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UNIVERSITI PUTRA MALAYSIA

MATHEMATICAL MODELING AND ANALYSIS OF DENGUE TRANSMISSION DYNAMICS

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By

SALISU MOHAMMED GARBA

Thesis submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

October 2008

DEDICATION

This thesis is dedicated in memory of my late brother, Rabiu Garba Mohammed, who passed away on Friday, 9th May, 2008 in a tragic car accident in Nigeria. My heart, love and prayers are always with him. May his soul rest in peace, Amin.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosaphy.

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October 2008

Chairman: Mohd Rizam Bin Abu Bakar, PhD.

Faculty: Science.

The work in this thesis is based on the design and analysis of suitable compartmental deterministic models for the transmission dynamics of dengue fever in a population. A basic dengue model which allows transmission by exposed humans and mosquitoes is developed and rigorously analysed. The model, consisting of seven mutually-exclusive compartments representing the human and vector dynamics, has a locally-asymptotically stable (LAS) disease-free equilibrium (DFE) whenever a certain epidemiological threshold, known as the basic *reproduction number* (R_o) is less than unity. Further, the model exhibits the phenomenon of backward bifurcation, where the stable DFE co-exists with a stable endemic equilibrium. The epidemiological consequence of this

phenomenon is that the classical epidemiological requirement of making R_o less than unity is no longer sufficient, although necessary, for effectively controlling the spread of dengue in a community. The model is extended to incorporate an imperfect vaccine against the strain of dengue. In both the original and the extended models, it is shown, using Lyapunov function theory and LaSalle Invariance Principle, that the backward bifurcation phenomenon can be removed by substituting the associated standard incidence function with a mass action incidence. In other words, in addition to establishing the presence of backward bifurcation in models of dengue transmission, this study shows that the use of standard incidence in modelling dengue disease causes the backward bifurcation phenomenon of dengue disease.

The model is extended to include the dynamics of two strains of dengue disease. The extended model has a locally-asymptotically stable, disease-free equilibrium (DFE) whenever the maximum of the associated *reproduction numbers* of the two strains (denoted by R_o) is less than unity. It is also shown, using a Lyapunov function and LaSalle Invariance Principle, that the DFE of the model, in the absence of dengue-induced mortality, is globally-asymptotically stable whenever $R_o<1$. The two strains co-exist if the reproduction number of each strain exceeds unity (and are different). For the case when the two reproduction numbers exceed unity but are equal, a continuum of co-existence equilibria exists. The impact of cross-immunity is explored for the case when $R_o >1$. It is shown that

the model can have infinitely many co-existence equilibria if infection with one strain confers complete immunity against the other strain. However, if infection with one strain has no effect on susceptibility to the other strain, the model can have a unique co-existence equilibrium. It is shown that cross-immunity could lead to disease elimination, competitive exclusion or co-existence of the strains. Further, the effect of seasonality on dengue transmission dynamics is explored using numerical simulations. It is shown that the oscillation pattern differs between the strains, both in their subharmonic periods and the relative phase of cycles, depending on the degree of the cross-immunity between the strains.

Finally, a deterministic model for monitoring the impact of treatment and vector control strategy on the transmission dynamics of dengue in the human and vector populations is formulated. In addition to having a locally-asymptotically stable disease-free equilibrium (DFE) whenever R_o is less than unity, it is shown, using a Lyapunov function and LaSalle Invariance Principle, and using comparison theorem that the DFE of both treatment-free and treatment model, in the absence of dengue-induced mortality, is globally-asymptotically stable whenever R_o <1; each of the models has a unique endemic equilibrium whenever its reproduction number exceed unity. Numerical simulations shows that, the use of vector control strategies can result in the effective control of dengue in a community by reducing the population of susceptible and exposed mosquitoes.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah.

