

An Epidemiological Model on the Impact of Relapse in Patients With chronic Hepatitis B Virus Infection, using Treatment Strategies as Control

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ABSTRACT

The Impact of Relapse in Patients With chronic Hepatitis B Virus Infection, using Treatment Strategies as Control is analyzed. The reproduction number is computed from which threshold ratios are obtained. Sensitivity indices of the effective reproduction number, establishes that, the transmission rate championed the disease outbreak. Numerical experiments were carried out using MATLAB program, the result uncovers that ineffective treatment slows down the capability of recovery from the disease and should be avoided to reduce the consequences of drug resistance. On the other hand, people that have adopted effective treatment strategies have shown greater potentials for recuperation from the infection. Also, new drugs with low resistance should be given, that will help to reduce the risk of relapse. Hence, compliance to highly effective treatment strategy is needed to control relapse in patients with persistent HBV infection.

1.0 INTRODUCTION

Hepatitis B is one of such deadly diseases that is caused by hepatitis B virus (HBV). Presently, regardless of the use of a preventive vaccine for several decades as well as the use of effective and well tolerated viral suppressive medications since 1998, approximately 250 million people are chronically infected with the virus and a lot of people die every year from hepatitis belated liver failure and liver cancer (Nguyen *et al.*, 2020). In the domain of medicine, the impact of ill-advised treatment, self-medication, or visually impaired remedy are liable for viral persistence in the host genome. In this manner, setting off relapse in patients and subsequently lead to complication and mortality (Yao *et al.*, 2017; Sonneveld *et al.*, 2019; Kuo *et al.*, 2021; Hall *et al.*, 2022). For this research, relapse alludes to the reappearance of infection because of drug resistance (Kuo *et al.*, 2021). It is seen that the people who go through successful treatment tend not to encounter resistance and do recuperate rapidly (Choi *et al.*, 2022). Assuming the viral burden increases, it implies that it is resistant to the medications and ought to be altered (Pan *et al.*, 2021; Xu *et al.*, 2021), however assuming that it fails to reproduce, it implies the medications are effective and the infection is not resistant.

Notwithstanding, regardless of numerous analysts that have made endeavors to model HBV. HBV as seen in (Nwaokolo *et al.* 2020, 2022), none as far as I could possibly know have displayed the impact of relapse in patients with chronic hepatitis b virus infection, using treatment strategies as control

Hence, guided by the model of Nwaokolo *et al.* (2020) on the impact vaccination and therapy in the control of HBV within the sight of infective immigrants; however, this research is interested in examining the impact of treatment strategies in controlling relapse in patients with chronic HBV infection independent of vaccination, using the above model. Hence, a relapsed subject does not undergo vaccination. Therefore, the current work means to look at the impact of relapse in patients with chronic hepatitis b virus infection, using treatment strategies as control

1.1 Aim and Objectives of the Study

The aim of this study is to model the impact of relapse in patients with chronic hepatitis b virus infection, using treatment strategies as control

The specific objectives are to:

- i. compute the effective reproduction number from the model of Nwaokolo *et al.* (2020);
- ii. carry out sensitivity analysis on the effective reproduction number in order to determine the parameters of the model that are most sensitive and targeted by way of intervention strategies;
- iii. carry out numerical simulation of the model;
- iv. interpret results in (ii)-(iii) in biological terms.

2.0 METHODOLOGY

The methods necessary for analysis of the existing Hepatitis B virus deterministic model of Nwaokolo *et al.* (2020) are presented.

2.1 The Existing Model

Nwaokolo *et al.* (2020) presented a work on the impact immunization and therapy on the control of HBV within the sight of infective immigrants. We state the assumptions, parameters and the equations of their model below.

2.2 Assumptions of the Model by Nwaokolo *et al.* (2020)

The following are the assumptions of the existing model by Nwaokolo *et al.* (2020):

- i. The population is compartmentalized into eight groups namely: Susceptible individuals, $S(t)$, Exposed individuals $E(t)$, Acutely infected individuals, $A(t)$, Chronic carriers, $C(t)$, Immunised individuals, $V(t)$, treated individuals $T(t)$, recovered individuals $R(t)$ and Migrated individuals, $M(t)$, all at time t .
- ii. The population is mixed homogeneously, that is, all people are equally likely to be infected by the infectious individuals in case of contact.
- iii. The newborns to carrier mothers infected at birth are latently infected individual.
- iv. A proportion of susceptibles are vaccinated per unit time and the vaccinated individuals do not acquire permanent immunity.

