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Sensitivity Analysis of Hepatitis B Virus Epidemic Model

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Authors' contributions

This work was carried out in collaboration among all authors. Author FSA designed the study, performed the sensitivity analysis, wrote the protocol and wrote the first draft of the manuscript. Authors OOK and SA managed the analyses of the study. Author ADA managed the literature searches. All authors read and approved the final manuscript.

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Abstract

The aim of this work is to carry out detailed sensitivity analysis of each parameter in order to know their relative importance in the epidemiological model. This mathematical model for hepatitis B virus is a system of non-linear differential equations which represents the interaction between diseases classes and other epidemiological parameters. The disease free equilibrium points and basic reproduction number of the cases were analyzed using the next generation matrix method. Sensitivity analysis of R_0 with respect to the model parameters was carried out using normalized forward sensitivity index with graphical illustrations for clarity on the effects of these parameters. This analysis showed transmission rate β as the most sensitive parameter which means a reduction to zero of the transmission rate could lead to eradicating HBV infection. It was deduced that sensitivity analysis of these model parameters gives an insight into how best the spread of Hepatitis B Virus could be curtailed.

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1 Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the HBV and is a major global health problem and the most serious type of viral hepatitis [1]. It has caused epidemics in parts of Asia and Africa [2]. Worldwide, about 2 billion people have been infected with the virus and about 360 million live with chronic infection. With this information, it is important to study ways by which this real world problem can be solved using mathematical modeling.

Mathematical modeling of infectious diseases is a tool which had been used to study the mechanisms by which diseases spread, to predict the future course of an outbreak and to evaluate strategies to control an epidemic [3,4]. Mathematical models can project how infectious diseases progress to show the likely outcome of an epidemic and help inform public health interventions. Models use some basic assumptions and mathematics to find parameters for various infectious diseases and use those parameters to calculate the effects of possible interventions like mass vaccination programmes [5,6].

Abdulrahaman [3] discussed the importance of sensitivity analysis of each parameter in a mathematical model. In their work, they used normalized forward sensitivity analysis to discover parameters that have high impact on the basic reproduction number R_0 of Hepatitis B model which must be targeted by intervention strategies. It is worthy to note that sensitivity Analysis of models in mathematical epidemiology aims to study the effect of each parameters of the model [7,8,9,10]. Helena [11] explained that sensitivity indices was used to measure the relative change in a variable when a parameter changes. They defined the reproductive number R_0, as the expected number of secondary cases that one infected individual would cause through the duration of the infectious period and also used the normalized forward sensitivity index to compute the sensitivity indices of R_0.

In this way, close collaborations between experimentalists/clinicians and mathematical epidemiologists have become an important instrument, leading to faster progress in our understanding of these infections. In view of this, a mathematical model for the transmission dynamics of Hepatitis B Virus is presented and the importance of the most sensitive parameter will be examined.

2 Model Formulation

A model equation for the transmission dynamics and characteristics of Hepatitis B virus infection was formulated using first order ordinary differential equation. The population was divided into seven compartment namely: Susceptible S(t) who are not yet infected but can be infected by hepatitis B virus through various mode of transmission, Latent L(t) denote part of the population who came in contact with the virus but have no serologic alteration in their blood (Incubation Phase), Acute A(t) infected population have asymptomatic cases of the infection and may become silent carriers of the virus and has the ability of spreading the infection to those in the susceptible class, Chronic infected C(t) population are known as asymptomatic carriers who develop significant and potentially fatal diseases, Treatment T(t) population denote detected cases of chronic HBV infection undergoing treatment [12]. Recovered R(t) population denote the number of individual that completely recovered from the disease through natural healing and treatment while V(t) is the compartment for individuals who have been vaccinated. Individual in this class have temporary immunity for a period of 25years and cannot be infected with HBV until the vaccine wane out. Let the total population at any time (t) be denoted by N(t).

The rate of transfer between the compartments consist of several epidemiological parameters which include recruitment by birth represented by π and λ represents recruitment by immigration, proportion of birth without vaccination is denoted by ω and $(1-\omega)$ represent birth successfully vaccinated. ρ denotes birth to carrier mothers i.e vertically infected birth rate, β represent the transmission rate, k shows the reduced transmission rate from chronic infectiousness to acute infection, μ represent natural death rate for all compartments, δ_1 is the vaccination rate of susceptible population and δ_2 represents loss of immunity of the vaccinated class. The transmission dynamics of hepatitis B virus is presented in the flow chart of Fig. 2.1,

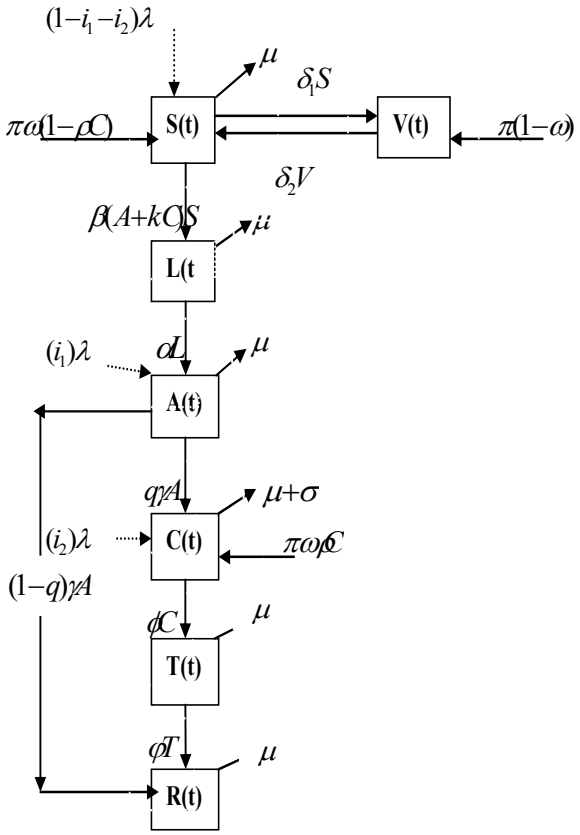

Fig. 2.1. Flow chart of hepatitis B model with infective migrant

The rate at which latent class becomes infectious and progress to acute class is denoted α, i_1 and i_2 are proportion of immigrant with Acute and chronic HBV infection respectively, q is the proportion of Acute that fails to clear HBV infection and become chronic, γ is the progression rate of Acute class, σ represent HBV induced death rate and the rate of flow from chronic to treatment class is ϕ, φ is the rate of progressing from treatment class to recovered class after HBV elimination while $(1-q)$ represents proportion of Acute class who cleared the infection and progress to the recovered class.

