



CONTROLLING THE SPREAD OF MALARIA: A MATHEMATICAL MODELLING APPROACH

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ABSTRACT

A mathematical model for the transmission dynamics and control of Malaria was developed incorporating the impact of vaccination, standard incidence function, mass treatment and insecticide treatment controls. The effective reproduction number (R_c) was obtained and used to find the best strategy for curbing transmission of the disease. Using Nigerian demographic data, numerical simulations revealed that having a vaccination rate of 50%, insecticide control rate of 25% and a 75% mass treatment control rate, the morbidity of infected humans that are vaccinated will drop significantly to the disease-free equilibrium in less than 10 days while infected humans that are not vaccinated will drop to the disease-free equilibrium in the first 60 days.

Keywords: *Disease-free equilibrium, effective reproduction number, vaccination*

INTRODUCTION

Malaria is a widely spread deadly infectious disease caused by the protozoan parasite of the genus Plasmodium which is transmitted to humans through bites from infected female Anopheles mosquitoes. There exist over one hundred species of the genus Plasmodium involved in malaria infection out of which only five cause malaria in humans. The five species are *P. falciparum*, *P. vivax*,

P. ovale, *P. malariae* and *P. knowlesi*. *Plasmodium falciparum* is the most deadly genus that causes malaria in humans and it predominates in Africa (Olaniyi & Obabiyi, 2013). This genus accounts for over 90% all malaria-attributed deaths and *Plasmodium vivax* accounts for much of the remaining disease burden and it is the dominant *Plasmodium* species in sub-Saharan Africa (Mendis, Sina, Marchesini, & Carter, 2001).

Based on 2013 data, WHO estimated that approximately 584 000 deaths per year were attributable to malaria, with over 90% of these deaths occurring in sub-Saharan Africa, and nearly all of the remaining occurring in South-East Asia, the Indian subcontinent and South America (WHO, 2014). According to the latest estimates from WHO, there were 214 million new cases of malaria worldwide in 2015 (range 149–303 million). The African Region accounted for most global cases of malaria (88%), followed by the South-East Asia Region (10%) and the Eastern Mediterranean Region (2%). In 2015, there were an estimated 438 000 malaria deaths (range 236 000–635 000) worldwide. Most of these deaths occurred in the African Region (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%) (WHO, 2015). Data on malaria from 2015-2017 according to WHO (2018), highlight that no significant progress in reducing global malaria cases was made in this period. There were an estimated 219 million cases and 435,000 related deaths in 2017. This was further emphasized in WHO (2019).

Malaria is a major public health problem in Nigeria where it accounts for more cases and deaths than any other country in the world. Malaria is a risk for 97% of Nigeria's population. The remaining 3% of the population live in the malaria free highlands. Malaria is also the leading cause of clinic attendance and absenteeism in Nigeria. There are an estimated 100 million malaria cases with over 300,000 deaths per year in Nigeria. This compares with 215,000 deaths per year in Nigeria from HIV/AIDS. Malaria contributes to an estimated 11% of maternal mortality (WHO, 2015).

Malaria is probably the only infection that can be treated in just three days but still kills millions every year. Without prompt and appropriate treatment, malaria may become a medical emergency by rapidly progressing to complications and death. Malaria can also aggravate certain pre-existing illnesses and may even prove fatal for patients with end stage organ disease. As a result of the spread of drug-resistant parasites and insecticide-resistant

mosquitoes, in many respects there are now fewer tools to control malaria than existed even 25 years ago. Because of malaria's growing global burden, its control is essential. Historically, vaccines have been one of the most cost-effective and easily administered means of controlling infectious diseases.

In July 2015, RTS,S/AS01 was approved for use by European regulators as not only the world's first malaria vaccine, but the first vaccine licensed for use against a parasitic disease of any kind (Walsh, 2015). Vaccine development efforts have focused on *P. falciparum* and, to a lesser extent, on *P. vivax* (Good, 2011). RTS,S/AS01 is a vaccine against *Plasmodium falciparum*, the most deadly malaria parasite globally, and the most prevalent in Africa. It offers no protection against *P. vivax* malaria, which predominates in many countries outside of Africa. The vaccine is being considered as a complementary malaria control tool in Africa that could potentially be added to – and not replace – the core package of proven malaria preventive, diagnostic and treatment interventions (WHO, 2016).

During the past two decades, Gebremeskel and Krogstad (2015), Olabiyi and Obabiyi (2013), Xiao (2011), Mandal, Sarkar and Sinha (2011), Tumwiine, Luboobi, and Mugisha, (2005), and Ngwa (2004) have designed mathematical models of malaria transmission and control in different parts of the world. Considering the works of the aforementioned authors, a new mathematical model was developed to complement and extend on their works by incorporating the impact of vaccination, standard incidence function mass, treatment and insecticide treatment controls. These factors are very vital in the transmission dynamics and control of malaria especially in developing countries where the disease is endemic.

