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ON THE EXISTENCE, UNIQUENESS AND POSITIVITY OF SOLUTION OF THE EFFECT OF VACCINATION AND TREATMENT ON HEPATITIS B VIRUS TRANSMISSION WITH INFECTIVE MIGRANTS.

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Abstract

In this paper, we modify a mathematical model of Hepatitis B Virus transmission with infective migrants incorporating vaccination and treatment as control measures. Finally, we transform the model into proportions where we investigate and prove a theorem on the existence, uniqueness and positivity of the solution of the governing model in a positive invariant region.

Keywords: Hepatitis B Virus, migrant, vaccination, treatment, positivity, uniqueness and invariant region.

1.0 Introduction

Hepatitis B is a liver disease that results from infection with the Hepatitis B Virus (HBV). It belongs to the family of hepadnaviridae and genus orthohepatodna virus [1]. It is the only resilient- hepadna virus causing infection in humans [2] with double- shelled dane particles of diameter 42-47 nanometers, which is present in serum of infected host. Once infected with HBV, there is an incubation period of four to ten weeks; the hepatitis B surface antigen (HBsAg) becomes detectable in the blood, and then Hepatitis B envelope antigen (HBeAg) occur, which is a marker of increased infectivity [3]. The release of HBeAg into the blood indicates that the virus is infecting the liver cells and will often persist in high titres for years in perinatally acquired infections. Antibodies to hepatitis B core antigen (anti-HBc) appear at the early stage of infection and can be used to distinguish between acute and chronic infections. Immunoglobulin M class (IgM) anti-HBc appears and is associated with acute infection and will be replaced by immunoglobulin G (IgG) class during chronic infection [4] and persists in the majority of person for life.

Acute hepatitis B is a short term illness that occurs with symptoms like jaundice, fatigue, appetite loss, nausea, vomiting, dark urine, pale-coloured stool or abdominal pain within the first six months after an individual is exposed to HBV. Chronic hepatitis B (CHB) is marked by persistent presence of HBsAg in serum for greater than six months, which will clear naturally over time (1-6%), in a majority of CHB patients, either spontaneously or through treatment.

Currently, there are approximately 2 billion people around the World that have been infected with HBV. Over 350 million are chronic carriers and 500,000 to 1.2 million die annually due to chronic active hepatitis, cirrhosis or primary liver failure annually [5]. The prevalence of chronic HBV infection varies throughout regions of the World [5] and could be categorized as low (0.5-2%) in Northern and Western Europe, intermediate (2-8%) in Eastern and southern Europe, and high prevalence (>8%) in China and Sub-sahara Africa.

HBV is transmitted by birth (from mother to child), sex and exchange of blood and body fluids. The spread of HBV could be enhanced through non-standard conditions and structure of migration process. Therefore, in an effort to control HBV progression in the presence of infective migrants, vaccination and treatment would be required for both migrants and resident population. However, HBV control measures include vaccination, education, screening of blood and blood products and treatment [7].

Vaccination as a control measure helps the immune system to develop protective antibodies against the virus. Current dosing recommendations are 0.13ml/kg Hepatitis B immune globulin (HBIG) immediately after delivery or within 12 hours after birth, followed by a second dose at 1-2 months and a third dose not earlier than 6 months in combination with recombinant vaccine[8,9]. The combination results in a higher-than-90% level of protection against HBV infection [10]. Despite the use of vaccines the devastating effect of HBV has increased, thus, the need for treatment of chronic carriers.

Treatment as a control strategy help to reduce viral loads to undetectable (≤ 20IU/ML) or nearly undetectable levels (< 69 IU/ML or 400 Copies/ML) in most treated persons, depending on medication and genotype [11]. The research carried out in [12], recommend treatment to be administered when ALT concentrations are greater than 2 times the upper limit of normal (>30 IU/L for men and 19IU/L for women) and HBV DNA have values that are persistently >2,000IU/ML.

