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EXISTENCE, UNIQUENESS AND POSITIVITY OF SOLUTION OF THE IMPACT OF VACCINATION AND TREATMENT IN CONTROLLING THE SPREAD OF HEPATITIS B VIRUS WITH INFECTIVE MIGRANTS.

Nwaokolo M. A.[1], Oguche A. J.[2], and Twan S. M.[3]

[1]Department of Mathematics, Federal University Wukari, Taraba State, Nigeria.

[2&3]Department of Biological Sciences, Federal University Wukari, Taraba State, Nigeria.

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ABSTRACT: *In this paper, we extend a mathematical model on the impact of vaccination and treatment in controlling the spread of Hepatitis B Virus with infective migrants. 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.

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INTRODUCTION

Hepatitis B is a disease that is characterized by inflammation of the liver and results from infection with the Hepatitis B Virus (HBV). This DNA virus was first identified in 1960s and belongs to the family of hepadnaviridae and genus orthohepatodnavirus [1]. It is the only hepadnavirus 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 and later acute symptoms like jaundice, appetite loss, fatigue, pale-coloured stool, nausea, vomiting, dark urine, abdominal pain begins to occur 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 over six months, which will clear in most CHB patients through treatment.

Currently, about 2 billion people worldwide have been infected and approximately 350 million are chronically infected with HBV. The majority of those infected live in developing countries with few incidences in western countries. HBV is ranked among the highest cause of mortality worldwide and is responsible for 687000 deaths per year [5].

However, HBV can be transmitted by blood, birth or sex and exchange of blood and the spread can be enhanced through non-standard conditions and structure of migration process. Hence, in an effort to control the spread of HBV with infective migrants, a wide range of interventions are now available to prevent and treat HBV infection worldwide.

Vaccination as a control measure is the administration of antigenic material to stimulate the immune system to develop protective antibodies (>10 million IU/ML or 10 IU/L) against the virus. The use of monovalent HB vaccine (engerix-B, recombinant HB regimen) or combination vaccine (twinrix, convex, pediarix) for immunization of children and adults at risk, is administered with Hepatitis B Immune Globulin (HBIG) in other to produce immunity against HBV (USFDA, 2011). Current dosing recommendations are 0.13ml/kg 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 (24 weeks) in combination with recombinant vaccine (Ma *et al.*, 2014; CDC, 2013). The combination results in a higher-than-90% level of protection against HBV infection (Ikobah *et al.*, 2016). Despite some successes associated with the use of vaccines and supportive therapies for acute infection, the devastating effect of HBV has increased, thus, the need for treatment of chronic carriers.

Treatment as a control strategy helps 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 (Lai and Yuen, 2007). Treatment decisions are made on the basis of Hepatitis B Virus Deoxyribonucleic Acid (HBVDNA) viral load, Hepatitis B envelope antigen (HBeAg) status, Alanine aminotransferase (ALT), moderate to severe active necroinflammation and/or at least moderate liver fibrosis severity (EASL, 2012; Lampertico and Liaw, 2012; Scaglione and Lok, 2012; Buti, 2014; Kao, 2014), the age of patient, stage of liver disease and other factors (Weinbaum *et al.,* 2008). The research carried out by Asian liver center at Stanford University in 2018, recommend treatment to be administered when ALT concentrations are greater than 2 times the upper limit of normal (> 30 IU/l for men and 19 IU/l for women) and HBeAg negative(HBVDNA >2,000IU/ml) or HBeAg positive (HBVDNA >20,000IU/ml) for 3-6 months.

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Currently, the first line drugs approved globally include immune stimulators (interferon Alfa-2b and pegylated interferon-2a) and oral antiviral such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF) (Weinbaum *et al.*, 2008). Although, combination therapy, such as TDF in combination with ETV or emtricitabine (FTC), Encapsidation and entry inhibitors, TLR7 agonists, and therapeutic vaccines can be considered if drug-resistant mutants are present or for patients with failing first line therapy (Zhang *et al*., 2012, Kosinska *et al*., 2013). Therefore, adherence to anti-HBV therapies has > 95% effectiveness for maintaining maximal suppression (Zoulim and Locarnini, 2009; Gish, 2012; Viagono *et al.*, 2014). However, small tumors 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% (Jaclyn, 2010). Once you recover from Hepatitis B, you develop antibodies that protect you from the virus for life (CDC, 2008).

