analysis also shows the cumulative number of cases is reduced with the increased education of the community (Figure 4.14).

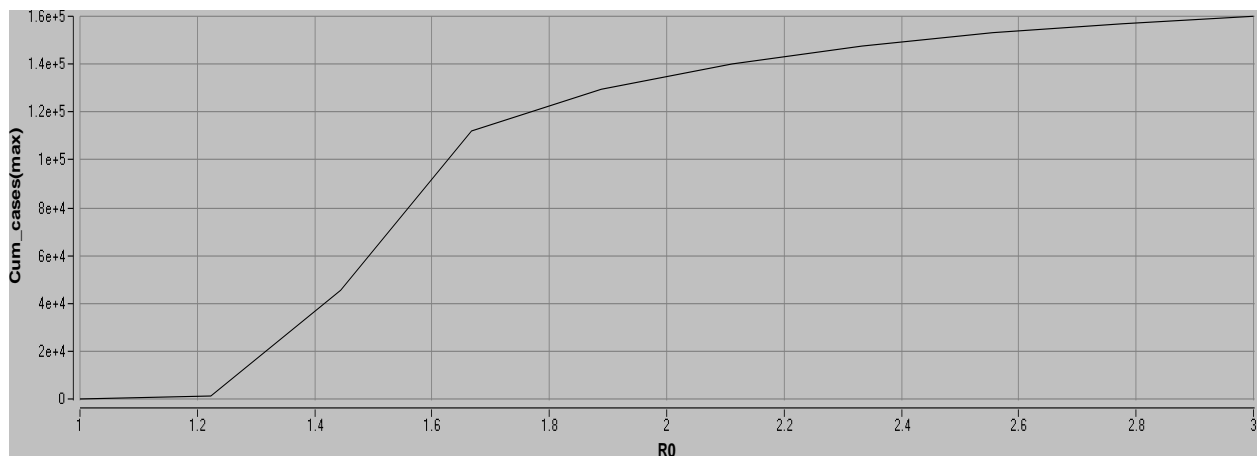


Figure 4.13: The sensitivity test of R_0 with the cumulative cases (rural and urban).

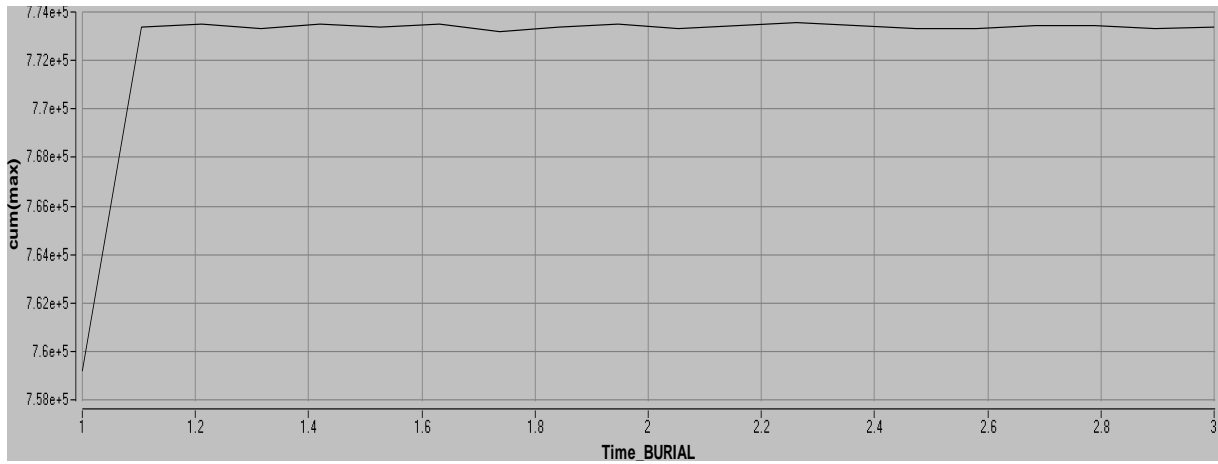


Figure 4.14: Sensitivity test of time to burial with the proportion of infected people in rural and urban regions.

The cumulative cases are reduced with the education of the community (Figure 4.15).