MATERIALS AND METHODS

Model Development

The total human population (N_H) is divided into five (5) compartments of Susceptible individuals (S), Vaccinated individuals (V), Individuals infected with any of the five genus of Plasmodium (I_1), Individuals infected with any of the four genus of Plasmodium apart from *P. falciparum*, (I_2) and Recovered individuals with substantial immunity (R). The Vector population (N_M) is

divided into two (2) compartments of Susceptible female anopheles mosquitoes (S_M) and Infected female anopheles mosquitoes (I_M). The following assumptions were considered in the construction of the model:

- i. The age structure of the population is not considered
- ii. The latent stage of both human and mosquitoes are not considered

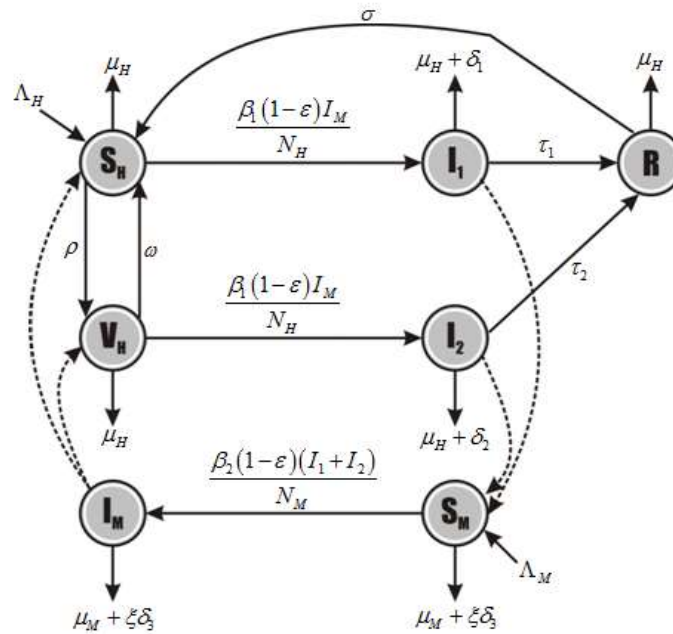


Figure 2.1: Schematic Diagram of Malaria Transmission Dynamics and Control

The corresponding mathematical equations of the schematic diagram is described by a system of ordinary differential equations below:

$$\frac{dS_H}{dt} = \Lambda_H - \frac{\beta_1(1-\varepsilon)S_H I_M}{N_H} + \omega V + \sigma R - (\rho + \mu_H)S_H \quad (1)$$

$$\frac{dV_H}{dt} = \rho S_H - \frac{\beta_1(1-\varepsilon)V_H I_M}{N_H} - (\omega + \mu_H)V_H \quad (2)$$

$$\frac{dI_1}{dt} = \frac{\beta_1(1-\varepsilon)S_H I_M}{N_H} - (\tau_1 + \delta_1 + \mu_H)I_1 \quad (3)$$

$$\frac{dI_2}{dt} = \frac{\beta_1(1-\varepsilon)V_H I_M}{N_H} - (\tau_2 + \delta_2 + \mu_H)I_2 \quad (4)$$

$$\frac{dR}{dt} = \tau_1 I_1 + \tau_2 I_2 - (\sigma + \mu_H) R \quad (5)$$

$$\frac{dS_M}{dt} = \Lambda_M - \frac{\beta_2(1-\varepsilon)(I_1 + I_2)S_M}{N_M} - (\xi\delta_3 + \mu_M) S_M \quad (6)$$

$$\frac{dI_M}{dt} = \frac{\beta_2(1-\varepsilon)(I_1 + I_2)S_M}{N_M} - (\xi\delta_3 + \mu_M) I_M \quad (7)$$

where

$$N_H = S_H + V_H + I_1 + I_2 + R \quad (8)$$

and

$$N_M = I_M + S_M \quad (9)$$

so that

$$\frac{dN_H}{dt} = \Lambda_H - \mu_H N_H - \delta_1 I_1 - \delta_2 I_2 \quad (10)$$

and

$$\frac{dN_M}{dt} = \Lambda_M - (\xi\delta_3 + \mu_M) N_M \quad (11)$$

in the biological-feasible region:

$$\left. \begin{aligned} \Omega &= \{ \Omega_H \cup \Omega_V \subset \mathfrak{R}_+^5 \times \mathfrak{R}_+^2 \} \\ \text{with} \\ \Omega_H &= \left\{ (S_H, V_H, I_1, I_2, R) \in \mathfrak{R}_+^5 : S_H + V_H + I_1 + I_2 + R \leq \frac{\Lambda_H}{\rho + \mu_H} \right\} \\ \Omega_N &= \left\{ (S_M, I_M) \in \mathfrak{R}_+^2 : S_M + I_M \leq \frac{\Lambda_M}{\xi\delta_3 + \mu_M} \right\} \end{aligned} \right\} \quad (12)$$

