DETERMINISTIC MODEL FOR WEST AFRICAN EBOLA EPIDEMIC GROWTH DYNAMICS

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I thank God for everything in my life. I appreciate the immense support and guidance of my supervisor, Dato' Prof. Dr. Zuhaimy Ismail. I will ever be thankful to him for weaning me to scholarship. I am so thankful to my wife and children for being there in my aloneness. I thank my brothers and sisters for refreshing my home and family while being away. I thank you all, my friends.

ABSTRACT

Previous models of Ebola epidemic growth in the affected populations of West Africa such as found in the literature have insufficient consideration of the preventive and control compartments for the models. This had led to inaccurate estimation of Ebola virus disease reproduction number and insufficient quantitative information for policy decision making of Ebola outbreak control. An improvement over those models by using additional class specifications that fully represent the Ebola epidemic dynamics is necessary. In this research, a new deterministic epidemic growth model which explains Ebola growth dynamics alongside preventive and control strategies was proposed. The Susceptible-Vaccined-Exposed-Quarantine-Infected-Hospitalised-Funeral-Recovered (SVEQIHFR) stability analysis showed that the disease-free equilibrium and the unique endemic equilibrium are asymptotically stable both locally and globally. Next generation matrix was used to determine the model threshold parameter. The threshold was found to represent the average individuals infected due to transmission from the community, hospitals and funeral events. The SVEQIHFR model was fitted to the Ebola cumulative incidence and death data of Guinea, Liberia and Sierra Leone outbreaks, collected from World Health Organization (WHO) and Center for Disease Control (CDC). Nonlinear least square method was used to estimate the model parameters and their confidence intervals were calculated using the bootstrapping method. Ebola epidemic growth threshold was estimated to be 1.28, 1.72 and 1.89 for outbreaks in Guinea, Liberia and Sierra Leone respectively. The model predicted the Ebola epidemic final size in Guinea, Liberia and Sierra Leone with 98%, 99.03% and 98.4% precision and Root Mean Square Error (RMSE) values of 0.1135, 0.1216 and 0.1167, respectively. Meanwhile the Mean Average Percentage Error (MAPE) were 22.1%, 33.2% and 20.2% for infected cases in the respective countries. Latin Hypercube Sampling (LHS) or Partial Rank Correlation Coefficient (PRCC) procedure was implemented to carry out uncertainty analysis for the model's estimated parameters of Ebola transmission and prevalence outcome variables. It was proven that transmission coefficients and effective isolation, safe burial, effective identification and tracking of Ebola victims are critical to breaking Ebola transmission and prevalence. This model has comprehensively represented the dynamics of Ebola virus disease growth in the populations. It can help international agencies and affected countries' public health administrators to plan for prevention and control of the spread of Ebola virus disease. The model can also be used to study similar outbreaks in the future.