In order to improve understanding on the dynamics of HBV infection, several mathematical models have been formulated (Zou *et al.*, 2009; Pang *et al.*, 2010; Kimbir *et al.*, 2014; Khan *et al.*, 2016). This study is motivated by the work of Khan *et al.* (2016) which is centered on the transmission model of Hepatitis B virus with the migration effect. They assumed a situation where the total population was compartmentalized into six classes, namely: the susceptible S, Exposed E, Acutely infected A, Chronic carrier C, Immunity class V and Migrated M individuals. They also considered γ_{3}, as the rate at which chronic carriers acquire immunity and move to the immunized class. They assumed that a proportion of susceptible individuals are vaccinated across all age groups. 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.

Against this background, the present study intends to extend the work of Khan *et al.* (2016) by incorporating treatment, which was not considered in their model, but is proved effective in eliminating hepatitis B virus (Kimbir *et al.*, 2014; Nayagam *et al.*, 2016). Therefore, we intend to show that, if this health control measures adopted in countries like China when applied here, would help to improve the health condition in Nigeria. Hence, this study will model the effect of vaccination and treatment on HBV transmission with infective migrants.

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.

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MODEL FORMULATION

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), Immunized 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 susceptible 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. Migrants are adults hence; the natural birth rate of the migrated class is neglected.
vii. There is a transmission rate from exposed to migrated class and vice–versa.
viii. There is a transmission rate from migrated class to susceptible class and migrated class to acutely infected class.
ix. There is a stable population with equal precipitant 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
$S(t)$	Number of Susceptible individuals at time t
$E(t)$	Number of Exposed individuals at time t
$A(t)$	Number of Acute infective at time t
$C(t)$	Number of Chronic carriers at time t
$V(t)$	Number of Immunized individuals at time t
$M(t)$	Number of Migrated individuals at time t
δ	Equal per capita birth and death rate (as disease-induced death rate is not considered in the system)
π	The 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 chronic carriers acquire immunity and move to the immunized class
β	The transmission coefficient
κ	The infectiousness of carriers relative to acute infections
q	Proportion of acute infected individuals that become carriers
$1-q$	Proportion of acute infected individuals that move to the immunity class.
δ_0	The loss of immunity from the immunized class to susceptible class

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ρ	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