Let

$$\left. \begin{aligned} \eta &= 1 - \varepsilon \\ k_1 &= \rho + \mu_H \\ k_2 &= \omega + \mu_H \\ k_3 &= \tau_1 + \delta_1 + \mu_H \\ k_4 &= \tau_2 + \delta_2 + \mu_H \\ k_5 &= \sigma + \mu_H \\ k_6 &= \xi\delta_3 + \mu_M \end{aligned} \right\} \quad (13)$$

so that (1) – (7) becomes

$$\frac{dS_H}{dt} = \Lambda_H - \frac{\beta_1 \eta S_H I_M}{N_H} + \omega V_H + \sigma R - k_1 S_H \quad (14)$$

$$\frac{dV_H}{dt} = \rho S_H - \frac{\beta_1 \eta V_H I_M}{N_H} - k_2 V_H \quad (15)$$

$$\frac{dI_1}{dt} = \frac{\beta_1 \eta S_H I_M}{N_H} - k_3 I_1 \quad (16)$$

$$\frac{dI_2}{dt} = \frac{\beta_1 \eta V_H I_M}{N_H} - k_4 I_2 \quad (17)$$

$$\frac{dR}{dt} = \tau_1 I_1 + \tau_2 I_2 - k_5 R \quad (18)$$

$$\frac{dS_M}{dt} = \Lambda_M - \frac{\beta_2 \eta (I_1 + I_2) S_M}{N_M} - k_6 S_M \quad (19)$$

$$\frac{dI_M}{dt} = \frac{\beta_2 \eta (I_1 + I_2) S_M}{N_M} - k_6 I_M \quad (20)$$

Table 2.1 Parameters of the Model

S/N	Parameter	Description
1	Λ_H	Human recruitment number
2	Λ_M	Mosquito recruitment number
3	μ_H	Natural death rate of humans
4	β_1	Contact rate between uninfected humans and infected mosquitoes
5	β_2	Contact rate between infected humans and susceptible mosquitoes
6	μ_M	Natural death rate of mosquitoes
7	δ_1	Malaria induced death rate from all five plasmodium
8	δ_2	Malaria induced death rate from other four plasmodium except P. falciparum
9	δ_3	Mosquito death rate from insecticide
10	ξ	Insecticide control rate
11	ρ	Rate of vaccination
12	ω	Waning rate of vaccine

13	ε	Mass treatment control rate
14	τ_1	Treatment rate of individuals infected with all five plasmodium
15	τ_2	Treatment rate of individuals infected with other four plasmodium except <i>P. falciparum</i>
16	σ	Rate at which recovered individuals lose acquired immunity

Effective Reproduction Number (R_C)

The basic reproduction rate (R_0) is used to measure the ability of a disease to invade the entire population. It is the number of secondary infections produced by a typical case of an infection in a population where all individuals are susceptible and no one has immunity against the disease. It can therefore be measured by counting the number of secondary cases following the introduction of an infection into a totally susceptible population. In general, for an epidemic to occur in a susceptible population, the basic reproduction number must be greater than one (*i.e* $R_0 > 1$), so the number of new cases of infection is increasing. On the converse, If $R_0 < 1$, the infection will die out in the population because an infected individual cannot produce up to one new case of infection. A population will rarely be totally susceptible to an infection in the real world. That is, some contacts will be immune, for example due to prior infection which has induced immunity, or as a result of previous immunisation. Therefore, not all contacts will become infected and the average number of secondary cases per infectious case will decrease. This is measured by the effective reproduction number (R_C). The effective reproduction number (R_C) estimates the average number of secondary cases per infectious case in a population made up of both susceptible and non-susceptible hosts. It can be thought of as the number of secondary infections produced by a typical infective.

Herd immunity occurs when a significant proportion of the population (or the herd) has been vaccinated, and this provides protection for unprotected individuals. The larger the number of people who are vaccinated in a population, the lower the likelihood that a susceptible (unvaccinated) individual will come into contact with the infection. It is more difficult for diseases to

spread between individuals if large numbers are already immune, and the chain of infection is broken. The herd immunity threshold is the proportion of a population that need to be immune in order for an infectious disease to become stable in that community. If this is reached, for example due to immunisation, then each case leads to a single new case and the infection will become stable within the population (i.e $R_0 = 1$). Herd immunity is given by $\frac{1-R_0}{R_0}$. The herd

immunity is an important measure as it is used in eradication programmes to control infectious diseases.

