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A Graph-Theoretic Method for the Basic Reproduction Number in Age-Structured HBV Model

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Abstract
In this paper, we present an Age-Structured hepatitis B model. This epidemic model investigates different classes of infectious diseases that can be transmitted through an effective contact with infective individuals, who are contagious. The Graph-Theoretic Method for the Basic Reproduction Number was obtained. In addition, the numerical simulation is used to verify the model predictions. The result suggest that the endemic nature of the model is approaching equilibrium with increase immunization program and other control measures put in place.

Key words: Hepatitis B, endemic, immunization, equilibrium.

1. Introduction

In the last two decades, mathematical models have frequently been used to study the transmission dynamics of HBV in several regions. Anderson and May (1991) used a deterministic, compartmental mathematical model to illustrate the influences of carriers on the transmission of Hepatitis B virus (HBV). Anderson *et al.* (1992) and Williams *et al.* (1996) described models of the sexual transmission of HBV, which include heterogeneous mixing on age and sexual activity. Edmunds *et al.* (1993) illustrated the relation between the age at infection with HBV and the development of the carrier state. In 2007, Stanca *et al.* (2007) modeled the mechanisms of acute hepatitis B virus infection, they discovered that a cell-mediated immune response plays a significant role in controlling the virus. Also, Stanca *et al.* (2007) observed in the study of role of cells refractory to productive infection in acute hepatitis B viral dynamics that the number of infected cells declined fast after the peak in viral load in the refractory cell.

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Thornley *et al*. (2008) applied the model of Medley *et al*. (2001) to predict chronic hepatitis B infection in New Zealand. Hepatitis B is a severe liver disease caused by the hepatitis B virus (HBV) (Edmund *et al*., 1993). It is a primary global health problem and the most severe type of viral hepatitis. Formerly known as "serum hepatitis," the infection has caused epidemics in parts of Africa and Asia; moreover, it is endemic in China (Williams, 2006). In a study by Zou *et al*. (2010) they use a model of six subclasses to analysis the transmission of HBV by stratifying the age of the host population. They suggested that the optimal control of HBV should be the combination of retroactive vaccination of susceptible adults and vaccination of newborns.

Recently, Zhang and Zhang (2018) opined that optimal control techniques are of great use in developing optimal strategy and that since control of newborn immunization combined with treatment minimize the given objective. Also, Wangen *et al*. (2019) observed that vaccination of newborn depends mostly on the mother's education level, family income level and knowledge of transmission routes.

2. Materials and Methods

We propose a mathematical model to understand the transmission dynamics and prevalence of HBV. The model is constructed based on the characteristics of HBV transmission and the model of Sirajo *et al*. (2013). The model comprises of nine compartments, here we see the need of treatment of carrier above 15 years of age, because of the need to procure a therapeutic treatment for the infected individuals in the population. Susceptible individual below 15 years of age ($S_U(t)$), Susceptible individual 15 years and above ($S_F(t)$), Vaccinated V, Infectious individual below 15 years of age ($I_U(t)$), Infectious individual 15 years and above ($I_F(t)$), Chronically infected individual below 15 years of age ($C_U(t)$), Chronically infected individual above 15 years of age ($C_F(t)$), Treatment of chronically infected individual above 15 years of age and above ($T_F(t)$), Recovered (R(t)), and Vaccinated (V(t)).

The following assumptions were made: There exist disease induced deaths due to chronic (via single and dually HBV/HIV co-infections). Treatment should be for a long time and

uninterrupted, as virological relapses after discontinuation of treatment are frequent. Wanning of HBV vaccination takes 25 years, and it has not been established to be life-long.

