Original Article

Study of Ebola Virus Outbreak Dynamics, Impact of Vaccination and Other Preventive Measures on Transmission Control

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ABSTRACT

Ebola virus disease (EVD) is an emerging and remerging zoonosis associated with high fatality rate, mainly caused by the Zaire Ebola virus (ZEBOV) and Sudan Ebola virus (SEBOV) strains. Approximately 20 epidemics of EVD have been documented mainly in Central African countries since 1976. Currently, there are no therapeutics agents and vaccines yet approved for EVD. However, several promising therapeutics and vaccines candidates are actively undergoing various phase of clinical development. This study aims to study the EVD dynamics and evaluate the potential impacts of vaccines and other preventive measures on EVD transmission control and significance of medical intervention on outcome of the disease. An initial branch chain model of EVD dynamics was built based on data obtained from previous study. Different epidemiological scenarios for EVD with impacts of intervention were simulated using Berkeley-Madonna Version 8.3.18 software. Every reduction in the exposure rate of EBV infection by 10% produces two- to five-fold improvement in protection against EVD. Transmission control is optimum when the rate of exposure to EBV infection is reduced below 1%. Optimal control of EVD transmission can be achieved through strategic implementation of successful vaccination programme, and other preventive measures as well as rapid delivery of supportive medical care.

Keywords: Ebola virus disease, Zaire Ebola Virus, Sudan Ebola Virus, epidemics, vaccines, epidemiological model

INTRODUCTION

Ebola virus disease (EVD) is a severe haemorrhagic febrile illness caused by Ebola virus (EBV) infection. It is an emerging and re-emerging zoonosis and associated with high mortality rate[1, 2]. EVD first appeared in 1976, with two simultaneous outbreaks; one in Nzara, Sudan involving 284 cases with 151 deaths (53%), and another in Yambuku (near Ebola River) in Democratic Republic of Congo where 318 cases were reported with 280 casualties (88%)[3]. Since the first two-epidemics, approximately another 20 outbreaks were recorded in the following years mostly involving Central African countries, until the recent largest and most complex outbreak of EVD in West African countries (2014 – 2016).

The recent EVD outbreak recorded higher number of deaths than all previous outbreaks combined. The outbreak started in Guinea before spreading across the land borders to Sierra Leone, Liberia, Mali, and Senegal and later to Nigeria, Europe and North America by the mean of air travellers (Figure 1). A total of 28,616 cases were reported as of March 2016 with 11,005 fatalities (39%)[4].

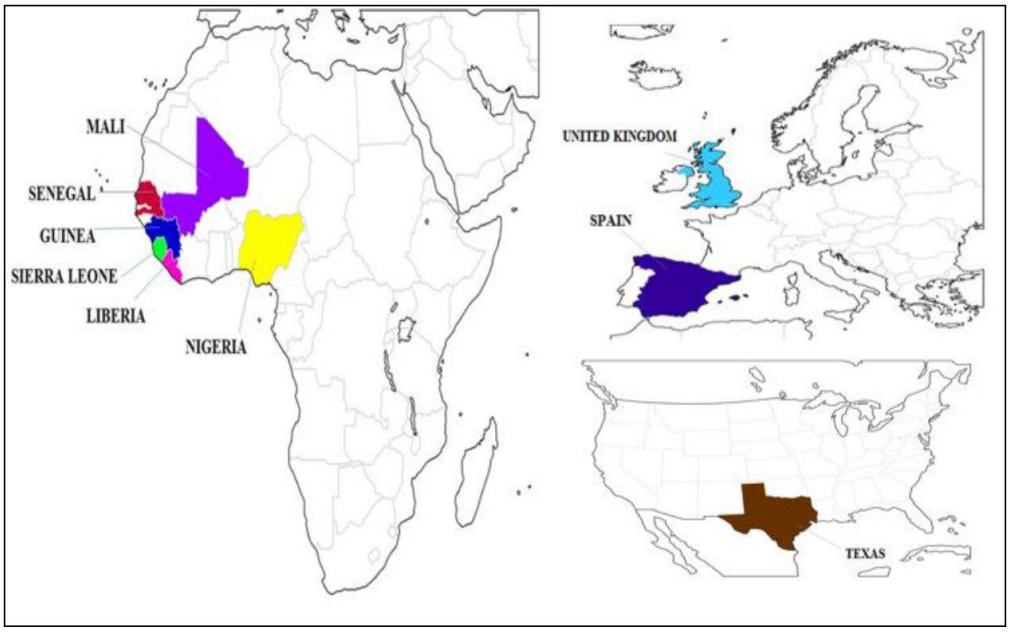
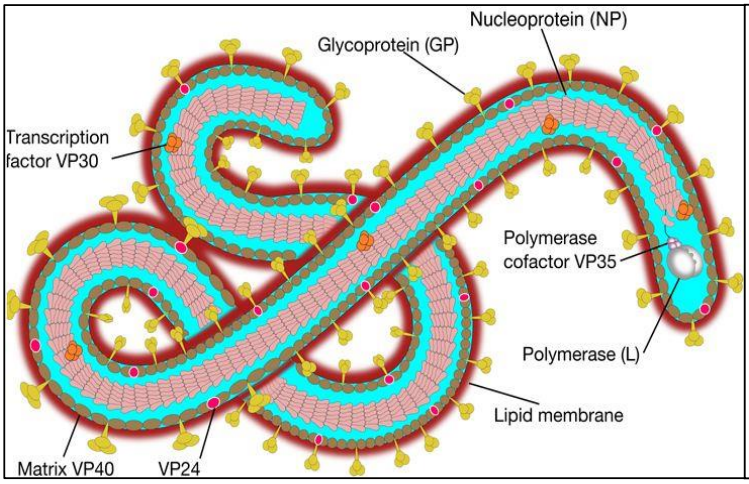