- v. Migrants are adults hence; the natural birth rate of the migrated class is neglected.
- vi. There is a transmission rate from exposed to migrated class and vice-versa.
- vii. There is a transmission rate from migrated class to susceptible class and migrated class to acutely infected class.
- viii. There is a stable population with equal percapita birth and death rate δ (as disease-induced death rate is not considered in the system).
- ix. We assume that the chronic carriers do not acquire immunity until they are treated and recruited into the treated class, whereas not all treated individuals progress to the recovery class, some relapse to chronic if drug resistant mutants are present.
- x. We split the immunized class and redefined the recovery of chronic carriers as, treated subjects who progress to recovery class and those who relapse to chronic.

Subsequently, inspired by the work of Nwaokolo *et al.* (2020), the overseeing model equations have the accompanying variables and parameters.

Table 1. Variables and Parameters of the Model

S/N	Parameters	Interpretation
1.	$S(t)$	Number of Susceptible persons at time t .
2.	$E(t)$	Number of Exposed persons at time t .
3.	$A(t)$	Number of Intense infective at time t .
4.	$C(t)$	Number of persistent (Chronic) carriers at time t .
5.	$V(t)$	Number of immunized persons at time t .
6.	$M(t)$	Number of migrated persons at time t .
7.	$T(t)$	Number of treated persons at time t .
8.	$R(t)$	Number of recuperated persons at time t .
9.	δ	Equal per capita birth and demise rate
10.	Π	The proportion without immunization
11.	γ_1	The rate at which exposed persons become infectious and move to the intensely infected class.
12.	γ_2	The rate at which intensely infected persons move to the chronic carrier class.
13.	γ_3	The rate at which chronic carriers secure immunity and move to the vaccinated class.
14.	β	The transmission coefficient
15.	κ	The irresistibility of carriers comparative with intense infections.
16.	q	The proportion of intensely infected persons that become chronic disease carriers.
17.	$1 - q$	The proportion of intensely infected persons that move to the immunity class.
18.	δ_o	The loss of immunity from the immunized class to susceptible class.
19.	α_o	The ratio of chronic carriers that are treated per unit time.
20.	ϕ	The rate at which treated persons relapse and continue to the chronic class.
21.	ρ	The proportion of immunized susceptible per unit time.

22.	ξ	Rate of flow from exposed class to migrated class.
23.	α	The flow from migrated class 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 intensely infective class.
26.	η	The proportion of the immunized kids born by carrier mothers.
27.	$\delta(1 - \pi)$	The babies that are effectively immunized.
28.	$\delta\pi(1 - \eta)C(t)$	Birth transition into the susceptible class.

The governing model equations are as follows (Nwaokolo *et al.* 2020).

$$\frac{dS}{dt} = \delta\pi(1 - \eta)C - \delta S - \beta(A + kC)S + \delta_0 V - pS + \alpha M, \quad (3.17)$$

$$\frac{dE}{dt} = \beta(A + kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M, \quad (3.18)$$

$$\frac{dA}{dt} = \gamma_1 E - (\delta + \gamma_2)A + \mu_2 M, \quad (3.19)$$

$$\frac{dC}{dt} = q\gamma_2 A + \varphi T - (\delta + \alpha_0)C, \quad (3.20)$$

$$\frac{dT}{dt} = \alpha_0 C - (\delta + \varphi + \gamma_3)T, \quad (3.21)$$

$$\frac{dM}{dt} = \xi E - (\mu_1 + \mu_2 + \delta + \alpha)M, \quad (3.22)$$

$$\frac{dV}{dt} = \delta(1 - \pi) + pS - (\delta + \delta_0)V. \quad (3.23)$$

with

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

Hence, the laid out reproduction number of the model (3.17-3.23) as contained in Nwaokolo *et al.* (2020) is

$$R_{rc} = \frac{[\beta S^0(c + Kq\gamma_2(\delta + \varphi + \gamma_3)) + e(\delta + \varphi + \gamma_3)](\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc}{dbca} \quad (3.24)$$

where,

$$S^0 = \frac{\delta\pi + \delta_0}{\delta + \delta_0 + p}, a = (\alpha + \delta + \mu_1 + \mu_2), b = (\delta + \gamma_2), c = (\delta + \gamma_3)(\delta + \alpha_0) + \delta\varphi,$$

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

Notwithstanding, we are keen on looking at the effect of viable (effective) and ineffective therapy system in controlling relapse in patients with chronic HBV disease, free of immunization, utilizing the above model.