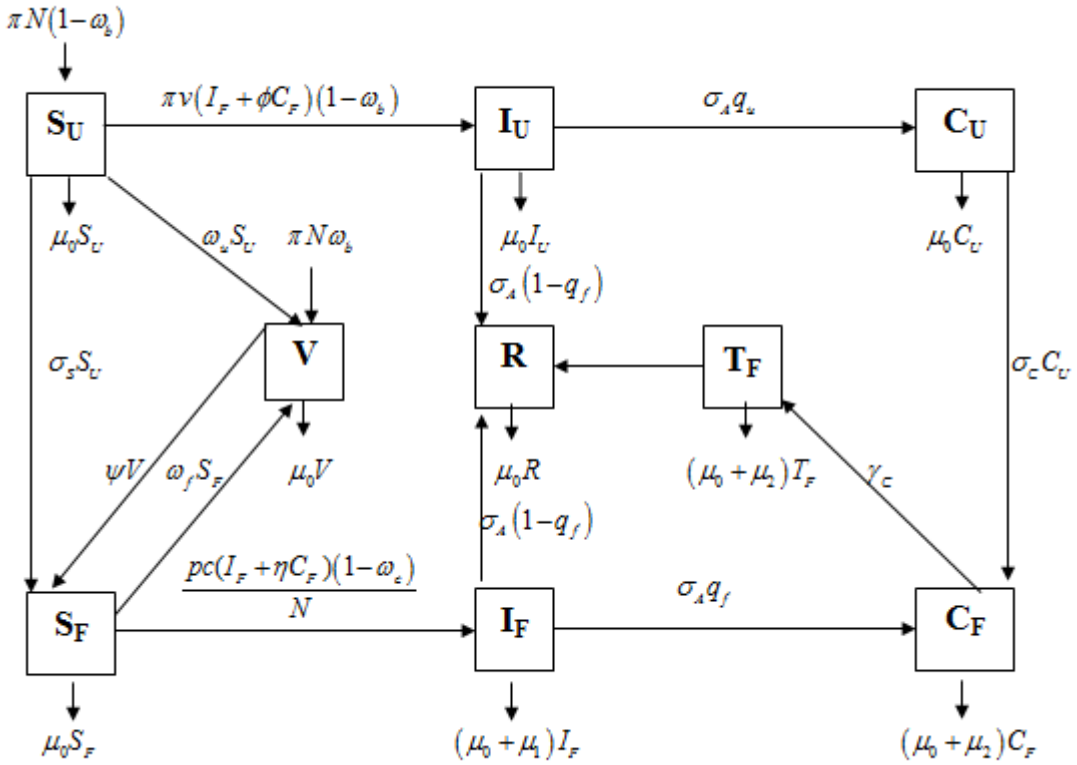


Figure 1: Schematic representation of interactions of HBV transmission.

$$\frac{dS_U}{dt} = \pi N\left(1-\omega_b\right) - \pi\nu\left(I_F + \phi C_F\right)\left(1-\omega_b\right)S_U - \left(\sigma_s + \omega_u + \mu_0\right)S_U \quad (2.1)$$

$$\frac{dS_F}{dt} = \sigma_s S_U + \psi V - \frac{pc\left(I_F + \eta C_F\right)\left(1-\omega_c\right)}{N}S_F - \left(\omega_f + \mu_0\right)S_F \quad (2.2)$$

$$\frac{dV}{dt} = \pi N\omega_b + \omega_u S_U + \omega_f S_F - \left(\mu_0 + \psi\right)V \quad (2.3)$$

$$\frac{dI_U}{dt} = \pi\nu\left(I_F + \phi C_F\right)\left(1-\omega_b\right)S_U - \left(\sigma_A + \mu_0\right)I_U \quad (2.4)$$

$$\frac{dI_F}{dt} = \frac{pc\left(I_F + \eta C_F\right)\left(1-\omega_c\right)}{N}S_F - \left(\mu_0 + \mu_1 + \sigma_A\right)I_F \quad (2.5)$$

$$\frac{dC_U}{dt} = \sigma_A q_u I_U - \left(\sigma_C + \mu_0\right)C_U \quad (2.6)$$

$$\frac{dC_F}{dt} = \sigma_A q_f I_F + \sigma_C C_U - \left(\mu_0 + \mu_2 + \gamma_c\right)C_F \quad (2.7)$$

$$\frac{dT_F}{dt} = \gamma_c C_F - \left(\mu_0 + \mu_2 + \gamma_T\right)T_F \quad (2.8)$$

$$\frac{dR}{dt} = \sigma_A\left(1-q_u\right)I_U + \sigma_A\left(1-q_f\right)I_F + \gamma_T T_F - \mu_0 R \quad (2.9)$$