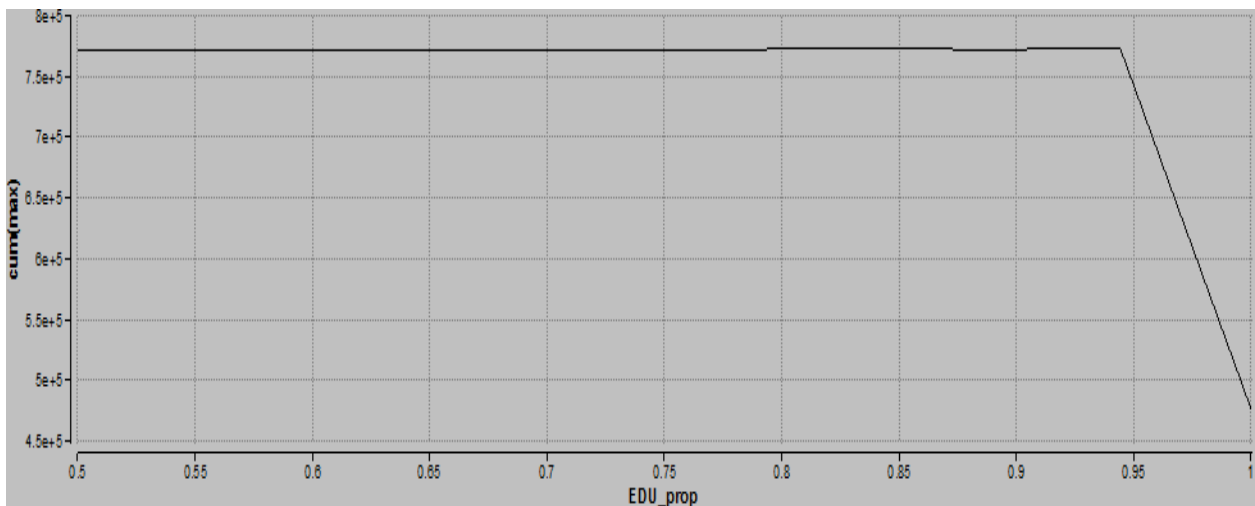


Figure 4.15: The sensitivity test of community education with the cumulative cases (rural and urban).

CHAPTER FIVE

5.0 DISCUSSION

Using known epidemiological data of EVD, we developed a dynamic model for its spread within Serenje District (rural area) and subsequently to Lusaka District (urban area). We modeled the course of the outbreak using two approaches: firstly without interventions and secondly with interventions.

Biological plausibility of disease spread involves the-contacts, the exposed, the actual infected to be constantly interacting. In the absence of this phenomenon, the disease spread is brought into a naïve population by an index case which in this case is likely to be imported into Lusaka District. Given the high propensity of travels towards Lusaka, there is a probability that more than one index case will bring the disease into Lusaka.

Using the same basic reproductive number ($R_0 = 3$), the model developed predicted an early peak (day 40) of the outbreak in the urban area (Lusaka District) as compared to the rural area (day 46) (Serenje District). These findings are in agreement with those of the 1995 EVD outbreak in Bandundu Province of the DRC, where the peak was observed earlier in the urban area (Kikwit) than in the surrounding rural area (Mosango). This was despite the fact that the epidemic started in the rural area (Khan *et al.*, 1999).

The model also predicted that the epidemic would last longer in Serenje District (148 days) than in Lusaka District (67 days). This could be due to the socio-cultural factors such as; level of education, misconception of the disease and the beliefs that will favor the non-compliance of the rural population to the disease control measures being implemented (Hewlett *et al.*, 2003).

The proportion of cases predicted in the model was not the same throughout the two districts. From the onset of the outbreak up to the peak day, 67.2 percent (114,308 persons) of the total population of Serenje District were predicted to be affected by the disease where as a larger proportion, 75.4 percent (1,320,000 persons), of the total population of Lusaka District were predicted to be affected. In most of the previous reported EVD outbreaks, the proportion of infected people was higher in the urban areas compared to the rural areas (Muyembe *et al.*, 2012). Furthermore, in the 1996, the WHO reported a high proportion of cases (80.7 percent) in Kikwit (urban area) as compared to the rural areas surrounding Kikwit (18.9 percent) (Kibari *et al.*, 2011). The urban areas seemed to be more affected because they are characterized by a high demographic density which facilitates the easiest spread of communicable diseases (Alirol *et al.*, 2010). However, some studies including those in Guinea (Bah *et al.*, 2014) and in Republic of Congo (Formenty *et al.*, 2003) reported a higher incidence of the disease in the rural areas as compared to the urban areas.