The importance of the aforementioned is that relapse is the re-emergence of a diseased condition on one that was previously infected. Hence, a relapsed subject does not undergo vaccination; therefore we set vaccinated related parameters in (3.24) to zero ($p = \delta_0 = 0$) to derive the effective reproduction ratios with treatment and relapse given by:

$$R_\varphi = \frac{[\beta S_1(c + Kq\gamma_2(\delta + \varphi + \gamma_3)) + e(\delta + \varphi + \gamma_3)](\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc}{dbca} \quad (3.25)$$

where,

$$S_1 = \pi, a = (\alpha + \delta + \mu_1 + \mu_2), b = (\delta + \gamma_2), c = (\delta + \gamma_3)(\delta + \alpha_0) + \delta\varphi,$$

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

Therefore, $R_\varphi < 1$ implies that

$$\beta_\varphi < \frac{dbca - (e(\mu_2\xi + \gamma_1 a)(\delta + \varphi + \gamma_3) + \xi\mu_1 bc)}{S_1((c + Kq\gamma_2(\delta + \varphi + \gamma_3)) + e(\delta + \varphi + \gamma_3))(\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc} \quad (3.26)$$

Also, the effective reproduction number with treatment only ($\varphi = 0$) becomes

$$R_{\alpha_0} = \frac{[\beta S_1(\delta + \alpha_0 + Kq\gamma_2) + e](\mu_2\xi + \gamma_1 a) + \xi\mu_1 b(\delta + \alpha_0)}{dba(\delta + \alpha_0)} \quad (3.27)$$

Therefore, $R_{\alpha_0} < 1$ implies that

$$\beta_{\alpha_0} < \frac{dba(\delta + \alpha_0) - (e(\mu_2\xi + \gamma_1 a)(\delta + \gamma_3) + \xi\mu_1 b(\delta + \alpha_0))}{S_1((\delta + \alpha_0 + Kq\gamma_2) + e)(\mu_2\xi + \gamma_1 a) + \xi\mu_1 b(\delta + \alpha_0)} \quad (3.28)$$

In this way, successful treatment system (treatment without relapse) assumes a basic role in decreasing the frequency of HBV disease in the populace. Since the chronic carriers change their behaviour which results in a reduction in the spread of HBV infection, it is noted that $R_{\alpha_0} < R_{\varphi}$.

Likewise, the essential reproduction number (without treatment) is given by,

$$R_0 = \frac{[\beta S_1(\delta + Kq\gamma_2) + e](\mu_2\xi + \gamma_1a) + \xi\mu_1b\delta}{dba\delta} \quad (3.29)$$

The computation of the various reproductions numbers using MAPLE satisfies the inequality $R_{\alpha_0} < R_{\varphi} < R_0$. However; the presence of relapse posed a threat to HBV control measures if not adequately checked.

2.3 Numerical Simulation

We apply the fourth order Runge-kutta technique coded by the aid of MATLAB program to simulate the model, while the table of values is given below;

Table 3: Parameters Values utilized in Numerical Simulation

Parameters	Range	Value	Source
β		0.8	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
δ		0.0143	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
γ_1		6 per year	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
γ_2		4 per year	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
γ_3		0.34	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
k		0.1	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
π	0-1	0.001	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
η		0.7	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
μ_1		0.001	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
μ_2		0.001	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
α	0-1	0.8	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
ξ	0-1	0.8	Khan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
q	0.005-0.9	0.005	WHO in Nwaokolo <i>et al</i> (2022)
φ		0.393	Pan <i>et al</i> in Nwaokolo <i>et al</i> (2022)
S_0		0.493	Medley <i>et al</i> in Nwaokolo <i>et al</i> (2022)
E_0		0.0035	Medley <i>et al</i> in Nwaokolo <i>et al</i> (2022)
A		0.0035	Medley <i>et al</i> in Nwaokolo <i>et al</i> (2022)

C_0	0.25	Assumed
M_0	0.003	Assumed
α_0	0.8	Assumed

2.4 Sensitivity Analysis

We investigate the sensitivity, to determine the significant importance of model parameters liable for disease transmission. The analysis will empower us to figure out parameters that profoundly affect the effective reproduction number and which ought to be focused on by mediation strategies. We calculate the sensitivity indices of the effective reproduction number with relapse R_ϕ to decide if HBV can be eradicated in the populace or not. These indices let us know how indispensable every parameter is to hepatitis B transmission.