PEMODELAN BERMATEMATIK DAN PENGANALISISAN TERHADAP KEDINAMIKAN PENULARAN DENGGI

Oleh

SALISU MOHAMMED GARBA

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Hasil kerja tesis ini berdasarkan kepada reka bentuk dan analisis terhadap kesesuaian model berbahagian ketentuan untuk dinamik penularan demam denggi pada populasi. Model asas denggi yang melibatkan penularan oleh manusia dan nyamuk yang terdedah dibina dan dianalisis secara rapi. Model ini, yang mengandungi tujuh bahagian saling-eksklusif mewakili manusia dan dinamik vektor, stabil secara asimptot-setempat (LAS) keseimbangan bebas-jangkitan (DFE) bila mana ambang wabak tertentu, yang dikenali sebagai nombor asas pembiakan (R_o), kurang dari unitari. Selanjutnya, model mempamerkan fenomenon percabangan ke belakang, yang mana kestabilan DFE

wujud bersama dengan keseimbangan endemik stabil. Akibat fenomena epidemiologi ini yang mana epidemiologi klasik memerlukan $R_o < 1$ adalah tidak lagi cukup, walaupun perlu, untuk mengawal penularan denggi dalam komuniti secara berkesan. Model diperluas dengan menggabungkan vaksin yang tidak sempurna menentang strain denggi. Menggunakan teori manifold berpusat, model yang diperluas juga cenderung untuk mengalami fenomena pendwicabangan ke belakang. Dalam kedua-dua model asal dan model yang diperluas, ia tertunjuk, menggunakan teori fungsi Lyapunov dan prinsip tak varian LaSalle, yang fenomena pendwicabangan ke belakang boleh dihapuskan dengan pengantian fungsi kejadian piawai bersekutu dengan insidens tindakan jisim. Dengan kata lain, selain dari pengujudan kehadiran percabangan ke belakang di dalam model penularan denggi, kajian ini menunjukkan penggunaan insidens piawai di dalam pemodelan jangkitan denggi menyebabkan fenomena pendwicabangan ke belakang jangkitan denggi.

Model diperluas dengan memasukkan dinamik dua strain jangkitan denggi. Model yang diperluas mempunyai kestabilan asimptot-tempatan keseimbangan bebas-jangkitan (DFE) bila mana nombor maksimum pembiakan bersekutu oleh dua strain (ditandakan oleh R_o) adalah kurang dari unitari. la juga menunjukkan, menggunakan fungsi Lyapunov dan prinsip tak varian LaSalle, DFE terhadap model, dalam ketiadaan kematian denggi-teraruh, adalah stabil secara asimptot-sejagat bila mana $R_o < 1$. Dua strain wujud bersama jika nombor pembiakan

setiap strain melebihi unitari (dan berbeza). Untuk kes, apabila kedua-dua nombor pembiakan melebihi unitari dan sama, wujud kontinum kewujudan bersama. Kesan keimunan-silang diterokai untuk kes apabila $R_o > 1$. Ia menunjukkan model boleh mempunyai keseimbangan wujud bersama tak terhingga banyak jika jangkitan dengan satu strain saling keimunan sepenuhnya terhadap strain yang lain. Walau bagaimana pun, jika jangkitan dengan satu strain tidak mempunyai kesan terhadap rentanan terhadap strain yang lain, model boleh mempunyai keseimbangan kewujudan-bersama yang unik. Ia tertunjuk bahawa keimunan-silang boleh menyebabkan penghapusan wabak penyakit, penghapusan secara kompetitif atau kewujudan-bersama wabak. Seterusnya, kesan bermusim bagi dinamik penularan denggi dijelajahi menggunakan simulasi berangka. Ia menunjukkan pola gerakan berkala tidak sama antara dua strain, kedua-dua di dalam tempoh subharmonik dan kitaran fasa relatif, bergantung kepada darjah keimunan-silang di antara dua strain.

Akhir sekali, model ketentuan untuk pengawasan kesan rawatan dan strategi kawalan vektor terhadap penularan dinamik denggi terhadap manusia dan populasi vektor dirumus. Selain mempunyai kestabilan asimptot-tempatan keseimbangan bebas-jangkitan (DFE) bila mana R_o kurang dari unitari, ia tertunjuk, menggunakan fungsi Lyapunov dan prinsip tak varian LaSalle dan mengunakan teori perbandingan yang mana DFE bagi kedua-dua model bebas rawatan dan model rawatan, di dalam ketidak hadiran kematian denggi-teraruh,

stabil secara asimptotik-sejagat apabila $R_o < 1$; setiap model mempunyai keseimbangan endemik unik apabila nombor pertumbuhan melebihi unitari. Simulasi berangka menunjukkan, penggunaan strategi kawalan vektor boleh membawa kepada kawalan denggi yang efektif di dalam komuniti dengan mengurangkan populasi nyamuk yang rentan dan yang terdedah kepada denggi.