where

$\omega_u = \varepsilon_p\tau_u,\ \omega_b = \varepsilon_p\tau_b,\ \omega_f = \varepsilon_p\tau_f, \omega_c = \varepsilon_c\tau_c, \pi_A = \pi\nu\left(1-\omega_b\right), \pi_C = \pi\nu\phi\left(1-\omega_b\right), \beta_A = pc\left(1-\omega_b\right),$
$\beta_C = pc\eta\left(1-\omega_c\right), \gamma_{AU} = \sigma_A\left(1-q_u\right), \gamma_{AF} = \sigma_A\left(1-q_f\right), Z_0 = \mu_0 + \sigma_A, Z_1 = \mu_0 + \sigma_s + \omega_u, Z_2 = \mu_0 + \omega_f,$
$Z_3 = \mu_0 + \psi, Z_4 = \mu_0 + \mu_1 + \sigma_A, Z_5 = \mu_0 + \sigma_C, Z_6 = \mu_0 + \mu_2 + \gamma_C, Z_7 = \mu_0 + \mu_2 + \gamma_T,$

The total population N(t) can be obtained from

$$N(t) = S_U(t) + S_F(t) + V(t) + I_U(t) + I_F(t) + C_U(t) + C_F(t) + T_F(t) + R(t)$$
$$\frac{dN}{dt} = \pi N - \mu_0 N - \mu_2\left(C_F + T_F\right)$$
$$N(t) = N(0)e^{(\pi-\mu_0)t}$$

(2.10)

in the absence of disease $N(t) \to \frac{\pi}{\mu_0}$. Moreover, under the dynamics described by the above systems of equations, the region

Table 1: The list of parameters / notations

Parameter	Interpretation	Value	Reference
μ	birth rate	0.0121	MOHC (2009)
μ_0	Natural mortality rate	0.00693	MOHC (2009)
μ_1	HBV related mortality rate by I U and I F	0.007	MMWR (2007)
μ_2	HBV related mortality rate by C F and T F	0.00131	Sirajo *et al*. (2013)
ψ	Rate of waning of vaccine-induced immunity	0.04	Sirajo *et al*. (2013)
Q	Average probability an individual fail to clear an acute infection and develops to carrier state	0.885	Sirajo *et al*. (2013)
π	birth rate	0.036	Sirajo *et al*. (2013)
C	Average number of sexual partner	3.233	Sirajo *et al*. (2013)
P	HBV-Sexual transmission risk rate and pc is the effective contact rate	0.6	Sirajo *et al*. (2013)
η	Modification Parameter that suggest reduce sexual transmission rate by chronic individual	0.667	Sirajo *et al*. (2013)
ε_c	Condom efficacy	0.8	Sirajo *et al*. (2013)
ε_p	Vaccine efficacy	0.9	Sirajo *et al*. (2013)
v	Proportion of perinatal infected HBV positive birth	0.724	Sirajo *et al*. (2013)
ϕ	Modification Parameter that suggest reduction in HBV-positive birth by chronic individual	0.159	Sirajo *et al*. (2013)
σ_s	Rate of moving from S U to S F	0.0667	Sirajo *et al*. (2013)
σ_A	Rate of moving from acute to chronic infection	2.667	Sirajo *et al*. (2013)
σ_C	Rate of moving from C U to C F	0.069	Sirajo *et al*. (2013)
γ_T	Rate of moving from T F to R		Hypothetical
γ_C	Rate of moving from C F to T F	0.015	Sirajo *et al*. (2013)
q_u	Proportion of I U which progress to C U	0.885	Hahnea *et al*. (2004)
q_f	Proportion of I F which progress to C F	0.1	Sirajo *et al*. (2013)
$\tau_c, \tau_b, \tau_u, \tau_f$	Condom, Vaccine(birth), Vaccine (below15), Vaccine (above 15), compliance	0.1	Sirajo *et al*. (2013)

$$\Omega = \left\{ \begin{array}{l} x = \left(S_U, S_F, V, I_U, I_F, C_U, C_F, T_F, N\right) \in \Re_+^9 \mid S_U > 0, S_F > 0, V \geq 0, I_U \geq 0, I_F \geq 0, C_U \geq 0, \\ C_F \geq 0, T_F \geq 0, N \leq \dfrac{\mu}{\mu_0} \end{array} \right\} \tag{2.11}$$

is positively invariant. Hence the system is both mathematically and epidemiologically well-posed. Therefore, for initial starting point $x \in \Re_+^9$, the trajectory lies in Ω. Thus we restrict our analysis to the region Ω. (where the models make biological sense)

2.1 Positivity of Solutions

Lemma 1: All the solution of the equations 2.1 - 2.9 are positive for all time t ≥ 0 provided the initial condition are positive.