Figure 1 Distribution of EVD outbreaks in 2014 – 2015. The outbreak begins in West African countries before it spread to other distant countries by the means of air travelling[5].

EVD outbreak occurs mostly in African countries. The natural environment in the continent favours the survival of Ebola virus. This includes wide distribution of EBV natural and alternate hosts such as fruit bats, apes and monkeys, and suitable temperature for the virus to survive throughout the year[6]. In addition, poor healthcare system, lack of basic infrastructures, human and economic resources and political instability in African countries further complicates the control of the outbreak.

EBV is a polymorphic, negative sense RNA virus belongs to the (family) *Filoviridae* (Figure 2). There are five identified strain of EBV; Zaire Ebola Virus (ZEBOV), Sudan Ebola Virus (SEBOV), Bundibugyo Ebola Virus (BEBOV), Tai Forest Ebola Virus (TEBOV) and Reston Ebola Virus (REBOV)[7]. The first three have been responsible for the large outbreaks in Africa in which ZEBOV identified causing the recent epidemic in Africa[1]. REBOV is not associated with human disease while ZEBOV is the most virulent and causes the highest fatality rate (more than 90%)[8, 9].



The 19-kb long EBV genome has seven open reading frames encoding structural proteins that include nucleoprotein (NP), virion envelope glycoprotein (eGP), matrix protein VP24 and VP40, non-structural proteins such as VP30 and VP35, and viral polymerase. These ribonucleoproteins complex have distinct roles in pathogenesis of EVD[10].

Figure 2 Schematic diagram of the structure of EBV

The high fatality rate associated with Zaire Ebola Virus strain is related to its ability to initiate intense innate immune response which characterized by the 'cytokine storm', as observed in some other severe form and fatal case of infection (e.g. H5N1 Influenza, smallpox, etc.). It also causes global suppression of adaptive immunity which is characterized by very low-level circulating cytokines produced by T-lymphocytes and massive loss of peripheral CD4 and CD8 lymphocytes[11].

Transmission of EBV to humans can occur by indirect contact with contaminated environment or direct contact with body fluids of infected patients[12]. The main routes of entry of EBV infection into human body are the mucous membrane, conjunctiva and skin abrasions[13]. Healthcare workers and family members of infected persons are particularly at risk of acquiring infection.

Through skin and mucosa access, EBV disseminates into blood stream by infecting target monocytes, macrophages and dendritic cells before it spreads to the liver and spleen and regional lymph nodes. The infected macrophages and monocytes will release a very high concentration of pro-inflammatory cytokines in blood stream, which then initiate inflammatory reaction causing damage to the affected normal tissues and microcirculation[5, 14]. Extensive damage to endothelial vessel will leads to massive haemorrhage.

The incubation period following infection is usually five to nine days but can vary between two to twenty-one days[12]. The symptoms may initially appear as flu-like symptoms and gastrointestinal symptoms such as stomach ache, vomiting and diarrhoea. At a later stage, complications may occur with evidence of internal or external bleeding and multi-organ failure and finally death[5].

