

## **Sensitivity Analysis Applied to the Progression (Deterioration) Rate of Hepatitis 'B' to Primary Liver Cancer Model**

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### **Abstract**

*We aimed at studying the sensitivity analysis of the parameters to the effective reproduction number for the rate of progression of Hepatitis B Virus (HBV) to primary liver cancer. The effect of vaccination, sensitization and proper education on HBV transmission is considered as control strategies on the transmission rate of the disease. Also, the effect of therapeutic treatment is considered on the rate at which the patients living with HBV progresses to a primary liver cancer patients. Positivity of solution of the model as well as the disease free equilibrium and endemic equilibrium states of the model were discussed. Threshold analysis of some of the parameters were analysed and discussed.*

**Keywords:** Sensitivity Analysis, Reproduction Number, HBV, Primary Liver Cancer. Threshold analysis.

### **Introduction**

Hepatitis is a virus disease that affect the liver. The word "Hepatitis" is believed to be coined from two different languages; which are 'hepar' (Greek root word; hepat) which means 'liver' and the Latin 'itis' which is interpreted as 'inflammations' [10]. Hence, it is convenient to describe Hepatitis as an injury to the liver with inflammation of the liver cells. Five major types of Hepatitis has been diagnosed by laboratory test, they are: Hepatitis A, B, C, D, E with clinical explanation that one can lead to another and some may occur independently. Our focus in this research work is on Hepatitis B which is generally taken as the deadliest of all the hepatitis type. Clinically, mode of transmission of Hepatitis B includes sexual transmission, lateral transmission (Mother-Child), horizontal transmission (which include, contact with infected blood or semen and some other body fluid). The acute phase of Hepatitis B may include symptoms like mild flu, Diarrhea, fatigue, loss of appetite etc. whereas the chronic stage may include symptoms like

drowsiness, dark urine, headache etc. An estimated 686,000 of people living with chronic Hepatitis B die annually according to WHO [3]. Liver cirrhosis and Primary liver cancer is a product of chronic hepatitis B.

Mathematical model is an interpretation of physical, biological, economic or social problems using mathematical expressions with the aim of performing qualitative analysis in order to gain insight on which solution can be proffer to the studied problem(s). Over the year, Mathematical Biologist are becoming instrumental to make the world free of infections. Hence, this work aimed at exposing the effect of defined parameter in order to curb the spread of Hepatitis B in the population using sensitivity analysis approach.

### Model formulation

The model divides the entire human population into six compartments which are  $M-S-E-I_1-I_2-R$ . Movement into the compartment  $M$  is as a result of children born with partial immunity due to vaccine given to their mother during pregnancy. The compartment reduces by natural death rate ( $\mu$ ) and by the expiration of the vaccine at the rate  $\delta$  (either due to time frame or due to constant contact with the HB Virus). Susceptible compartment increases due to influx of people from recruitment at rate  $k$  and expiration of immunity of the vaccine from compartment  $M$  while  $S$  reduces by natural death rate and contact with an infectious Hepatitis B patient at the rate  $\beta$ .