Then, $\pi\omega(1-\rho C)$ show the new born who are unimmunized and become Susceptible, $\pi(1-\omega)$ represents successful immunization of new birth, $\pi\omega\rho C$ measures the new birth who are born to carrier mothers and cannot be vaccinated.

From Fig. 2.1, the system of equations modified which represents the transmission dynamics of hepatitis B with immigrant and treatment/detected class is presented thus:

$$\begin{aligned}
S' &= \pi\omega(1-\rho C) + \lambda(1-i_1-i_2) - \beta(A+kC)S - (\mu+\delta_1)S + \delta_2 V \\
L' &= \beta(A+kC)S - (\mu+\alpha)L \\
A' &= \lambda i_1 + \alpha L - (\mu+\gamma)A \\
C' &= \lambda i_2 + \pi\omega\rho C + q\gamma A - (\mu+\sigma+\phi)C \\
T' &= \phi C - (\mu+\varphi)T \\
R' &= \varphi T + (1-q)\gamma A - \mu R \\
V' &= \pi(1-\omega) + \delta_1 S - (\mu+\delta_2)V
\end{aligned} \tag{1}$$

Subject to initial conditions,

$$S(0) \geq 0,\ L(0) \geq 0,\ A(0) \geq 0,\ C(0) \geq 0,\ T(0) \geq 0,\ R(0) \geq 0,\ V(0) \geq 0.$$

The following assumptions were made:

I. The Population is assumed not to be constant since birth, immigration and death occur in the population.
II. The natural death of all classes is the same except for chronic class.
III. The vaccinated individuals become temporary immune for a period of 25 years.
IV. The recovered individuals become permanently immune to the disease for life.
V. The chronic infected individual have a diseases induced death rate of σ.
VI. This model is assume to be homogeneous mixing of individuals in the population where all individuals have equal likelihood of getting infected if they come in contact with infectious individuals.

Then, consider a scenario where no migrant is present in the population i.e $\lambda = 0,$ in equation (1), then equation (2) is obtained,

$$\begin{aligned}
S' &= \pi\omega(1-\rho C) - \beta(A+kC)S - (\mu+\delta_1)S + \delta_2 V \\
L' &= \beta(A+kC)S - (\mu+\alpha)L \\
A' &= \alpha L - (\mu+\gamma)A \\
C' &= \pi\omega\rho C + q\gamma A - (\mu+\sigma+\phi)C \\
T' &= \phi C - (\mu+\varphi)T \\
R' &= \varphi T + (1-q)\gamma A - \mu R \\
V' &= \pi(1-\omega) + \delta_1 S - (\mu+\delta_2)V
\end{aligned} \tag{2}$$

With the initial conditions,

$$S(0) \geq 0,\ L(0) \geq 0,\ A(0) \geq 0,\ C(0) \geq 0,\ T(0) \geq 0,\ R(0) \geq 0,\ V(0) \geq 0.$$

3 Methodology

3.1 Positive invariant region

Consider equation (2), it is important to show that all the state variable and parameters are non- negative with respect to time (t) such that $t \geq 0$. The total population in each compartment of the model is denoted by N(t). Let $\{S(t), L(t), A(t), C(t), T(t), R(t), V(t)\} \in \Re^7$. be any solution of equation (2), given by $N(t) = S(t) + L(t) + A(t) + C(t) + T(t) + V(t) + R(t)$ where $S > 0, L \geq 0, A \geq 0, C \geq 0, T \geq 0, V \geq 0, R \geq 0$, then all feasible solutions are uniformly bounded in $\Gamma \in \Re_+^7$. To show that all feasible solutions are uniformly-bounded in a proper subset of $\Gamma \in \Re_+^7$, then

From equation (2),

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dL}{dt} + \frac{dA}{dt} + \frac{dC}{dt} + \frac{dT}{dt} + \frac{dR}{dt} + \frac{dV}{dt}$$

$$\frac{dN}{dt} = \pi - \mu(S + L + A + C + T + V + R) - \sigma C$$

$$N' = \pi - \mu(N) - \sigma C$$

Assume no induced death rate, then

$$N'(t) = \pi - \mu N(t)$$

then, $N(t) = \frac{\pi}{\mu} + C_1 e^{\mu t}$

Where C_1 is the constant of integration. At $t \to \infty$ and applying theorems on differential inequalities then, the seven dimensional simplex is positively invariant with respect to equation (2), this means for starting point $x \in \Re^7$., the trajectories lie in Γ.

$$\Gamma = \left\{ (S, L, A, C, T, R, V) \in \Re_+^7 / S > 0, L \geq 0, A \geq 0, C \geq 0, T \geq 0, R \geq 0, V \geq 0, S + L + A + C + T + R + V \leq \frac{\pi}{\mu} \right\}$$

This implies that the mathematical model is well posed and epidemiologically meaningful.