Using the next generation operator technique described by Diekmann and Heesterbeek (2000) and subsequently analysed by Van de Driessche and Watmough (2002), we obtained the effective reproduction number (R_c) of our model has the spectral radius (ρ) of the next generation matrix, G , i.e $\rho(FV^{-1})$. The matrix F is the matrix of the new infection terms and V the matrix of the transition terms. The both matrices are obtained from the infected compartments (i.e I_1, I_2 and I_M) at the disease-free equilibrium (E^0).

The disease-free equilibrium of the model exist at the point

$$E^0 = \begin{pmatrix} S_H^0 \\ V_H^0 \\ I_1^0 \\ I_2^0 \\ R^0 \\ S_M^0 \\ I_M^0 \end{pmatrix} = \begin{pmatrix} \frac{k_2 \Lambda_H}{k_1 k_2 - \rho \omega} \\ \frac{\rho \Lambda_H}{k_1 k_2 - \rho \omega} \\ 0 \\ 0 \\ 0 \\ \frac{\Lambda_M}{k_6} \\ 0 \end{pmatrix} \quad (21)$$

and thus we have

$$F = \begin{pmatrix} 0 & 0 & \frac{\beta_1 \eta S_H^0}{N_H^0} \\ 0 & 0 & \frac{\beta_1 \eta V_H^0}{N_H^0} \\ \frac{\beta_2 \eta S_M^0}{N_M^0} & \frac{\beta_2 \eta S_M^0}{N_M^0} & 0 \end{pmatrix} \quad (22)$$

and

$$V^{-1} = \begin{pmatrix} \frac{1}{k_3} & 0 & 0 \\ 0 & \frac{1}{k_4} & 0 \\ 0 & 0 & \frac{1}{k_6} \end{pmatrix} \quad (23)$$

The effective reproduction number is thus given as

$$R_c = \sqrt{\frac{\beta_1 \beta_2 (1-\varepsilon)^2 \lambda [(\omega + \mu_H)(\tau_2 + \delta_2 + \mu_H) + \rho(\tau_1 + \delta_1 + \mu_H)]}{(\tau_1 + \delta_1 + \mu_H)(\tau_2 + \delta_2 + \mu_H)(\xi \delta_3 + \mu_M)[(\omega + \mu_H) + \rho]}} \quad (24)$$

RESULTS AND DISCUSSIONS

Estimation of Variables and Population-dependent Parameters Values

The standard incidence function used in this model allows it to fit any population (country) of interest, no matter the size of the population. Every disease epidemiology has its variables and population-dependent parameters. In this paper, the malaria demographic profile of Nigeria is considered.

As at the year 2015, the total population of Nigeria was 181,562,056 (CIA, 2016). There is no record on malaria vaccination in the entire country as at when this model was designed (to the best of our knowledge). Thus 100,000 individuals are assumed to have been vaccinated. According to WHO (2015), there is an estimate of over 100 million malaria cases in Nigeria annually and Olaniyi & Obbiyi (2013) explained that Plasmodium falciparum is the most deadly genus that causes malaria in humans and it predominates in Africa. Hence, we assume 65% of the total infected population for (I_1) i.e

$$I_1 = \frac{65}{100} \times 100,000,000, \text{ which is } 65,000,000 \text{ and the remaining } 35,000,000$$

represent infection from other sources of human malaria, i.e $I_2 = 35,000,000$.

The majority of malaria cases are uncomplicated, and if diagnosed and treated early enough and correctly, the patient has every chance of making a full recovery from the infection. Artemisinin-combination Therapy (ACT) is about 90% effective when used to treat uncomplicated malaria (Howitt *et al.*, 2012). Thus we assumed a recovery rate of 90% in 60 days i.e $R = 0.015 \times (90,000,000)$, which gives 1,300,000. Thus, $S = 80,162,056$. The life expectancy of a

Nigerian is 53.02 years (CIA, 2016). Thus the natural death rate is equal to $\frac{1}{53.02} \times \frac{1}{366}$, which is 0.000052 per day. The life expectancy of a female mosquito is between 42 – 56 days (Andrew, 2001). Thus its natural death rate is equal to $\frac{2}{42+56}$, which gives 0.0408 per day.

The contact rate between uninfected humans and infected mosquitoes (β_1), the contact rate between infected humans and susceptible mosquitoes (β_2), Rate at which recovered individuals lose acquired immunity (σ), and Mosquito death rate from insecticide (δ_3) are all cited from (Fatmawati, 2013). Malaria-induced death rates of I_1 and I_2 are cited from (Smith & Hove-Musekwa, 2008). The efficacy of RTS,S/AS01 vaccine is 7 years if administered properly (Olotu *et al.*, 2016). Thus the waning rate of vaccine is $\frac{1}{7} \times \frac{1}{366}$, which gives 0.00039 per day.