There are no effective vaccines and therapeutic agents available for EVD before, but several therapeutics and vaccines candidates are currently undergoing various phase of clinical development. Two of most promising vaccine candidates are ChAd3-ZEBOV and rVSV-ZEBOV. rVSV-ZEBOV is a replication-competent, life attenuated, recombinant vesicular stomatitis virus, which genetically engineered to express ZEBOV strain glycoprotein as immunogen[15, 16]. Result from Phase III open-label, cluster-randomised clinical trial conducted in Guinea in 2016 by WHO and collaborators show that the vaccine is highly protective against EBV[17].

While ChAd3-ZEBOV is a vaccine derived from chimpanzee adenovirus, Chimp Adenovirus type 3. The vaccine genetically engineered to express glycoprotein from two EBV strains, ZEBOV and SEBOV. It provokes immune response against EBV and have demonstrated 100% efficacy in previous non-human primates' study[18, 19].

The mainstay treatment of EVD begins with an early recognition of the disease and delivery of effective supportive care. Supportive medical care, when given early can significantly improve survival[20]. The lack of availability of medical facilities or difficulties in getting the access to medical care in poor African countries may contribute to high fatality cases in previous outbreaks[21, 22].

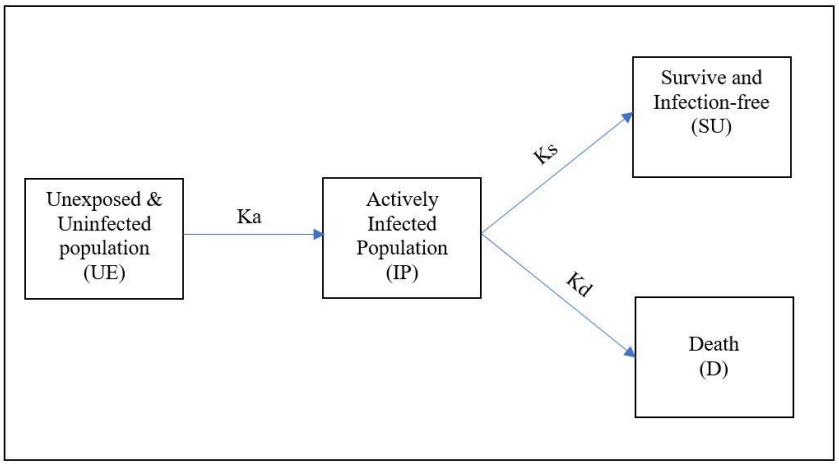
The main objective of this study is to explore the nature of EVD dynamics through construction of mathematical modelling. It allows for critical analysis of EVD dynamics based on different epidemiological scenarios generated by various key factors. The hypothetical scenarios to be tested include when the exposure rate is at 30% before it is being reduced to 20%, 10% and 1%, while the death and survival rate are fixed. Other aim is to investigate the significance of time intervention when the outbreak is fully controlled at different time intervals. This model could help researchers and public healthcare providers to understand the dynamics of EVD better and it potentially becomes a useful tool for early assessment of impact of vaccination and other preventive measures on EBV transmission control.

METHODOLOGY

An initial branch-chain epidemiological model was developed which consists of initial unexposed and uninfected population (UE) and post exposure group which were classified into three categories; infected population (IP), survivors of the disease (SU) and death (D). Epidemiological parameters tested include exposure rate constant (Ka), survivals rate constant (Ks) and death rate constant (Kd).

This epidemiological model was fitted on, where applicable, data published from previous EVD outbreaks. Data used from literature review include; EVD fatality rate (Kd) range from 20% to 90% and EVD survival rate (Ks) range from 10% to 80%[2]. Ka value was based on estimation to simulate few theoretical environments for EVD. In this model, following assumptions were also been made; the initial population in a region is 100 000 people, entire population was considered susceptible to the infection, the nett of birth rate and death case due to natural cause as well as immigration or emigration rate within the year to be zero.

The model is represented in the schematic diagram as shown in Figure 3.



UE = Unexposed and uninfected population, IP = Actively infected population, SU = Survived patient, D = Death, Ka = Exposure rate constant, Ks = Survival rate constant, Kd = Death rate constant

Figure 3 Schematic diagram of proposed basic epidemiological modelling of EVD

From the model in Figure 3, following differential equations (Figure 4) were derived and tested with Berkeley Madonna Version 8.3.18 software, for simulation of various epidemiological scenarios. Graphs of number of healthy people, infected people, survivals, death vs time were then generated for interpretation.

