A MATHEMATICAL MODEL ON THE CONTROL AND SIMULATION OF HEPATITIS B VIRUS (HBV) INFECTION TRANSMISSION DYNAMICS IN A POPULATION

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Abstract
In this paper, a new mathematical model for Hapatitis B Virus (HBV) infection with controls (enlightenment, condom use and vaccine/therapy) was developed. We showed that the HBV model is biologically meaningful and epidemiologically well posed. Furthermore, we carried out simulation on the equations of the model using Matlab. The simulation results showed that when phi (Infectivity control) is increased, then the exposed treated individuals in the population will decrease. On the contrary, if phi is increased, then the number of individuals who recover from HBV will also increase. The impact of phi (infectivity control: enlightenment, vaccine, condom use and therapy) as a control measure of HBV in the population is remarkable. However enlightenment and vaccine are better control strategies which we can use to effectively control HBV infection in a population than condom and therapy.

Keywords: *Hapatitis B Virus , Simulation, Matlab , control strategies, enlightenment , vaccine.*

1. Introduction

Hepatitis B, caused by the Hepatitis B virus (HBV) is a major global health problem and the most serious type of viral hepatitis. Worldwide about 240 million people live with chronic infection and an estimation of 780,000 people die each year due to the acute or chronic consequences of hepatitis B ([28], [30]). Hepatitis B is a disease that is characterized by inflammation of the liver and is caused by the hepatitis B virus [15]. Hepatitis may be caused by drugs or viral agents. These viral agents include the hepatitis A, B, C, D, E, F, G and H viruses ([23], [27]). Hepatitis B is one of the world's most serious health problems. More than a billion people around the world have serological indicators of past or present infection with hepatitis B virus (HBV). Over 300 million people are chronic carriers of the virus ([22], [20], [8], [13], [19]). HBV infection can be transmitted from mother to child (vertical), contact with an infected person (horizontal transmission), sexual contact (homosexual and heterosexual transmission) with infected partners, exposure to blood or other infected fluids and contact with HBV contaminated instruments ([23], [27]).

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It is a viral infection that attacks the liver and can cause both acute and chronic disease ([23], [27]). About 2 billion people worldwide have been infected with the virus and about 350 million live with chronic infection [9]. An estimated 600 000 persons die each year due to the acute or chronic consequences of hepatitis B [25]. About 25% of adults who become chronically infected during childhood later die from liver cancer or cirrhosis (scarring of the liver) caused

by the chronic infection [9]. HBV is 50 to 100 times more infectious than HIV [25]. HBV is an important occupational hazard for health workers, and 50 million new cases are diagnosed annually ([9], [25]).

Epidemiological models help to capture infection or disease transmission mechanisms in a population in a mathematical frame-work in order to predict the behavior of the disease spread through the population [15]. Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Understanding the transmission characteristics of infectious diseases in a population (communities, regions and countries) in mathematical frame works can lead to better approaches to decreasing the transmission of these diseases [6].

Re c e n t l y, mathematical models have been used to study the transmission dynamics of HBV in various communities, regions and countries [15]. [6], used a simple deterministic, compartmental mathematical model to study the effects of carriers on the transmission of HBV [15]. ([7], [26]) presented models of sexual transmission of HBV, which include heterogeneous mixing with respect to age and sexual activity. [10], investigated the relation between the age at infection with HBV and the development of the carrier state. [17], proposed a model to show that the prevalence of infection is largely determined by a feedback mechanism that relates the rate of transmission, average age at infection and age-related probability of developing carriage following infection. [21], applied the model of [17] to predict chronic hepatitis B infection in New Zealand. The prevalence of HBV in developing countries is different from that in developed countries, since it appears that the rate of transmission in childhood is the major determinant of the level of HBV endemicity and little is known on the rates and patterns of sexual contact in developing countries [12]. ([16], [11]) studied models of HBV transmission in developing countries and [26] described a model of HBV in United Kingdom. [29], proposed a mathematical model to investigate the transmission dynamics and prevalence of HBV in mainland China. Their model was formulated from that of [17] based on the characteristics of HBV in China.

Public health policy on the design of various HBV control programs has benefitted a lot from the recommendations of the previous mathematical modellers and much success has been recorded [15]. However, available data in various regions on the prevalence of HBV infection shows a slow pace of control ([15], [24]). Much still needs to be done until HBV infection is eradicated from the global community [15].