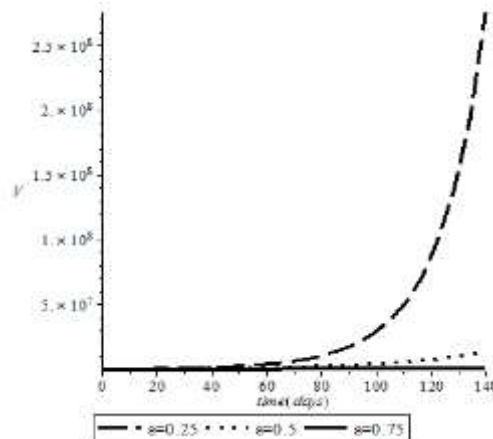
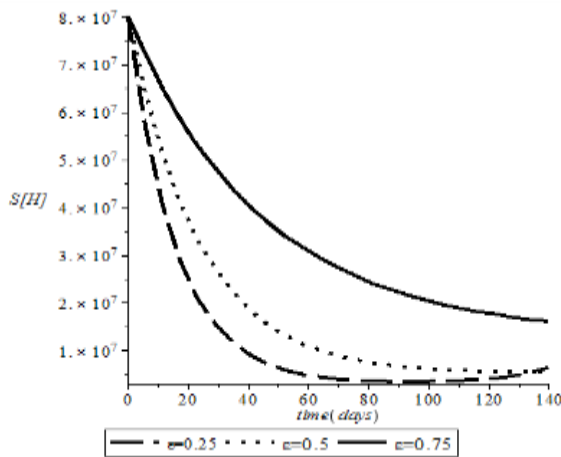
As at the time this model was developed, no record of the population of mosquitoes in Nigeria was available (to the best of our knowledge). But a female mosquito lays about 300 eggs at a time and each mosquito will lay eggs up to three times before it dies (Andrew, 2001). Hence, we assumed that $\Lambda_M = 600,000$, which gives a $N_M = 14,705,882$. We also assumed $I_M = 500,000$. Thus $S_M = 14205882$.

Table 3.1 Values of Variables and Parameters of the Model

S/ N	Variable/Parameter	Value	S/ N	Variable/Parameter	Value
1	S_H	80,162,056	14	β_1	1day ⁻¹
2	V_H	100,000	15	β_2	1.5day ⁻¹
3	I_1	65,000,000	16	δ_1	0.0045day ⁻¹
4	I_2	35,000,000	17	δ_2	0.05day ⁻¹
5	R	1,300,000	18	δ_3	0.1day ⁻¹
6	S_M	14,205,882	19	ξ	(0,1)

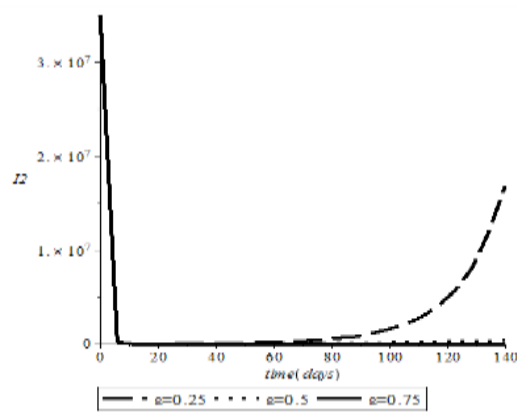
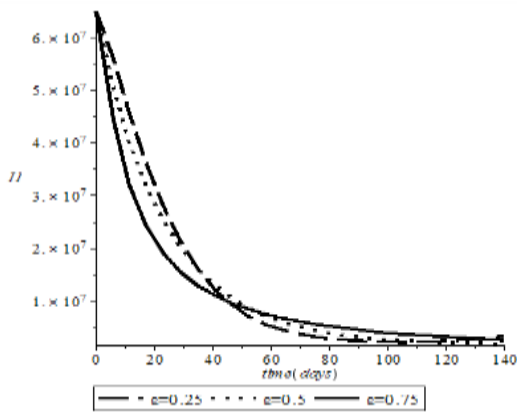
7	I_M	500,000	20	ρ	(0,1)
8	N_H	181,562,056	21	ω	0.00039day ⁻¹
9	N_M	14,705,882	22	ε	(0,1)
10	Λ_H	9,441day ⁻¹	23	τ_1	(0,1)
11	Λ_M	600,000day ⁻¹	24	τ_2	(0,1)
12	μ_H	0.000052day ⁻¹	25	σ	0.333day ⁻¹
13	μ_M	0.0408day ⁻¹			

Numerical Simulations



a

b



a

b

Figure 3.1: A Comparison between the effects of different levels of mass treatment control rates on the morbidity of (a) susceptible humans, (b) vaccinated humans, (c) humans infected with any of the five genus of plasmodium, and (d) humans infected with any of the four genus of plasmodium apart from *P. falciparum*. Initial variables and parameters value used are as in Table 3.1 above.

