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NUMERICAL SIMULATION OF THE IMPACT OF RELAPSE ON HEPATITIS B VIRUS TRANSMISSION DYNAMICS.

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ABSTRACT In this study, we present a numerical simulation of the impact of relapse on Hepatitis B virus transmission dynamics. The sensitivity analysis result establishes that relapse rate increases the value of the effective reproduction number when it is increased. Similarly, the result of the numerical simulation reveals that relapse increases the number of infected persons and thus the spread of the Hepatitis B Virus. Also, it delays the quick response to the treatment regimen which consequently slows down the potential of recovery from the infection. However, new drugs with low resistance should be provided, that will help to minimize the risk of relapse / re-emergence of the infection due to drug resistance.

Keywords: Hepatitis B Virus, treatment, relapse.

INTRODUCTION

Hepatitis B is a liver disease that results from the infection with hepatitis B virus (HBV) and is spread by the body fluid of an infected person. Hepatitis B can be acute or chronic, and about 25% of the chronic carriers will relapse as a result of drug-resistant (Nowak and May 2005).

Relapse refers to the reemergence of infection due to drug resistance. Primarily, drug resistance is the reduction in the effectiveness of a medication to cure a disease (HBV) (Zoulim, 2009). Relapse is one of the most challenging aspects of anti-viral therapy which can occur as a result of previous treatment with suboptimal regiments (type of immunosuppression), increase in viral load (virologic factors), and alteration in immune function (patient factors) (Tseng *et al*., 2012), which often cause a flare of disease that can be severe resulting in liver failure (Hoofnagle *et al*., 2009).

The prevalence of relapse in patients with Hepatitis B occurs due to population growth, drug-resistant strains, co-infection with HIV, re-infection, cultural factors and the collapse of public health programs (Athena *et al*., 2012; Charan and Paramita, 2016) is on the increase globally mostly due to poor patient compliance to health-care services. The risk was classified as low when the incidence rate is less < 1%, moderate when it is between 1%-10%, and high when it exceeds 10% (Wu *et al*. 2019). Relapse in patients is one of the most challenging aspects of antiviral therapy, however, when these patients receive immunosuppressive therapy, HBV is likely to be activated, which would lead to acute hepatic failure (Karajibani *et al.*, 2018; Tseng *et al*., 2012). At the moment, the predictors of relapse in patients after cessation of nucleotides analogues remain unclear (Yao *et al.*, 2017).

Relapse could be intrinsic to the liver cells or acquired when drugs are exposed, misuse of chemical or cellular stress among other conditions which allow dormant HBV to flare. Also, some drugs (anti-CD20 monoclonal antibody, rituximab, ibrutinib, glucocorticoid, cisplatin, and imatinib) could induce relapse in patients directly which results in profound B-cell depletion and produce a strong immune-mediated reaction (Buti, 2014). These factors enable drugs to be nonresponsive to standard therapies and conversely, delay the effective treatment of patients and as such, the number of HBV infections is relatively large (Moore and Chang, 2010). However, it is more difficult is to decide who requires antiviral therapy, the time, dose, and duration of treatment are still uncertain. Hence, it will be necessary to understand the impact of relapse to avoid harm. Therefore, to study the impact of relapse on Hepatitis B virus transmission dynamics, a mathematical model has been developed (see Nwaokolo *et. al.*, 2020).

This study is motivated by the work of Nwaokolo *et al.* (2020), on the global stability analysis of the effect

of vaccination and treatment in controlling the spread of the hepatitis b virus with infective migrants.

Model formulation

The population is categorized into eight compartments; Susceptible, Exposed, Acutely infected, Chronic carrier, Treated individuals, Recovered individuals, Migrated and Vaccinated individuals. They assume that the treated subjects may relapse to chronic and others progress to recovery class respectively. A proportion of susceptible is vaccinated per unit time and the vaccinated individuals do not acquire permanent immunity. The result shows that HBV will be sustained if infective migrants are allowed and also, there is improper or no vaccination regiment, under steady-state conditions (that is, a situation where there is no vaccination and effective treatment options HBV will persist). Therefore, guided by the work of Nwaokolo *et al.* (2020) the present work intends to examine the numerical simulation of the impact of relapse on HBV transmission dynamics.