ABSTRAK

Model-model terdahulu bagi pertumbuhan epidemik Ebola dalam kalangan populasi Afrika Selatan yang terjejas seperti yang terdapat dalam literatur mempunyai aspek pencegahan dan kawalan yang kurang mencukupi bagi model tersebut. Ini telah membawa kepada ketidaktepatan anggaran angka pembiakan penyakit Ebola dan ketidakcukupan data kuantitatif untuk penggubalan dasar bagi pengawalan wabak Ebola. Penambahbaikan ke atas model-model tersebut dengan menggunakan spesifikasi kelas tambahan yang mewakili dinamik epidemik Ebola sepenuhnya adalah diperlukan. Dalam kajian ini, satu model baharu pertumbuhan epidemik berketentuan yang menerangkan tentang dinamik pertumbuhan Ebola di samping strategi pencegahan dan kawalan telah dicadangkan. Analisis kestabilan Susceptible-Vaccined-Exposed-Quarantine-Infected-Hospitalised- Funeral-Recovered (SVEQIHFR) menunjukkan bahawa keseimbangan bebas-penyakit dan keseimbangan wabak unik adalah stabil secara asimptot, kedua-duanya secara tempatan dan sejagat. Matriks generasi mendatang telah digunakan untuk menentukan model parameter ambang. Nilai ambangnya didapati mewakili purata individu yang dijangkiti akibat daripada aktiviti penjangkitan melalui komuniti, hospital dan acara pengebumian mayat. Model SVEQIHFR telah dipadankan dengan data kejadian dan kematian terkumpul Ebola di Guinea, Liberia dan Sierra Leone, dikumpul daripada Pertubuhan Kesihatan Dunia (WHO) dan Pusat Kawalan Penyakit (CDC). Kaedah kuadrat terkecil tak linear telah digunakan untuk menganggar parameter model dan selang keyakinannya dihitung menggunakan kaedah tarikan gantian rawak. Nilai ambang pertumbuhan epidemik Ebola dianggarkan bernilai 1.28, l.72 dan 1.89 bagi wabak masing-masing di Guinea, Liberia dan Sierra Leone. Model tersebut meramalkan saiz terakhir epidemik Ebola di Guinea, Liberia dan Sierra Leone masing-masing dengan ketepatan 98%, 99.03% dan 98.4% dan nilai Ralat Punca Min Kuasa Dua (RMSE) pada 0.1135, 0.1216 dan 0.1167. Manakala, Ralat Peratusan Purata Min (MAPE) adalah 22.1%, 33.2% dan 20.2% bagi kes jangkitan di negara masing-masing. Tatacara Hiperkubus Latin (LHS) atau Pekali Korelasi Pangkat Separa (PRCC) telah digunakan bagi menjalankan analisis ketakpastian ke atas model parameter anggaran bagi pembolehubah-pembolehubah anggaran penjangkitan dan hasil penyebaran Ebola. Terbukti bahawa pekali-pekali penjangkitan dan pengasingan yang berkesan, pengebumian yang selamat, pengenalpastian dan penjejakan mangsa Ebola yang berkesan sangat penting dalam menyekat penjangkitan dan penyebaran Ebola. Model ini telah dapat mewakili secara komprehensif dinamik pertumbuhan virus penyakit Ebola dalam kalangan populasi-populasi. Ia boleh membantu agensi- agensi antarabangsa dan kementerian kesihatan awam di negara-negara yang terjejas untuk merancang pencegahan dan pengawalan sebaran virus penyakit Ebola. Model ini juga boleh digunakan untuk mengkaji wabak serupa pada masa akan datang.

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LIST OF ABBREVIATIONS

EVD	-	Ebola Virus Disease
CFR	-	Case Fatality Ratio
CDC	-	Centre for Disease Control and Protection
WHO	-	World Health Organization
ETU	-	Ebola Treatment Unit
NMS	-	Nelder-Mead Simplex method
LSM		Least Square method
MLE		Maximum Likelihood Estimate
CI	-	Confidence Interval
RMSE	-	Root Mean Squared Error
MAPE	-	Mean Absolute Percentage Error
SA	-	Sensitivity Analysis
UA	-	Uncertainty analysis
LHS	-	Latin Hypercube Sampling
PRCC	-	Partial Rank Correlation Coefficient
MCMC	-	Markov Chain Monte Carlo
SEIHFR	-	Susceptible Exposed Infected Hospitalized Funeral Removed
SEIR	-	Susceptible Exposed Infected Removed
SEEIH(DB)R	-	Susceptible Exposed Exposed(hospital) Infected Hospitalized (Dead Buried) Recovered
SEIIIHHFR	-	Susceptible Exposed Infectious Infectious(dead) Infectious(recovered) Hospitalized(non) Hospitalized Funeral Removed
SEIIFR	-	Susceptible Exposed Infected Infectious Funeral Recovered
SEIIHHFRR	-	Susceptible Exposed Infected Infectious Hospitalized(non) Hospitalized Funeral Removed Recovered
SEIFRD	-	Susceptible Exposed Infected Funeral Removed