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Currently, the seven treatment options approved by the Food and Drug Administration (FDA) include injection immune stimulators (interferon Alfa-2b and pegylated interferon-2a) and oral antiviral such as lamivudine, telbivudine, adefovir dipoxil, entecavir and tenofovir disoproxil fumarate [4] . While, small tumours detected early can be cured through resection or ethanol injection. Moreover, with advances in surgical technique, immunosuppression and intensive care, liver transplants have become an effective treatment option for liver failure and hepatocellular carcinoma (HCC), with 5-year survival above 75% [13].
Once you recover from Hepatitis B, you develop antibodies that protect you from the virus for life [14].
To improve better understanding on the dynamics of HBV infection, several mathematical models have been formulated; see for example [15, 16,17 and 18] . This study is motivated by the work of [18], on the transmission model of hepatitis B virus with the migration effect. Their result suggests that migrants for short visit and students should be subjected to test to reduce the number of migrants with disease. The research further recommends a more advanced model on restraining HBV transmission through migration. Therefore, guided by the work of [18] as mentioned above, the present study intends to modify their work by incorporating treatment of chronic carriers. Hence, this study intends to investigate the region of biological interest, existence, uniqueness and positivity of solution of the effect of vaccination and treatment on Hepatitis B Virus transmission with infective migrants.

2.0 Model formulation

2.1 The Existing model

We consider the following assumptions of the existing model in [18] below.

i. The population is compartmentalized into six groups namely: Susceptible individuals, S(t), Exposed individuals E(t), Acutely infected individuals, A(t), Chronic carriers, C(t), Immunised individuals, V(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 is vaccinated per unit time and the vaccinated individuals do not acquire permanent immunity.
v. By vaccination coverage we assumed the complete three dose of HBV vaccine.
vi. There is a transmission rate from exposed to migrated class and vise–visa.
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).

Table 1: Parameters of the Existing Model

The existing model in [18] has the following parameters:

Parameters	Description
δ	Equal per cspita birth and death rate (as disease-induced death rate is not considered in the system)
π	The proportion of failure immunization or proportion without immunization
γ_1	Rate at which exposed individuals become infectious and move to the acute infected class.
γ_2	Rate at which acutely infected individuals move to the chronic carrier class
γ_3	Rate at which carriers acquire immunity and move to the immunized class
β	The transmission coefficient
K	The infectiousness of carrier relative to acute infections.
q	Proportion of acute infected individual that become carrier.
δ_0	The loss of immunity from the immunized class to susceptible class.
P	Proportion of vaccinated susceptible per unit time.
ξ	The rate of flow from exposed to migrated class.
α	The flow from migrated to susceptible class.
μ_1	The transmission rate from migrated class to exposed class.
μ_2	The transmission rate from migrated class to acute infected class
η	Proportion of the unimmunized children born to carrier mothers
$\delta(1-\pi)$	The newborns that are successfully immunized
$\delta\pi(1-\eta C(t))$	Births flux into the susceptible class

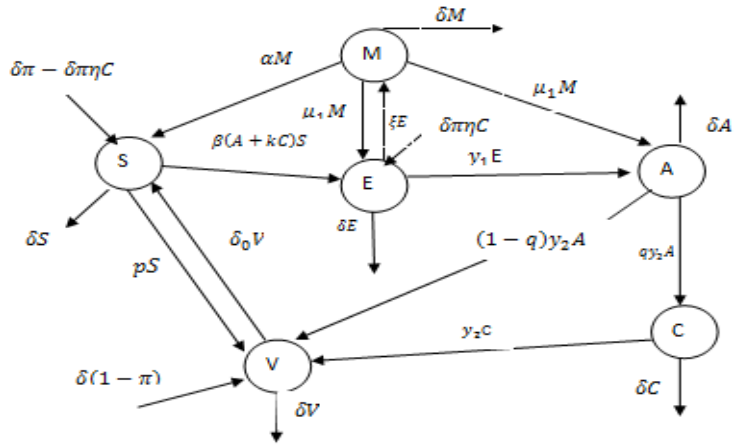

Figure 1: Flow diagram of HBV transmission dynamics for the existing model

With the above assumptions, parameters and flow diagram in [18], the following model equations were derived.

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+KC)S + \delta_0 V - pS + \alpha M$$
$$\frac{dE}{dt} = \beta(A+KC)S - \delta E + \delta\pi\eta C - \gamma_1 E + \mu_1 M - \xi E$$
$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M \qquad (2.1)$$
$$\frac{dC}{dt} = q\gamma_2 A - \delta C - \gamma_3 C$$
$$\frac{dV}{dt} = \gamma_3 C + (1-q)\gamma_2 A - \delta_0 V - \delta V + \delta(1-\pi) + pS$$
$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2)M - \delta M - \alpha M$$

2.2 The Modified Model

In addition to the assumptions of the existing model , we make the following assumptions.

i. The chronic carriers are treated at a rate α_0 and the treated individuals recover [19].