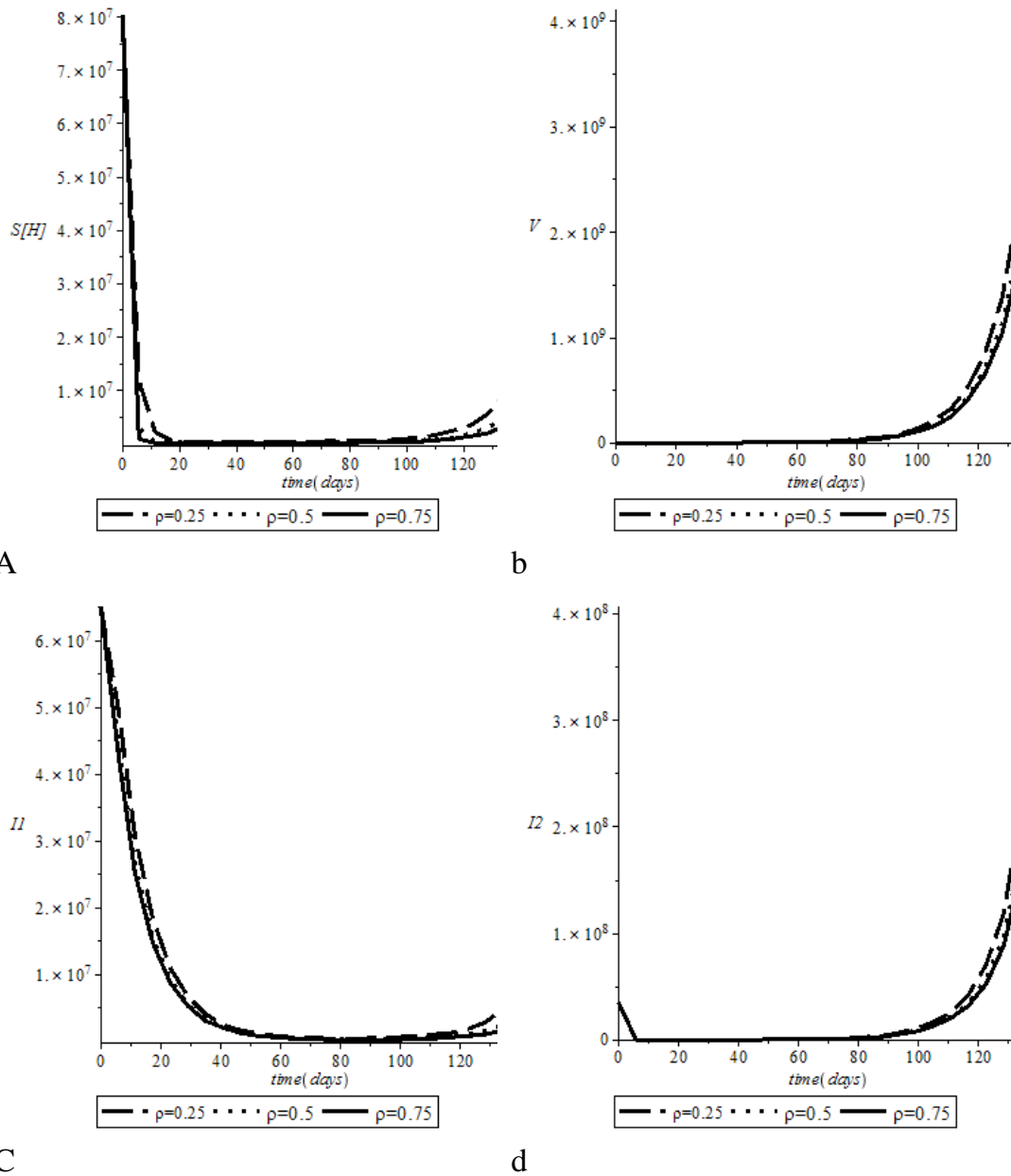


Figure 3.2: A Comparison between the effects of different levels of vaccination rates on the morbidity of (a) susceptible humans, (b) vaccinated humans, (c) humans infected with any of the five genus of plasmodium, and (d) humans infected with any of the four genus of plasmodium apart from *P. falciparum*. Initial variables and parameters value used are as in Table 3.1 above.