For unexposed and uninfected population (UE):
$UE = UE_0 - (IP_t + SU_t + D_t)$
with time; $d/dt(UE) = UE_t - (Ka \times UE_t)$

For infected population (IP):
$IP = (Ka \times UE) - (SU_t + D_t)$
with time; $d/dt(IP) = IP_0 + (Ka \times UE_t) - (Ks \times IP_t) - (Kd \times IP_t)$

For survival people (SU):
$SU = Ks \times IP$
with time; $d/dt(SU) = SU_0 + (Ks \times IP_t)$

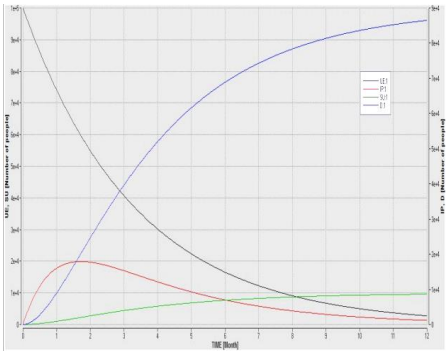
For death case (D):
$D = Kd \times IP$
with time; $d/dt(D) = D0 + (Kd \times IP_t)$

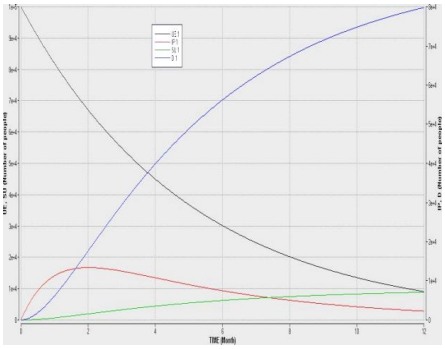
Initial UE =100000
Initial IP = 0
Initial SU = 0
Initial D = 0

Figure 4 Differential equations derived from the model for estimation number of protected and affected population

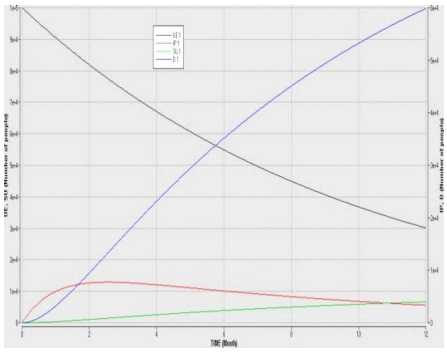
RESULTS

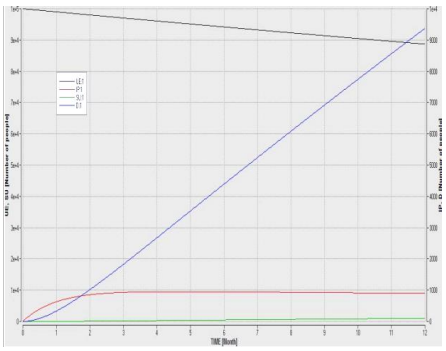
(A) (B)





(C) (D)





The left axis of the graph represents the number of people for uninfected population (UE: black line) and survivals (SU: green line), while on the right axis of the graph it represents the number of people for infected population (IP: red line) and number of people died (D: blue line) over one-year outbreak.

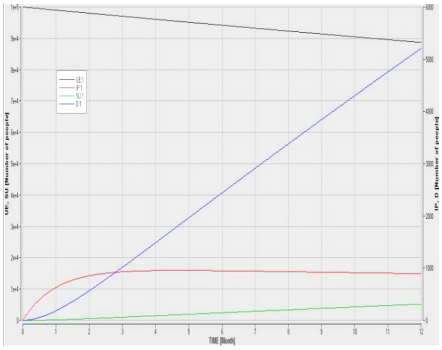
(A) When Ka = 0.2, Ks = 0.1 and Kd = 0.9, the EVD-free population had declined to 12% from the initial population comprising both of uninfected people (2732 people) and survivors of EVD (9610 people). About 1% (1171) of the population remain actively infected.

(B) When Ka = 0.2, Ks = 0.1 and Kd = 0.9, the number of EVD-free population declined to 18% from initial number of population over the year, comprising both uninfected population (9072) and EVD survivors (8866). There are about 2% (2268) of the population who remain actively infected.

(C) When Ka = 0.1, Ks = 0.1, and Kd = 0.9, the number of EVD-free population declined to 37% from initial number of population over the year, comprising both uninfected population (30119) and EVD survivors (6653). There are about 3% (3347) of the population remain actively infected.