3.2 Diseases-Free Equilibrium (DFE)

The diseases free equilibrium (E_0) is a point at which the population is free from Hepatitis B Virus infection. Consider equation (2), the disease free equilibrium of model equation (2) was obtained by setting $S' = L' = A' = C' = T' = R' = V' = 0$. At HBV-free equilibrium point there is no infection, then we set all state variables except susceptible and vaccinated to be zero [13,14]. Such that, $L = A = C = T = R = 0$ and $S = S_0$ and $V = V_0$

Then, $S = S_0, V = V_0, L = A = C = T = R = 0,$

equation (2) gives

$$\pi\omega(1-0) - \beta(0) - (\mu + \delta_1)S_0 + \delta_2 V_0 = 0$$

$$\pi(1-\omega) + \delta_1 S_0 - (\mu + \delta_2)V_0$$

then, $S_0 = \dfrac{\pi\omega + \delta_2 V_0}{\mu + \delta_1}$, $V_0 = \dfrac{\pi(1-\omega) + \delta_1 S_0}{(\mu + \delta_2)}$

substituting V_0 into S_0, then

$$S_0 = \frac{\pi\omega + \delta_2\left(\dfrac{\pi(1-\omega) + \delta_1 S_0}{(\mu + \delta_2)}\right)}{(\mu + \delta_1)}$$

$$S_0 = \frac{\pi\omega(\mu + \delta_2) + \delta_2(\pi(1-\omega) + \delta_1 S_0)}{(\mu + \delta_2)(\mu + \delta_1)}$$

$$S_0(\mu + \delta_1)(\mu + \delta_2) = \pi\omega(\mu + \delta_2) + \delta_2\pi(1-\omega) + \delta_1\delta_2 S_0$$

Collect like terms,

$$S_0(\mu + \delta_2)(\mu + \delta_1) - \delta_2\delta_1 S_0 = \pi\omega\mu + \pi\omega\delta_2 + \delta_2\pi - \delta_2\pi\omega$$

$$S_0(\mu^2 + \mu\delta_1 + \mu\delta_2 + \delta_1\delta_2 - \delta_1\delta_2) = \pi\omega\mu + \delta_2\pi$$

$$S_0(\mu^2 + \mu\delta_1 + \mu\delta_2) = \pi(\delta_2 + \omega\mu)$$

Hence, $$S_0 = \frac{\pi(\delta_2 + \omega\mu)}{\mu(\mu + \delta_1 + \delta_2)}$$

On the other hand, V_0 gives

$$V_0 = \frac{\pi(1-\omega) + \delta_1\left(\dfrac{\pi\omega + \delta_2 V_0}{\mu + \delta_1}\right)}{\mu + \delta_2}$$

$$V_0 = \frac{\pi(1-\omega)(\mu+\delta_1)+\delta_1(\pi\omega+\delta_2 V_0)}{(\mu+\delta_2)(\mu+\delta_1)}$$

$$V_0(\mu+\delta_2)(\mu+\delta_1) = \pi(1-\omega)(\mu+\delta_1)+\delta_1\pi\omega+\delta_1\delta_2 V_0$$

$$V_0(\mu\delta_1+\mu^2+\delta_1\delta_2+\mu\delta_2)-\delta_1\delta_2 V_0 = \pi(1-\omega)(\mu+\delta_1)+\delta_1\pi\omega$$

Collect like term, hence,

$$\Rightarrow \qquad V_0 = \frac{\pi(\delta_1+\mu(1-\omega))}{\mu(\mu+\delta_1+\delta_2)}$$

Therefore, the disease free equilibrium E_0 of the working model is

$$E_0 = (S_0, L_0, A_0, C_0, T_0, R_0, V_0) = \left(\frac{\pi(\mu\omega+\delta_2)}{\mu(\mu+\delta_1+\delta_2)}, 0, 0, 0, 0, 0, \frac{\pi(\delta_1+\mu(1-\omega))}{\mu(\mu+\delta_1+\delta_2)}\right) \tag{3}$$

3.3 Basic reproduction number

In general, the basic reproduction number (R_0) of an infection, is the effective number of secondary infection caused by an infected individual during his/her period of infectiousness. This makes it an important measure of transmissibility of a disease. We use the next generation matrix operator technique for analyzing the reproduction number of Hepatitis B Virus model of equation (2). Consider the mathematical expression in equation (4),

$$R_0 = F_i V_i^{-1} \tag{4}$$

F_i is the rate of appearance of new HBV infection in the infected compartment, V_i is the transfer of individuals out of compartment I by all other means and E_0 is the disease-free equilibrium. Therefore, the spectral radius of the next generation matrix is the basic reproduction number [13,15]. From equation (2),

$$F_i = \begin{pmatrix} F_1 \\ F_2 \\ F_3 \end{pmatrix} = \begin{pmatrix} \beta(A+kC)S \\ 0 \\ 0 \end{pmatrix}$$

Then, the Jacobian derivative of F_i is given as

$$\begin{pmatrix} 0 & \beta S_0 & \beta k S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Where $S_0 = \frac{\pi(\mu\omega+\delta_2)}{\mu(\mu+\delta_1+\delta_2)}$

The transfer of individual out of the compartment i is given by

$$V_i = \begin{pmatrix} V_1 \\ V_2 \\ V_3 \end{pmatrix} = \begin{pmatrix} (\mu+\alpha)L \\ (\gamma+\mu)A - \alpha L \\ -\pi\omega\rho C - q\gamma A + (\mu+\sigma+\phi)C \end{pmatrix}$$

Therefore, the Jacobian derivative of V_i is

$$V = \begin{pmatrix} \mu+\alpha & 0 & 0 \\ -\alpha & \mu+\gamma & 0 \\ 0 & -q\gamma & \mu+\sigma+\phi-\pi\omega\rho \end{pmatrix} \tag{5}$$

and then equation (5) implies

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\alpha} & 0 & 0 \\ \frac{\alpha}{(\mu+\gamma)(\mu+\alpha)} & \frac{1}{\mu+\gamma} & 0 \\ \frac{\alpha q\gamma}{(\mu+\gamma)(\mu+\alpha)(\mu+\sigma+\phi-\pi\omega\rho)} & \frac{q\gamma}{(\mu+\gamma)(\mu+\sigma+\phi-\pi\omega\rho)} & \frac{1}{(\mu+\sigma+\phi-\pi\omega\rho)} \end{bmatrix}$$