Proof: Let $\left\{\left(S_U(0), S_F(0), V(0), I_U(0), I_F(0), C_U(0), C_F(0), T_F(0), R(0)\right) \geq 0\right\} \in \Re_+^9$

$$\frac{dS_U}{dt} = \pi N(1-\omega_b) - \pi\nu\left(I_F + \phi C_F\right)(1-\omega_b)S_U - \left(\sigma_s + \omega_u + \mu_0\right)S_U \qquad (2.12)$$

$$\geq -\pi\nu\left(I_F + \phi C_F\right)(1-\omega_b)S_U - \left(\sigma_s + \omega_u + \mu_0\right)S_U \qquad (2.13)$$

This implies $S_U'(t) \geq -\pi\nu\left(I_F + \phi C_F\right)(1-\omega_b)S_U - \left(\sigma_s + \omega_u + \mu_0\right)S_U$, integrating we have

$$S_U(t) \geq S_U(0)e^{-\pi\nu(1-\omega_b)\int(I_F+\phi C_F)dt-(\sigma_s+\omega_u+\mu_0)t} \geq 0. \qquad (2.14)$$

similarly, it can be shown that:

$S_U > 0, S_F > 0, V \geq 0, I_U \geq 0, I_F \geq 0, C_U \geq 0, C_F \geq 0, T_F \geq 0, R \geq 0,$ for all time t > 0. Hence all solutions of the HBV model remain positive for all non-negative initial conditions.

2.2 Basic Reproduction Number (Graph-Theoretic Method)

A graph-theoretic method for calculating R_0 was discussed exclusively in de-Camino-Beck *et al*. (2007, 2009). From the definition of $R_0 = \rho(FV^{-1})$, they are able to derive a series of rules for reducing the digraph associated with $F\lambda^{-1} - V$ to a digraph with zero weight, from which $\lambda = R_0$ is given. The rules are as follows:

Rule 1: To reduce the loop $-a_{ii} < 0$ to - 1 at node i, every arc entering i has weight divided by a_{ii}.

Rule 2: For a trivial node i on a path j → i → k, the two arcs are replaced by j → k with weight equal to the product.

Using Graph Theoretic Method

Taking the infective classes of the model;

$$\frac{dI_U}{dt} = \pi\nu\left(I_F + \phi C_F\right)\left(1-\omega_b\right)S_U - \left(\sigma_A + \mu_0\right)I_U$$
$$\frac{dI_F}{dt} = \frac{pc\left(I_F + \eta C_F\right)\left(1-\omega_c\right)}{N}S_F - \left(\mu_0 + \mu_1 + \sigma_A\right)I_F$$
$$\frac{dC_U}{dt} = \sigma_A q_u I_U - \left(\sigma_C + \mu_0\right)C_U$$
$$\frac{dC_F}{dt} = \sigma_A q_f I_F + \sigma_C C_U - \left(\mu_0 + \mu_2 + \gamma_c\right)C_F$$

We have four infected classes in this model, Infectious individual below 15 years of age ($I_U(t)$), Infectious individual 15 years and above ($I_F(t)$), Chronically infected individual below 15 years of age ($C_U(t)$), Chronically infected individual 15 years and above ($C_F(t)$), hence our m = 4.

$$F = \begin{bmatrix} 0 \\ \left(\beta_A I_F + \beta_C C_F\right)S_F \\ 0 \\ 0 \end{bmatrix}, \quad V = \begin{bmatrix} Z_0 I_U - \pi_A I_F S_U - \pi_C C_F S_U \\ Z_4 I_U \\ Z_5 C_U - \sigma_A q_u I_U \\ Z_6 C_F - \sigma_A q_f I_F - \sigma_C C_U \end{bmatrix} \tag{3.15}$$

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & \beta_A S_F & 0 & \beta_C S_F \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{3.16}$$