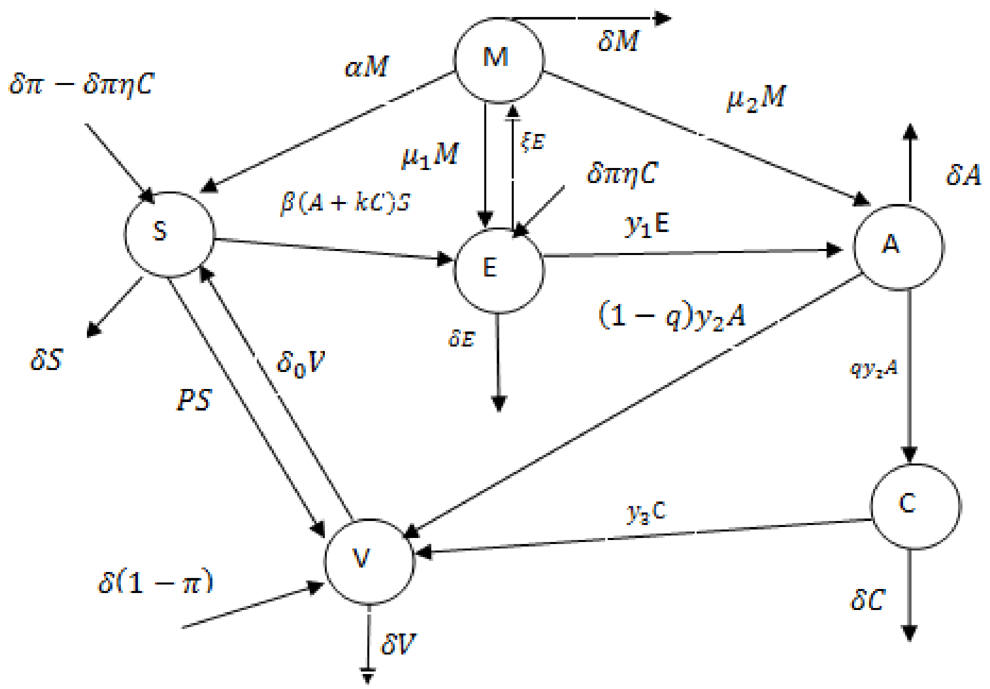

Figure 1: Flow Diagram of HBV transmission Dynamics for the Existing Model

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

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

The Modified Model

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

We assume that the chronic carriers do not acquire immunity accept they are treated (O'Leary *et al*., 2008) and recruited into the treated class. Whereas, not all treated individuals recovers and progress to the recovery class, some relapse to chronic if drug resistant mutants are present (Zhang et al., 2012, Kosinska et al., 2013). In addition, we change the notation of the immune class to vaccinated class and redefined the parameters of the extended model in table 2.

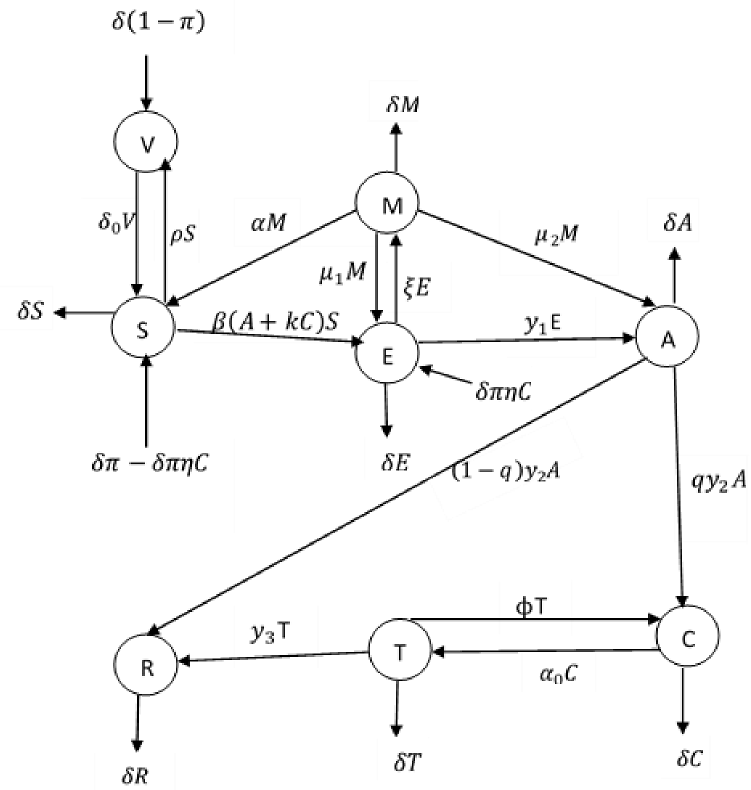

Figure 2: Flow diagram of HBV transmission dynamics for the modified model

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

$$\begin{aligned}
\frac{dS}{dt} &= \delta\pi(1-\eta C) - \delta S - \beta(A+kC) - pS + \delta_0 V \ + \alpha M \\
\frac{dE}{dt} &= \beta(A+kC)S - (\delta+\xi+\gamma_1)E + \delta\pi\eta C + \mu_1 M \\
\frac{dA}{dt} &= \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M \\
\frac{dC}{dt} &= q\gamma_2 A + \ \varphi T - (\delta+\alpha_0)C \\
\frac{dT}{dt} &= \alpha_0 C - (\delta+\varphi+\gamma_3)T \\
\frac{dR}{dt} &= (1-q)\gamma_2 A + \gamma_3 T - \delta R \\
\frac{dM}{dt} &= \xi E - (\mu_1+\mu_2+\delta+\alpha)M \\
\frac{dV}{dt} &= \delta(1-\pi) + pS - (\delta+\delta_0)V,
\end{aligned} \qquad (2.2)$$

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

The total population $N(t)$, is defined by

$N(t) = S(t) + E(t) + A(t) + C(t) + T(t) + R(t) + M(t) + V(t)$, So that

$$\frac{dN}{dt} = \delta - \delta N.$$

Therefore,

$$\frac{dN}{dt} = \delta(1-N). \qquad (3.15)$$

Using variable separable method, we have

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

Integrating both side yield

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

$$-In(1-N) = \delta t + C$$

Multiplying through by -1

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$$In(1-N)=-\delta t-C$$

Taking exponential of both side

$1-N=Ae^{-\delta t}$, where $A=e^{-c}$

$$N(t)=1-Ae^{-\delta t},$$

At time $t=0$, we have

$$N(0)=N_0=1-A$$

$$A=1-N_0$$

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

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

Since $S+E+A+C+T+R+M+V=1$, we have

$$R=1-S-E-A-C-T-M-V \tag{3.16}$$

Hence, the governing equations become

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

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

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

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

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

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

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

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The initial conditions for the modified model are non-negative. $S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, M(0) \geq 0, V(0) \geq 0$, and all the parameters of the extended model are also assumed to be non-negative.