The model by Nwaokolo *et al.* (2020) has the following variable and parameters.

Table 1. Variables and Parameters of the Model

S/N	Parameters	Interpretation
1.	S (t)	Number of Susceptible individuals at time *t.*
2.	E (t)	Number of Exposed individuals at time *t.*
3.	A (t)	Number of Acute infectives at time *t.*
4.	C (t)	Number of Chronic Infections at time *t.*
5.	V (t)	Number of immunized individuals at time *t.*
6.	M (t)	Number of Migrated individuals at time *t.*
7.	T (t)	Number of treated individuals at time *t*
8.	R (t)	Number of recovered individuals at time *t*
9.	δ	Equal per capita birth and death rate disease-(as induced death is not considered in the system)
10.	π	The proportion without immunization
11.	γ_1	The rate at which exposed individuals become infectious and move to the Acutely infected class.
12.	γ_2	The rate at which acutely infected individuals move to the chronic carrier class.
13.	γ_3	The rate at which chronic carriers acquire immunity and move to the immunized class.
14.	β	The transmission coefficient
15.	κ	The infectiousness of carriers relative to acute infections.
16.	q	The proportion of acutely infected individuals that become chronic carriers.
17.	1 - q	The proportion of acutely infected individuals that move to the immunity class.
18.	δ_o	The loss of immunity from the immunized class to susceptible class.
19.	α_0	The proportion of chronic carriers that are treated per unit time.
20.	φ	The rate at which treated individual relapse and proceed to the chronic class.
21.	ρ	The proportion of vaccinated susceptible per unit time.
22.	ξ	Rate of flow from exposed to migrated class.
23.	α	The flow from migrated to susceptible class.
24.	μ_1	The transmission rate from migrated class to exposed class.
25.	μ_2	The transmission rate from migrated class to acutely infected class.
26.	η	The proportion of the immunized children born to carrier mothers.

27.	δ(1 - π)	The newborns that are successfully immunized.
28.	δπ(1 – η*C*(t))	Birth flux into the susceptible class.