Then,

$$FV^{-1} = \begin{pmatrix} 0 & \beta S_0 & \beta k S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} * \begin{bmatrix} \frac{1}{\mu+\alpha} & 0 & 0 \\ \frac{\alpha}{(\mu+\gamma)(\mu+\alpha)} & \frac{1}{\mu+\gamma} & 0 \\ \frac{\alpha q\gamma}{(\mu+\gamma)(\mu+\alpha)(\mu+\sigma+\phi-\pi\omega\rho)} & \frac{q\gamma}{(\mu+\gamma)(\mu+\sigma+\phi-\pi\omega\rho)} & \frac{1}{(\mu+\sigma+\phi-\pi\omega\rho)} \end{bmatrix}$$

$$\Rightarrow FV^{-1} = \begin{bmatrix} M & N & P \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

$$M = \frac{\beta S_0 \alpha}{(\mu+\alpha)(\mu+\gamma)} + \frac{\beta k S_0 \alpha q\gamma}{(\mu+\alpha)(\mu+\gamma)(\mu+\sigma+\phi-\pi\omega\rho)}$$

$$N = \frac{\beta S_0}{(\mu+\gamma)} + \frac{\beta k S_0 \alpha q\gamma}{(\mu+\gamma)(\mu+\sigma+\phi-\pi\omega\rho)}$$

$$P = \frac{\beta k S_0}{(\mu+\sigma+\phi-\pi\omega\rho)}$$

The basic reproduction number R_0 is the dominant eigenvalue of matrix FV^{-1}, then

$$R_0 = \frac{\beta S_0 \alpha}{(\mu+\alpha)(\mu+\gamma)} + \frac{\beta k S_0 \alpha q \gamma}{(\mu+\alpha)(\mu+\gamma)(\mu+\sigma+\phi-\pi\omega\rho)} \tag{6}$$

From the above, the basic reproduction number R_0, is given by the largest eigenvalue of the working model [16]. If $R_0 < 1$, then, on average, HBV infected individual produces less than one new infected individual over the course of its infectious period, and the disease cannot grow. Conversely, if $R_0 > 1$, then HBV infected individual infects more than one person, and the disease invades the population.

4 Results for Sensitivity Analysis

The normalized forward sensitivity index of a variable with respect to a parameter is the ratio of the relative change in the variable to the relative change in the parameter [11]. Let φ represent any of the thirteen non-negative parameter $\beta, \pi, \alpha, \omega, \mu, \delta_1, \delta_2, k, \sigma, \phi, \rho, q, \gamma$ that define the basic reproduction number of the model.

$$R_0 = \frac{\beta S_0 \alpha}{(\mu+\alpha)(\mu+\gamma)}\left(1 + \frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)$$

Where $S_0 = \left(\frac{\pi(\delta_2+\omega\mu)}{\mu(\mu+\delta_1+\delta_2)}\right)$

Then, $R_0 = \frac{\beta\pi\alpha(\delta_2+\omega\mu)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1 + \frac{kq\gamma}{\mu+\sigma+\phi-\pi\omega\rho}\right)$

If a small perturbation $\delta\varphi$ is made to the parameter φ, a corresponding change will occur in R_0 as δR_0, where

$$\delta \mathrm{R}_0 = R_0(\varphi+\delta\varphi) - \mathrm{R}_0(\varphi) = \delta\varphi \frac{\partial R_0}{\partial \varphi} \tag{7}$$

The normalized sensitivity index $\Omega_\varphi = \frac{\partial R_0}{R_0} \div \frac{\partial \varphi}{\varphi} = \frac{\varphi \partial R_0}{R_0 \partial \varphi}$

An approximation of the perturbed value of R_0, in terms of the sensitivity index is given as

$$R_0(\psi+\delta\psi) = \left(1 + \frac{\delta\psi}{\psi}\Omega_\psi\right)\mathrm{R}_0(\psi)$$

The sensitivity indices are obtained by substituting values of each parameter from Table 1.

Table 1. Parameter values used for numerical simulation

Parameter	Value	Source
β	0.8	[17]
k	0-1, 0.16	[18]
π	0.0143	[17]
ρ	0.7	[17]
ω	0-1	[19]
μ	0.0121, 0.00693	[19]
σ	0.002, 0.2%	[19]
δ_1	0.3	[17]
δ_2	0.1	[19]
α	6/year, 0.0166	[17]
q	0.855	[19]
γ	4/year	[17]
$1-q$	0.1-0.95, 0.115	[19]
ϕ	9/years/0.025	Estimated
φ	0.01	Estimated

4.1 Index for parameter β

Solving for Ω_β, then $\Omega_\beta = \dfrac{\beta \partial R_0}{R_0 \partial \beta}$

Where, $R_0 = \dfrac{\beta S_0 \alpha}{(\mu+\alpha)(\mu+\gamma)}\left(1+\dfrac{kq\gamma}{\mu+\sigma+\phi-\pi\omega\rho}\right)$ where $S_0 = \dfrac{\pi(\mu\omega+\delta_2)}{\pi(\mu+\delta_1+\delta_2)}$

then $\dfrac{\partial R_0}{\partial \beta} = \dfrac{\pi\alpha(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\dfrac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)$

$$\Omega_\beta = \frac{\beta}{R_0}\times\frac{\partial R_0}{\partial \beta} = \left[\frac{\beta}{\left(\dfrac{\beta\pi\alpha(\mu+\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\right)\left(1+\dfrac{kq\gamma}{(\mu+\delta+\phi-\pi\omega\rho)}\right)}\times\right.$$
$$\left.\left[\frac{\pi\alpha(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)\right]\right]$$

simplify the above and substituting parameters in Table 1,

then, $\Omega_\beta = 1$

4.2 Index for parameter π

The sensitivity index of π is $\Omega_\pi = \frac{\pi}{R_0} \times \frac{\partial R_0}{\partial \pi}$

$$R_0 = \frac{\beta\pi\alpha(\mu\omega + \delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2 + \mu\delta_1 + \mu\delta_2)}\left(1 + kq\gamma(\mu + \sigma + \phi - \pi\omega\rho)^{-1}\right)$$

$$\frac{\partial R_0}{\partial \pi} = \left[\frac{\beta\alpha(\mu\omega + \delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2 + \mu\delta_1 + \mu\delta_2)}\left(1 + \frac{kq\gamma}{(\mu + \sigma + \phi - \pi\omega\rho)}\right)\right] +$$
$$\left[\frac{\beta\pi\alpha(\mu\omega + \delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2 + \mu\delta_1 + \mu\delta_2)}\left(\frac{kq\gamma}{(\mu + \sigma + \phi - \pi\omega\rho)^2}\right)\right]$$