BASIC PROPERTIES OF SOLUTION OF THE GOVERNING MODEL

Invariant region

Since, the model system $(3.17) - (3.23)$ 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 $(3.17) - (3.23)$ it is imperative to show that the state variables of the model remains positive for all positive initial conditions,

$(S(0) \geq 0, E(0) \geq 0, A(0) \geq 0, C(0) \geq 0, T(0) \geq 0, M(0) \geq 0, V(0) \geq 0,)$. Therefore, we state the proposition below:

Proposition 1

The model system $(3.17) - (3.23)$ has solutions which are contained in the region $\Omega = \{(S, E, A, C, T, M, V): N(t) \leq 1\} \epsilon R_+^7$

Proof:

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

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dA}{dt} + \frac{dC}{dt} + \frac{dT}{dt} + \frac{dM}{dt} + \frac{dV}{dt},$$

that is

$$\frac{dN}{dt} = \delta - \delta(S + E + A + C + T + M + V) + q\gamma_2 A - \gamma_3 T$$

$$\frac{dN}{dt} = \delta - \delta N + q\gamma_2 A - \gamma_3 T \,. \qquad (3.24)$$

In disease-free population, $S \leq N$ at the initial point, therefore equation (3.24) takes the form

$$\frac{dN}{dt} \leq \delta - \delta N,$$

$$\frac{dN}{dt} + \delta N \leq \delta.$$

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

$$N(t) \leq \frac{\delta}{\delta} + Ce^{-\delta t}, \quad as \quad t \to \infty \,. \qquad (3.25)$$

where C is a constant of integration.

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

$N_0 - 1 \leq C$

Thus equation(3.25), becomes

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

$N(t) \rightarrow 1, as\ t \rightarrow \infty$

By using the theorem of differential inequality (Birkhoff and Rota, 1989), we have $0 \leq N(t) \leq 1\ as\ t \rightarrow \infty$. (3.26)

To be precise, $N(t) \leq 1$ if $N_0 \leq 1$. Therefore, Ω is positively invariant.

Also, if $N(t) \geq 1$, then $\frac{dN}{dt} < 0$ and the feasible solution either approaches

1or enter Ω in finite time. Hence Ω is attracting and all the feasible solution of the model with initial condition in R_+^7 enters or stays in the region Ω. Hence, the system is biologically meaningful and epidemiological well posed in the region Ω (Hethcote, 2000).

Positivity of the solution

For the model $(3.17) - (3.23)$ to be mathematically well posed, we need to prove that all the state variables are non-negative for all $t \geq 0$.

Proposition 2

Given non-negative initial data $\{S(0), E(0), A(0), C(0), T(0), M(0), V(0)\} c\ \Omega$, the feasible solution $\{S, E, A, C, T, M, V\}$ of the model system $(3.17) - (3.23)$ is positive for all $t \geq 0$.

Proof

To prove Proposition 2, we will use the approach as outlined in the work of Sharomi *et al.* (2008) by considering all the equations of the model.

Beginning with (3.17), we have

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

or

$$\frac{dS}{dt} \geq -(\delta + \beta A + \beta KC + P)S. \quad (3.27)$$

Integrating (3.27) by separation of variables and applying the initial condition yields

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$$S(t) \geq S(0)e^{-(\delta+\beta A+\beta KC+P)t} > 0 \text{ for t} > 0. \tag{3.28}$$

From equation (3.18), we have

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

$$\frac{dE}{dt} \geq -(\delta + \gamma_1 + \xi)E. \tag{3.29}$$

Integrating (3.29) by separation of variables and applying the initial condition consequently yields

$$E(t) \geq E(0)e^{-(\delta+\gamma_1+\xi)t} > 0 \quad \text{for} \quad t > 0\,. \tag{3.30}$$