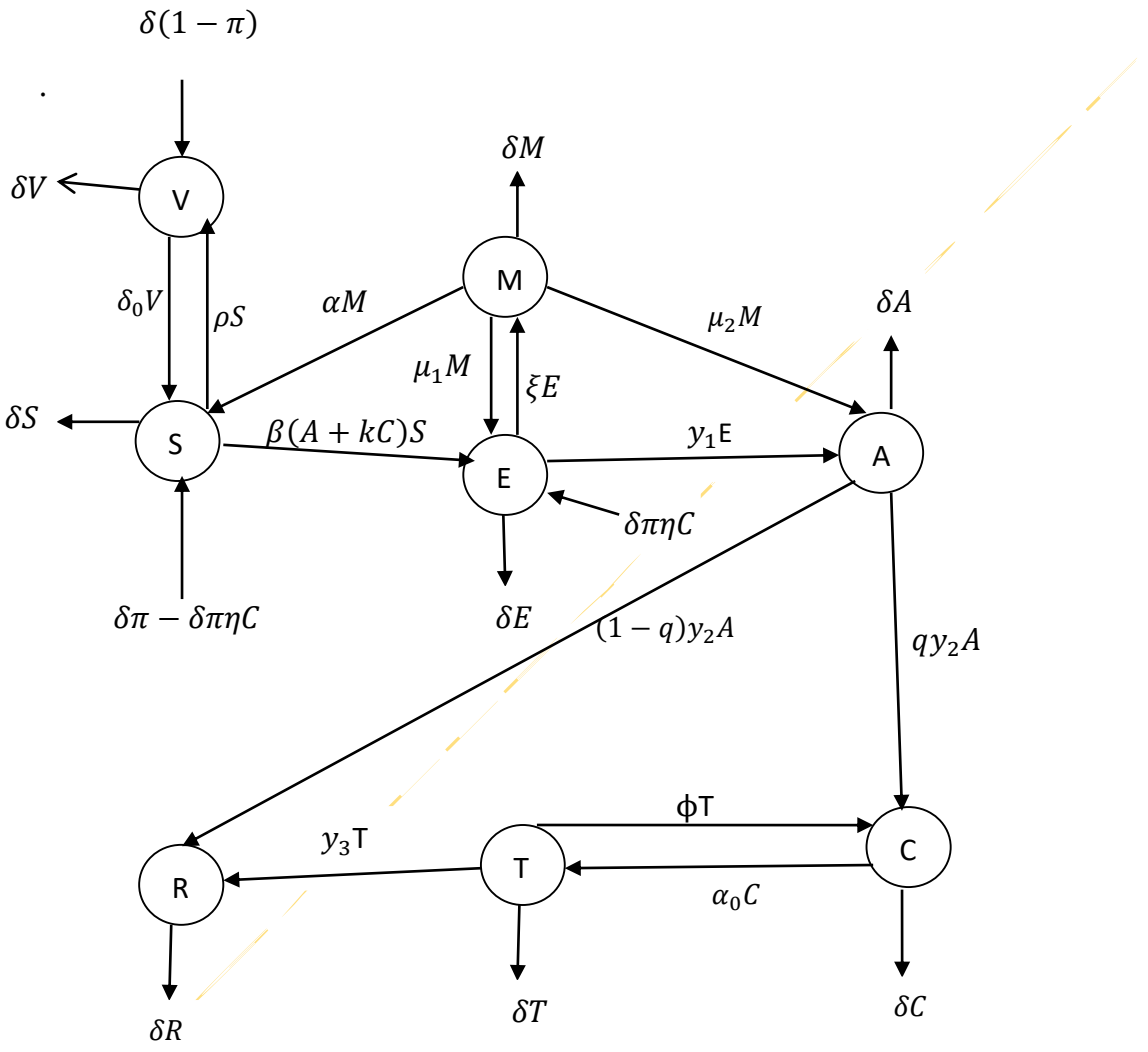

Figure 1: The Model Flow diagram of HBV Transmission Dynamics.

The Model Equation

Our governing model was based on the influence of vaccination and treatment on the dynamics of HBV in the presence of infective immigrants. The transformed governing model equations are as follows (Nwaokolo *et al*., 2020)

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+kC)S + \delta_0 V - pS + \alpha M, \quad (1)$$

$$\frac{dE}{dt} = \beta(A+kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M, \quad (2)$$

$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M, \quad (3)$$

$$\frac{dC}{dt} = q\gamma_2 A + \varphi T - (\delta+\alpha_0)C\,, \quad (4)$$

$$\frac{dT}{dt} = \alpha_0 C - (\delta+\varphi+\gamma_3)T, \quad (5)$$

$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2+\delta+\alpha)M, \quad (6)$$

$$\frac{dV}{dt} = \delta(1-\pi) + pS - (\delta+\delta_0)V. \quad (7)$$

Where,

$$R = 1 - S - E - A - C - T - M - V \quad (8)$$

and

$$S(0) > 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, M(0) \geq 0, V(0) \geq 0$$

Thus, the established reproduction number of the model (1-7) as contained in Nwaokolo *et al.* (2020) is

$$R_{r^c} = \frac{\left[\beta S^O\left(c + Kq\gamma_2(\delta+\varphi+\gamma_3)\right) + e(\delta+\varphi+\gamma_3)\right](\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc}{dbca} \quad (9)$$

Where,

$$S^O = \frac{\delta\pi+\delta_0}{\delta+\delta_0+p}, a = (\alpha+\delta+\mu_1+\mu_2), b = (\delta+\gamma_2), c = (\delta+\gamma_3)(\delta+\alpha_0) + \delta\varphi,$$

$$d = (\delta+\xi+\gamma_1), e = \delta\pi\eta q\gamma_2, f = (\delta+\varphi+\gamma_3), g = (\mu_2\xi+\gamma_1 a)$$

However, we are interested in examining the impact of relapse even though it was captured in the model but has not been fully explored. The importance of the aforementioned is that relapse is the re-emergence of a diseased condition on one that was previously infected. Based on the gap, we are motivated to examine the numerical simulation of the impact of relapse on HBV transmission dynamics.