		Dead
SEI-(CCC/ETC)R	-	Susceptible Exposed Infected -(Community Care Centre/Ebola Treatment Centre) Removed
SEI(LH)BRC	-	Susceptible Exposed Infected (Latent Hospital) Buried Recovered Completely (Removed).
SSEIHR	-	Susceptible (probable) Susceptible(confirmed) Exposed Infected Hospitalized Recovered
SEIHCR	-	Susceptible Exposed Infected Hospitalized Control Recovered
SEIIHFR	-	Susceptible Exposed Infected Infectious Hospitalized Funeral Recovered
SVEEIJDR	-	Susceptible Vaccinated Exposed Exposed Infected Isolated Dead Recovered
SEIHRDB	-	Susceptible Exposed Infected Hospitalized Removed Dead Buried
SEIT	-	Susceptible Exposed Infected Treatment
SEIRD	-	Susceptible Exposed Infected Removed Dead
SSEQIHR	-	Susceptible Exposed Quarantined Infected Hospitalized Recovered
SSVEIHR	-	Susceptible(probable) Susceptible(confirmed) Vaccine Exposed Infected Hospitalized Recovered
SEIIFDR	-	Susceptible Exposed Infected Infectious Funeral Dead Recovered
SEI(HF)R	-	Susceptible Exposed Infected (Hospital Funeral) Recovered
SSEEIIR	-	Susceptible(unvaccinated) Susceptible(vaccinated) Exposed Exposed(quarantined) Infected Infectious Removed
$SS_NS_QP_NP_QC_NC_QR_RR_DR_ND$	-	Susceptible (Non-quarantine Quarantine) Probable(Quarantined Non-quarantine) Confirmed (Quarantined Non-quarantined)

		Removed (Recovered Death Natural Death) Dead
SEIDUQPHRK	-	Susceptible Exposed Infected Dead Unclear Qualified Probable Hospital Recovered (infectious) K(recovered non-infectious)
SEIIRRD	-	Susceptible Exposed Infected(Early) Infectious (Late)Recovered Recovered(Immuned) Dead
SEIRRRH	-	Susceptible Exposed Infectious Removed (Buried)Removed (Infectious) Removed(Recovered)Hospitalized

LIST OF SYMBOLS

N	-	total population size of a country
λ	-	force of infection
β_I	-	transmission coefficient in the community at the onset of the epidemic
β_H	-	transmission coefficient in the hospital
β_F	-	transmission coefficient during unsafe burial
ψ	-	safe burial efficiency
ρ	-	isolation efficiency
γ	-	rate of probable individuals being quarantined
ξ	-	vaccination rate
η	-	efficacy of the vaccine
α_1	-	the rate at which non-quarantined become infectious
α_2	-	the rate which quarantined individuals are isolated
θ	-	the proportion of infectious individuals that are isolated
χ	-	rate asymptomatic latent individuals are quarantined
δ_1	-	the case fatality rate of non-isolated individuals
δ_2	-	the case fatality rate of isolated individuals
γ_I^{-1}	-	average time from symptoms onset to recovery (in days)
γ_H^{-1}	-	average time from hospitalization to recovery (in days)
γ_F^{-1}	-	average time from death to burial/removal (in days)
γ_{IF}^{-1}	-	average time from symptoms onset to death (in days)
γ_{IH}^{-1}	-	average time from symptoms onset to hospitalization
γ_{HF}^{-1}	-	mean duration from hospitalization to deaths
R_0	-	basic reproduction number

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CHAPTER 1

INTRODUCTION

1.0 Introduction

This chapter introduces the thesis. It describes the background to the research problem. It further explains the research problem statement, the aim and objectives of the study, scope and limitation of the study, significance and motivation of study. The chapter finally outlines the thesis structure by summarizing each chapter.

1.1 Motivation

The Guinea Ebola outbreak infected over 28,000 individuals and killed nearly half the number infected in the West African region. Even though WHO declared West Africa Ebola epidemic to be a 'public health emergency of international concern', on August 8th, 2014 (WHO Ebola Response Team, 2014), it spread to more than 5 countries in the region (Guinea, Liberia, Sierra Leone, Nigeria Mali and Senegal), adversely affecting Guinea, Sierra-Leone, and Liberia. It became clear for every nation to be watchful and proactively plan to contain the epidemic, should the disease be transmitted into a country (Gomes *et al.*, 2014). Ebola is an extensively, severe and uncontrollable infectious disease (Poletto *et al.*, 2014; Shrivastava *et al.*, 2015) that broke out from 22nd March 2014 until September 2015.