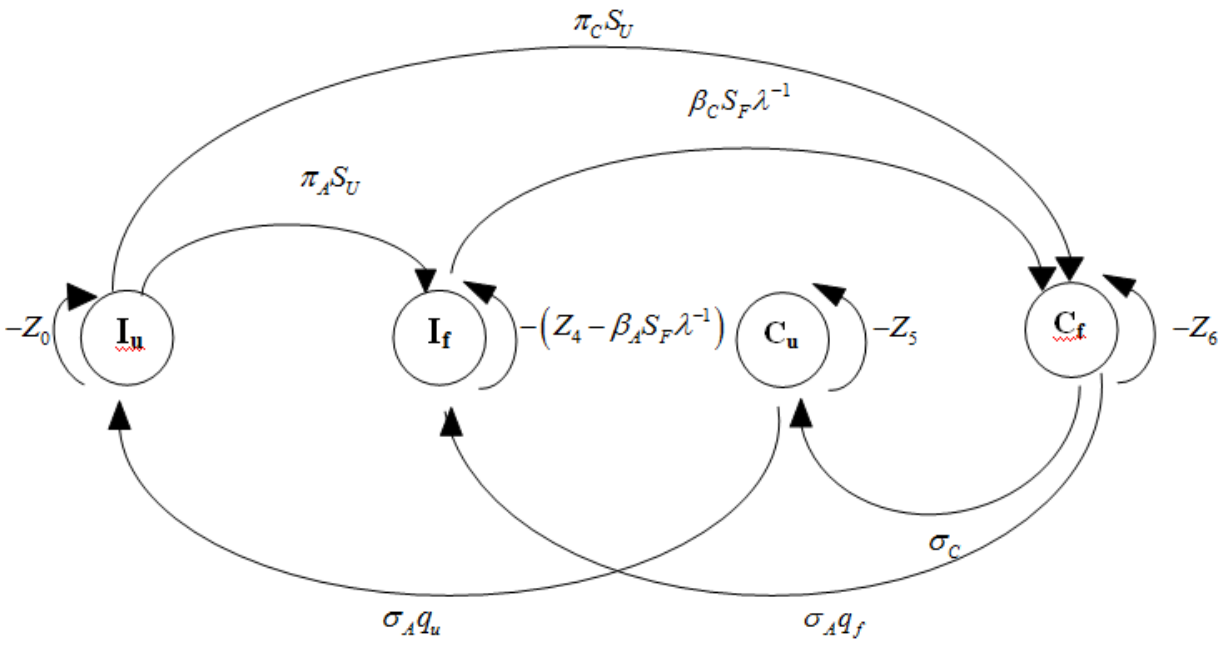
$$V = \begin{bmatrix} Z_0 & -\pi_A S_U & 0 & -\pi_C S_U \\ 0 & Z_4 & 0 & 0 \\ -\sigma_A q_u & 0 & Z_5 & 0 \\ 0 & -\sigma_A q_f & -\sigma_C & Z_6 \end{bmatrix} \tag{3.17}$$

For the disease-free equilibrium point of the system of equations, which has the coordinates:

