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Mathematical Modelling of Hepatitis B transition to Primary Liver Cancer with consideration of partial immunity

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Abstract

This work study the rate of progression of Hepatitis B to Primary Liver Cancer, the effect of therapeutic treatment on the HBV and the role of vaccination of pregnant woman as a passive immunity for the unborn child. The equilibria states of both the disease free and the endemic were calculated. Positivity of solution of the model was analysed and the effective reproduction number was computed. The analysis of the reproduction number at the DFE indicate a substantial decrease in the number of secondary infection rate as a result of passively acquired immunity of the infant and the therapeutic treatment now available to HBV. However, the study show that the rate of progression to Primary Liver Cancer (PLC) will be on the increase if the treatment is not affordable to all HBV patients.

Keywords: Hepatitis B, Primary Liver Cancer, Passive immunity, Reproduction number, Positivity of solution

1.0 Introduction

Hepatitis B was adjudge to be the most common serious liver infection in the world nowadays [1]. The word Hepatitis was coined from two words: Greek word 'Hepar' (root word hepat) which means 'liver' and the Latin word 'itis' that mean 'inflammation' [10]. Even though it is a vaccine preventable disease, up to 400million people have the disease worldwide with the largest population of patient in Asian countries. Modes of transmission include vertical transmission (Mother-child), unprotected sex with a carrier, direct contact with blood of an infected person, misuse of anaesthesia etc. Chronic Hepatitis B is the cause of a whooping eighty percent (80%) case of primary liver cancer in the world and second only to tobacco in causing the most cancer deaths in the world [1]. Although, scientists have discover up to five main types of hepatitis virus, hepatitis B is said to be the deadliest which can also result to another deadly disease known as Cancer.

Mathematical modelling denotes a representation of issue affecting mankind in a Mathematical language (with the use of expression known as equations) so that Mathematical analysis can be performed in other to gain insight on the cause, effect and making a solid foundation on which a solution can be established.

The study of infectious diseases was simplified by the use of Mathematical models to understand the dynamics of its epidemics, to identify potential public health interventions, and to assess their impact on the population at large [2].

This work study the progression rate of Chronic Hepatitis B into Primary Liver Cancer using the compartmental model $MSEI_1I_2R$, where M denotes the compartment with passively acquired immunity from birth as a result of mother being vaccinated during pregnancy, S denote the compartment of the susceptible individuals, E denote the latently infected individuals with Hepatitis B but no clinical symptoms, I_1 denote the infected and infectious individuals, I_2 denote the Primary liver cancer compartment while R denote the Removed class.

2.0 Model Formulation

The model divides the entire human population into six compartments which are
$M\text{-}S\text{-}E\text{-}I_1\text{-}I_2\text{–}R$. 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 (μ) and by the expiration of the vaccine at the rate δ (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 β.

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Similarly, the population dynamic of the Exposed class (E) grows with the incidence rate of infection βSI and decreases by natural death rate (μ) and progression rate (ϵ)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 (μ), death due to the disease (ω_1), recovery rate (σ_1) and progression to Primary Liver cancer at the rateϑ. The only means of entry into I_2 compartment in this model is ϑ and the exit are natural death, death as a result of primary liver cancer ω_2, and recovery rate σ_2 . The removed class (R) increases through recovery rate (σ_1) of I_1 class and recovery rate (σ_2) of I_2 class and decreases by natural death rate.

3.0 Model Assumptions

1. Recruitment into the population can either be into susceptible compartment or infected HBV compartment.
2. The assumption is that more people are recruited into susceptible compartment more than the infected compartment such that $k > x$ and $k + x = 1$.
3. 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.
4. We assume that latently infected individuals cannot transmit the disease.
5. We assume two forms of death, natural death that occurs to all compartments and death due to the disease.
6. It was assumed that only partial immunity is available to children born from a vaccinated mother.
7. We assume an even interaction in the population such that everyone has a chance of interacting with the infected individuals
8. All parameters are assumed non-negative

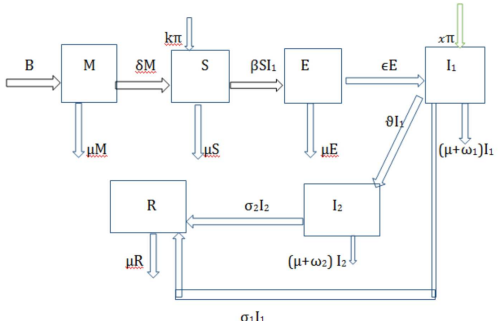

Fig. 1: Flow diagram showing transmission rate of Hepatitis B to Primary Liver Cancer