Therefore, as a result of this new assumption, we change the notation of vaccinated class to remove class and redefined γ_3 as the rate at which carriers move to the removed class. Also, we redefined δ_0 as the loss of immunity from the removed class to the susceptible class.

The flow diagram for the existing model is now modified to obtain the flow diagram for the modified model as follows;

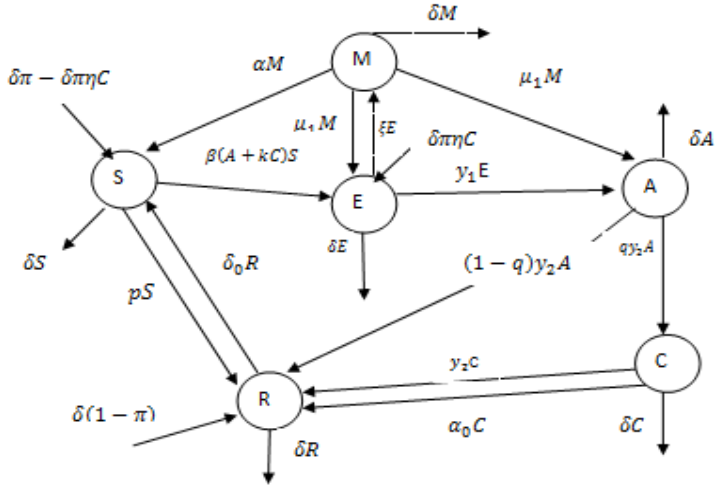

Figure 2: Flow diagram of HBV transmission dynamics for the modified model

The modified model equations are derived based on the above assumptions, parameters and flow diagram in figure 2.

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+kC)S - pS + \delta_0 R + \alpha M$$
$$\frac{dE}{dt} = \beta(A+kC)S - (\delta+\varepsilon+\gamma_1)E + \delta\pi\eta C + \mu_1 M$$
$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M \qquad (2.2)$$
$$\frac{dC}{dt} = q\gamma_2 A - (\delta+\alpha_0+\gamma_3)C$$
$$\frac{dR}{dt} = (\alpha_O+\gamma_3)C + (1-q)\gamma_2 A - (\delta_0+\delta)R + pS + \delta(1-\pi)$$
$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2+\delta+\alpha)M$$

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

The total population $N(t)$, therefore becomes

$$\frac{dN}{dt} = \delta(1-N) \qquad (2.3)$$

If $e^{\int p dt} = e^{\int \delta dt} = e^{\delta t}$

Multiply both sides of (2.3) by $e^{\delta t}$ and integrate, we have

$$e^{\delta t}N = \delta \int e^{\delta t}\, dt$$
$$N(t) = 1 + Ce^{-\delta t}$$

At time $t = 0$, we have

$$N_0 - 1 = C$$
$$N(t) = 1 + (N_0 - 1)e^{-\delta t}$$

$N(t) \to 1$as $t \to \infty$, it means that

$$S + E + A + C + R + M = 1$$

or

$$R = 1 - S - E - A - C - M \qquad (2.4)$$

Hence, substituting (2.4) in equation(2.2), the governing equation becomes

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+kC)S + \delta_0(1-S-E-A-C-M) - pS + \alpha M$$
$$\frac{dE}{dt} = \beta(A+kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M$$
$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M \qquad (2.5)$$
$$\frac{dC}{dt} = q\gamma_2 A - (\delta+\alpha_0+\gamma_3)C$$
$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2+\delta+\alpha)M$$

3.0 Basic properties of solution of the governing model

3.1 Invariant Region

Since, the model system (2.5) under consideration monitors a human population; we assume that all state variables and parameters of the model are positive for all $t \geq 0$. For any standard analysis to be conducted on the model system (2.5) it is imperative to show that the state variables of the model system remain positive for all positive initial conditions $(S(0) > 0, E \geq 0, A \geq 0, C \geq 0, M \geq 0$. Therefore, we state the proposition below;

Proposition 1:

The model system (2.5) has solutions which are contained in the region

$$\Omega = \left\{\left((S,E,A,C,M)\epsilon R_+^5 : N(t) \leq \tfrac{\delta\pi+\delta_0}{\delta_0+\delta+P}\right), \left(S+E+A+C+M \leq \tfrac{\delta\pi+\delta_0}{\delta_0+\delta+P}\right)\right\}$$

Proof:

Let $N(t) = S(t) + E(t) + A(t) + C(t) + M(t)$, then we have

$$\frac{dN}{dt} = \delta\pi + \delta_0 - (\delta_0+\delta)N - pS - (1-q)\gamma_2 A - (\alpha_0+\gamma_3)C \qquad (2.6)$$

In disease-free population, $S \leq N$ at the initial point, therefore equation (2.6) takes the form

$$\frac{dN}{dt} \leq (\delta\pi + \delta_0) - (\delta_0 + \delta + p)N$$

Using the method of integrating factor, we obtain the solution as follows;

$$N(t) \leq \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P} + Ce^{-(\delta_0+\delta+P)t} \qquad t \to \infty \qquad (2.7)$$

Where C is a constant of integration.