However, our work mimics the model presented by [29]. In their work, a mathematical model was proposed to study the transmission dynamics and prevalence of HBV infection in mainland China. They assumed that the newborns to carrier mothers infected at birth do not stay in a latent period, so that they instantaneously become carriers. However, as pointed out by [6] and [22], an HBV carrier must have harboured the virus in the blood for at least six months. By this newborns to carrier mothers infected at birth are latently infected individuals. [18], supported the same view in his study and assumed that the proportion of the infected newborns to carrier mothers is latent. The role of treatment of HBV carriers as a measure of control was not considered in their model.

A new mathematical model for HBV infection transmission incorporating control strategies (enlightenment, use of condom and vaccine/therapy) in a population was developed by [4]. Like [29], [4] assumed that the newborns to carrier mothers infected at birth do not stay in a latent period, so that they instantaneously become carriers and also individuals that enter into the population will either go into the susceptible class or into the infectious class depending on their

epidemiological condition as at the time of entering. [4], calculated the basic reproduction number R_0 of the new model and consequently carried out the sensitivity analysis on the parameters of the model using Mathcad. Furthermore, the stability analysis in the occurrence of the HBV was verified using the Jacobian method by [5] for the new model, it was shown that the disease occurrence was unstable. In this paper, the role of control strategies (enlightenment, use of condom and vaccine/therapy) in Hepatitis B virus infection transmission dynamics in a population was investigated. We carried out simulation on the equations of the model using Matlab in order to investigate the impact of various control strategies on HBV transmission dynamics in the population. Useful and valid results were obtained and discussed.

2. Model formulation

Assumptions of the Model

The model is based on the following assumptions:

1. The individuals that make up the population can be grouped into different compartments or groups according to their epidemiological state
2. The population size in a compartment varies with respect to time.
3. The population mixes homogeneously. That is, all susceptible individuals are equally likely to be infected by infectious individuals if they come in contact with one another.
4. The infection does not confer immunity to the recovered individuals and so they can go back to the susceptible class at any given time.
5. The individuals in each compartment have equal natural death rate given as μ
6. The gain in the infectious class is at a rate proportional to the number of infectious and susceptible individuals, that is, βSI, where $\beta > 0$ is a contact parameter (effective contact rate).The susceptible are lost at the same rate
7. The rate of removal of infectious to the recovered or removed class is proportional to the number of infectious individuals.
8 Individuals that enter into the population will either go into the susceptible class or into the infectious class depending on their epidemiological condition as at the time of entering.

Model Variables

The following variables will be used in this model:
$\boldsymbol{S}$: The number of susceptible individuals.
$\boldsymbol{E}$: The number of exposed individuals.
$\boldsymbol{I}$: The number of infectious individuals.
$\boldsymbol{R}$: The number of individuals who have been treated and have recovered from the infection.
$\boldsymbol{E_T}$: The number of exposed individuals who are receiving treatment.
$\boldsymbol{I_T}$: The number of infectious individuals who are receiving treatment.
$\boldsymbol{I_N}$: The number of infectious individuals who are not receiving treatment.

Model Parameters

We shall use the following parameters in this model, they are:
π: The number of people that enter into the population or the number of individuals that enter into the susceptible class(recruitment).
β : Contact rate for HBV infectious individuals with the susceptible individuals. i.e., the rate at

which susceptible individuals who had contact with the infected become exposed to HBV.
τ: The rate at which latently infected individuals become infectious (actively infected).
ω: The rate at which exposed individuals enter the exposed and treated class (E_T).
ρ_2: The rate at which infectious individuals enter into the infectious and treated class (I_T).
α: The rate at which infectious and treated individuals go back to exposed class (E)
ρ_1: The rate at which infectious individuals enter into the class of infected and not treated.
λ: The rate at which infectious and treated individuals recover from HBV (the rate at which infectious and treated individuals move to the recovered class R).
ϕ: The rate at which recovered individuals become susceptible to HBV again.
δ: HBV-induced mortality/death rate for the class of infectious and treated individuals.
δ_1: HBV-induced mortality/death rate for the class of infectious and not treated individuals μ: The natural mortality/death rate.
$\psi(1+\varphi)$: The rate at which exposed and treated individuals recover.
φ: Infectivity control; which include enlightenment, vaccine and the use of condom.
θ : The number of individuals already infected with HBV that goes into the population
ψ : Cure rate

Model Description of HBV

Base on the standard SEIR model, the population is partitioned into seven compartments or classes namely: Susceptible(S), Exposed(E), Infectious(I), Exposed and Treated(E_T), Infectious and Treated(I_T), Infectious and not Treated(I_N) and Recovered(R) Compartments.