The model equations

$$\frac{dM}{dt} = B - (\mu + \delta)M$$
$$\frac{dS}{dt} = k\pi + \delta M - \beta S I_1 - \mu S$$
$$\frac{dE}{dt} = \beta S I_1 - (\mu + \epsilon)E \qquad (1.0)$$
$$\frac{dI_1}{dt} = x\pi I_1 + \epsilon E - (\vartheta + \mu + \omega_1 + \sigma_1)I_1$$
$$\frac{dI_2}{dt} = \vartheta I_1 - (\mu + \omega_2 + \sigma_2)I_2$$
$$\frac{dR}{dt} = \sigma_1 I_1 + \sigma_2 I_2 - \mu R$$

Table 1: Parameters, Interpretation, value and source

Symbol	Interpretation	Values	Source
π	Recruitment rate	29	[3]
x	Probability of recruiting infected individuals	[0, 0.4]	Hypothetical
k	Probability of recruiting susceptible individuals	0.85	[4]
B	Birth with partial immunity	0.2	[3]
β	Effective contact rate	(0, 1]	[5]
μ	Natural mortality rate	0.2	[5]
δ	Rate of losing partial immunity	0.1	[4]
ϵ	Transmission rate of exposed class to infected class	0.016	[4]
ϑ	Rate of transmission of chronic hepatitis B into primary liver cancer	0.4	[4]
σ_1	Recovery rate of hepatitis B due to treatment	0.5	[3]
σ_2	Recovery rate of Primary Liver Cancer due to treatment	(0, 0.3]	Hypothetical
ω_1	Hepatitis B induced death	0.47	[6]
ω_2	Primary Liver cancer induced death	0.30	Hypothetical

4.0 Existence of the Disease Free Equilibrium of the Model

The system of equations (1.0) has a unique disease free equilibrium given as:
$\{S^0, E^0, M^0, I_1^0, I_2^0, R^0\}$
At equilibrium, let

$$\frac{dM}{dt} = \frac{dS}{dt} = \frac{dE}{dt} = \frac{dI_1}{dt} = \frac{dI_2}{dt} = \frac{dR}{dt} = 0$$

Then the system of equation becomes

$$B - (\mu + \delta)M = 0 \quad (1.1)$$
$$k\pi + \delta M - \beta S I_1 - \mu S = 0 \quad (1.2)$$
$$\beta S I_1 - (\mu + \epsilon)E = 0 \quad (1.3)$$
$$x\pi I_1 + \epsilon E - (\vartheta + \mu + \omega_1 + \sigma_1)I_1 = 0 \quad (1.4)$$
$$\vartheta I_1 - (\mu + \omega_2 + \sigma_2)I_2 = 0 \quad (1.5)$$
$$\sigma_1 I_1 + \sigma_2 I_2 - \mu R = 0 \quad (1.6)$$

At disease free, we assume the absence of Hepatitis B virus, hence $I_1 = 0$.
From equation (1.1),

$$M^0 = \frac{B}{(\mu + \delta)}$$

Using (1.4),
$x\pi I_1 + \epsilon E - (\vartheta + \mu + \omega_1 + \sigma_1)I_1 = 0$
But $I_1 = 0$ implies that
$\epsilon E = 0$
$E^0 = 0$
Since ϵ is assumed to be a positive parameter.
Using equation (1.5), we have $I_2^0 = 0$ since $I_1 = 0$
Similarly, from equation (1.6), $R^0 = 0$, since $I_1 = I_2 = 0$
From equation (1.2)
$\mu S = k\pi + \delta M$

$$S^0 = \frac{1}{\mu}\left[k\pi + \delta\frac{B}{(\mu + \delta)}\right]$$

Hence, $\{M^0, S^0, E^0, I_1^0, I_2^0, R^0\} = \left\{\frac{B}{(\mu+\delta)}, \frac{1}{\mu}\left[k\pi + \delta\frac{B}{(\mu+\delta)}\right], 0,0,0,0\right\}$