Numerical Simulation

Numerical Simulations is used to illustrate some of the analytical results and verify theoretical predictions of the model (1)-(7) using a set of parameter values (Table 2). These parameter values are gotten from the epidemiology of HBV and the demographic profile of the population which is obtained from the literature (Khan *et al.*, 2016; Pan *et al*., (2013)).

In this section, we indeed demonstrate numerically using the fourth-order Runge-Kutta method coded by the aid of MATLAB program in Appendix A to simulate the model (1)-(7).

Table 2: Parameters Values used in Numerical Simulation

Parameters	*Range*	Value	Source
β		0.8	Khan *et al.*(2016)
δ		0.0143	Khan *et al.*(2016)
δ_0	0.03-0.06	0.03	Khan *et al.*(2016)
γ_1		6 per year	Khan *et al.*(2016)
γ_2		4 per year	Khan *et al.*(2016)
γ_3		0.34	Khan *et al.*(2016)
k		0.1	Khan *et al.*(2016)
π		0.8	Khan *et al.*(2016)
η		0.7	Khan *et al.*(2016)
μ_1		0.1	Khan *et al.*(2016)
μ_2		0.1	Khan *et al.*(2016)
α	0-1	0.1	Khan *et al.*(2016)
ξ	0-1	0.1	Khan *et al.*(2016)
q	0.05-0.9	0.05	WHO (2002)
φ		0.393	Pan *et al* .(2013)
S_O		0.493	Medley *et al* . (2001)
E_O		0.0035	Medley *et al* . (2001)
A_O		0.0035	Medley *et al* . (2001)
C_O		0.25	Assumed
M_O		0.003	Assumed
P		0.8	Assumed
α_o		0.8	Assumed

The results of the numerical experiments are meant to study the following cases (a)-(d).

a) The behaviour of chronic carriers in the absence of relapse. This is shown in Figure 2.
b) The impact of different relapse rates on the chronic carriers. This is shown in Figure 3.
c) The impact of different relapse rates on Acute infection. This is shown in Figure 4.
d) The impact of reproduction number against relapse. This is shown in Figure 5.

Sensitivity Analysis

We perform sensitivity analysis to determine the relative importance of model parameters responsible for disease transmission. The analysis will enable us to find out parameters that have a high impact on the effective reproduction number and which should be targeted by intervention strategies. We perform sensitivity analysis by calculating the sensitivity indices of the effective reproduction number with relapse R_r^c to determine whether HBV can be eradicated in the population or not. These indices tell us how vital each parameter is to hepatitis B transmission and prevalence.

Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values because there are usually errors in data collection and presumed parameter values (Chitnis *et al.*, 2008). To investigate which parameters in the model system have a high impact on the R_r^c and should be targeted by intervention strategies, we apply the approach presented by Chitnis *et al.* (2008). The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives as follows.

Definition 1: The normalized forward sensitivity index of a variable, τ that depends differentiable on the index of a parameter p is defined as

$$r_\tau^\rho = \frac{\partial \rho}{\partial \tau} \times \frac{\tau}{\rho} \tag{10}$$

From the formula of effective reproduction, R_r^c in equation (9), we derive an analytical expression for the sensitivity of R_r^c as

$$r_\tau^{R_r^c} = \frac{\partial R_r^c}{\partial \tau} \times \frac{\tau}{R_r^c} \tag{11}$$

where τ denotes the parameter. We compute the sensitive indices of the model system for some parameters involved in R_r^c. For example the sensitivity index of R_r^c with respect to β is given by

$$r_\beta^{R_r^c} = \frac{\partial R_r^c}{\partial \beta} \times \frac{\beta}{R_r^c} \tag{12}$$

Also, the sensitivity index of R_r^c with respect to α_0 is given by

$$r_{\alpha_0}^{R_r^c} = \frac{\partial R_r^c}{\partial \alpha_0} \times \frac{\alpha_0}{R_r^c} \tag{13}$$

Furthermore, the sensitivity index of R_r^c with respect to φ is given by

$$r_\varphi^{R_r^c} = \frac{\partial R_r^c}{\partial \varphi} \times \frac{\varphi}{R_r^c} \tag{14}$$

RESULTS AND DISCUSSION

In this section, we present the main findings of the study under the following sub-headings.