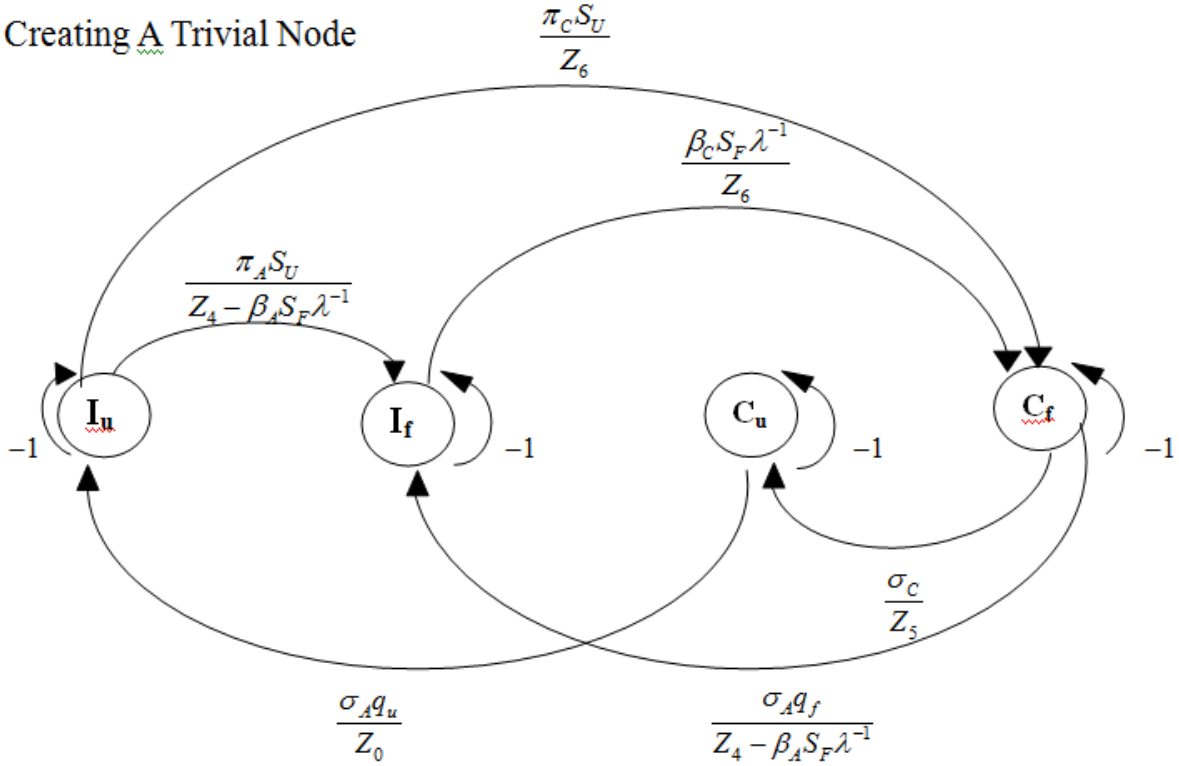
$$S_U^* = \frac{\pi N\left(1-\omega_b\right)}{Z_1}, \qquad S_F^* = \frac{Z_4\left(-q_u\pi_c\sigma_A\sigma_C + Z_6 Z_5 Z_4\right)}{\pi_A q_u \beta_c \sigma_A \sigma_C - \pi_C q_u \beta_A \sigma_A \sigma_C + Z_4 Z_5 q_f \beta_C \sigma_A + \beta_A Z_6 Z_5 Z_4}$$

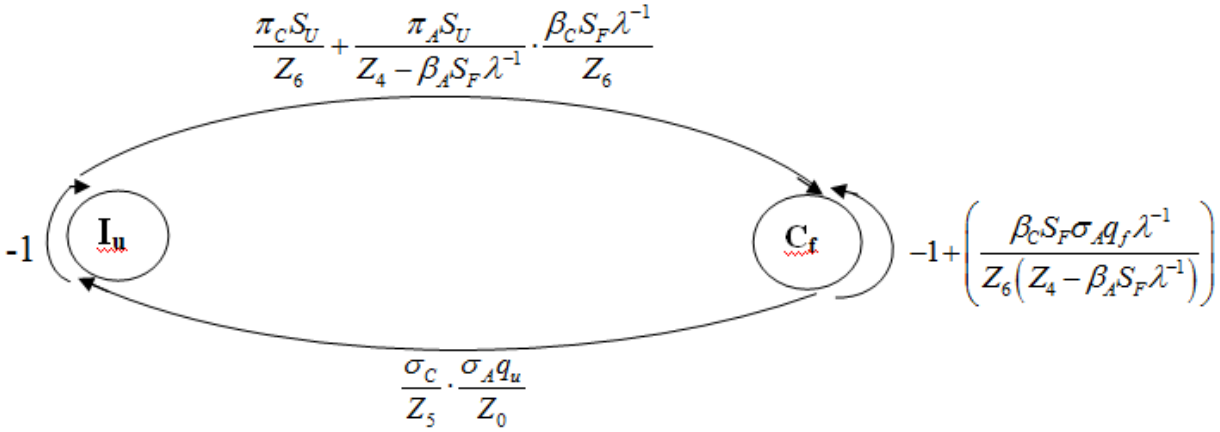
$$F\lambda^{-1} - V = \begin{bmatrix} -Z_0 & \pi_A S_U & 0 & \pi_C S_U \\ 0 & \beta_A S_F \lambda^{-1} - Z_4 & 0 & \beta_C S_F \lambda^{-1} \\ \sigma_A q_u & 0 & -Z_5 & 0 \\ 0 & \sigma_A q_f & \sigma_C & -Z_6 \end{bmatrix} \tag{3.18}$$