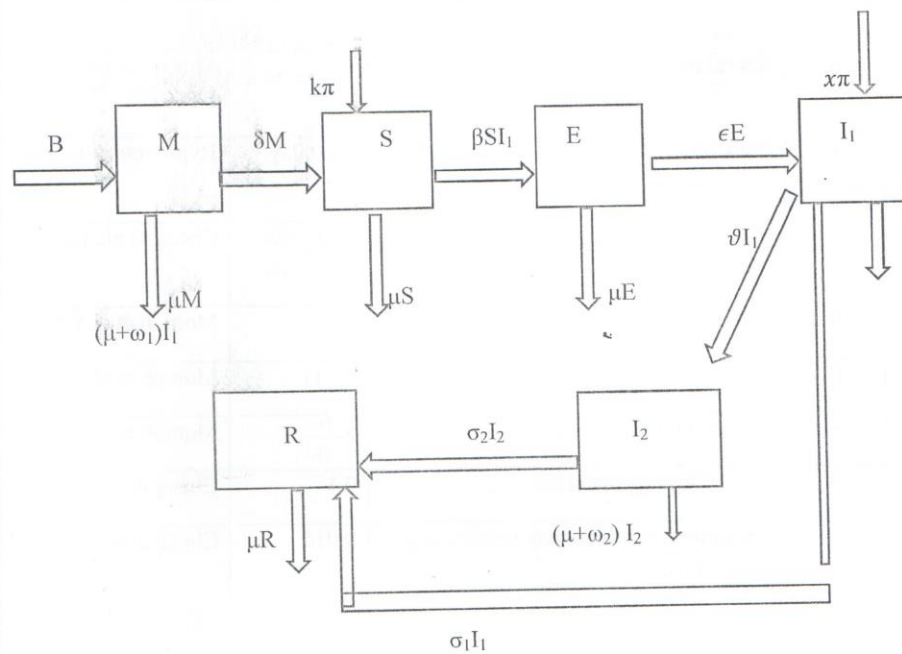
Similarly, the population dynamic of the Exposed class ( $E$ ) grows with the incidence rate of infection  $\beta SI$  and decreases by natural death rate ( $\mu$ ) and progression rate ( $\epsilon$ ) to infectious hepatitis B. The  $I_1$  class increase as a result of recruitment of infected individuals into the population at the rate  $x\pi$  and also due to influx from the exposed compartment.  $I_1$  decreases by natural death ( $\mu$ ), death due to the disease ( $\omega_1$ ), recovery rate ( $\sigma_1$ ) and progression to Primary Liver cancer at the rate  $\vartheta$ . The only means of entry into  $I_2$  compartment in this model is  $\vartheta$  and the exit are natural death, death as a result of primary liver cancer  $\omega_2$ , and recovery rate  $\sigma_2$  [1]. The removed class ( $R$ ) increases through recovery rate ( $\sigma_1$ ) of  $I_1$  class and recovery rate ( $\sigma_2$ ) of  $I_2$  class and decreases by natural death rate.

### Model Assumptions

- Recruitment into the population can either be into susceptible compartment or infected HBV compartment.
- The assumption is that more people are recruited into susceptible compartment more than the infected compartment such that  $k > x$  and  $k + x = 1$ .
- That primary liver cancer compartment ( $I_2$ ) is a result of chronic Hepatitis B left untreated, hence does not cause the epidemic of HBV in the population.
- We assume that latently infected individuals cannot transmit the disease.

- We assume two forms of death, natural death that occurs to all compartments and death due to the disease.
- It was assumed that only partial immunity is available to children born from a vaccinated mother.
- We assume an even interaction in the population such that everyone has a chance of interacting with the infected individuals
- All parameters are assumed non-negative

#### Flow diagram of the Rate of Hepatitis B to Primary Liver Cancer



The model equations

$$\begin{aligned}
 \frac{dM}{dt} &= B - (\mu + \delta)M \\
 \frac{dS}{dt} &= k\pi + \delta M - \beta SI_1 - \mu S \\
 \frac{dE}{dt} &= \beta SI_1 - (\mu + \epsilon)E
 \end{aligned}
 \tag{1}$$

$$\frac{dI_1}{dt} = x\pi I_1 + \epsilon E - (\vartheta + \mu + \omega_1 + \sigma_1)I_1$$

$$\frac{dI_2}{dt} = \vartheta I_1 - (\mu + \omega_2 + \sigma_2)I_2$$

$$\frac{dR}{dt} = \sigma_1 I_1 + \sigma_2 I_2 - \mu R$$

**Table 1: Parameters, Interpretation, value and source**

| Symbol      | Interpretation                                                        | Values    | Source                     |
|-------------|-----------------------------------------------------------------------|-----------|----------------------------|
| $\pi$       | Recruitment rate                                                      | 29        | Mukandavire et al., (2010) |
| $x$         | Probability of recruiting infected individuals                        | [0, 0.05] | Hypothetical (varied)      |
| $k$         | Probability of recruiting susceptible individuals                     | $1 - x$   | Cheng et al., (2014)       |
| $B$         | Birth with partial immunity                                           | 0.2       | Momoh et al., (2012)       |
| $\beta$     | Effective contact rate                                                | (0, 1]    | Momoh et al., (2012)       |
| $\mu$       | Natural mortality rate                                                | 0.2       | Momoh et al., (2012)       |
| $\delta$    | Rate of losing partial immunity                                       | 0.1       | Cheng et al., (2014)       |
| $\epsilon$  | Transmission rate of exposed class to infected class                  | 0.016     | Cheng et al., (2014)       |
| $\vartheta$ | Rate of transmission of chronic hepatitis B into primary liver cancer | 0.4       | Cheng et al., (2014)       |
| $\sigma_1$  | Recovery rate of hepatitis B due to treatment                         | 0.5       | Momoh et al., (2012)       |
| $\sigma_2$  | Recovery rate of Primary Liver Cancer due to treatment                | (0, 0.3]  | Hypothetical               |
| $\omega_1$  | Hepatitis B induced death                                             | 0.47      | N. Shaban (2015)           |