Ebola outbreaks have been studied based on SEIR-variant epidemic models (Legrand *et al.*, 2007; Althaus, 2014; Rivers, 2014; Browne *et al.*, 2015; Shen *et al.*, 2015; G. Chowell *et al.*, 2015). Re-emergent of Ebola outbreak and its rapid spread

across borders having high case fatality rate makes it suitable for investigation. Ebola epidemic outbreak is currently ravaging the Democratic Republic of Congo (Gatherer, 2018; Barry *et al.*, 2018).

The need for quantitative information is enormous for epidemic control decisions. How brief and sufficient information is, depends on the dimension of an epidemic model. If a model considered more disease stages, control measures and population dynamics, the model will explain the biological reality of the disease better, and the derived information will accurately gauge control decisions.

Ebola epidemic model should have sufficient parameters characterising preventive and control strategies, disease characteristic and population dynamics. It should also accurately assess final outbreak scale and the sensitivity of the model to changes in the model parameters. Therefore epidemic model should be refined, without compromising reality with simplification, to include disease characteristic in the population amidst preventive or control measures.

Until recently, Ebola had no vaccine, among other interventions for effective prevention of the outbreak. Assessing the impact of this measure will provide information on the effective plan for providing vaccine among the affected populations.

1.2 Research Background

Outbreaks of detected and undetected infectious diseases will continue to shock humanity. Knowledge has to envision the future and carry out investigations to cope with dreadful or tragic days of epidemic outbreaks. Therefore studies to overcome epidemic predicament by proactively modelling epidemic dynamics in

order to optimally quantify preventive and controls interventions strategies for stalling ongoing or future outbreaks is necessary. Moreover, when an epidemic spreads relatively quickly across a large number of susceptible individuals, public health administrators need timely and accurate information that enables them to effectively manage the growth of the epidemic.

At the onset of Ebola virus disease outbreak, there had been attempts by researchers, making use of interim data, to study and estimate disease incidences using different epidemiological methods. Their findings had helped determine the type and degree of intervention control measures required to prevent the spread of Ebola disease.

Foretelling the future of epidemic is important in assessing the impact of preventive or control practices upon the disease growth. Correct prediction depends on correct estimation of model parameter values using the existing outbreak data. Therefore appropriate choice of parameters to be estimated or prefixed will essentially reduce epidemic forecast imprecision. Epidemic models that incorporated sufficient disease state variables and parameters can provide a high forecast precision of Ebola epidemic growth.

Until recently there had not been vaccines for Ebola epidemic among humans except for animals (Ye and Yang, 2015) with the trial for humans being underway, Galvani *et al*.(2014) attempts to model disease control using vaccine. Trials of Ebola vaccine had been conducted in Guinea, Liberia and Sierra Leone (Bellan *et al.*, 2014; Henao-restrepo *et al.*, 2015; David *et al.*, 2017) with some degrees of efficacy. While some studies had considered some control measures (Chowell and Nishiura, 2014; Rivers *et al.*, 2014; Eisenberg *et al.*, 2014; Webb *et al.*, 2015), they did not incorporate all technically feasible intervention and control measures that were deployed. Therefore controlling Ebola epidemic requires concerted efforts through aggressive implementation of more comprehensive control strategies including public enlightenment, contact tracing, isolation and reformed burial practices.

Undertaking an erroneous procedure to investigating a disease dynamics will adversely affect planning and efficient management of the outbreaks. Consequently, studies have to formulate models and accurately assess the growth of Ebola based on comprehensive implementable prevention and control factors including vaccine, contact tracing, quarantine, isolation and safe burial. In addition to understanding the transmission dynamics of Ebola, the epidemic models will provide quality and quantitative information for proper management of the outbreak. This study attempts to incorporate intervention measures than were ever attempted.

1.3 Problem Statement

Studies had been undertaken to investigate growth of Ebola disease outbreak in populations. These attempts to model Ebola are based on some factors while not considering some disease and prevention or control compartments, thereby inadequately representing disease dynamics amidst population and control factors. Such models do not provide detail quantitative information for managing Ebola outbreak. In the high-dimensioned Ebola dynamics models there had not been analytical proves of stability to validate the application of the model on the growth dynamics of Ebola in a population.

