PAN AFRICAN UNIVERSITY

INSTITUTE FOR BASIC SCIENCES, TECHNOLOGY AND INNOVATION

MATHEMATICAL MODELS FOR INFLUENZA A VIRUS AND PNEUMOCOCCUS: WITHIN–HOST AND BETWEEN–HOST INFECTION

By

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Award of the Degree of Doctor of Philosophy in Mathematics of Pan African University Institute for Basic Sciences, Technology and Innovation

April 1, 2019

DECLARATION

I, **Fulgensia Kamugisha Mbabazi** declare that this submission is my own work towards the Ph.D mathematics and that, to the best of my knowledge it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University or College elsewhere, except where due acknowledgment has been made in the text.

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DEDICATION

I dedicate this research work to my dear parents late Gabrael Rwitoka, Tekyera Beturumura and Mary Kebita Okuja. May their souls rest in peace.

ACKNOWLEDGMENT

I give glory to the Almighty God who has made it possible for me to accomplish this research and wish to extend my sincere thanks and appreciation to the following people and institutions.

Pan African University Institute for Basic Sciences, Technology and Innovation, Nairobi–Kenya, Busitema University, Tororo–Uganda and Uganda Martyrs University, Nkozi–Uganda, for the financial support.

My Supervisors Professor Joseph Y.T. Mugisha and Doctor Kimathi Mark for their dedicated guidance, encouragement, devotion, tolerance and all the necessary support rendered to me especially in the field of Mathematical Modeling and Computational Mathematics. May God, bless you plentifully. Professor L.S. Luboobi, your parental guidance and technical support has been a road mark in my achievement, be blessed always!

My husband Major Kamugisha Joram Kembo for loving, encouraging, supporting and accepting me to undertake the programme; may God bless you. My children: Asea James, Kyokusiima Racheal, Kagaiga Joel and Katungi Emmanuel for the care, encouragement, prayers, jokes and loving stories you have always offered; may God guide you to grow into responsible citizens. My friends, thank you for your support in advising me during the programme and paying visits to my children. May God reward you abundantly.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACRONYMS

ODE	Ordinary Differential Equation
DDE	Delay Differential Equation
MATLAB	Matrix Laboratory
HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
IAV	Influenza A Virus
IBV	Influenza B Virus
ICV	Influenza C Virus
IDV	Influenza D Virus
NA	Neuraminidase
HA	Hemagglutinin
IPD	Invasive Pneumococcal Diseases
AM	Alveolar Macrophages
PCV's	Pneumococcal Conjugate Vaccines
SP	Streptococcus Pneumoniae
SIS	Susceptible–Infective–Susceptible
SEI	Susceptible–Exposed–Infective
SIR	Susceptible–Infective–Recovered
SEIR	Susceptible–Exposed–Infective–Recovered

NOMENCLATURE

Withinhost co–infection model of IAV and pneumococcus

S	Population density of uninfected cells
I_v	Population density of infected cells not yet producing IAV
I_b	Density of infected cells not yet producing pneumococcus
I_{vb}	Population density of co–infected cells
V	Total number of influenza A virus
B	Total number of pneumococcus bacteria
A	Alveolar macrophage population
Λ	Recruitment of epithelial cells from the pool of precursor cells
μ_s	Natural death rate for uninfected epithelial cell
r	Bacterial growth rate
γ_a	Phagocytosis rate
τ_b	Creation rate of bacterium by infected epithelial cells
μ_b	Mortality rate of pneumococcus infected cells
β_b	Epithelial cell infection rate per bacterium
δ_b	Toxic death rate due to pneumococcus bacterium
n_b	Released pneumococcus particles from lysis of infected cells

n_v	Released infectious IAV particles from lysis of infected cells
n_{vb}	Free co–infected particles liberated from lysis of infected cells
β_v	Epithelial cell infection rate per virion
β_v^*	Infectivity rate of infected cells by pneumococcus with IAV
β_b^*	Infectivity rate of infected cell by IAV with pneumococcus
α_v	Loss of IAV due to interaction of uninfected cells with SP
α_b	Loss of SP due interaction of uninfected cell with IAV
τ_v	IAV production rate
τ_{vb}	Creation rate of co–infected cells
δ_v	Toxic death rate due to influenza A virus
μ_v	Mortality rate of influenza A virus infected cells
μ_{vb}	Mortality rate of co–infected cells
m	Maximum number of bacteria an AM can catch in a unit time