|            |                                    |      |              |
|------------|------------------------------------|------|--------------|
| $\omega_2$ | Primary Liver cancer induced death | 0.30 | Hypothetical |
|------------|------------------------------------|------|--------------|

### Qualitative Analysis of the biological model:

First, we established the positivity of solution to the above biological model (1) using the total population as  $N = M + S + E + I_1 + I_2 + R$ , hence,  $\frac{dN}{dt} = \frac{dM}{dt} + \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI_1}{dt} + \frac{dI_2}{dt} + \frac{dR}{dt}$

Thus,

$$\frac{dN}{dt} = B + (k + x)\pi - \omega_1 I_1 - \omega_2 I_2 - \mu N$$

But  $k + x = 1$

Hence,

$$\frac{dN}{dt} = B + \pi - \omega_1 I_1 - \omega_2 I_2 - \mu N$$

So that

$$\frac{dN}{dt} \leq \pi - \mu N$$

$$\frac{dN}{dt} + \mu N \leq \pi$$

Where the integrating factor is given as:  $I.F = e^{\int \mu dt}$

$$I.F = e^{\mu t}$$

Thus the above differential equation becomes:

$$\frac{d}{dt}(Ne^{\mu t}) \leq \pi e^{\mu t}$$

$$d(Ne^{\mu t}) \leq \pi e^{\mu t} dt$$

$$\int d(Ne^{\mu t}) \leq \pi \int e^{\mu t} dt + C$$

On integration, the above integral becomes

$$Ne^{\mu t} \leq \frac{\pi}{\mu} e^{\mu t} + C$$

$$N(t) \leq \frac{\pi}{\mu} + Ce^{-\mu t} \quad (2)$$

Where  $C$  is the constant of integration. Given that at time  $t = 0$ ,  $N(t) = N(0)$ , then

$$N(0) \leq \frac{\pi}{\mu} + C$$

Where;  $C = N(0) - \frac{\pi}{\mu}$

Hence, equation (2) becomes

$$N(t) \leq (1 - e^{-\mu t}) \frac{\pi}{\mu} + N(0)e^{-\mu t}$$

By applying Birkoff and Rota's theorem on the above inequality as  $t \rightarrow \infty$ , we obtain  $N(t) \leq \frac{\pi}{\mu}$ . Hence all the feasible solution of system (1) enters the region  $D = \{(M, S, E, I_1, I_2, R): N \leq \frac{\pi}{\mu}\}$  which is positive invariant, attracting and its sufficient to consider solutions in  $D$  [9].

Secondly, we analyzed the stability points of the model for both the disease free and endemic equilibria. Denoting DFE by  $\Psi_0$  and the EE by  $\Psi_*$ , using [12], we obtain;

$$\begin{aligned} \Psi_0 &= \{M_0, S_0, E_0, I_{10}, I_{20}, R_0\} \\ &= \left\{ \frac{B}{\mu + \delta}, \frac{k\pi(\mu + \delta) + \delta B}{\mu(\mu + \delta)}, 0, 0, 0, 0 \right\} \end{aligned} \quad (3)$$