The model predicted that without any interventions, almost the entire population of Serenje and Lusaka districts (1,917,320) would be affected by the disease by day 100. This prediction is in agreement with Rachah *et al.* (2015), who reported that in the absence of any intervention the epidemic of EVD could be out of control.

A simulation model using the same basic reproductive number ($R_0=3$), but with the implementation of control measures (community education and reduction of the burial time), revealed a significant change on the peak day of the epidemic, the number of cases who would be infected by the EVD and the length of the epidemic in both districts. The peak days would be delayed by 25 days and 22 days in Serenje and Lusaka districts, respectively. As reported by Khan *et al.* (1999) the control measures implemented during the 1995 EVD outbreak in Kikwit reduced the speed of disease transmission.

Furthermore, with an intervention, the model predicted that the number of EVD cases would be reduced by 10.5 percent (17,879 cases prevented) and seven percent (121,827 cases prevented) in Serenje and Lusaka districts, respectively. This agrees with several observations made during several past outbreaks where control measures reduced the number of infected people (Khan *et al.*, 1999; Legrand *et al.*, 2007; Rachah *et al.*, 2015).

Nevertheless, the intervention would extend the length of the outbreak by 35 days and 72 days in Serenje and Lusaka districts, respectively. The intervention reduces R_0 of the disease by reducing the transmissibility. When the R_0 is close to one, the epidemic is more likely to last longer (Jones, 2007).

However, the extension of the epidemic is almost twice in Lusaka District (urban area) as compared to Serenje District. Moreover, the model predicts that the overall effect of an intervention would be more optimal in Serenje District than in Lusaka District. The high demographic density in the urban setup has been described as some of the factors making the control of communicable diseases in an urban area difficult (Alirol *et al.*, 2010). However, in both urban and rural areas, the overall effect of intervention could only be achieved with compliance of the community which is influenced by their socio-cultural factors and perception of the disease (Hewlett *et al.*, 2003).

Our model also predicted that community education would have the largest effect in the reduction of the number of cases during the outbreak as compared to the effect of reducing the burial time of person deceased from EVD. Previous studies which assessed the impact of several types of interventions in the control of EVD revealed that education of the population has a significant contribution in the control of an outbreak due to Ebola virus (Formenty *et al.*, 2003; Legrand *et al.*, 2007; WHO, 2015). However, taken together, adequate public awareness will ensure safe burial.

A sensitivity analysis was performed for single parameter of the model in order to identify important parameters for the control of the outbreak. For the pattern of transmission identified it appeared that the R_0 , meaning the transmissibility, the time to burial and the community education were related to the epidemic size.

Study limitations

The model assumed the introduction of one infected person in the total population of Serenje District but in reality there can be several persons that get infected at the same time. A direct exposure to migrating fruit bats massively hunted and sold by villagers to the community was suspected during the 2007 EVD in Luebo, DRC, resulting in several persons being infected simultaneously (Leroy *et al.*, 2009). If this could be the case in real situation, the pattern of disease transmission would be different from that predicted in this model.

It was assumed that the recovered become immune for life to the virus species that caused the disease. Evidence demonstrates that people who recover from EVD develop antibodies that last for at least 10 years, possibly longer (CDC, 2015). However, the study on immune memory to SUDV suggested that the same strain of the virus may not yield identical memory responses (Sobarzo *et al.*, 2015). Furthermore, it is still unknown if people who survive are immune for life (CDC, 2015). This would have an influence on the number of susceptible in this model; hence the number of cases might change in the real situation.

It was further assumed that the population was homogenous (rural community, urban community and rural-urban community). This assumption may not be very realistic, particularly in African countries where the structure of the communities favors person-to-person transmission (Legrand *et al.*, 2007).

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Considering the exposure risk to annual migratory fruit bats which come into Serenje District of Zambia, a simulation transmission model for EVD was developed. The model predicted that following the introduction of one infected person into Serenje District, and without any interventions an epidemic would reach its peak after 46 days. It was further assumed that the epidemic would spread to Lusaka District where it would reach its peak by day 40. The model also demonstrated that the epidemic would have a devastating impact on the community with increasing devastation in the absence of implementation of effective intervention measures. The predictive model also revealed that introduction of community education would have a large beneficial effect than the reduction of the burial time in the control of the outbreak. These results suggest that the size of the epidemic could be reduced further by reinforcing other interventions such as quarantine which could allow stopping the transmission cycle.