Numerical Results

We begin this sub-section by presenting the numerical results of the above experiments (a-d).

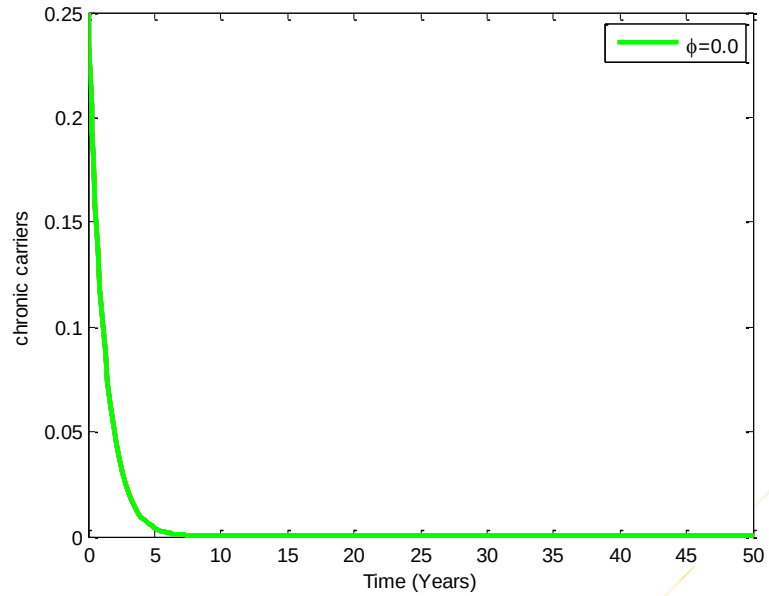

Figure 2: A situation where there is no relapse on Chronic Carriers($\varphi = 0,0$)

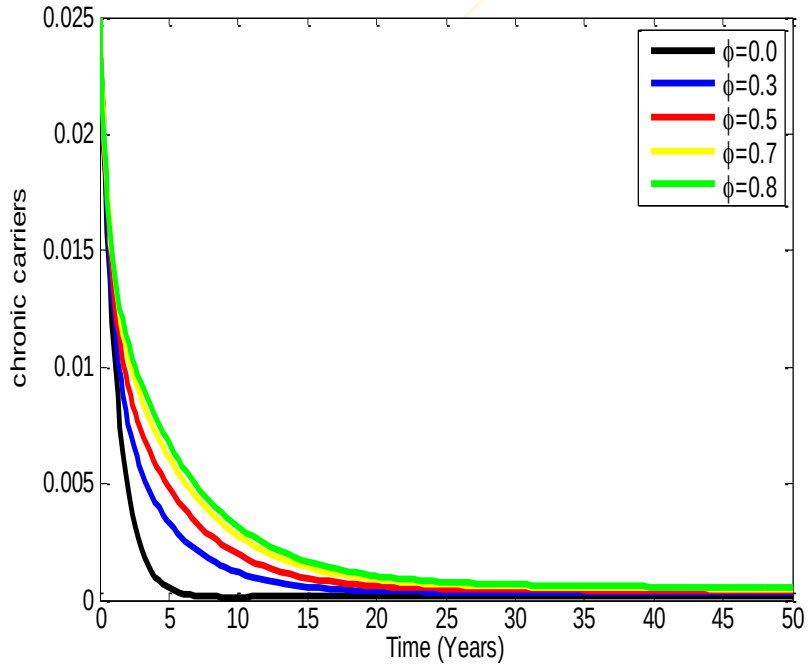

Figure 3: Impact of increasing Relapse Rate on Chronic Carriers($\varphi = 0, 0.3, 0.5, 0.7, 0.8$)