And

$$\Psi_* = \{M_*, S_*, E_*, I_{1*}, I_{2*}, R_*\} = \left\{ \frac{B}{\mu + \delta}, \frac{(\mu + \delta)(\vartheta + \mu + \omega_1 + \sigma_1)}{\beta \epsilon}, \frac{\mu(\vartheta + \mu + \omega_1 + \sigma_1)(R_0 - 1)}{\beta \epsilon}, \frac{\mu(R_0 - 1)}{\beta}, \frac{\mu\vartheta(R_0 - 1)}{\beta(\mu + \omega_2 + \sigma_2)}, \frac{(R_0 - 1)(\vartheta + \mu + \omega_2 + \sigma_2)}{\beta(\mu + \omega_2 + \sigma_2)} \right\} \quad (4)$$

We obtained the effective reproduction number of the model as:

$$R_0 = \frac{\epsilon\beta S_0}{(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)} = \frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}$$

Where,  $\vartheta + \mu + \omega_1 + \sigma_1 > x\pi$

### Sensitivity Analysis of the Reproduction Number

We now compute the sensitivity indices of the reproduction number  $R_0$  to the parameters in the model. These indices will show how critical each parameters is to disease transmission and prevalence. Sensitivity analysis showcase the parameters with high impact on  $R_0$ . It allow us to measure the relative change in a state variable when a parameter changes. The sensitivity index of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. Given a variable which is differentiable with respect to the function of the parameter, the sensitivity index may be alternatively defined using partial derivatives as follows:

The sensitivity index of a state variable  $q$  that depends on a differentiable parameter  $p$  can be written as:

$$X_p^q = \frac{\partial q}{\partial p} \times \frac{p}{q}$$

Before proceeding to obtain the sensitivity indices of the model, we first evaluate the threshold analysis with respect to parameters concern and deduce its influence on the number of secondary infection in the population.

#### (a) Threshold analysis with respect to recruitment of infected individual ( $x$ )

$$\frac{\partial R_0}{\partial x} = \frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]\pi}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} > 0$$

Hence, the larger the influx of infected individual into the population, the greater the prevalence of the disease in the society.

#### (b) Threshold analysis of $R_0$ with respect to $\vartheta$

$$\frac{\partial R_0}{\partial \vartheta} = -\frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} < 0$$

Deterioration rate of hepatitis B to primary liver cancer reduces the number of secondary infection of hepatitis B because the model assumed that people with primary liver cancer cannot transmit Hepatitis B disease. However, the increase in

deterioration rate leads to increase in death and reduction in number of infectious individuals in the society.

(c) Threshold analysis of  $R_0$  with respect to  $\sigma_1$

$$\frac{\partial R_0}{\partial \sigma_1} = - \frac{\epsilon \beta [k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} < 0$$

In the presence of effective treatment, hepatitis B disease will reduce as depicts by the expression of  $\frac{\partial R_0}{\partial \sigma_1}$

(d) Threshold analysis of  $R_0$  with respect to  $\beta$

$$\frac{\partial R_0}{\partial \beta} = \frac{\epsilon [k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)} > 0$$

More contact rate between susceptible and infectious individuals increases the spread of the disease in the population. Without enough sensitization about the disease, more contact rate breeds more disease in the population as the above expression depict.

(e) Threshold analysis of  $R_0$  with respect to  $\omega_1$

$$\frac{\partial R_0}{\partial \omega_1} = - \frac{\epsilon \beta [k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} < 0$$

Increase in the death rate due to Hepatitis B disease in the population can bring the population to extinct and thereby reduces the number of secondary infection that may arise from the infectious individuals. If an infected individual can be quarantined and treated, with/without the success of the treatment, the population can be free of the spread due to removal of the infected person.

(f) Threshold analysis of  $R_0$  with respect to  $\delta$

$$\frac{\partial R_0}{\partial \delta} = \frac{\epsilon \beta [k\pi + B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)} - \frac{\epsilon \beta [k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)^2(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}$$

The expression does not give a basis for conclusion as it depends on two different expressions.

$\frac{\partial R_0}{\partial \delta} > 0$  if and only if

$$\frac{\epsilon\beta[k\pi + B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)} > \frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)^2(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}$$

We now take a look at the sensitivity indices of the parameters above with respect to the effective reproduction number.