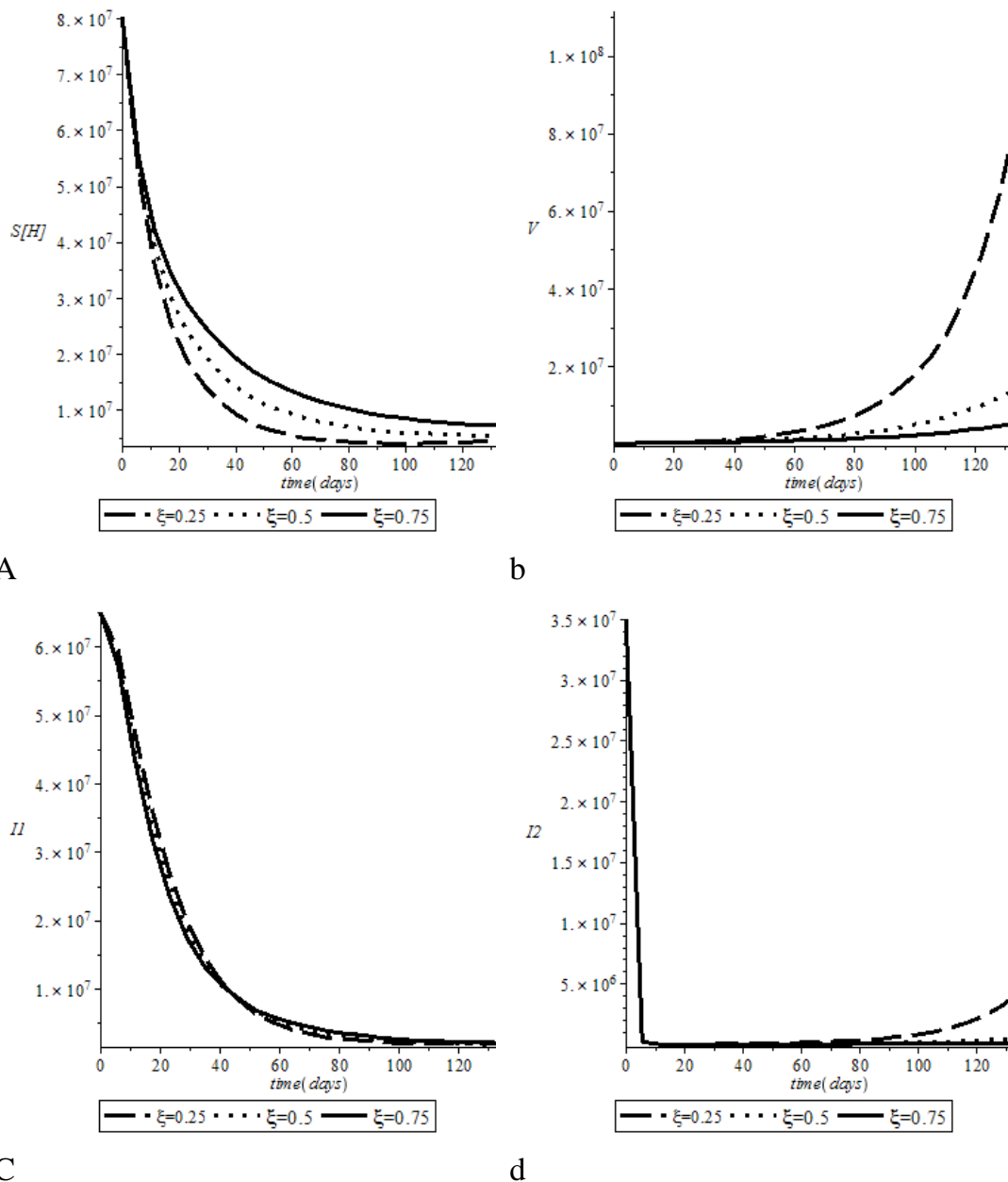


Figure 3.3: A Comparison between the effects of different levels of insecticide control rates on the morbidity of (a) susceptible humans, (b) vaccinated humans, (c) humans infected with any of the five genus of plasmodium, and (d) humans infected with any of the four genus of plasmodium apart from *P. falciparum*. Initial variables and parameters value used are as in Table 3.1 above.