(D) When Ka = 0.01, Ks = 0.1 and Kd = 0.9, almost 89% of population are free from the disease. However, about 11% from total population affected by EBV infection resulted with 9371 deaths and 1041 survivals. Less than 1% of population remain actively infected.

Figure 5 Graph population vs time (month) with fixed Ks = 0.1 and Kd = 0.9



When Ka = 0.01, Ks, Kd = 0.5. Improvement in survival rate up to 50%, thus reducing the fatality rate to 50%, and with infection rate kept at 1%, the impact of EBV on population is minimal. Almost 89% of population are free from the disease (blue line). From 11% affected population, 5206 of them survives and less than 1% of population remain actively infected.

Figure 6 Graph population vs time (month) with fixed Ka = 0.01

Table 1 Summary of cumulative impacts on population density when there is changes in exposure rate constant (Ka) in one-year EVD outbreak.

	Number of people/cases			
Epidemiological Variables	**Uninfected & Unexposed population [UE]**	**Actively infected population [IP]**	**Survivals [SU]**	**Death [D]**
Ka = 0, Ks = 0, Kd = 0	100 000	0	0	0
Ka = 0.3, Ks = 0.1, Kd = 0.9	2732	1171	9610	86487
Ka = 0.2, Ks = 0.1, Kd = 0.9	9072	2268	8866	79794
Ka = 0.1, Ks = 0.1, Kd = 0.9	30119	3347	6653	59881
Ka = 0.01, Ks = 0.1, Kd = 0.9	88692	896	1041	9371
Ka = 0.01, Ks = 0.5, Kd = 0.5	88692	896	5206	5206

Table 2 Summary of cumulative number of uninfected people and number of death case according to time interval when Ka = 0.01, Ks = 0.1, Kd = 0.9

Time interval	Cumulative number of uninfected people	Cumulative number of death case
3 months	97045	1823
6 months	94177	4387
9 months	91393	6915
12 months	88692	9371

The model was first tested against different values of exposure rate constant, Ka (0.3, 0.2, 0.1 and 0.01), while survival rate (Ks) and death rate constant (Kd) remain the same, at 0.1 and 0.9 respectively.

When Ka value was set at 0.3 (Figure 5-A), i.e. the population was exposed to 30% infection rate, a huge change in demographic pattern can be observed. The population density had drastically decreased to about 12% from initial total population, comprising both healthy uninfected individuals and survivor of the disease; with another 1% of population remain actively infected.

When Ka was tested at 0.2 i.e. 20% exposure rate (Figure 5-B) similar changes in demographic pattern also can be seen. Less than 10% of population being protected and 8% were survivals from the disease. However, a further reduction by 10%, i.e. when Ka = 0.1, the study shows there was significant improvement in terms of impact on population and disease survivals. 31% of population were protected from disease, 7% are survivals from the disease, while 3% remain actively infected.

The model was then tested with Ka value being reduced to 0.01 i.e. 1% of exposure rate (Figure 5-C). Tremendous improvement can be observed, in which almost 90% of population are protected from the disease throughout the epidemics, with less than 1% remain actively infected.

In second test, the model was tested against different values of survival rate, Ks and death rate constant, Kd. Ks and Kd value was changed to 0.5 respectively, while Ka value is kept at 0.01 (Figure 5-D). When Ks is change from 0.1 to 0.5 (thus Kd value from 0.9 to 0.5), there was five-fold increase in number of disease survivors (from 1041 to 5206) and the number of death case reduced to halve.

Another noteworthy observation made here is the significant of time of intervention (Table 2). If effective measures taken to halt the outbreak within 3 months, about 97% of population can be protected from the disease. At 6 months, about 94% of population are still free from the disease. However, if the outbreak continues, it will claim more casualties. It is estimated that, by 9 months, 10% of population will be affected with the disease with 6915 death cases, and by 12 months interval, more than 11% of the population will be affected with 9371 deaths.

DISCUSSION

An initial branch-chain epidemiological model was constructed as a basis to understand EVD dynamics, identifying different epidemiological variables and its influence on epidemics, and early assessment of potential impact of intervention particularly vaccination and other preventive measures.

On the first set of tests, the study aims to establish dynamics of EVD when there is a change in exposure towards EBV infection. The assessment was done by observing in terms of cumulative impacts on population density, number of survivors, number of actively infected population and number of death case.