Applying the initial condition at $t = 0$ we have,

$$N_0 - \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P} \leq C$$

Thus equation(2.7), becomes

$$N(t) \leq \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P} + \left(N_0 - \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P}\right) e^{-(\delta_0+\delta+P)t}$$

$$N(t) \to \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P}, as\ t \to \infty$$

By using the Theorem of differential inequality by [19], we have

$$0 \leq N(t) \leq \frac{\delta\pi + \delta_0}{\delta_0 + \delta + P}\ as\ t \to \infty \qquad (2.8)$$

To be precise, $N(t) \leq \frac{\delta\pi+\delta_0}{\delta_0+\delta+P}$ if $N_0 \leq \frac{\delta\pi+\delta_0}{\delta_0+\delta+P}$. Therefore, Ω is positively invariant.

Also, if $N(t) \geq \frac{\delta\pi+\delta_0}{\delta_0+\delta+P}$, then $\frac{dN}{dt} < 0$ and the feasible solution either approaches $\frac{\delta\pi+\delta_0}{\delta_0+\delta+P}$ or enter Ω in finite time. Hence Ω is attracting and all the feasible solution of the model with initial condition in R_+^5 enters or stays in the regionΩ. Hence, the system is biologically meaningful and epidemiological well posed in the region Ω [21]

.3.2 Positivity of the solution

For the model (2.5) to be mathematically well posed, we need to proof that all state variables are non-negative for all $t \geq 0$.

Proposition 2:

Let the initial data $\{S(0) > 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, M(0) \geq 0\} \epsilon\ \Omega$, Then, the feasible solution $\{S, E, A, C, M\}$ of the model system (2.5) is positive for all $t \geq 0$.

Proof:

To prove Proposition 2, we will use the approach of [22] by considering all the equations of the model.

Beginning with the first equation of model (2.5), we have

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

or

$$\frac{dS}{dt} \geq -(\delta + \beta A + \beta KC + \delta_0 + P)S \qquad (2.9)$$

Integrating (2.9) by separation of variables and applying the initial condition yields

$$S(t) \geq S(0)e^{-(\delta+\beta A+\beta KC+\delta_0+P)t} > 0 \text{ for t} > 0 \qquad (3.0)$$

From the second equation of the model (2.5), we have

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

$$\frac{dE}{dt} \geq -(\delta + \gamma_1 + \xi)E \qquad (3.1)$$

Integrating (3.1) by separation of variables and applying the initial condition consequently yields

$$E(t) \geq E(0)e^{-(\delta+\gamma_1+\xi)t} > 0 \quad \text{for} \quad t > 0 \qquad (3.2)$$

and so on up to the fifth equation where

$$\frac{dM}{dt} \geq -(\mu_1 + \mu_2 + \delta + \alpha)M \qquad (3.3)$$

yields

$$M(t) = M(0)e^{-(\mu_1+\mu_2+\delta+\alpha)dt} \qquad (3.4)$$

Therefore, all the solution set of the model (2.5) are positive for all $t > 0$ which ends the proof.

3.3 Existence and uniqueness of the solution

The ideas and techniques adopted in this section are motivated from the work of Derick *et al*., in [23]. Using their approach, we formulate theorem on existence of unique solution of the model system (2.5) and we establish the proof.

We consider the system of ordinary differential equations below:

$$\left.\begin{aligned} x_1{}' &= f_1(t, x_1, x_2, \dots, x_n) \\ x_2{}' &= f_2(t, x_1, x_2, \dots, x_n) \\ &\vdots \\ x_n{}' &= f_n(t, x_1, x_2, \dots, x_n) \end{aligned}\right\} \quad (3.5)$$

We may write equation(3.5) in compact form as

$$x' = f_n(t, x), x(t_0) = x_0 \quad (3.6)$$

Theorem 1

Let Ω denoted the region

$|t - t_0| \leq \alpha, \|x - x_0\| \leq b, x = (x_1, x_2, \dots, x_n), x_0 = (x_{10}, x_{20}, \dots, x_{n0})$

and suppose that $f(t, x)$ satisfies the Lipschitz condition

$$\|f(t, x_1) - f(t, y)\| \leq K\|x_1 - y\| \quad (3.7)$$

Whenever the pairs (t, x_1) and (t, x_2) belong to Ω, where K is a positive constant. Then, there is a constant $\delta > 0$ such that there exist a unique continuous vector solution $x(t)$ of the system (3.6) in the interval $|t - t_0| \leq \delta$.