From equation (3.19), we have

$$\frac{dA}{dt} = \gamma_1 E - \delta A - \gamma_2 A + \mu_2 M$$
$$\geq -(\delta + \gamma_2)A \tag{3.31}$$

Integrating (3.31) and applying the initial condition we have

$$A(t) \geq A(0)e^{-(\delta+\gamma_2)t} \quad \text{for } t > 0. \tag{3.32}$$

From equation (3.20), we get

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

or

$$\frac{dC}{dt} \geq -(\delta + \alpha_0)C. \tag{3.33}$$

Integrating (3.33) yields

$$C(t) \geq C(0)e^{-(\delta+\alpha_0)t} > 0 \quad \text{for } t > 0. \tag{3.34}$$

From equation $(3.18B)$, we get

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

$$\geq (\delta + \varphi + \gamma_3)T \tag{3.35}$$

Integrating (3.35) and applying the initial condition we have

$$T(t) \geq T(0)e^{-(\delta+\varphi+\gamma_3)t} \quad \text{for } t > 0. \tag{3.36}$$

from equation (3.22), we have

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

or

$$\frac{dM}{dt} \geq -(\mu_1 + \mu_2 + \delta + \alpha)M \tag{3.37}$$

Integrating (3.37) and applying the initial condition yields

$$M(t) \geq M(0)e^{-(\mu_1+\mu_2+\delta+\alpha)t} \quad \text{for } t > 0. \tag{3.38}$$

Lastly, from equation (3.23), we have

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

$$\geq -(\delta + \delta_0)V \tag{3.39}$$

Integrating (3.39) and applying the initial condition we have

$$V(t) \geq V(0)e^{-(\delta+\delta_0)t} \quad \text{for } t > 0. \tag{3.40}$$

Therefore, from $(3.28), (3.30), (3.32), (3.34), (3.36), (3.38)$ and (3.40), the solution set of the model $(3.17) - (3.23)$ is positive for all $t > 0$ which ends the proof.

Existence and uniqueness of the solution

The ideas and techniques adopted in this section are motivated from the work of Derick *et al*.(1976). Using their approach, we formulate theorem on existence of unique solution of the model system $(3.17) - (3.23)$ and we establish the proof.

We may write the model system $(3.17) - (3.23)$ in compact form as

$$x' = f(t, x), x(t_0) = x_0 \tag{3.41}$$

Where,

$$x = (S, E, A, C, T, M, V)$$

and

$$f(t, x) = \frac{dx}{dt}$$

$$f_1 = \frac{dx_1}{dt} = \frac{ds}{dt}$$

and so on to f_7.

Theorem 1

Let Ω denoted the region

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$$|t-t_0|\le \alpha, \|x-x_0\|\le b, x=(x_1,x_2,\dots,x_n), x_0=(x_{10},x_{20},\dots,x_{n0}) \quad (3.42)$$

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

$$\|f(t,x)-f(t,y)\|\le K\|x-y\| \quad (3.43)$$

Where the pairs (t,x) and (t,y) 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 (3.42) in the interval $|t-t_0|\le\delta$.

The condition (3.43) from the above theorem can be alternatively proven using the following result:

Proposition 3

The Lipschitz condition (3.43) is satisfied if the partial derivatives $\left(\frac{\partial f_i}{\partial x_j}\right), i,j=1,2,\dots,7$ are continuous and bounded in Ω. Thus, we shall state and prove the following result.

Theorem 2

Let $\Omega=\{\mathrm{x(t)}: |\, a\le t\le b,\ \ |x|<\infty|\}$. Then model equation $(3.17)-(3.23)$ has a unique solution provided $f(t,x)$ is continuous and satisfies Lipschitz condition in Ω.