Model Equations

$$\frac{dS}{dt} = \pi + \phi R - \beta SI - \mu S \quad (1)$$
$$\frac{dE}{dt} = \beta SI + \alpha I_T - \omega E - \tau E - \mu E \quad (2)$$
$$\frac{dE_T}{dt} = \omega E - \psi(1+\varphi)E_T - \mu E_T \quad (3)$$
$$\frac{dI}{dt} = \tau E + \theta I - \rho_1 I - \rho_2 I \quad (4)$$
$$\frac{dI_N}{dt} = \rho_1 I - \mu I_N - \delta_1 I_N \quad (5)$$
$$\frac{dI_T}{dt} = \rho_2 I - \alpha I_T - \lambda I_T - \mu I_T - \delta I_T \quad (6)$$
$$\frac{dR}{dt} = \lambda I_T + \psi(1+\varphi)E_T - \phi R - \mu R \quad (7)$$
$$N = S + E + E_T + I_N + I_T + R \quad (8)$$

Susceptible individuals acquire HBV infection following effective contact with individuals infected with HBV (i.e., those in the $E, I_N \; and \; I_T$ classes) at a rate β, given by $\beta = \frac{\chi_B(E+\mu_1 I_N+\mu_2 I_T)}{N}$;

$N = S + E + I_N + I_T$ where χ_B is the effective contact rate for HBV transmission. Further, the modification parameters $\mu_1 \geq 1 \; and \; \mu_2 < 1$ account for the relative infectiousness of individuals in the I_N and I_T classes in comparison to those in the E class. That is individuals in the I_N class are more infectious than those in the E class (because of their higher viral load), and likewise, I_T are less infectious than those in I_N class (because the use of treatment significantly reduces the viral load in those treated).

3. Well-Posedness of the Model of HBV

The well-posedness of the model is done by proving the positivity and boundedness of the solutions of the model with the non-negative initial solution for all time.

Theorem 1: (Boundedness). The solution set $\{S(t), E(t), E_T(t), I(t), I_N(t), I_T(t), R(t)\}$ is contained and bounded in the feasible region D.

Proof

The total human population can be determined by

$N(t) = S(t) + E(t) + E_T + I(t) + I_N + I_T + R(t)$.

So, the time derivatives, $\frac{dN}{dt}$, along solutions of system is obtained as

$\frac{dN}{dt} = \pi - \mu N - \delta_1 I_N - \delta I_T \leq \pi - \mu N$.

Assume that the initial condition for model satisfies $N(0) \leq \frac{\pi}{\mu}$, where $N(0) = S(0) + E(0) + E_T(0) + I(0) + I_N(0) + I_T(0) + R(0)$.

Then, applying the Gronwall's inequality gives

$N(t) \leq \frac{\pi}{\mu} + \left(N(0) - \frac{\pi}{\mu}\right) e^{-\mu t}$ whenever $(0) \leq \frac{\pi}{\mu}$.

So, taking the limit as $t \to \infty$ yields $(t) \leq \frac{\pi}{\mu}$. This shows that the feasible region for the model exists and is bounded by $N(t) \leq \frac{\pi}{\mu}$. It means that all the solutions of system are nonnegative in D for any time $t > 0$ and this represents human population.

Lemma 1 (Positivity of solutions)

Let the set of initial solution be $\{(S(0), E(0), E_T(0), I(0), I_N(0), I_T(0), R(0)) \in \Phi\}$. Then, the solution set $\{S(t), E(t), E_T(t), I(t), I_N(t), I_T(0), R(t)\}$ of the Hepatitis B virus transmission model is non-negative for $t > 0$.

Proof

Assume that the set of initial solutions, $\{(S(0), E(0), E_T(0), I(0), I_N(0), I_T(0), R(0)) \geq 0\}$, then the first equation can be written as

$\frac{dS}{dt} \geq \pi - (\beta I + \mu)S = \pi - \beta(t)S$ (9)

where $\beta(t) = \beta I + \mu$.