5.0 Positivity Solution of the Model

Given the initial value set to be $\{M(0), S(0), E(0), I_1(0), I_2(0), R(0) \geq 0\}$. Then the solution set $\{M(t), S(t), E(t), I_1(t), I_2(t), R(t)\}$ of the system of equation (1.0) is positive for all $t > 0$.
Proof
From the first equation

$$\frac{dM}{dt} = B - (\mu + \delta)M$$
$$\frac{dM}{dt} + (\mu + \delta)M = B$$

The integrating factor is $e^{(\mu+\delta)t}$

$$\frac{d}{dt}\{M * e^{(\mu+\delta)t}\} = B * e^{(\mu+\delta)t}$$
$$M(t) = \frac{B}{(\mu + \delta)} + ce^{-(\mu+\delta)t}$$

Using the initial condition that, t=0 implies M(t)=M(0), then

$$M(t) = \frac{B}{(\mu + \delta)} + \left[M(0) - \frac{B}{(\mu + \delta)}\right]e^{-(\mu+\delta)t}$$

Which is greater than zero at any time $t > 0$.
Similarly,

$$\frac{dS}{dt} = k\pi + \delta M - \beta S I_1 - \mu S$$
$$\frac{dS}{dt} \geq k\pi - (\beta I_1(t) + \mu)S$$

$\frac{dS}{dt} + (\beta I_1(t) + \mu)S \geq k\pi$

Integrating factor; I.F = $e^{\mu t + \int_0^t \beta I_1(u)du}$

$S(t) \geq \int_0^t k\pi \left(e^{\mu t + \int_0^t \beta I_1(u)du}\right) dv + ce^{-(\mu t + \int_0^t \beta I_1(u)du)}$

Which is positive for any time t.

From the third equation

$\frac{dE}{dt} = \beta S I_1 - (\mu + \epsilon)E$

$\frac{dE}{dt} \geq -(\mu + \epsilon)E$

$\frac{dE}{E} \geq -(\mu + \epsilon)dt$

$E(t) \geq E(0)e^{-(u+\epsilon)t} \geq 0$

From the next equation

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

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

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

$I_1(t) \geq I_1(0)e^{-(\vartheta+\mu+\omega_1+\sigma_1-x\pi)t} \geq 0$

From the fifth equation;

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

$\frac{dI_2}{dt} \geq -(\mu + \omega_2 + \sigma_2)I_2$

$\frac{dI_2}{I_2} \geq -(\mu + \omega_2 + \sigma_2)dt$

$I_2(t) \geq I_2(0)e^{-(\mu+\omega_1+\sigma_1)t} \geq 0$

Lastly,

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

$\frac{dR}{dt} \geq -\mu R$

$\frac{dR}{R} \geq -\mu dt$

$R(t) \geq R(0)e^{-\mu t} \geq 0$

Hence, the solution set {M(t), S(t), E(t), I_1(t), I_2(t), R(t)} of the model system is positive for all t ≥ 0

6.0 The Endemic Equilibrium point of the Model

There exist a unique endemic equilibrium for the system of the equation (1.0) in the presence of Hepatitis B virus infection.

Recall the system of equations (1.1 – 1.6) and by making the substitution:

$y_1 = (\mu + \delta)$, $y_2 = (\mu + \epsilon)$, $y_3 = (\vartheta + \mu + \omega_1 + \sigma_1)$, $y_4 = (\mu + \omega_2 + \sigma_2)$

The system then becomes:

$B - y_1 M = 0$ (1.7)

$k\pi + \delta M - \beta S I_1 - \mu S = 0$ (1.8)

$\beta S I_1 - y_2 E = 0$ (1.9)

$x\pi I_1 + \epsilon E - y_3 I_1 = 0$ (2.0)

$\vartheta I_1 - y_4 I_2 = 0$ (2.1)

$\sigma_1 I_1 + \sigma_2 I_2 - \mu R = 0$ (2.2)

The endemic equilibrium after computation are given as:

$M = \frac{B}{y_1} = \frac{B}{(\mu + \delta)}$

$S = \frac{(x\pi - y_3)y_2}{\beta\epsilon} = \frac{(x\pi - (\vartheta + \mu + \omega_1 + \sigma_1))(\mu + \epsilon)}{\beta\epsilon}$

$$E = \frac{k\pi\beta\epsilon y_1 + x\pi\mu y_1 y_2 + B\beta\delta\epsilon - \mu y_1 y_2 y_3}{\beta\epsilon y_1 y_2}$$
$$= \frac{k\pi\beta\epsilon(\mu+\delta) + x\pi\mu(\mu+\delta)(\mu+\epsilon) + B\beta\delta\epsilon - \mu(\mu+\delta)(\mu+\epsilon)(\vartheta+\mu+\omega_1+\sigma_1)}{\beta\epsilon(\mu+\delta)(\mu+\epsilon)}$$