This implies

$$\Omega_\pi = \frac{\pi}{R_0}\left[\frac{\beta\alpha(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)+\left(\frac{\pi kq\gamma\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho)^2}\right)\right]$$

$$\Omega_\pi = \left[\begin{array}{l}\dfrac{\beta\pi\alpha(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\dfrac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}+\dfrac{\pi kq\gamma\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho)^2}\right)\times \\ \left(\dfrac{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}{\beta\pi\alpha(\mu\omega+\delta_2)}\right)\left(\dfrac{1}{1}+\dfrac{kq\gamma}{\mu+\sigma+\phi-\pi\omega\rho}\right)\end{array}\right]$$

$$\Rightarrow \Omega_\pi = \frac{\pi kq\gamma\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho)^2} \times \frac{1}{1+\dfrac{kq\gamma}{\mu+\sigma+\phi-\pi\omega\rho}}$$

$$= \frac{\pi kq\gamma\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho)^2} \times \frac{\mu+\sigma+\phi-\pi\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho+kq\gamma)}$$

$$\Omega_\pi = \frac{\pi kq\gamma\omega\rho}{(\mu+\sigma+\phi-\pi\omega\rho)((\mu+\sigma+\phi-\pi\omega\rho)+kq\gamma)}$$

Substituting values for the parameters provided in Table 1, then Ω_π gives

$$\frac{2\cdot 0731656\times 10^{-6}}{(0\cdot 032599)(0\cdot 0341476)} = 0\cdot 001862$$

Hence, Ω_π =0.001862.

4.3 Index for parameters α

The sensitivity index is given as $\Omega_\alpha = \frac{\alpha}{R_0} \times \frac{\partial R_0}{\partial \alpha}$

$$\frac{\partial R_0}{\partial \alpha} = \frac{\partial}{\partial \alpha}\left[\frac{\beta\alpha\pi(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)\right]$$

$$\frac{\partial R_0}{\partial \alpha} = \left[\frac{\beta\alpha\pi(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)\right]$$

$$\Omega_\alpha = \frac{\alpha}{R_0}\left[\frac{\beta\alpha\pi(\mu\omega+\delta_2)}{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)\right]$$

$$\Omega_\alpha = \frac{\pi\beta\alpha(\mu\omega+\delta_2)}{(\mu+\alpha)^2(\mu+\gamma)(\mu^2+\delta_1+\delta_2)}\left(1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}\right)\times$$

$$\frac{(\mu+\alpha)(\mu+\gamma)(\mu^2+\mu\delta_1+\mu\delta_2)}{(\alpha\beta\pi(\mu\omega+\delta_2))}\left(\frac{1}{1+\frac{kq\gamma}{(\mu+\sigma+\phi-\pi\omega\rho)}}\right)$$

$$\Omega_\alpha = \frac{\mu}{\mu+\alpha}$$

$$\Omega_\alpha = \frac{0\cdot00693}{0\cdot00693+0\cdot016667} = \frac{0\cdot00693}{0\cdot0235967}$$

Hence, $\Omega_\alpha = 0\cdot293685$.

Following the same procedure, the sensitivity index for other parameters of the model was obtained and presented in Table 2.

Considering β in Table 2 its sensitivity index evaluated is $\beta = +1$ meaning that, increasing β by 10% increases R_0 by 10% and vice-versa. On the contrary, the negative sign of sensitivity index of R_0 to the model parameters indicate that an increase in the value of each of the parameter in this case leads to a corresponding decrease in R_0 of the model and vice-versa.

Note that the sensitivity index may be a complex expression, depending on different parameters of the system, but can also be a constant value, not depending on any parameter value in the case of β. With sensitivity analysis, one can get insight on the appropriate intervention strategies to prevent and control the

spread of the disease described by model (2) [20]. Hence, a highly sensitive parameter should be carefully estimated, because a small variation in that parameter will lead to large quantitative changes. On the other hand, an insensitive parameter does not require as much effort to estimate, because a small variation in that parameter will not produce large changes to the quantity of interest. This results show that big changes in the parameter that affects the basic reproduction number produce significant changes in R_0 , and consequently, in the behavior of the disease development.

Table 2. Sensitivity indices of each parameter in the model

Parameter	Sensitivity index for parameter values
β	$+1$
μ	$-0\cdot968227$
σ	$-0\cdot825904$
δ_2	$+0.68447$
γ	$-0\cdot541856$
α	$+0.29368$
ρ	$+0.05014$
k	$+0.045998$
q	$+0.045998$
ϕ	$-0\cdot035276$
δ_1	$-0\cdot00500$
π	$+0.00186$
ω	$+0.00003$

The model equation (2) is solved numerically using Runge-Kutta method of order 4, then the effect of varying transmission rate and vaccination rate was presented graphically