Equation (2) is a linear first order ordinary differential equation in S with the solution

$S(t) = S(0)exp\left(\int_0^t -\beta(S)ds\right) \times \int_0^t \Lambda exp\left(\int_0^u \beta(\omega)d\omega\right) \geq 0$.

Hence, $S(t) \geq 0 \; \forall \; t \geq 0$.

In similar way, the remaining state variables are obtained such that

$E(t) \geq E(0)\, Exp(-(\mu + \tau + \omega)) \geq 0$,

$E_T(t) \geq E_T(0)\, Exp(-(\psi(1+\varphi) + \mu)) \geq 0$,

$I(t) \geq I(0) Exp\left(-(\mu + \theta + \rho_2 + \rho_1)\right) \geq 0$,

$I_N(t) \geq I_N(0)\, Exp(-(\mu + \delta_1)) \geq 0$,

$I_T(t) \geq I_T(0)\, Exp(-(\mu + \alpha + \lambda + \delta)) \geq 0$,

$R(t) \geq R(0)\, Exp(-(\mu + \phi)) \geq 0$.

This completes the proof of the lemma 1.

Therefore, the biological validity of the HBV model is stated in lemma 2.

Lemma 2: The HBV model is well posed and valid in the set $D = \left\{S(t), E(t), E_T(t), I(t), I_N(t), I_T(0), R(t) \in \mathbb{R}_+^7 : N(t) \leq \frac{\pi}{\mu}\right\}$. According to [14], the HBV model is biologically meaningful and epidemiologically well posed in the region D.

4. Simulation Results and Discussion

In this section we used MATLAB to simulate the Model.

We formulated and analysed a mathematical Model for the transmission dynamics of HBV infection in a population with controls. The main objective of this part of the research is to assess the impact of the parameters (control strategies) on the transmission dynamics of the infection. Graphical representations showing the impact of various parameters in the population is much needed. This will provide the best framework for understanding the control strategies of the disease in the population. Table1 shows the set of parameter values used in the simulation for HBV infection.

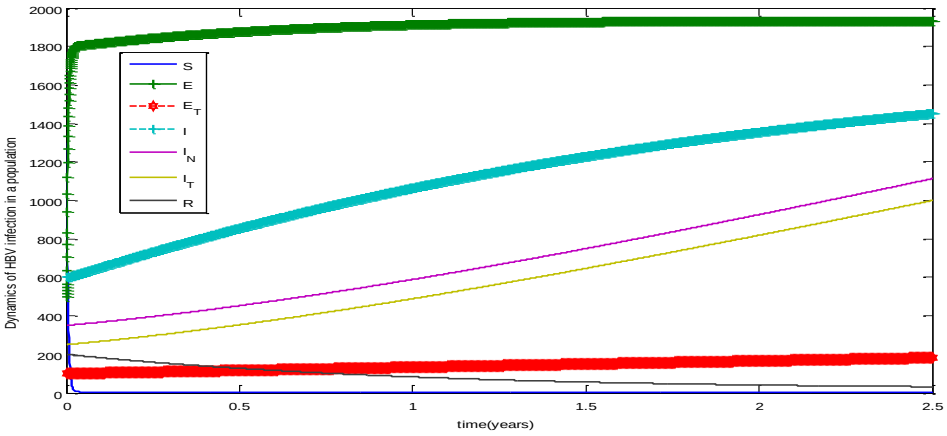
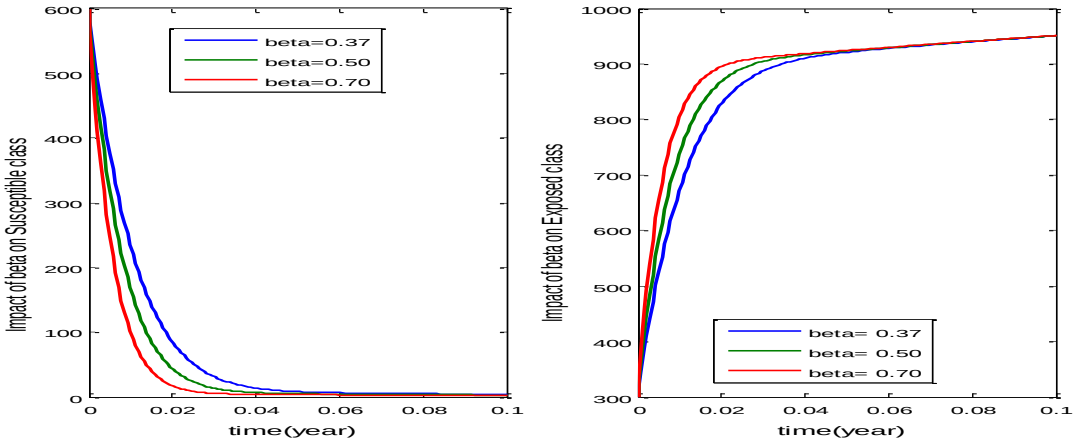