Sensitivity analysis is generally used to decide the robustness of model predictions to parameter values since there are normally mistakes in information assortment and assumed parameter values (Chitnis *et al* in nwaokolo 2022).

To explore which parameters in the model system (3.18) – (3.22) exceptionally affect R_ϕ and ought to be targeted by mediation technique, we apply the methodology introduced by (Chitnis *et al* in nwaokolo 2022). The normalized forward sensitivity index of a variable to a parameter is a proportion of the relative change in the parameter. At the point when a variable is a differentiable function of the parameter, the sensitivity index may be on the other hand defined using partial derivatives as follows.

Definition 4: The normalized forward sensitivity index of a variable τ that depends differentiable on the index on a parameter p is defined as $r_\tau^p = \frac{\partial \tau}{\partial p} \times \frac{p}{\tau}$

From the formula of effective reproduction, R_ϕ in condition (3.25), we determine an analytical expression for the sensitivity of R_ϕ as $r_\tau^{R_\phi} = \frac{\partial R_\phi}{\partial \tau} \times \frac{\tau}{R_\phi}$, where τ signifies the parameter. We compute the sensitive indices of the model system (3.17) – (3.23) or certain parameters involved in R_ϕ . For instance the sensitivity index of R_ϕ regarding to β is given by

$$r_\beta^{R_\phi} = \frac{\partial R_\phi}{\partial \beta} \times \frac{\beta}{R_\phi} \quad (3.30)$$

3.0 RESULT AND DISCUSSION

In this segment, we present the primary discoveries of the findings under the accompanying sub-headings.

3.1 Numerical Results

Based on the numerical simulation done, the following graphs and discussion of numerical results of the model were presented.

Figure 2 illustrate the dynamical behaviour of chronic carrier with respect to the parameters, α_0 and ϕ . With no treatment rate, the chronic carriers will persist in the population, implying that the disease fails to be eradicated at that point and begins to decline as the value of effective treatment increases from 0.3 to 0.8. Figure 2 (from 0.3 to 0.8) demonstrates the effectiveness of treatment without relapse in controlling chronic HBV infection.

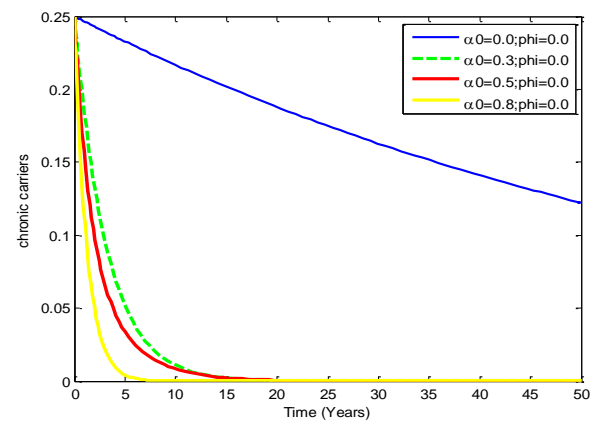


Figure 2: Effect of different treatment strategies on chronic carriers without relapse rate.

Figure 3 shows the behaviour of chronic carriers who have gone out for treatment and indicates a similar scenario only that the number of treated individuals with an ineffective treatment strategy, who relapse, has a less comparative advantage to those treated individuals without relapse. That is, ineffective treatment strategy increases the time or may not allow the infection to be put under control on time.