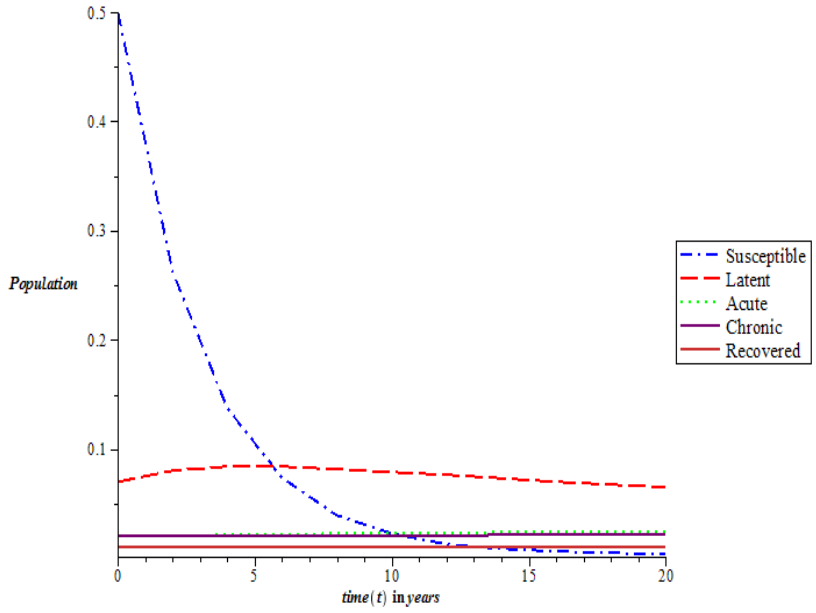

Fig. 4.1. Hepatitis B virus dynamic model against time (t)

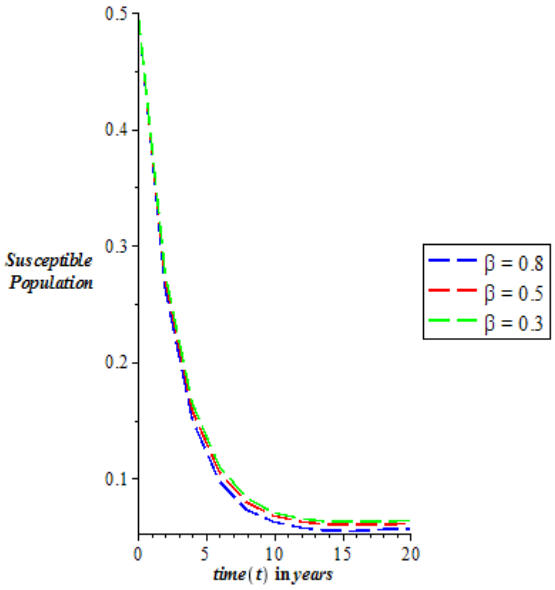

Fig. 4.2. Susceptible population with various transmission rate (β) against time (t)

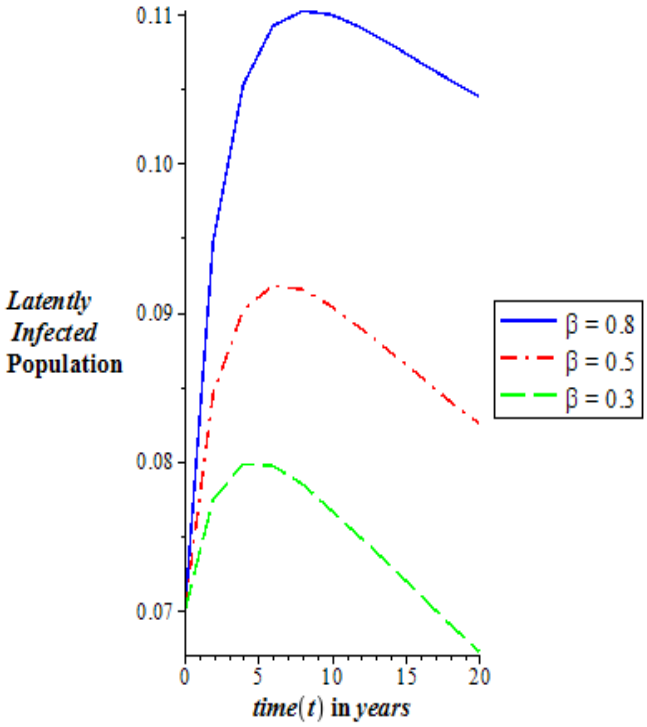

Fig. 4.3. Latent population with various transmission rate (β) against time (t)

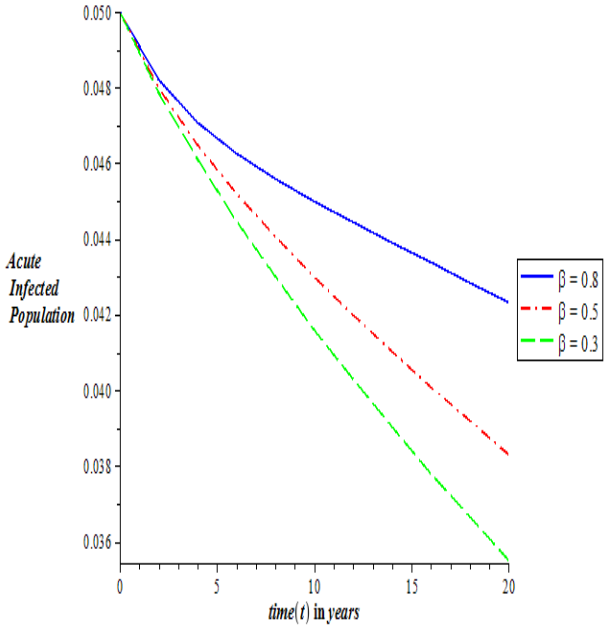

Fig. 4.4. Acute population with various rate (β) against time (t)