Figure 1: A graph showing the dynamics of HBV infection in a population.

Graph above shows all the equations describing the dynamics of HBV infection in a population.



(a) (b)

Figure 2: Graphs showing the impact of beta(contact rate of the disease) on the population.
Figure 2(a): The graph on the left, showing the impact of beta on the susceptible class.
Figure 2(b): The graph on the right, showing the impact of beta on the exposed class.

From the above graphs, as beta increases, the number of susceptible individuals in the population decreases. Conversely, increasing beta , increases the number of exposed individuals in the population. Therefore, as a control strategy, efforts should be geared towards ensuring that the contact rate is drastically reduced. This is achievable if more susceptible individuals are immunized against HBV infection. This is so because upon immunization the individual will lose his/her potency of contacting the disease. Active vaccination (Energix-B and Recombivax-HB) is recommended, this will offer long lasting active immunity against HBV and invariably will help control the spread of HBV in the population.

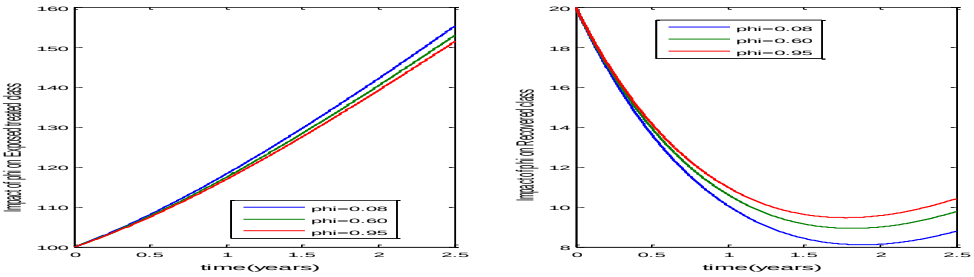


Figure 3: Graphs showing the impact of phi(Infectivity control) on the population .
Figure 3(a): The graph on the left, showing the impact of phi on exposed treated class.
Figure 3(b): The graph on the right, showing the impact of phi on the recovered class.

From the graphs displayed in figure3 above, if phi is increased, then the exposed treated individuals in the population will decrease (see graph on the left). On the contrary, if phi is increased, then the number of individuals who recover from HBV will also increase. This increase in the number of recovered HBV individuals is highly noticeable (see graph on the

right). The impact of phi (infectivity control: enlightenment, vaccine and condom use) as a control measure of HBV in the population is noteworthy. Therefore, to effectively control HBV in any given population, we must increase awareness of the disease amongst the people. Once people are aware of the disease, then they can indulge on other diligent preventive measures: condom use, not sharing needles or other drug paraphernalia, not sharing items such as tooth brushes and razors. Individuals can also get vaccinated against HBV once they become aware. Therefore, efforts should be targeted at increasing the above mentioned strategies for effective control of HBV in the population.