Proof

We show that $\frac{\partial f_i}{\partial x_j}, i,j=1,2,3,4,5,6,7$ are continuous and bounded in Ω.

$$f_1=\delta\pi(1-\eta C)-\delta S-\beta(A+kC)S+\delta_0 V-pS+\alpha M, \quad (3.44)$$

$$f_2=\beta(A+kC)S-\delta E+\delta\pi\eta C-\gamma_1 E-\xi E+\mu_1 M, \quad (3.45)$$

$$f_3=\gamma_1 E-(\delta+\gamma_2)A+\mu_2 M, \quad (3.46)$$

$$f_4=q\gamma_2 A+\varphi T-(\delta+\alpha_0)C\ , \quad (3.47)$$

$$f_5=\alpha_0 C-(\delta+\varphi+\gamma_3)T \quad (3.48)$$

$$f_6=\xi E-(\mu_1+\mu_2+\delta+\alpha)M. \quad (3.49)$$

$$f_7=\delta(1-\pi)+pS-(\delta+\delta_0)V, \quad (3.50)$$

Differentiating each of $f_1, f_2, f_3, f_4, f_5, f_6$ and f_7 partially with respect to $S, E, A, C, T, M and\ V$

respectively and taking their norms gives

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$$\left|\frac{\partial f_1}{\partial S}\right| = |(\delta + \beta(A + kC) + P)| < \infty, \left|\frac{\partial f_1}{\partial E}\right| = |0| < \infty, \left|\frac{\partial f_1}{\partial A}\right| = |(\beta S)| < \infty,$$

$$\left|\frac{\partial f_1}{\partial C}\right| = |-(\delta\pi\eta)| < \infty, \left|\frac{\partial f_1}{\partial T}\right| = |0| < \infty, \left|\frac{\partial f_1}{\partial M}\right| = |(\alpha)| < \infty, \left|\frac{\partial f_1}{\partial V}\right| = |(\delta_0)| < \infty$$

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

$$\left|\frac{\partial f_2}{\partial C}\right| = |\beta kS + \delta\pi\eta| < \infty, \left|\frac{\partial f_2}{\partial T}\right| = |0| < \infty, \left|\frac{\partial f_2}{\partial M}\right| = |\mu_1| < \infty, \left|\frac{\partial f_2}{\partial V}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_3}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_3}{\partial E}\right| = |\gamma_1| < \infty, \left|\frac{\partial f_3}{\partial A}\right| = |-(\delta + \gamma_2)| < \infty, \left|\frac{\partial f_3}{\partial C}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_3}{\partial T}\right| = |0| < \infty, \left|\frac{\partial f_3}{\partial M}\right| = |\mu_1| < \infty, \left|\frac{\partial f_3}{\partial V}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_4}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_4}{\partial E}\right| = |0| < \infty, \left|\frac{\partial f_4}{\partial A}\right| = |q\gamma_2| < \infty, \left|\frac{\partial f_4}{\partial C}\right| = |(\delta + \alpha_0)| < \infty$$

$$\left|\frac{\partial f_4}{\partial T}\right| = |\varphi| < \infty, \left|\frac{\partial f_4}{\partial M}\right| = |0| < \infty, \left|\frac{\partial f_4}{\partial V}\right| = |0| < \infty$$

$$\left|\frac{\partial f_5}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial E}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial A}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial C}\right| = |\alpha_0| < \infty,$$

$$\left|\frac{\partial f_5}{\partial T}\right| = |-(\delta + \varphi + \gamma_3)| < \infty, \left|\frac{\partial f_5}{\partial M}\right| = |0| < \infty, \left|\frac{\partial f_5}{\partial V}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_6}{\partial S}\right| = |0| < \infty, \left|\frac{\partial f_6}{\partial E}\right| = |\xi| < \infty, \left|\frac{\partial f_6}{\partial A}\right| = |0| < \infty, \left|\frac{\partial f_6}{\partial C}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_6}{\partial T}\right| = |0| < \infty, \left|\frac{\partial f_6}{\partial M}\right| = |(\mu_1 + \mu_2 + \delta + \alpha)| < \infty, \left|\frac{\partial f_6}{\partial V}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_7}{\partial S}\right| = |\rho| < \infty, \left|\frac{\partial f_7}{\partial E}\right| = |0| < \infty, \left|\frac{\partial f_7}{\partial A}\right| = |0| < \infty, \left|\frac{\partial f_7}{\partial C}\right| = |0| < \infty,$$

$$\left|\frac{\partial f_7}{\partial T}\right| = |0| < \infty, \left|\frac{\partial f_7}{\partial M}\right| = |0| < \infty, \left|\frac{\partial f_7}{\partial V}\right| = |-(\delta + \delta_0)| < \infty,$$

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

Therefore, the model $(3.17) - (3.23)$ has a unique solution.

CONCLUDING REMARKS

In this paper, we extend the work of [18] by incorporating treatment class and its relapse effect. 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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