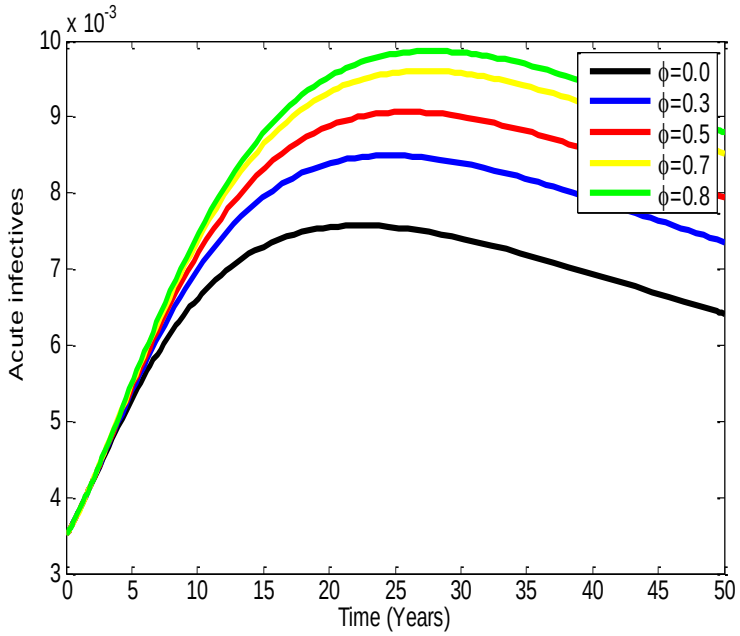

Figure 4: Impact of Relapse Rates on Acute Infectives ($\varphi = 0, 0.3, 0.5, 0.7, 0.8$).

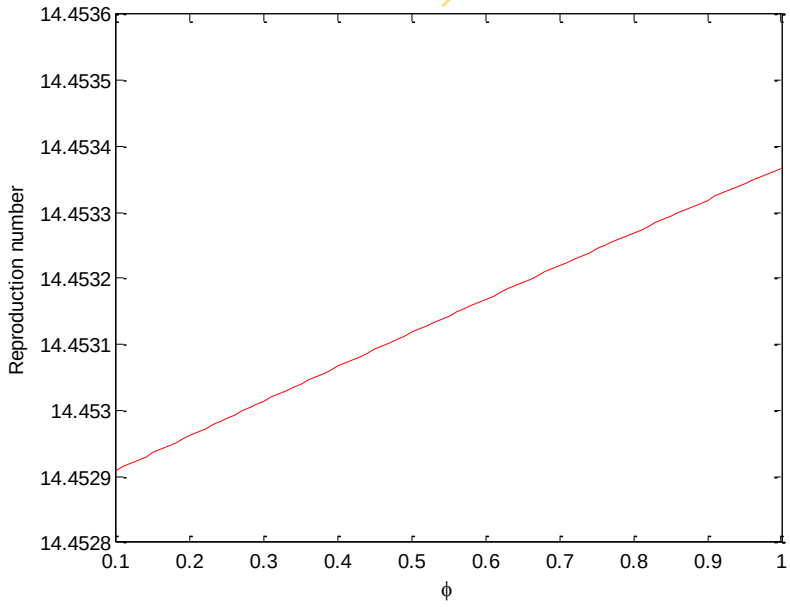

Figure 5: Impact of reproduction number against relapse rate

Sensitivity Results

We use the parameter values displayed in Table 1 to obtain the numerical value, therefore, the sensitivity index of R_r^c with respect to β is given by

$$r_{\beta}^{R_r^c} = 1$$

the sensitivity index of R_r^c with respect to α_0 is given by

$$r_{\alpha_0}^{R_r^c} = -0.0000342508$$

Furthermore, the sensitivity index of R_r^c with respect to φ is given by

$$r_{\varphi}^{R_r^c} = 0.00001801218$$

The sensitivity indices results of R_r^c are given in Table 3 and are arranged from the highest sensitivity value to the lowest value. The indices with positive signs show that the value of R_r^c increases when the corresponding parameters are increased and those having negative signs indicate that the value of R_r^c decreases when the parameters are increased.