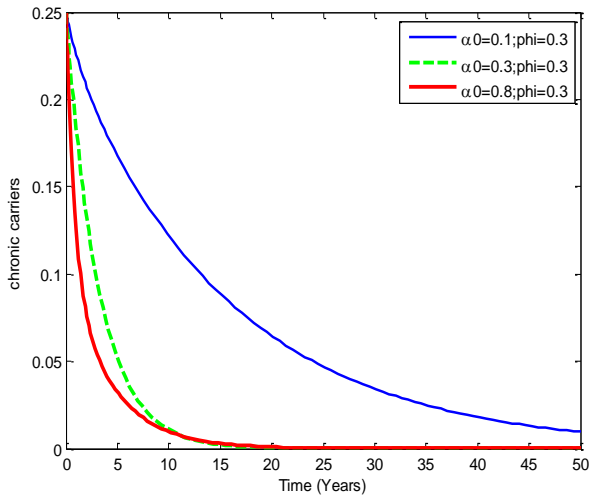


Figure 3: Effect of different treatment strategies on chronic carriers with constant relapse rate.

Figure 4. Shows a clear difference between the above two experiments, where treatment $\alpha_0 = 0.3$ and relapse ranges from $\varphi = 0$ to $\varphi = 0.3$. This result shows the significance of effective treatment ($\alpha_0 = 0.3, \varphi = 0$) as an essential for reducing relapse in patients with persistent HBV infection and further beats down ineffective treatment (blind prescription, or self-medication) ($\alpha_0 = 0.3, \varphi = 0.3$). This result agrees with the work of (Guo, 2018) that adherence to effective anti- HBV therapy prevents relapse and encourages timely cure.

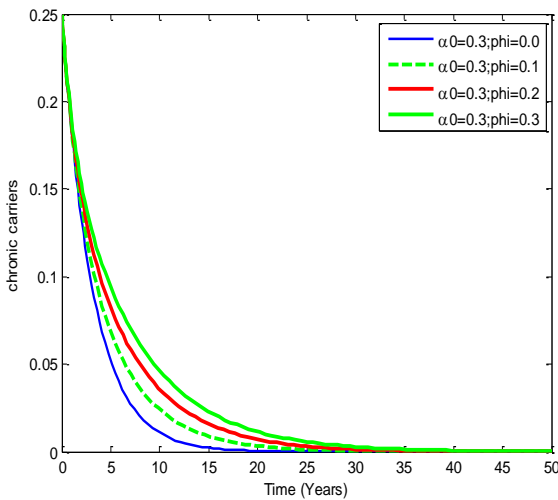


Figure 4: Effect of a treatment strategy on chronic carriers with different relapse rates.

Figure 5: Demonstrate the impact of α_0 on patients, who relapse to chronic carrier at different rates. The higher one embraces treatment with less or no relapse

at all, the better for chronic infection to be halted. On the other hand, the infection will prove difficult to curtail for those who have gone for ineffective treatment (self-medication).

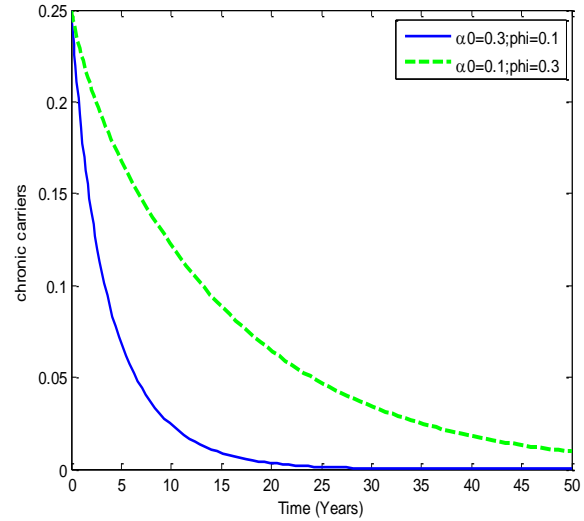


Figure 5: Effect of two different treatment and relapse strategies on chronic carriers.

Figure 6 shows that R_φ increase in the presence of relapse (treatment failure, φ). Therefore, φ increases HBV infection. On the other hand, the treatment rate α_0 decreases the spread of the disease in the population. Hence, it will be profitable if the causes of treatment failure are checked.