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Praise and thanks to Almighty ALLAH for the wonderful guidance, good health and direction (Alhamdulillah).

I certify that an Examination Committee met on 9th October, 2008 to conduct the final examination of Salisu Mohammed Garba on his Doctor of Philosophy thesis entitled "mathematical modeling and analysis in dengue transmission dynamics" in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The committee recommends that the candidate be awarded the relevant degree.

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This thesis was submitted to the senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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SALISU MOHAMMED GARBA

Date:

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GLOSSARY OF TERMS

DFE	Disease Free Equilibrium
LAS	Locally Asymptotically Stable
GAS	Globally Asymptotically Stable
EEP	Endemic Equilibrium Point
DF	Dengue Fever
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
SI	Susceptible-infectious
SIS	Susceptible-Infectious- Susceptible
SIR	Susceptible-Infectious- Recovered/immune
SIRS	Susceptible-Infectious-Recovered/immune-Susceptible
SEIR	Susceptible-Exposed-Infectious- Recovered/immune
SEIRS	Susceptible-Exposed-Infectious-Recovered/immune-Susceptible
CDC	Center for Disease Control
CVD	Center for Vaccine Development
IPCC	Intergovernmental Panel on Climate Change
WHO	World Health Organization
CFR	Case Fatality Rate

CHAPTER 1

INTRODUCTION

1.1 Introduction

Dengue, a mosquito-transmitted disease caused by any of four closely-related virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) of the genus *Flavivirus*, is endemic in at least 100 countries in Africa, the Americas, the Eastern Mediterranean and subtropical regions of the world [35, 107], inhibited by over 2.5 billion people. Dengue ranks second to malaria amongst deadly mosquito-borne diseases, each year claiming about 100 million infections and 20,000 deaths globally [107]. Classical dengue fever causes relatively mild morbidity and mortality, and sufferers recover within one to two weeks after the onset of fever [63]. However, some individuals develop dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) [71], where the severity of the disease is drastically increased (with mortality ranging from 5-15%) [63, 79]. Figures from the World Health Organization show that hundreds of thousands of cases of DHF are recorded annually [16, 17, 117].

Dengue is transmitted to humans through mosquito bites. Female mosquitoes (of the genus Aedes (Stegomyia), mainly the *Aedes aegypti* [9]) acquire infection by taking a blood meal from an infected human (in the viremic phase of illness). These mosquitoes, after becoming infectious, then pass the disease to suscep-

tible humans. Individuals who recover from one serotype become permanently immune to it, but may become partially-immuned or temporarily-immuned (or both) to the other serotypes [117].

Unfortunately, there is still no specific effective treatment for dengue. Persons with dengue fever should rest and drink plenty of fluids. They should be kept away from mosquitoes for the protection of others [30, 44]. Dengue hemorrhagic fever is treated by replacing lost fluids. Some patients need transfusions to control bleeding.

Although there is no effective and safe vaccine for dengue at the moment, a number of candidate vaccines (including live attenuated mono- and tetra-valent formulation, inactivated whole virus vaccines, and recombinant subunit vaccines) are undergoing various phases of clinical trials ([16, 17, 30, 31, 45, 73, 84, 104, 117, 118]) However, it is believed that any future dengue vaccine would not be able to offer perfect protection against all serotypes. Thus, any future dengue vaccine is expected to be imperfect [31]. Efficacy trials in human volunteers have yet to be initiated. Research is also being conducted to develop second-generation recombinant vaccine viruses. Therefore, an effective dengue vaccine for public use will not be available for 5 to 10 years. Prospects for reversing the recent trend of increased epidemic activity and geographic expansion of dengue are not promising. New dengue virus strains and serotypes will likely continue to be introduced into many areas where the population densities