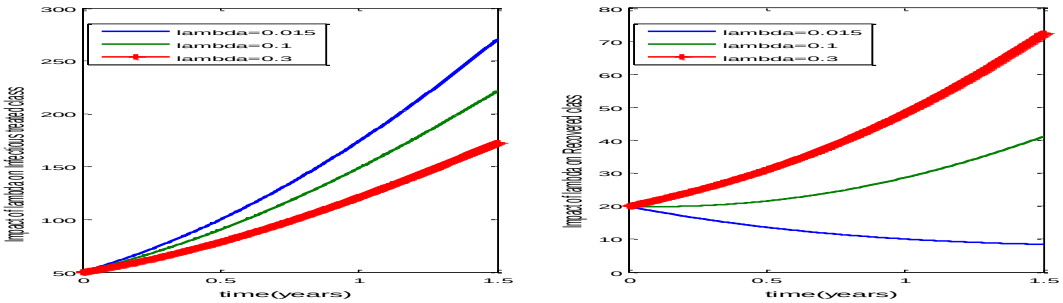


Figure 4: Graphs showing the impact of lambda (the rate at which infectious and treated individuals recover from HBV) on the population
Figure 4(a): The graph on the left, showing the impact of lambda on infectious treated class.
Figure 4(b): The graph on the right, showing the impact of lambda on the recovered class.

From Figure 4(a) above, if lambda increases then the number of infectious treated people decreases in the population. On the other hand, in Figure 4 (b), increasing lambda also increases the number of recovered individuals in the population. This implies that treatment of HBV infected people has a positive impact on the population as more infected individuals will recover after treatment as shown in the graph (Figure 4b) above. If the infection of HBV is acute, then enough rest is highly recommended and also care should be taken to treat the exhibited symptoms. But on the other hand, if the infection of HBV is chronic, then the use of HBV drugs is recommended. The available drugs for the treatment of HBV are: (1) Lamivudine (LMV) or Ribavirine (2) Eggylated Alpa-interferon (IFN). If more infected HBV people are treated, it will help control HBV infection in the population . The recovered individuals can even get immunized to avoid contracting it again since treatment does not offer immunity.

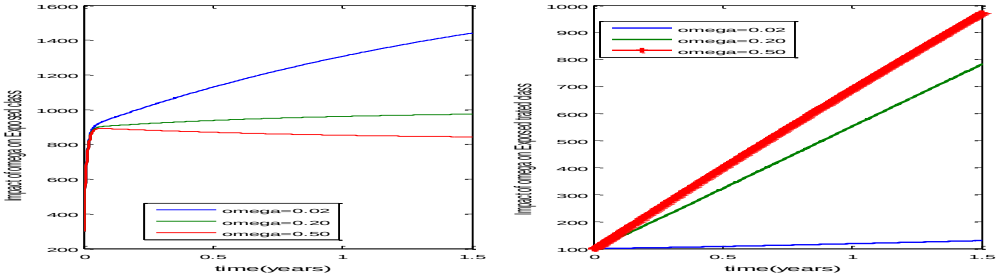


Figure 5: Graphs showing the impact of omega (the rate at which exposed individuals enter the

exposed and treated class)on the population.
Figure 5(a): The graph on the left, shows the impact of omega on exposed class.
Figure 5(b): The graph on the right, shows the impact of omega on the exposed treated class.

In Figure 5(a), from zero, increasing omega does not show any impact or difference in the population may be due to the fact that the number of exposed people are very few or due to the fact that the exposed individuals are not aware that they are exposed of the disease. However, as time progresses, we notice that an increase in omega brought a decrease in the exposed HBV class. In figure 5 (b), an increase in omega shows a great increase on the number of exposed treated individuals in the population, that is increasing the rate at which people go for treatment (omega) reduces the exposed individuals in the population. The reason for the increase on the number of treated people in the population could be as a result of awareness. When more people are aware of the disease and go for screening, the infected ones will start treatment, this will eventually lead to recovery. Often time, people may not know that they are exposed of HBV until irreversible damage is done to the Liver before they will become aware of the infection So as a control strategy, awareness is strongly recommended.

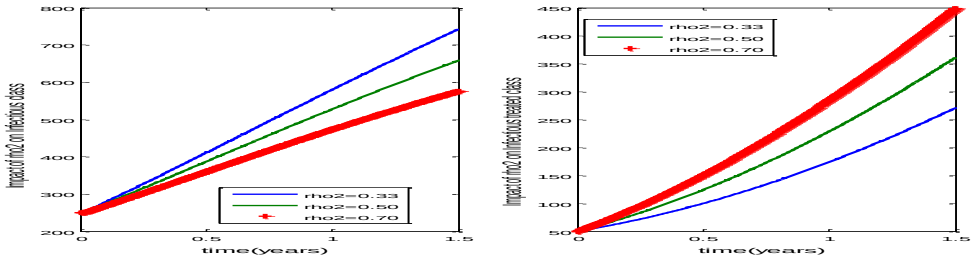


Figure 6: Graphs showing the impact of rho2(The rate at which infectious individuals enter into the infectious and treated class) on the population
Figure 6(a): Graph on the left, shows the impact of rho2 on the infectious class.
Figure 6(b): Graph on the right, shows the impact of rho2 on the infectious treated class.