Due to some model structures and assumptions adopted in estimating model parameters and epidemic size in other studies, the Ebola disease transmission rate and Ebola epidemic size in the affected populations had been inaccurately estimated. Furthermore, sensitivity analysis of Ebola prevalence to model parameter changes, which can help understand behaviour of the endemic equilibrium state of infectious state variables, have never been attempted for Ebola outbreak analysis.

This study will model Ebola outbreak based on comprehensive preventive and control factors employed amidst the population dynamics. The study will proof the stability of the high-dimensioned epidemic model at both disease-free and endemic equilibria. Furthermore a newer technique for sensitivity analysis of the model's state variables at endemic equilibrium points will be developed to investigate the changes of endemic equilibrium points as model parameters change.

1.4 Research Questions

The study seeks to respond to the following research questions:

i. Is the Ebola growth dynamics model stable at both disease free equilibrium and endemic equilibrium?
ii. How accurate can Ebola growth dynamics model estimate the final size of the outbreak?
iii. How influential are model parameters to Ebola virus disease transmission and prevalence?
iv. How significant is the uncertainty associated with a model parameter to model outcome variables' estimation?

1.5 Objectives of the Study

The objectives of this study are to:

i. Design and construct an Ebola epidemic growth model for West Africa Ebola outbreak that is stable and robust
ii. Prove the model stability at disease-free and endemic equilibrium

iii. Design a new algorithm that optimises the model parameters using Least Squares Method

iv. Perform uncertainty and sensitivity analysis (perturbation) for determining the most influential parameters affecting Ebola disease transmission and prevalence.

1.6 Scope and Limitation of Study

In the past, several Ebola outbreaks had been recorded on different scales and geographic spread, but the extent of West Africa Ebola outbreak had surpassed all. Therefore Ebola outbreak cannot be fully investigated due to diversity and complicity in the outbreaks across different countries and continents. This study focuses on the three most affected countries - Guinea, Liberia, and Sierra Leone. This is partly justified by the severity of the outbreak, volume and availability of data from these countries compared to other affected West African countries like Nigeria, Mali, Senegal and Cote d'Ivoire.

The model is structured based on SEIR-variant epidemic model structure. Though there are other forms (object, droplet, aerosol, reservoir-to-human, environment-to-human)(Judson *et al.*, 2015) through which Ebola virus can be transmitted, the model considered the human-to-human transmission of Ebola virus in the community, hospital and during funeral by coming in contact with body fluid of infected infectious individual or Ebola-induced death victim.

This research covered 541 days of Ebola epidemic starting from 22nd March 2014 to 14th September 2015. This study uses outbreak dataset of cumulative infected and deaths case collected from Centre for Disease Control (CDC, 2016). The data is used to estimate parameters for the disease progression and control parameters in the affected countries. Though our model made use of data covering a

long period of the outbreak, our estimates could be marred with some degree of errors that affected data collection. It is due to the fact that Ebola incidence and deaths cases are collected while the outbreak was ongoing, under extreme conditions therefore inherent data collection errors will affect epidemic size estimates.

Deterministic epidemic models provide quantitative information for large community or population, in deterministic models disease states and control factors are compartmentalized. In stochastic models, states of individuals change at every discrete-time step in a probabilistic manner. Though stochastic modelling of disease is preferred when studying a small community, deterministic epidemic models are suitable for large scale spatiotemporal epidemic outbreak analysis.

Assumptions influence epidemic model formulation and performances because they specify and limit approaches to formulation and analysis procedure. In this study homogenous mixing among the population, immunity after recovery from the disease, and methods of disease transmission also dictated the Ebola virus disease model structure.

The uncertainty associated with prefixed parameters influences performances of epidemic models. In this study simulation is carried out using a range of parameter's value, in order to minimize the influence of variance on estimated parameters. Analyzing the uncertainty and sensitivity of the model performance to parameter changes only provides insight but not correcting the deviation. This study provided a wider overview of uncertainty analysis of parameter changes to model response variables in order to ascertain the influence of model parameters changes.