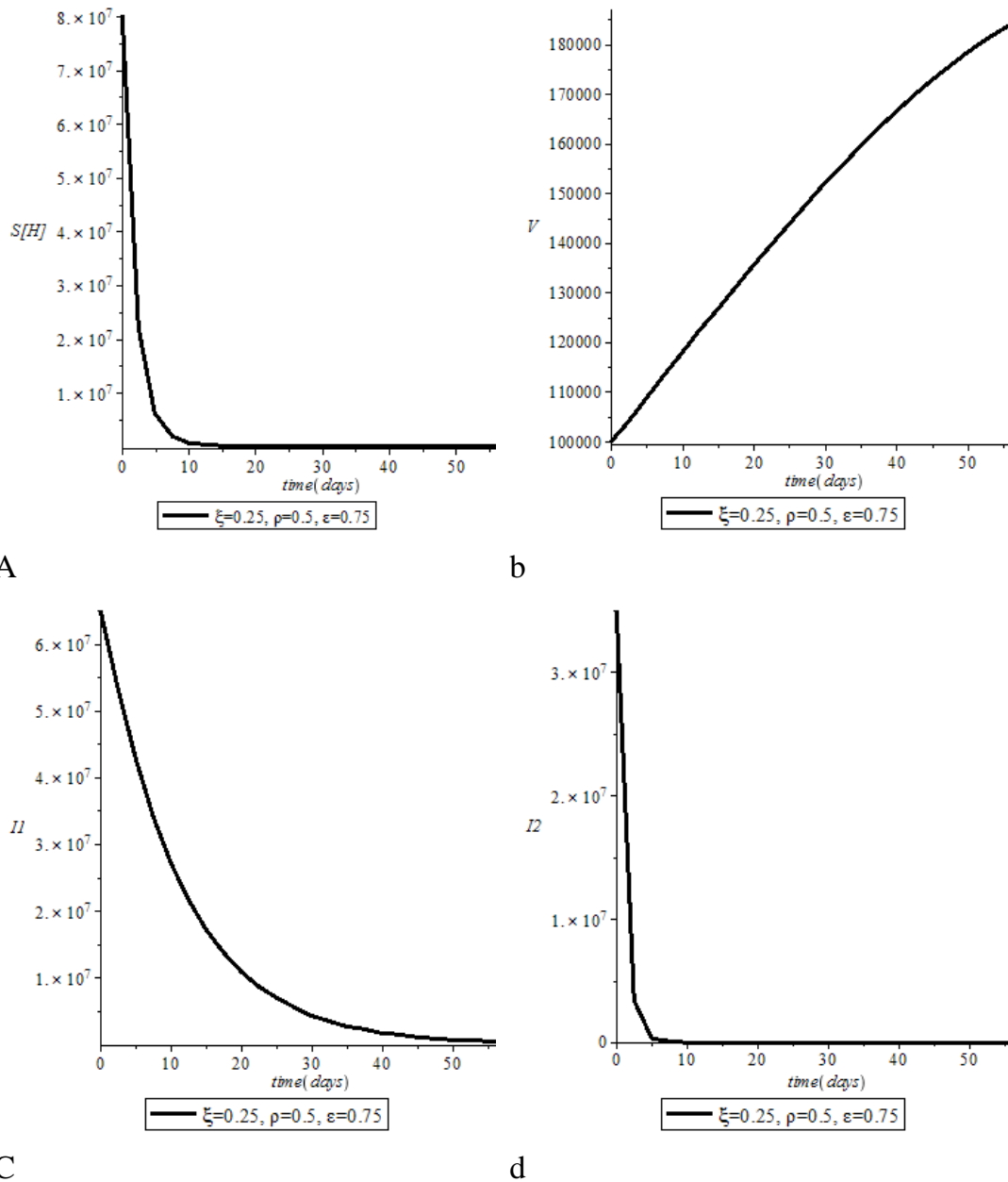


Figure 3.4: A Comparison between the effects of different levels of the three control rates on the morbidity of (a) susceptible humans, (b) vaccinated humans, (c) humans infected with any of the five genus of plasmodium, and (d) humans infected with any of the four genus of plasmodium apart from *P. falciparum*. Initial variables and parameters value used are as in Table 3.1 above.

CONCLUSION

A mathematical model was developed and analyzed as a strategy to curtail the transmission dynamics of Malaria. The disease-free equilibrium state (E^0) and effective reproduction number (R_c) was obtained. Our results revealed that if there is a vaccination rate of 50%, insecticide control rate of 25% and a 75% mass treatment control rate, the morbidity of infected humans that are vaccinated will drop significantly to the disease-free equilibrium in less than 10 days while infected humans that are not vaccinated will drop to the disease-free equilibrium in the first 60 days. The goal of this model is to curb the spread of malaria to a bearable minimum by vaccinating more of the susceptible individuals. It is therefore recommended that:

- (i) Nigerian government should include malaria vaccine as part of its routine immunization programmes.
- (ii) Since the model can fit any population of interest, government of such country should create awareness through public enlightenment campaign on the importance of mass treatment control (which include mass drug administration, distribution of mosquito net and personal hygiene). This is because if the mass treatment is poorly implemented, it could lead to the resistance of *Plasmodium* spp. to anti-malarial drugs in the population.

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