However, this model like all others is a simplification of a complex process, founded on many assumptions and may not reflect an actual outbreak scenario. Therefore, the observations made in this study need to be taken with caution.

6.2 Recommendations

Arising from this study that an outbreak of EVD in Serenje and Lusaka districts would have devastating effects on the community, the following recommendations are made:

1. Community education on the preventive measures should always be conducted to avoid such an outbreak from occurring
2. A good EVD preparedness plan should always be in place for effective risk management and control
3. Exposure to bats should be avoided
4. Studies on modelling that can explore the effect of other intervention measures such as movement restriction, vaccination and drug administration should be undertaken while taking into consideration the cost effectiveness of each intervention type

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APPENDIX

{Top model}

{Reservoirs}

$$d/dt (\text{Sus}_u) = - \text{new_infn}_u$$

$$\text{INIT Sus}_u = \text{Sus}_u0$$

$$d/dt (\text{Preinfous}_u) = + \text{new_infn}_u - \text{new_infous}_u$$

$$\text{INIT Preinfous}_u = \text{Preinfous}_u0$$

$$d/dt (\text{Infous}_u) = + \text{new_infous}_u - \text{newly_recovered}_u - \text{new_deaths}_u$$

$$\text{INIT Infous}_u = \text{Infous}_u0$$

$$d/dt (\text{Recovered}_u) = + \text{newly_recovered}_u$$

$$\text{INIT Recovered}_u = \text{Rem}_u0$$

$$d/dt (\text{Sus}_r) = - \text{new_infn}_r$$

$$\text{INIT Sus}_r = \text{Sus}_r0$$

$$d/dt (\text{Preinfous}_r) = + \text{new_infn}_r - \text{new_infous}_r$$

$$\text{INIT Preinfous}_r = \text{Preinfous}_r0$$

$$d/dt (\text{Infous}_r) = - \text{newly_recovered}_r + \text{new_infous}_r - \text{new_deaths}_r$$

$$\text{INIT Infous}_r = \text{Infous}_r0$$

$$d/dt (\text{Recovered}_r) = + \text{newly_recovered}_r$$

$$\text{INIT Recovered}_r = \text{Rem}_r0$$

$$d/dt (\text{Cum_reported_u}) = + \text{new_reported_cases_u}$$

$$\text{INIT Cum_reported_u} = \text{Cum_u0}$$

$$d/dt (\text{Cum_reported_r}) = + \text{new_reported_cases_r}$$

$$\text{INIT Cum_reported_r} = \text{Cum_r0}$$

$$d/dt (\text{Dead_but_not_buried_u}) = + \text{new_deaths_u} - \text{newly_buried_u}$$

$$\text{INIT Dead_but_not_buried_u} = \text{Deadbnb_u0}$$

$$d/dt (\text{Dead_but_not_buried_r}) = + \text{new_deaths_r} - \text{newly_buried_r}$$

$$\text{INIT Dead_but_not_buried_r} = \text{Deadbnb_r0}$$

$$d/dt (\text{Buried_u}) = + \text{newly_buried_u}$$

$$\text{INIT Buried_u} = \text{Buried_u0}$$

$$d/dt (\text{Buried_r}) = + \text{newly_buried_r}$$

$$\text{INIT Buried_r} = \text{Buried_r0}$$

{Flows}

$$\text{new_infn_u} = \text{Sus_u} * \text{force_of_infn_u}$$

$$\text{new_infous_u} = \text{Preinfous_u} * \text{infous_rate}$$

$$\text{newly_recovered_u} = \text{Infous_u} * \text{rem_rate} * (1 - \text{prop_die})$$

$$\text{new_infn_r} = \text{Sus_r} * \text{force_of_infn_r}$$

$$\text{new_infous_r} = \text{Preinfous_r} * \text{infous_rate}$$

$$\text{newly_recovered_r} = \text{Infous_r} * \text{rem_rate} * (1 - \text{prop_die})$$

$$\text{new_reported_cases_u} = \text{new_infous_u} * \text{frac_rep}$$

$$\text{new_reported_cases_r} = \text{new_infous_r} * \text{frac_rep}$$

$$\text{new_deaths_u} = \text{Infous_u} * \text{rem_rate} * \text{prop_die}$$

$$\text{new_deaths_r} = \text{Infous_r} * \text{rem_rate} * \text{prop_die}$$

$$\text{newly_buried_u} = \text{Dead_but_not_buried_u} * \text{burial_rate_u}$$

$$\text{newly_buried_r} = \text{Dead_but_not_buried_r} * \text{burial_rate_r}$$

{Globals}

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{                                     INITIAL   CONDITIONS
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Sus_u0 = pop_u - Rem_u0 - Infous_u0 ; Number of susceptible
urban individuals in the population at the start