1.7 Significance of the Study

The Ebola outbreak in Guinea had prompted researchers to model the outbreak dynamics by incorporating preventive and control intervention strategies. In attempting to contain Ebola outbreak empirically, the evaluation of dynamics and growth of epidemic will be needed to provide quantitative information for policy making or outbreak management decision making. Estimated Ebola epidemic control parameter values will inform public health administrators on how much resources is required for Ebola control.

Over the years disease control agencies like the World Health Organization, (WHO) and Centre for Disease Control and Prevention (CDC) decide on optimal resource allocation for effective intervention, control implementation plans to contain epidemic outbreaks. They were been able to do so because of findings from studies that comprehensively modelled Ebola with control interventions amidst disease and population dynamics. Hence findings of this study will contribute to effective preventive or control interventions deployment strategy.

While SEIR epidemic model, had broadly classified epidemic dynamics of diseases, SEIR- variants are usually formulated to incorporate prevention and control factors that resulting into more compartments that represent the disease characteristics. This study adopted this advantage in order to investigate the Ebola growth in Guinea, Liberia and Sierra Leone. This study advances the course of research on infectious disease transmission dynamics. The model is expected to be used to study similar infectious disease outbreak in the future. Publications of this study will add to the literature of Ebola epidemic growth dynamics.

1.8 Thesis Organization

This section outlines the research process. It summarizes what is done in each chapter.

Chapter 1 introduces the thesis. It describes the overall research background. It describes the research problem statement, aim and objectives of the study, scope and limitation of the study, significance of the study and motivation. This chapter provides the overview, goal and purpose of this research.

Chapter 2 reviews related literature of this study, the review guided the development of the research problem and objectives. It reviewed methodologies, techniques, and guidelines that have been used to solve similar studies of Ebola growth. The disease epidemic and brief exposition on the cases of study is highlighted in this chapter. The review helped determine the solution approach adopted for the investigation of Ebola epidemic growth in this study.

Chapter 3 explains the methodology of the research including Ebola growth modelling process and mathematical background steps for performing epidemic model stability analysis. The chapter explained the next-generation matrix approach for determining the epidemic model threshold. Algorithm for least square parameter estimation, implementing Nelder-Mead simplex was also explained. The chapter also explained the methodology for normalized sensitivity index of state variables at endemic equilibrium points and Latin hypercube sampling/partial rank correlation coefficient (LHS/PRCC) procedure that is used for carrying out sensitivity and uncertainty analysis of Ebola epidemic model.

Chapter 4 accounts for the modelling process of Ebola growth. It provides a schematic flow diagram of the disease transmission and transition rates resulting into a system of ordinary differential equations explaining the dynamics of Ebola growth.

In this chapter, the threshold of Ebola model is determined using next-generation matrix approach. The model stability analysis is performed by proving mathematical theorems using the Routh-Hurwitz criterion and construction of Lyapunov functions.

Chapter 5 accounts for Ebola epidemic growth model parameter estimation. The estimation made use of nonlinear least square method that implemented the Nelder-Mead simplex (NMS) algorithm. In this chapter, the basic reproduction number of Ebola outbreaks in the affected countries is estimated. The 95% confidence interval of the estimated parameter and the basic reproduction are determined. Furthermore forecasting Ebola outbreak epidemic final size for each country is determined with forecast performance and forecast precision error of the model aptly evaluated.

In Chapter 6, sensitivity and uncertainty analysis of the model response to its parameter changes are analyzed. Sensitivity index of disease transmission and disease prevalence to model parameter changes are determined. For the sensitivity index of Ebola prevalence, a new approach is implemented to assess the sensitivity index of the state variables at equilibrium points. For uncertainty analysis, Latin hypercube sampling and partial rank correlation coefficient procedure are implemented to assess the strength and relationship of uncertainty in model parameters changes to model outcome variables (disease transmission, the total number infected and the total number hospitalized).

Finally, Chapter 7 summarizes the research, by providing the summary, conclusion and an outlined research findings and contributions to knowledge. It further suggests studies that can resolve some limitations of this research work in the future.

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