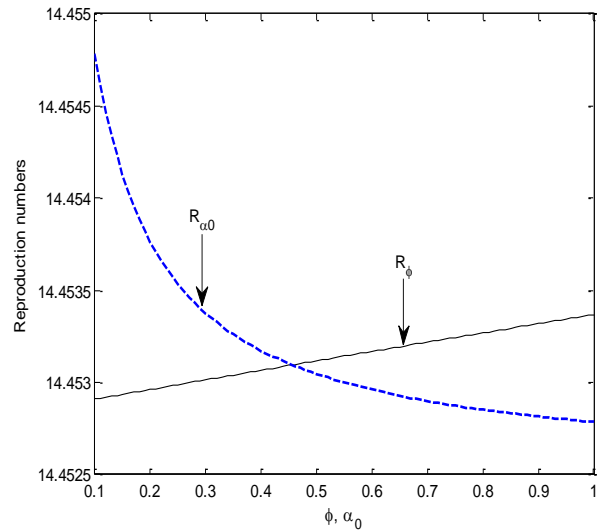


Figure 6: The impact of the reproduction numbers (R_φ on φ) and (R_{α_0} on α_0)



3.2 Sensitivity Results

We utilize the parameter value displayed in Table 3 to get the numerical values, therefore, the sensitivity index of R_ϕ and R_{α_0} with respect to β is given by

$$r_\beta^{R_\phi} = r_\beta^{R_{\alpha_0}} = 1$$

the sensitivity index of R_ϕ with respect to α_0 is given by

$$r_{\alpha_0}^{R_\phi} = -0.000008393$$

Likewise, the sensitivity index of R_{α_0} with respect to α_0 is given by

$$r_{\alpha_0}^{R_{\alpha_0}} = -0.00001532$$

The sensitivity indices results of R_ϕ are given in Table 4 and are arranged from the highest sensitivity value to the lowest value. The indices with positive signs show that the value of R_ϕ increases when the corresponding parameters are increased and those having negative signs indicate that the value of R_ϕ decreases when the parameters are increased.

Table 4: Sensitivity Indices of R_ϕ with respect to some Parameters

S/N	Parameter	Sensitivity Index	Sign
1	β	1.000000000	+
2	γ_2	0.43385442	-
3	μ_2	0.056317856	+
4	α	0.05641998	-
5	π	1.00000000	+
6	γ_1	0.92384591	+
7	ξ	0.90661118	-
8	μ_1	0.00111063	+

10	q	0.000008586	+
11	α_0	0.000008393	-
12	η	0.00000000712	+
13	ϕ	0.000001847	+
14	k	0.000008586	+
	γ_3	0.000001773	-

3.3 Sensitivity Analysis Result

Table 4 reveals that $\beta, \pi, \phi, q, \gamma_1$ and η increases the value of R_ϕ when they are increased. This suggests that the HBV disease will grow up in the populace when these parameters values are increased. Running against the norm, γ_2, α_0 and γ_3 decrease the value of R_ϕ when they are increased. This suggests that the disease can't grow in the populace when these parameters values are decreasing.

The transmission coefficient, β and the proportion without immunization π are the most, sensitive parameters. Decreasing or increasing the value of β and π leads to the decrease or increase of the value of R_ϕ with a similar extent since the sensitivity index is equivalent to one. Subsequently, as β and π increases, numerous people become infected, so HBV transmission increases in the population.

Moreover, when treatment rate, α_0 increases then R_{α_0} diminishes, this suggests that numerous persistent chronic carriers move to the removed class after treatment. Consequently, to limit HBV transmission in a populace, this study suggests that treatment ought to be carried out in light of the fact that treatment assists to prevent the spread of infection and its entanglements.

4.0 Conclusion

The objective of this paper is to show the effect of therapy in controlling relapse in patients with chronic HBV infection. To this end, we compute the effective reproduction ratios and the incidence function that account for the behaviour of subjects with and without relapse has been introduced. It was demonstrated that effective treatment (Hepatologist prescription) is extremely critical in mitigating and controlling relapse in subjects with chronic HBV infection than the subjects (model) with an ineffective treatment technique. Mathematical experiments were carried out using MATLAB program, the outcome uncovers that patients adopting ineffective treatment systems are inclined to delay in fast reaction to treatment regimens, which thusly slow down the capability of recuperation from the infection. The epidemiological result of the key discoveries is that controlling the illness with an insufficient treatment methodology (self-medicine and

visually impaired remedy) ought to be avoided to reduce the outcomes of drug resistance. Running against the norm, people that have embraced effective treatment strategies have shown more prominent possibilities for recuperation from the disease. The sensitivity indices of R_ϕ uncover that, transmission rate and the proportion without immunization advocated the disease outbreak and could be checked via occurrence of the infection or the number of infected person in the populace. Hence, compliance to highly effective treatment strategy is needed to control relapse in patients with persistent HBV infection.

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