Sus_r0 = pop_r - Rem_r0 - Infous_r0 ; Number of susceptible
rural individuals in the population at the start

$Preinfous_u0 = 0$; Number of urban individuals in the preinfectious category in the population at the start

$Preinfous_r0 = 0$; Number of rural individuals in the preinfectious category in the population at the start

$Infous_u0 = rep_u0 * infous_period / (frac_rep)$; Number of infectious urban individuals in the population at the start

$Infous_r0 = rep_r0 * infous_period / (frac_rep)$; Number of infectious rural individuals in the population at the start

$Deadbnb_u0 = 0$; Number who are dead but not buried in urban area at the start

$Deadbnb_r0 = 0$; Number who are dead but not buried in rural area at the start

$Rem_u0 = 0$; Number of urban individuals who are immune in the population at the start

$Rem_r0 = 0$; Number of rural individuals who are immune in the population at the start

Cum_u0 = Infous_u0*frac_rep ; number of urban
individuals reported as cases at the start

Cum_r0 = Infous_r0*frac_rep ; number of rural individuals
reported as cases at the start

Buried_u0 = 0 ; number of urban individuals
who have been buried

Buried_r0 = 0 ; number of rural individuals
who have been buried

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{ INFECTION-RELATED PARAMETERS
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{ (note that these are in DAILY units, unless otherwise specified)
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{
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total_deaths = (buried_u+dead_but_not_buried_u) +(buried_r+dead_but_not_buried_r)

preinfous_period = 6

infous_period = 10

infous_rate = 1/preinfous_period

rem_rate = 1/infous_period

frac_rep = 1.0 ; proportion of individuals those
infected who end case

force_of_infn_u = (b_uu*Infous_u + b_uu*rel_infousness_dead*Dead_but_not_buried_u +
b_ur*Infous_r + b_ur*rel_infousness_dead*Dead_but_not_buried_r)*community
; force of infection among urban individuals

force_of_infn_r = (b_ru*Infous_u + b_ru*rel_infousness_dead*Dead_but_not_buried_u +
b_rr*Infous_r + b_rr*rel_infousness_dead*Dead_but_not_buried_r)*community
; force of infection among rural individuals

b1 = 1.56e-11

b2 = 1.56e-11

b3 = 1.56e-11

b_uu = b1

b_rr = b2

b_ur = b3

b_ru = b3

prop_die = 0.81

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{                                INTERVENTION-RELATED    PARAMETERS
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{                (note that these are in DAILY units, unless otherwise specified )
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; EDUCATION

EDU = 0; switch

Community = IF (EDU=1) then .5 else 1

; BURIAL

BURIAL=0; BURIAL=0 if no burial intervention

time_to_burial_u = if (BURIAL=1) then 2 else 3

time_to_burial_r = if (BURIAL=1) then 2 else 3

burial_rate_u = 1/time_to_burial_u ; average time to

buried after death

burial_rate_r = 1/time_to_burial_r ; average time to buried
after death

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{          DEMOGRAPHIC  PARAMETERS  AND  VARIABLES
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tot_alive_urban = Sus_u + Preinfous_u + Infous_u + Recovered_u

tot_alive_rural = Sus_r + Preinfous_r + Infous_r + Recovered_r

tot_alive_all = tot_alive_urban + tot_alive_rural

pop_u = 1750000

pop_r = 170000

pop_all = pop_u+pop_r

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{          USEFUL  SUMMARY  VARIABLES
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Cum = (Cum_reported_u + Cum_reported_r) ; Cumulative number of
reported cases in population

Number_ever_infctd_u = Buried_u + Recovered_u

Number_ever_infctd_r = Buried_r + Recovered_r

Prop_ever_infctd_u = Number_ever_infctd_u/pop_u

Prop_ever_infctd_r = Number_ever_infctd_r/pop_r

Prop_ever_infctd_all = (Number_ever_infctd_u+Number_ever_infctd_r)/ (pop_u+pop_r);

reflects the proportion of the initial population that has been ever infected

cum_prop_reported = (Cum_reported_u + Cum_reported_r)/ (pop_u+pop_r)

new_infous_all = new_infous_u+new_infous_r

{End Globals}