$$I_1 = \frac{k\pi\beta\epsilon y_1 + x\pi\mu y_1 y_2 + B\beta\delta\epsilon - \mu y_1 y_2 y_3}{\beta y_1 y_2 (y_3 - x\pi)}$$
$$= \frac{k\pi\beta\epsilon(\mu+\delta) + x\pi\mu(\mu+\delta)(\mu+\epsilon) + B\beta\delta\epsilon - \mu(\mu+\delta)(\mu+\epsilon)(\vartheta+\mu+\omega_1+\sigma_1)}{\beta(\mu+\delta)(\mu+\epsilon)((\vartheta+\mu+\omega_1+\sigma_1) - x\pi)}$$

$$I_2 = \frac{\vartheta}{y_4}\left(\frac{k\pi\beta\epsilon y_1 + x\pi\mu y_1 y_2 + B\beta\delta\epsilon - \mu y_1 y_2 y_3}{\beta y_1 y_2 (y_3 - x\pi)}\right)$$
$$= \frac{\vartheta}{(\mu+\omega_2+\sigma_2)}\left(\frac{k\pi\beta\epsilon(\mu+\delta) + x\pi\mu(\mu+\delta)(\mu+\epsilon) + B\beta\delta\epsilon - \mu(\mu+\delta)(\mu+\epsilon)(\vartheta+\mu+\omega_1+\sigma_1)}{\beta(\mu+\delta)(\mu+\epsilon)((\vartheta+\mu+\omega_1+\sigma_1) - x\pi)}\right)$$

$$R = \frac{(k\pi\beta\epsilon y_1 + x\pi\mu y_1 y_2 + B\beta\delta\epsilon - \mu y_1 y_2 y_3)(\vartheta\sigma_2 + \sigma_1 y_4)}{\beta y_1 y_2 (y_3 - x\pi)\mu y_4}$$
$$= \frac{(k\pi\beta\epsilon(\mu+\delta) + x\pi\mu(\mu+\delta)(\mu+\epsilon) + B\beta\delta\epsilon - \mu(\mu+\delta)(\mu+\epsilon)y_3)(\vartheta\sigma_2 + \sigma_1(\mu+\omega_2+\sigma_2))}{\mu\beta(\mu+\delta)(\mu+\epsilon)(y_3 - x\pi)(\mu+\omega_2+\sigma_2)}$$

7.0 Reproduction Number of the Model (R_0)

The number of secondary infection generated by the introduction of an infectious individual into a population of susceptible group [7]

Let $i = 1,2,3$ represent the compartment with the diseases

Let f_i be the rate of appearance of new infection in compartment i

V_i be the transfer rate of individuals into and out of the infected compartment i

x_0 be the disease free equilibrium state, that is, $\{M^0, S^0, E^0, I_1^0, I_2^0, R^0\} = \left\{\frac{B}{(\mu+\delta)}, \frac{1}{\mu}\left[k\pi + \delta\frac{B}{(\mu+\delta)}\right], 0,0,0,0\right\}$

$$f_i = \begin{pmatrix} \beta S I_1 \\ 0 \\ 0 \end{pmatrix}$$

$$V_i = \begin{pmatrix} (\mu+\epsilon)E \\ (\vartheta+\mu+\omega_1+\sigma_1)I_1 - x\pi I_1 - \epsilon E \\ (\mu+\omega_2+\sigma_2)I_2 - \vartheta I_1 \end{pmatrix}$$

We obtain a non-negative matrix F and a non-singular matrix V such that;

$F = \frac{\partial f_i}{\partial x_j}$ and $V = \frac{\partial V_i}{\partial x_j}$ where $i, j = 1,2,3$(the infected compartment E,I_1,I_2)

Hence,

$$F = \begin{bmatrix} 0 & \beta S^0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

And

$$V = \begin{bmatrix} (\mu+\epsilon) & 0 & 0 \\ -\epsilon & (\vartheta+\mu+\omega_1+\sigma_1-x\pi) & 0 \\ 0 & -\vartheta & (\mu+\omega_2+\sigma_2) \end{bmatrix}$$

The effective reproduction number is define as the spectral radius (the largest eigenvalue) of the product of matrix F and V^{-1}, that is,