The condition (3.7) from the above theorem can be alternatively proven using the following result

Proposition 3

The Lipschitz condition (3.7) is satisfied if $\frac{\partial f_i}{\partial x_j}, i, j = 1,2, \dots, n$ are continuous and bounded in Ω.

Thus, we shall state and prove the following result.

Theorem 2

Let Ω denoted the region $0 \leq \alpha \leq \Omega$. Then equation (2.5) has a unique solution.

Proof

We show that $\frac{\partial f_i}{\partial x_j}, i, j = 1,2,3,4,5$ are continuous and bounded in Ω.

$$f_1 = \delta\pi(1 - \eta C) - \delta S - \beta(A + kC)S + \delta_0(1 - S - E - A - C - M) - pS + \alpha M$$

$$f_2 = \beta(A + kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M$$

$$f_3 = \gamma_1 E - (\delta + \gamma_2)A + \mu_2 M \quad (3.8)$$

$$f_4 = q\gamma_2 A - (\delta + \alpha_0 + \gamma_3)C$$

$$f_5 = \xi E - (\mu_1 + \mu_2 + \delta + \alpha)M$$

Differentiating f_1, f_2, f_3, f_4 and f_5 each partially with respect to S, E, A, C and M respectively and taking their norms gives

$\left|\frac{\partial f_1}{\partial S}\right| = |-(\delta + \beta(A + kC) + \delta_0 + P)| < \infty, \left|\frac{\partial f_1}{\partial E}\right| = |-(\delta_0)| < \infty, \left|\frac{\partial f_1}{\partial A}\right|$
$= |-(\beta S + \delta_0)| < \infty, \left|\frac{\partial f_1}{\partial C}\right| = |-(\delta\pi\eta)| < \infty, \left|\frac{\partial f_1}{\partial M}\right| = |(-\delta_0 + \alpha)| < \infty$

$\left|\frac{\partial f_2}{\partial S}\right| = |\beta(A + kC)| < \infty, \left|\frac{\partial f_2}{\partial E}\right| = |-(\delta + \gamma_1 + \xi)| < \infty, \left|\frac{\partial f_2}{\partial A}\right| = |\beta S| < \infty,$

$\left|\frac{\partial f_2}{\partial C}\right| = |\beta k S + \delta\pi\eta| < \infty, \left|\frac{\partial f_2}{\partial M}\right| = |\mu_1| < \infty,$

$\left|\frac{\partial f_3}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_3}{\partial E}\right| = |y_1| < \infty, \left|\frac{\partial f_3}{\partial A}\right| = |-(\delta + y_2)| < \infty, \left|\frac{\partial f_3}{\partial C}\right| = |0| < \infty,$

$\left|\frac{\partial f_3}{\partial M}\right| = |\mu_1| < \infty,$

$\left|\frac{\partial f_4}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_4}{\partial E}\right| = |0| < \infty, \left|\frac{\partial f_4}{\partial A}\right| = |qy_2| < \infty, \left|\frac{\partial f_4}{\partial C}\right| = |(\delta + \alpha_0 + y_3)|$
$< \infty, \left|\frac{\partial f_4}{\partial M}\right| = |0| < \infty,$

$\left|\frac{\partial f_5}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial E}\right| = |\xi| < \infty, \left|\frac{\partial f_5}{\partial A}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial C}\right| = |0| < \infty,$

$\left|\frac{\partial f_5}{\partial M}\right| = |(\mu_1 + \mu_2 + \delta + \alpha)| < \infty,$

Hence, since the partial derivatives exist and are continuous and bounded.

Therefore, the model (2.5) has unique solution.

5. CONCLUDING REMARKS

In this paper, we modify the work of [18] by incorporating treatment rate of chronic carriers and redefined the vaccinated class to remove class. The model is then transformed into proportions to reduce the number of equations, in order to define the prevalence of infection, where the model is biologically and mathematically well posed. The proofs for the invariant region, existence, uniqueness and positivity of solutions are adequately established.

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