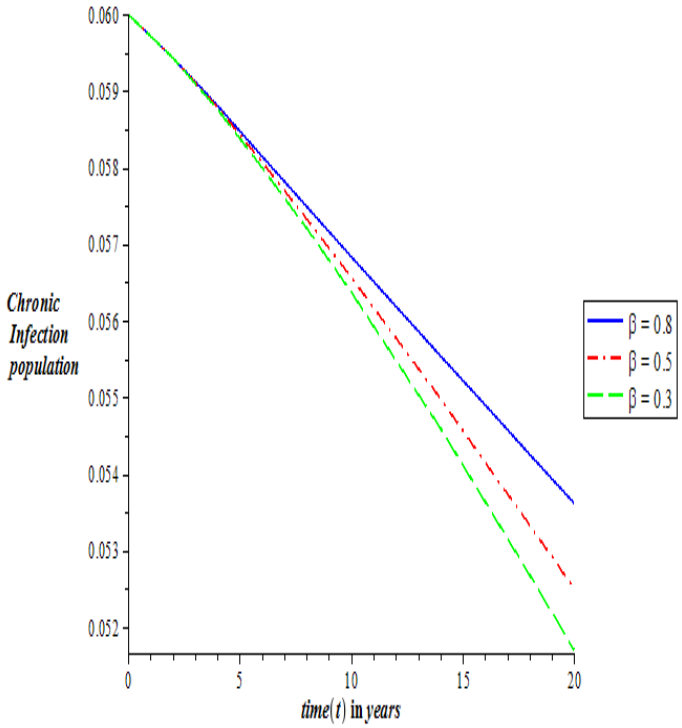

Fig. 4.5. Chronic population with various transmission transmission rate (β) against time (t)

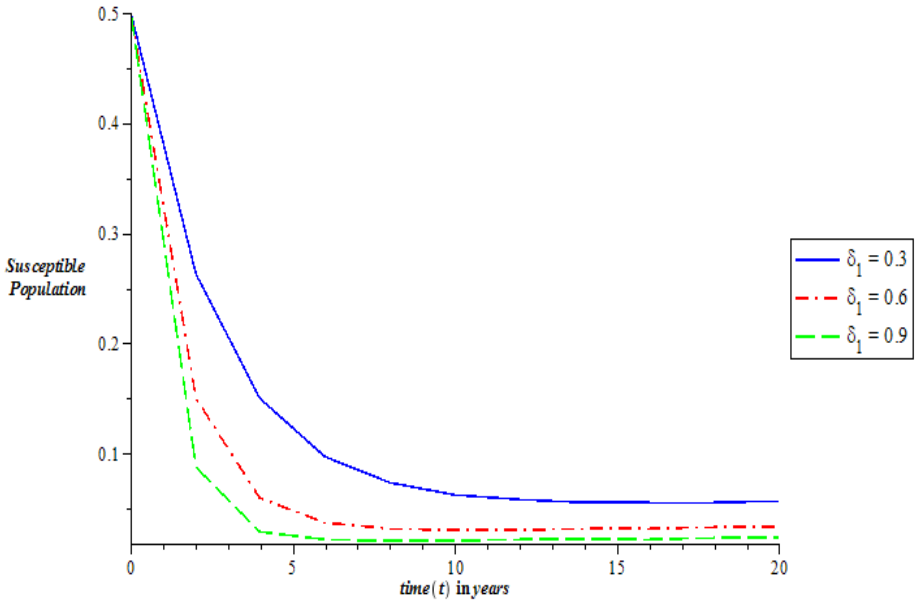

Fig. 4.6. Susceptible population against time (t) with various vaccination rate (δ_1)

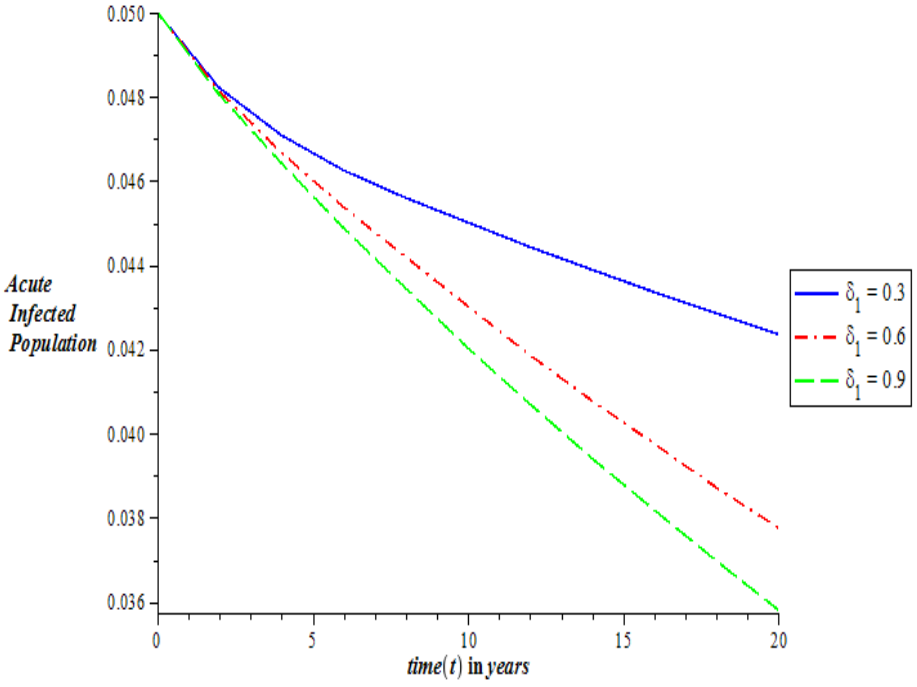

Fig. 4.7. Acute population against time (t) with various vaccination rate (δ_1)