From Figure 6(a), increasing rho2 shows a decrease in the number of infectious individuals in the population. Conversely, an increase in rho2 shows a very high increase on the number of infectious treated people in the population (see figure 6 b). From the above graphs, it is obvious that the more people who are infected with HBV go for treatment the less the number of HBV infected individuals in the population. Therefore, as a control strategy, people who are diagnose of HBV should be encouraged to go for treatment. Government should also help by providing free medical care for HBV infected persons. Also non-governmental organizations should even help in sponsoring medical treatment for HBV patients. Therefore, as a control measure, HBV infected individuals should be made to go for treatment this will help reduce HBV in a population.

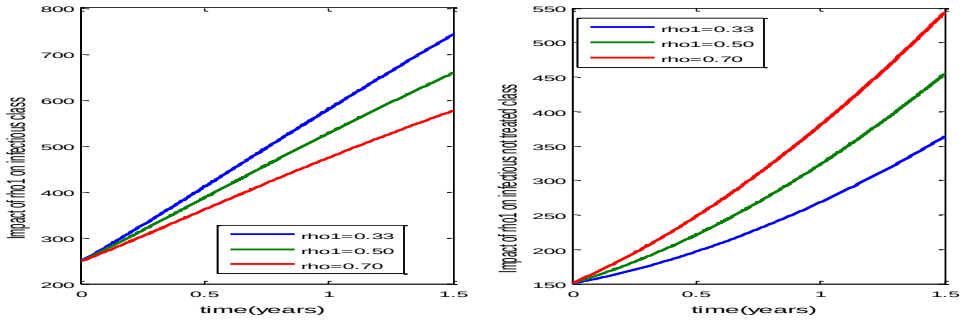


Figure 7: Graphs showing the impact of rho1 (the rate at which infectious individuals enter into the class of infected and not treated)on the population
Figure 7(a): Graph on the left, shows the impact of rho1 on the infectious class.
Figure 7(b): Graph on the right, shows the impact of rho1 on the infectious not treated class.

From figure 7 (a), increasing rho1 reduces the number of infectious individuals in the population.

Also in Figure 7(b), increasing rho1 increases the number of infectious not treated individuals in the population. Actually, rho1 has a very negative impact or effect on the population. People who are infectious of HBV should be encouraged to go for treatment as recommended earlier. For no reason should people who are diagnosed of HBV stay without going for treatment. Therefore, rho1is not contributing in any way to the control of HBV in the population, this should be avoided.

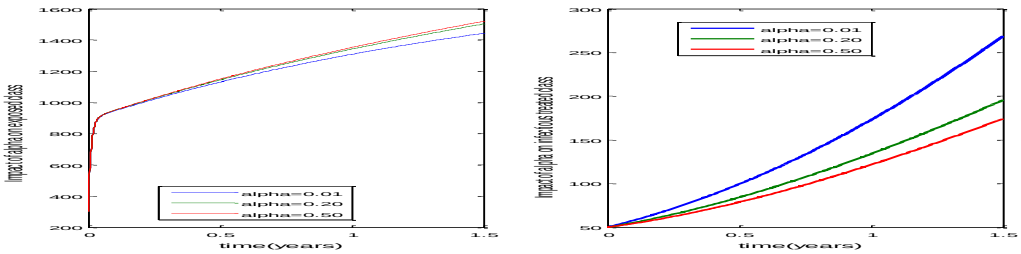


Figure 8: Graphs showing the impact of alpha (the rate at which infectious and treated individuals go back to exposed class) in the population
Figure 8(a): Graph on the left, shows the impact of alpha on the exposed class.
Figure 8(b): Graph on the right, shows the impact of alpha on the infectious treated class.