First, the result demonstrated the extent of devastating impacts of EVD when there was inefficiency in controlling the spread of infection. The density of population markedly reduced and casualty was very high. This simulation may reflect one of the worst possible case-scenarios. However, it is mere theoretical, as in real situation, spread of infection could reach saturation after certain period, and this huge outbreak will prompt global intervention to prevent uncontrolled spread of infection and improve survivals.

The study also made another significant observation from the first test; the reduction of Ka values has produced ‘point of inflexion’ especially when Ka value was reduced from

0.1 to 0.01, compared to when Ka value was reduced from 0.3 to 0.2 or 0.2 to 0.1. It produced more than double improvement in the number of uninfected population (increase of 58,843 populations) and reduction of death case (reduction of 50,510 case) compared to when Ka value being reduced from 0.2 to 0.1.

This could reflect the significant impact of preventive measures taken to halt the outbreak. One of the most effective way is vaccination programme. To be successful, it requires mass of population need to be vaccinated to produce herd immunity. However, in practical, it is almost impossible to vaccinate entire population for multiple reasons include logistic problem, socioeconomic burden, cultural beliefs and attitude towards vaccination.

The model however, shows that even when Ka is brought down to 1%, there are still considerable numbers of population are at risk for getting infection. This could reflect that in situation where population who do not receive vaccination potentially become the source of spreading of infection and further, diminish herd immunity. Moreover, around 5% to 15% vaccinated people may not successfully develop immunity against the disease[23].

Therefore, to aggressively control the outbreak, it is going to require not only a successful vaccination programme but combination strategy with other preventive measures. Dissemination of adequate information and raising public awareness about the nature of disease is very crucial. This includes information on the risk of dissemination of infection; from animals to human and human to human. People need to be advised to avoid eating raw bush meat, avoiding direct contacts with symptomatic patients, practising safe burial methods, abstaining sexual contact with actively infected patient or wearing condom for male[24].

Another integral element in controlling the infection is contact tracing. These include identification, assessment and follow up of persons who may have encountered with infected individual[25, 26]. Rapid identification of symptoms is critical and prompt isolation of suspected individuals can ensure successful interruption of Ebola virus transmission and control size of epidemics.

As human mobilisation is one of the identified factors that contribute to the spread of infection to distant countries, appropriate travel advice is necessary. Strict travel bans to or from affected countries are not recommended, except for those who are suspected or confirmed EVD patients, and corpse of EVD patients[27]. It also potentially disrupts medical volunteerism, essential trades such as medical supplies, food, and fuel[28].

Thermal screening which detects febrile cases at departure or arrival at airport could be costly and not effective to detect all infected cases[29]. This is given that the risk for getting infection for travellers is low and it also could not detect afebrile patient within the incubation period[30].

In the second batch of test, the study aims to demonstrate EVD dynamics when there were efforts carried out to improve patients' survivals and reducing the death rate, as well as the importance of time management of outbreak. It signifies the need of fast action to control the spread of infection, and prompt institution of medical care so that the negative impacts can be minimized (Table 2).

Optimal medical care requires close monitoring, conscientious correction of fluid and electrolytes losses, as well as treatment of any superinfection, respiratory failure, nutrition support, pain and anxiety control, psychosocial support and treatment of any complication with the present of well-trained staff[31, 32].

However, supportive treatment in the form of correction of electrolytes can be challenging. Delays in getting laboratory result may hasten the disease complication and fatality. To

improve the situation, the use of rapid test kit for electrolytes such as i-STAT Hand-held Point of Care Analyser could be very helpful. It is handy to use, result can be produced within 20 minutes and has demonstrated accuracy and precision comparable to standard laboratory methods[33].

This research has limitation in terms of establishing causal relationship between influencing factors with epidemiological variables (rate of exposure, survival and death rate). In future, the model could be expanded to explore these factors such as study the influence of traditional burial methods, or latent phase of infection on exposure control.

CONCLUSION

This mathematical model has provided an insight on how EVD transmission might evolve throughout the outbreak. It shows that the reduction in exposure rate to infection has produced 'point of inflexion' especially when the exposure rate was reduced from 10% to 1%; it produced more than double improvement in the number of protected population and number of death. The result also has demonstrated the significant of efforts carried out to improve patients' survivals and the importance of time of intervention of the outbreak. Though EVD is highly fatal, the number of casualties can be minimized when the outbreak is controlled as early as possible. In conclusion, this study emphasized that to achieve optimum control of infection; it is going to require not only a successful vaccination program but also strategic implementation of preventive measures and rapid delivery of medical care.

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