$R_0 = \rho(F * V^{-1})$

$$V^{-1} = \begin{bmatrix} \frac{1}{(\mu+\epsilon)} & 0 & 0 \\ -\frac{\epsilon}{(\mu+\epsilon)(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & -\frac{1}{(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & 0 \\ -\frac{\epsilon\vartheta}{(\mu+\epsilon)(x\pi-\vartheta-\mu-\omega_1-\sigma_1)(\mu+\omega_2+\sigma_2)} & -\frac{\vartheta}{(x\pi-\vartheta-\mu-\omega_1-\sigma_1)(\mu+\omega_2+\sigma_2)} & \frac{1}{(\mu+\omega_2+\sigma_2)} \end{bmatrix}$$

$$F * V^{-1} = \begin{bmatrix} 0 & \beta S^0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} * \begin{bmatrix} \frac{1}{(\mu+\epsilon)} & 0 & 0 \\ -\frac{\epsilon}{(\mu+\epsilon)(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & -\frac{1}{(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & 0 \\ -\frac{\epsilon\vartheta}{(\mu+\epsilon)(x\pi-\vartheta-\mu-\omega_1-\sigma_1)(\mu+\omega_2+\sigma_2)} & -\frac{\vartheta}{(x\pi-\vartheta-\mu-\omega_1-\sigma_1)(\mu+\omega_2+\sigma_2)} & \frac{1}{(\mu+\omega_2+\sigma_2)} \end{bmatrix}$$

$$= \begin{bmatrix} -\frac{\epsilon\beta S^0}{(\mu+\epsilon)(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & -\frac{\beta S^0}{(x\pi-\vartheta-\mu-\omega_1-\sigma_1)} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

The eigenvalues of the above matrix is given as:

$$\begin{bmatrix} \frac{\epsilon\beta S^0}{(\mu+\epsilon)(\vartheta+\mu+\omega_1+\sigma_1-x\pi)} \\ 0 \\ 0 \end{bmatrix}$$

Hence,

$$R_0 = \frac{\epsilon\beta S^0}{(\mu+\epsilon)(\vartheta+\mu+\omega_1+\sigma_1-x\pi)}$$

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

8.0 Local Stability of the Disease Free Equilibrium

Theorem 1:

The disease free equilibrium of the model is locally asymptotically stable if $R_0 < 1$

Proof:

We shall prove the above theorem using the Variational matrix approach.

Recall the system of equations (1.0) governing the model, let

$$\begin{aligned} f_1 &= B-(\mu+\delta)M \\ f_2 &= k\pi+\delta M-\beta SI_1-\mu S \\ f_3 &= \beta SI_1-(\mu+\epsilon)E \\ f_4 &= x\pi I_1+\epsilon E-(\vartheta+\mu+\omega_1+\sigma_1)I_1 \\ f_5 &= \vartheta I_1-(\mu+\omega_2+\sigma_2)I_2 \\ f_6 &= \sigma_1 I_1+\sigma_2 I_2-\mu R \end{aligned} \qquad (2.3)$$

The Jacobian matrix of the system of equations (2.3) above is given as:

$$J=\begin{bmatrix} -(\mu+\delta) & 0 & 0 & 0 & 0 & 0 \\ \delta & -(\mu+\beta I_1) & 0 & -\beta S & 0 & 0 \\ 0 & \beta I_1 & -(\mu+\varepsilon) & \beta S & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\vartheta+\sigma_1+\omega_1-x\pi) & 0 & 0 \\ 0 & 0 & 0 & \vartheta & -(\mu+\sigma_2+\omega_2) & 0 \\ 0 & 0 & 0 & \sigma_1 & \sigma_2 & -\mu \end{bmatrix}$$

Using the disease free equilibrium state: $\{M^0, S^0, E^0, I_1{}^0, I_2{}^0, R^0\} = \left\{\frac{B}{(\mu+\delta)}, \frac{1}{\mu}\left[k\pi+\delta\frac{B}{(\mu+\delta)}\right], 0,0,0,0\right\}$

$$J=\begin{bmatrix} -(\mu+\delta) & 0 & 0 & 0 & 0 & 0 \\ \delta & -\mu & 0 & -\beta S^0 & 0 & 0 \\ 0 & 0 & -(\mu+\varepsilon) & \beta S^0 & 0 & 0 \\ 0 & 0 & \varepsilon & -(\mu+\vartheta+\sigma_1+\omega_1-x\pi) & 0 & 0 \\ 0 & 0 & 0 & \vartheta & -(\mu+\sigma_2+\omega_2) & 0 \\ 0 & 0 & 0 & \sigma_1 & \sigma_2 & -\mu \end{bmatrix}$$

$|J-\lambda I| = 0$ gives