Table 3: Sensitivity Indices of R_r^c with respect to some Parameters

S/N	Parameter	Sensitivity Index	Sign
1	β	1.000000000	+
2	p	0.9475304984	−
3	δ_0	0.6884058306	+
4	γ_2	0.434756444	−
5	μ_2	0.3475541027	+
6	α	0.3123292643	−
7	π	0.2760833440	+
8	γ_1	0.1742824945	+
9	ξ	0.0296644089	−
10	μ_1	0.0094382464	+
11	q	0.00003554198	+
12	α_0	0.00003425081	−
13	η	0.00002156809	+
14	φ	0.00001801218	+
15	k	0.0000139739	+
16	γ_3	0.000001728521	−

Numerical Simulation Results

The behaviour of the model is shown in Figure 2 - 6 where we plot the prevalence of the population with time. The parameter values used in the numerical experiment are in Table 2.

Figure 2 shows clearly that when there is no relapse rate, the chronic carriers' declines over a short period. The medical implication is that the result in Figure 1 agrees with the report of Weinbaum *et al.* (2008) that HBeAg will clear in a short time, which leads to a marked reduction in disease activity, viral load, and histological improvement in the population. This agrees with the requirement for the global elimination of hepatitis B (WHO, 2015; Nayagam *et al.*, 2016).

Figure 3 demonstrates clearly that when the relapse rate is increased (0%, 30%, 50%, 70%, 80%), it takes a longer time for the infection (chronic carrier) to be curtailed. That is relapse slows down the potential of recovery from the infection. On the other hand, when the relapse rate is reduced by adhering to treatment it takes a short time for the infection to be curtailed as seen in figure 3. Therefore, for the infection to be put under control relapse in patients, need to be checked.

Figure 4 demonstrates clearly that when the relapse rate is increased, the number of acute infective increases.

Figure 5 shows clearly that R_r^c increases in the presence of relapse (treatment failure). Therefore, φ increases the spread of the disease in the population. Hence, it will be profitable if the impact of treatment failure is checked.

Sensitivity Analysis Result

In interpreting the sensitivity indices, we keep all other factors constant. Table 3 shows that parameters $\beta, \delta_0, \pi, q, \gamma_1, \varphi$ and η increase the value of R_r^c when they are increased. This implies that the HBV infection will grow up in the population when these parameters are increased. On the contrary, γ_2, p, α_0 and γ_3 decrease the value of R_r^c when they are increased. This implies that the disease cannot grow in the population when these parameters are increasing.

The most, sensitive parameter is the transmission coefficient β. Increasing or decreasing the value of β leads to the increase or decrease of the value of R_r^c with the same proportion since the sensitivity index is equal to one. Therefore, as β increases, many persons become infected, so HBV transmission increases in the population. Treatment rate α_0 is also sensitive, showing that as α_0 increases R_r^c decreases. This implies that treatment as a control strategy helps to reduce viral loads in most treated persons.

Furthermore, when relapse rate, φ increases then R_r^c increases, this implies that many treated individuals move to the chronic carrier-class after undergoing relapse. Therefore, to minimize HBV transmission in a population, this study recommends that relapse should be curtailed because it increases the livelihood of reoccurrences of the infection.

CONCLUSION AND RECOMMENDATION

Conclusion

In this study, we simulate a deterministic compartmental model on the impact of relapse on HBV transmission dynamics. The sensitivity analysis is carried out to show some important parameters that may cause an increase in the effective reproduction number, which could be checked by way of reoccurrences of the infection. The result of the numerical simulation reveals that relapse (reoccurrences of the infection) delays the quick response to a treatment regimen which consequently slows down the potential of recovery from the infection. Also, it increases the number of infected persons in the population and hence increases the spread of HBV.

Recommendations

Based on the findings of this research, to reduce the development of relapse as much as possible and to increase recovery, the study recommends that new drugs with low resistance should be provided, which will help to minimize the risk of relapse in controlling the spread of HBV.

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