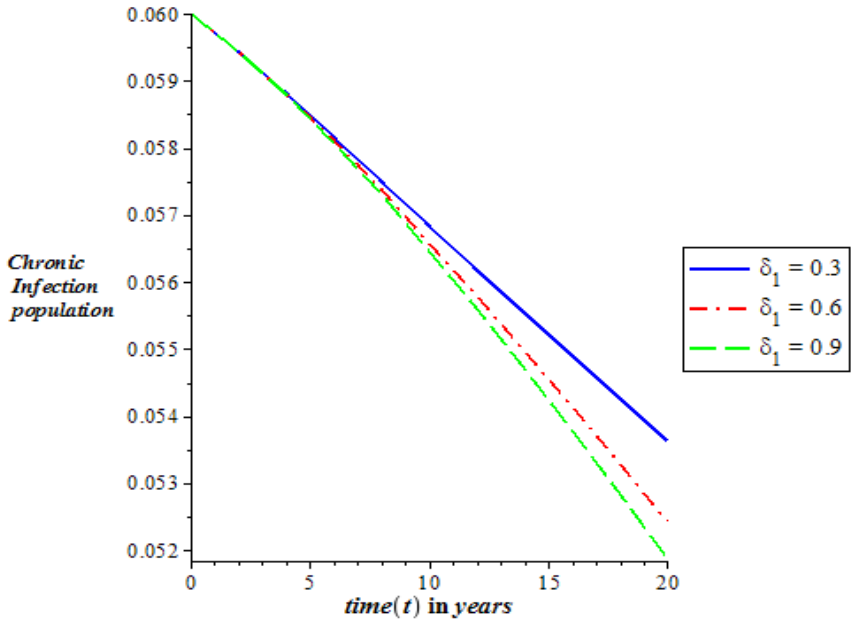

Fig. 4.8. Chronic population against time (t) with various vaccination rate (δ_1)

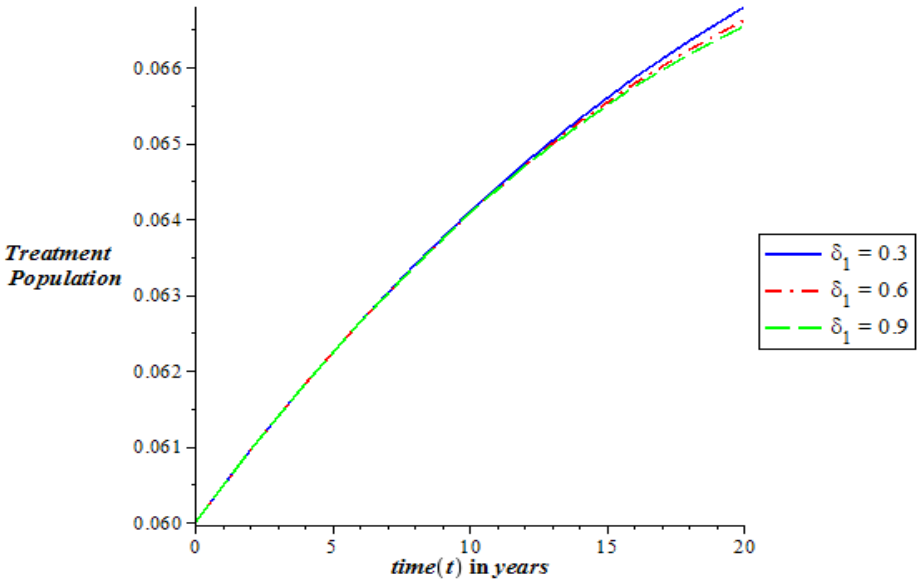

Fig. 4.9. Population undergoing treatment against time (t) with various vaccination rate (δ_1)

Fig. 4.1 explains the behavior of each population compartment of equation (2) without intervention which implies T(t)=0, V(t)=0 and $\delta_1 = 0$ within a period of 20 year. The figure shows a scenario where the entire population does not have any external forces for treatment or vaccination. It was observed that the

susceptible population decrease which also led to an increase in all other infected classes of HBV model due to high transmission coefficient.

The effect of varying transmission rate, β on the susceptible population was presented in Fig. 4.2. It was observed that an increase in the transmission rate, β of HBV infection led to a decline in the number of susceptible population which is as a result of the positive sensitivity indices of the β , that gives rise to an increase in threshold parameter R_0 . Figs. 4.3, 4.4 and 4.5 showed the effect of varying transmission rate β of Hepatitis B model in equation (2) on the Latent, Acute and Chronic population against time (t) respectively. Higher transmission rate, β led to a higher number of infective compare to a lower transmission rate. It was observed that when the transmission rate β of HBV infection becomes very small, the susceptible population increases, the number of latent, acute and chronic individuals decreases and vice-versa. However, it is difficult to control the transmission rate β . This result is supported by the claim of zou[19] that if the transmission coefficient β is sufficiently small then HBV could be eliminated.

The effect of varying vaccination rate, δ_1 on the model can be observed in Fig. 4.6. Increasing δ_1 led to a decrease in susceptible population and this means a higher vaccination coverage from the graph. High vaccination coverage implies a lower number of susceptible prone to being infected since the susceptible individuals would be transferred out of the compartment due to temporary immunity derived from vaccines. However, it is pertinent to note that if vaccination rate δ_1 is large enough, then R_0 might be less than 1 [19]. The effect of varying vaccination rate δ_1 on the model for acute and chronic population against time (t) was presented in Figs. 4.7 and 4.8. It was observed that an increase in vaccination parameter δ_1 reduced the Latent, Acute and the Chronic population since susceptible individuals who are vaccinated developed temporary immunity. [3]. From Fig. 4.9, it was observed that the vaccination rate, δ_1 has little or no effect on the treatment class since individual in this class are still undergoing treatment and cannot be vaccinated.

5 Conclusion

Detailed sensitivity analysis of parameters in the mathematical model for the dynamics of hepatitis B virus (HBV) transmission was analyzed and the basic reproduction number R_0 was obtained. The analysis showed that all the parameters are sensitive to the transmission and prevalence of HBV either positively or negatively. The most sensitive is the transmission rate β . These sensitivity indices allowed us to determine the most influential parameters in controlling disease transmission and prevalence. For optimum diseases control, intervention strategies should target those parameters with high sensitivity indices.

Competing Interests

Authors have declared that no competing interests exist.

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