In Figure 8 (a) above, we will observe that increasing alpha does not show any difference at time, zero. However, as time increases, we will notice that an increase in alpha showed an increase in the number of exposed individuals in the population. Similarly, in Figure 8 (b), it can be clearly seen that increasing alpha decreases the number of infectious treated individuals in the population. The condition such as depicted here occurs when the disease (HBV) goes into remission in the body of the HBV infected person who is receiving treatment for HBV. When this happens, the patient will not exhibit any symptom(s) of HBV again, and will conclude that he/she has recovered from the infection. From the graphs above, we can see that this situation

will arise when more people are infected of HBV and are being treated, some will recover fully and move to recovered class while very few will move to exposed class (that is the disease goes into remission in their body without their knowledge). This has a negative impact on the population and should be avoided. Therefore, as a control strategy, we recommend that the blood of HBV patients who is receiving treatment be screened thoroughly before they are certified recovered from HBV infection.

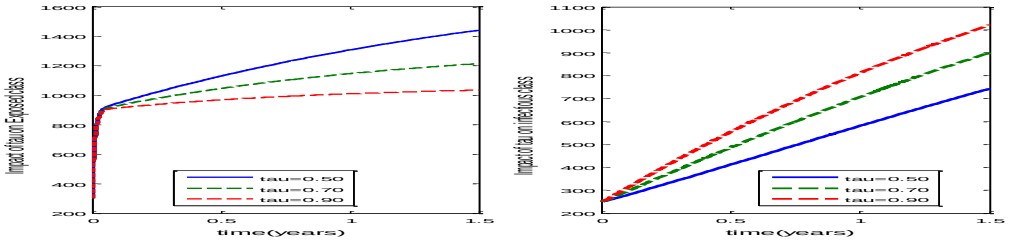


Figure 9: Graphs showing the impact of tau (the rate at which latently infected individuals become actively infected) on the population.
Figure 9(a): Graph on the left, shows the impact of tau on the exposed class.
Figure 9(b): Graph on the right, shows the impact of tau on the infectious class.

From Figure 9(a), increasing tau decreases the number of individuals who are exposed of HBV in the population. Conversely, increasing tau increases the number of infectious individual in the population (see Figure 9 b). Therefore, concerted effort should be made through enlightenment for people to know their HBV status. This if done will help individuals who are exposed of HBV to discover on time and go for treatment so that the person will not migrate to infectious stage. Therefore, as a control strategy, we recommend awareness and that people should go for screening of their blood against HBV. Early dictation of HBV is an advantage in curing the disease than when it has reached an advanced stage, often time the advance stage would have caused Fibrosis (scarring) and Cirrhosis (hardening of the liver). These conditions are too hard to reverse. This explains why persons diagnosed of HBV that has reached advanced stage often do not survive because of the irreversible damage already done to the liver as a result of the unawareness of the disease.

5. Conclusion

We developed a mathematical model for HBV infection in a dynamic population with controls. Simulations were carried out on the models with MatLab in order to investigate the impact of various control strategies on the disease transmission dynamics in the population. The impact of enlightenment, vaccine and condom use as a control measure of HBV in the population was remarkable. Therefore, to effectively control HBV in any given population, we must increase enlightenment (awareness) of the disease amongst the people. Once people are aware of the disease, then they can indulge on other diligent preventive measures: condom use, not sharing needles or other drug paraphernalia, not sharing items such as tooth brushes and razors. Individuals can also get vaccinated against HBV once they become aware. Active vaccination (Energix-B and Recombivax-HB) is recommended; this will offer long lasting active immunity

against HBV and invariably will help control the spread of HBV in the population. Therefore, efforts should be targeted at increasing the above mentioned strategies for effective control of HBV in a given population.

Table 1: Parameter values for HBV infection

S/N	Parameter	Value	Reference
1	μ	0.021	([1], [2]) and [3]
2	π	1000	Assumed
3	β	0.37	Assumed
4	τ	0.50	[29] and [15]
5	θ	10	Assumed
6	ω	0.02	Assumed
7	α	0.01	Assumed
8	λ	0.015	([1], [2])
9	ϕ	0.92	Assumed
10	ψ	0.015	([1], [2])
11	$\varphi \Rightarrow \Phi$	0.08	([1], [2])
12	ρ_1	0.33	[29] and [15]
13	ρ_2	0.33	[29] and [15]
14	δ	0.068	([1], [2])
15	δ_1	0.068	([1], [2])

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