Between–host pneumococcal pneumonia model with time delays

$S(t)$	Number of susceptible individuals at time t
$V(t)$	Number of vaccinated individuals at time t
$E(t)$	Number of asymptomatic individuals at time t
$C(t)$	Number of people with one sero–type not covered by the vaccine
$I(t)$	Number of infectious individuals at time t
b	Recruitment rate
ν	Effective vaccination rate
γ	Transfer rate from E to I class
μ	Natural mortality rate from causes unrelated to the infection
δ	Disease–induced mortality rate
ρ	Progression rate from C to I class
ϕ	Per capita rate of recovery
ζ	Waning rate of vaccine
ϑ	Proportion of the sero–type not covered by vaccine
β	Transmission coefficient
τ_1	Delay for the incubating individual
τ_2	Delay in seeking medical care

A model for the effect of antibiotic resistance awareness and saturated treatment for pneumococcal pneumonia

$S_u(t)$	Unaware individuals
$S_a(t)$	Aware individuals
$I(t)$	Infected individuals receiving treatment
$R(t)$	Infected individuals but resistant to first line of treatment
$N(t)$	Total population
B	Recruitment by birth/immigration
β	Maximal effective contact rate before awareness
β_1	Maximal reduced effective contact rate due to media alerts
β_2	Contact rate of aware susceptibles with infectives
γ	Rate of relapse encountered in administering treatment
m	Efficiency of awareness through media coverage
δ	Excess death due to disease
ξ	Loss of information about disease by aware susceptibles
Φ	Recovery rate due to treatment
D	Number of days delayed in receiving appropriate treatment
τ	Rate of delay to receive appropriate treatment

p	Probability of acquiring resistance during treatment
v	Rate at which unaware susceptibles become aware

ABSTRACT

Infectious diseases have become problematic throughout the world, threatening individuals who come into contact with pathogens responsible for transmitting diseases. Pneumoccocal pneumonia, a secondary bacterial infection follows an influenza A infection, responsible for morbidity and mortality in children, elderly and immuno–comprised groups. The aims of this Thesis are to; develop a mathematical model for within–host co–infection of influenza A virus and pneumococcus, model between–host pneumococcal pneumonia in order to determine the effect of time delays due to latency and seeking medical care, and study the effect of antibiotic resistance awareness and saturated treatment in the control of pneumococcal pneumonia. Analysis of the stability of steady states of influenza A virus and pneumococcal co–infection, pnemococcal pneumonia with time delays and antibiotic resistance awareness is done. The graph theoretic method, combined linear and quadratic Lyapunov functions, Goh–Voltera Lyapunov function are used to get suitable Lyapunov functions for global stability of steady states. The results show that the endemic equilibrium of pneumococcal pneumonia is locally stable without delays and stable if the delays are under conditions. The results suggest that as the respective delays exceed some critical value past the endemic equilibrium, the system loses stability and yields Hopf–bifurcation. The results of influenza A virus and pneumococcal co–infection show that, there exist a biologically important steady state where the two pathogens of unequal strength co–exist and replace each other in the epithelial cell population when the pathogen fitness for each infection exceeds unity. The impact of influenza A virus onto pneumococcus and vice–versa yields a bifurcation state. The results show that, the presence of antibiotic resistance awareness and treatment during the spread of pneumococcal pneumonia drastically reduces the basic reproduction number R_0 to less than unity, hence the disease could be eradicated.

CHAPTER 1

INTRODUCTION

1.1 Basic information about influenza A virus

Infectious diseases commonly known as communicable diseases, have always besieged animals and humans. Pathogenic microorganisms, such as bacteria, viruses, parasites or fungi spread diseases, directly or indirectly, from one person to another. Examples of bacterial diseases include pneumococcal, Tuberculosis ; Viral infections among others include influenza A virus and HIV/AIDS. Of the main important pathogens affecting humans today are influenza A virus and pneumococcus (Ackleh & Allen, 2003). Infectious diseases are significant and frequently cause human illness that lead to mortality across the globe.

Influenza commonly known as 'flu' is an infectious disease caused by a virus that is categorized in four different types A, B, C and D (IAV, IBV, ICV and IDV), but only influenza A and B viruses cause clinically significant human disease and seasonal epidemics (Ferguson et al., 2015). Influenza is one of the most studied viral infections, interactions and co–infections for respiratory viruses in general (Boianelli et al., 2015). It causes yearly chronic epidemic outbreaks, and individuals become infected several times over their lifetime (Beauchemin & Handel, 2011). They are distinguished by differences in two major virus surface proteins; HA and NA (Kamal et al., 2017). There are 16 diverse types of HA and 9 diverse types of NA. Thus there are potentially 144 diverse subtypes of influenza A viruses (Shi et al., 2010). With these types, virus A is epidemiologically essential for humans because it can recombine its genes with those of strains circulating in animal populations (birds, swine and horses).

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