Creating A Digraph $F\lambda^{-1} - V$



Creating A Trivial Node





equating the left hand-side to zero, we have:

$$\frac{\beta_C \sigma_A S_F \left(\pi_A S_U q_u \sigma_C + Z_5 Z_0 q_f \right)}{Z_6 \lambda \left(-\beta_A S_F + Z_4 \right) Z_5 Z_0} + \frac{\sigma_C \sigma_A q_u \pi_C S_U}{Z_6 Z_5 Z_0} = 1 \qquad (3.19)$$

$$R_0 = \lambda = \frac{S_F \left(\left(S_U q_u \left(-\pi_A \beta_C + \pi_C \beta_A \right) \sigma_C - \beta_C Z_5 Z_0 q_f \right) \sigma_A - \beta_A Z_6 Z_5 Z_0 \right)}{Z_4 \left(\pi_C \sigma_C \sigma_A q_u S_U - Z_6 Z_5 Z_0 \right)} \qquad (3.20)$$

3. Result and Discussion

Numerical Simulation

We simulated numerically with the aid of Maple software to check and determine the effect and behavior of the parameters of the model.

Table 2: Basic Reproduction Number (R_0) obtained for HBV.

Parameter	$R_0^{\tau_b}$		$R_0^{\tau_u}$		$R_0^{\tau_c}$		$R_0^{\tau_f}$	
τ_b, τ_u, τ_c, τ_f	DFE	Remark	DFE	Remark	DFE	Remark	DFE	Remark
0.1	0.4664	Stable	0.3767	Stable	0.6115	Stable	1.2621	Unstable
0.2	0.4454	Stable	0.3795	Stable	0.5752	Stable	0.8847	Stable
0.3	0.4244	Stable	0.3809	Stable	0.5389	Stable	0.6811	Stable

0.4	0.4033	Stable	0.3817	Stable	0.5026	Stable	0.5536	Stable
0.5	0.3823	Stable	0.3822	Stable	0.4663	Stable	0.4664	Stable
0.6	0.3612	Stable	0.3827	Stable	0.4301	Stable	0.4029	Stable
0.7	0.3400	Stable	0.3830	Stable	0.3938	Stable	0.3546	Stable
0.8	0.3188	Stable	0.3832	Stable	0.3576	Stable	0.3166	Stable
0.9	0.2976	Stable	0.3834	Stable	0.3213	Stable	0.2860	Stable
1.0	0.2763	Stable	0.3835	Stable	0.2850	Stable	0.2608	Stable

Discussion of Results

Simulations illustrate the asymptotic stability of DFE studied in Section 3. The model described by equations (2.1 - 2.9) exhibit a rich dynamic. We observed that varying these control parameters; τ_b, τ_u, τ_c, τ_f, when there is no control (effective immunization's and condom usage equal zero) our R_0 = 2.9479, at low rate (10 percent) R_0 = 1.6145, at moderate rate (50 percent) R_0 = 0.3823, at high rate (90 percent) R_0 = 0.0987, these suggests that the more we vaccinate and provide adequate treatment to the population and also enlighten them on its menace, this will bring the threshold value below unity, thus eradicating the disease. Moreover, other highly sensitive parameters are σ_A, σ_C, σ_S, η, γ_C and $\gamma_{TF.}$ For the parameters σ_A and q_f are the movement from an acute stage to a chronic stage and should be of high sensitivity. The acute stages have short duration (six months) while chronic stages have the long duration of years and in most cases, they are life-long. For η, it is the modification parameter that suggests the reduced sexual transmission rate by chronic individuals, and thus, it profoundly affects the transmission dynamics of the disease.

4. Conclusion

The positivity of the model considered was found. The use of Graph-Theoretic method was adopted in calculating the reproduction numbers of the model. For more complicated systems, the Graph-theoretic method might be simpler to apply since the matrix $F\lambda^{-1} - V$ has sparse structure, which avoids the dilemma associated with picking the dominant eigen-value from the matrix. Moreover, to quickly reduce the prevalence of the disease (HBV) in Nigeria, the nationwide public enlightenment campaign must be done, in other to raise awareness on national immunization days as in the case with polio immunization, to quickly combat the disease through children and adult vaccination.

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