(1). Sensitivity analysis with respect to recruitment of infected individual ( $x$ )

$$X_x^{R_0} = \frac{\partial R_0}{\partial x} \times \frac{x}{R_0}$$

$$X_x^{R_0} = \frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]\pi}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} \times \frac{x\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}$$

$$X_x^{R_0} = \frac{x\pi}{(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}$$

Using the values in the table of parameters while varying the value of  $x = [0, 0.05]$ , we obtain the following results:

$$X_x^{R_0} = 0, \text{ for } x = 0, X_x^{R_0} = 0.2265625000 \text{ for } x = 0.01, X_x^{R_0} = 0.5858585859, \text{ for } x = 0.02$$

$$X_x^{R_0} = 1.242857143, \text{ for } x = 0.03, X_x^{R_0} = 2.829268293, \text{ for } x = 0.04, X_x^{R_0} = 12.083333, \text{ for } x = 0.05$$

The numerical value obtained from the sensitivity analysis showcase the importance of reducing influx of infected individual into the population of unvaccinated susceptible individuals. As the recruitment rate of infected individuals' increases, so is the multiplicative increase in the sensitivity index. It is important to note that the sudden jump in the sensitivity index when the recruitment rate approach 0.05 indicate that the total population will go into extinct if nothing was done to curb the impact of the influx

of infected individual on the susceptible population. After the 0.05 mark, further analysis show that the sensitivity index tends to negative because the population is believed to be wiped out.

(2) Sensitivity analysis with respect to effective contact rate ( $\beta$ )

$$X_{\beta}^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0}$$

$$X_{\beta}^{R_0} = \frac{\epsilon[k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)} \times \frac{\beta\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}$$

$$\therefore X_{\beta}^{R_0} = 1$$

The value of the sensitivity index for the effective contact being a unity (contact rate approaches maximum value given in the table) established the fact that as long as human population exist, there will always be a contact since the population is evenly distributed. However, getting immunized through vaccination and/or being sensitized about the transmission dynamics of the disease could affect human attitude towards coming in contact with the infected individual.

(3) Sensitivity analysis with respect to recovery rate of Hepatitis B ( $\sigma_1$ )

$$X_{\sigma_1}^{R_0} = \frac{\partial R_0}{\partial \sigma_1} \times \frac{\sigma_1}{R_0}$$

$$X_{\sigma_1}^{R_0} = -\frac{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}{\mu(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)^2} \times \frac{\mu\sigma_1(\mu + \delta)(\mu + \epsilon)(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}{\epsilon\beta[k\pi(\mu + \delta) + \delta B]}$$

$$X_{\sigma_1}^{R_0} = \frac{\sigma_1}{(\vartheta + \mu + \omega_1 + \sigma_1 - x\pi)}$$

Numerical calculation of the expression above using the values as given in table 1 with the value of  $x = 0.01$ , give  $X_{\sigma_1}^{R_0} = 0.3906250000$ . Here, we observe that if the mortality rate of Hepatitis B disease is kept at high value  $\sigma_1 = 0.5$ , we are not guaranteed a disease eradication state at the long run due to the positive value of its sensitivity index.

Lowering the value of the mortality rate by effective treatment of the disease and other means reduce the sensitivity index as can be seen from the numerical simulation when  $\sigma_1 = 0.1$ , the value of  $X_{\sigma_1}^{R_0} = 0.1136363636$ .

### Discussion of Result

A deteriorating model of Hepatitis B virus (HBV) disease to Primary Liver Cancer (PLC) was proposed. The effective reproduction number of the model was established. This is the number of secondary infection of HBV that will be generated in a population of susceptible individuals by the introduction of one infected HBV patients. We established both the disease free and endemic equilibria states of the model. Threshold analysis of the model was calculated and analysed. The sensitivity indices with respect to some major parameters were discussed and evaluated numerically using values from the parameter table 1. Some of the main theoretical and epidemiological findings of the study are as follows:

1. All the feasible solution of system (1) enters the region  $D = \{(M, S, E, I_1, I_2, R) : N \leq \frac{\pi}{\mu}\}$  which is positive invariant, attracting and its sufficient to consider solutions in D
2. We observe that increase in the recruitment of the infected individual into the population can severely affect the outbreak of the disease with the possible risk of extinction of the entire population if no intervention was done.
3. Also, we note that effective contact rate attain its maximum value in the absence of no sensitization against the disease.
4. Lastly, high rate of mortality of the disease is not a means of reducing the spread as it was obtained in the study.

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