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An Age Structure Mathematical Model Analysis on the Dynamics of Chronic and Hyper Toxic Forms of Hepatitis B Virus by $SVEA_1A_2CR$ Model with Vaccination Intervention Control Strategy in Ethiopia

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Abstract

In our work we considered nonlinear ordinary differential equations to study the dynamics of hepatitis B virus (HBV) epidemics in Ethiopia. We proved that the invariant and bounded ness of the solution of the dynamical system. We used a nonlinear stability analysis method for proving the local and global stability of the existing equilibrium points. We have got that the diseases free equilibrium point and endemic equilibrium point exist for some conditions. We proved that the disease free equilibrium point is locally asymptotically stable and also globally asymptotically stable. We found that the effective reproduction number for the system is $R_{eff} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\theta+\lambda+H)(\psi+H)}\left[\frac{\theta\beta_1}{(\alpha+H)}+\frac{\lambda\beta_2}{(\delta+H)}+\frac{\theta\pi\alpha\beta_3}{(\alpha+H)(\eta+\gamma+H)}+\frac{\lambda\omega\delta\beta_3}{(\delta+H)(\eta+\gamma+H)}\right]$ which depends on fifteen parameters. On the other hand, the basic reproduction number is $R_0 = \frac{1}{(\theta+\lambda+H)}\left[\frac{\theta\beta_1}{(\alpha+H)}+\frac{\lambda\beta_2}{(\delta+H)}+\frac{\theta\pi\alpha\beta_3}{(\alpha+H)(\eta+\gamma+H)}+\frac{\lambda\omega\delta\beta_3}{(\delta+H)(\eta+\gamma+H)}\right]$. Using standard parameter estimation we found that the numerical value of the effective reproduction number is $R_{eff} = 3.37335245$ and $R_0 = 21.26273123$. From this numerical value we conclude that the disease spreads in the community and vaccination intervention strategy reduces the spread.

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Out of these fifteen parameters we identified five parameters which contribute significant role in control of the disease; and these are the rate of moving from exposed to acutely infected class with age below or equal to 5 years θ, the rate of moving from exposed to acutely infected class with age above 5 years λ, the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class π,the proportions of vaccinated newborns ρ and the ratio of vaccinated newborn to total population H; which influence the effective reproduction number. We also conduct numerical simulations which support the finding in the sensitivity analysis.

Key words: Age structure dynamical system; Hepatitis B virus; Vaccination intervention; Basic reproduction number; Effective reproduction number; Stability Analysis and Numerical simulation.

1. Introduction

The liver is the largest internal organ. It is reddish-brown, weighs approximately 1.5-3 kg and accounts for approximately 2.5% of adult body weight [26]. The surface of the liver is smooth and dome shaped, where it is related to the concavity of the inferior surface of the diaphragm. The liver lies mainly in the right upper quadrant of the abdomen where it is hidden and protected by the thoracic cage and diaphragm. The liver has the unique ability to regenerate its own tissue, as much as three-quarters of the liver can be lost, and the organ can grow back or expand to its original size within several weeks. This allows people who need transplants to receive part of a living or deceased donor's liver.

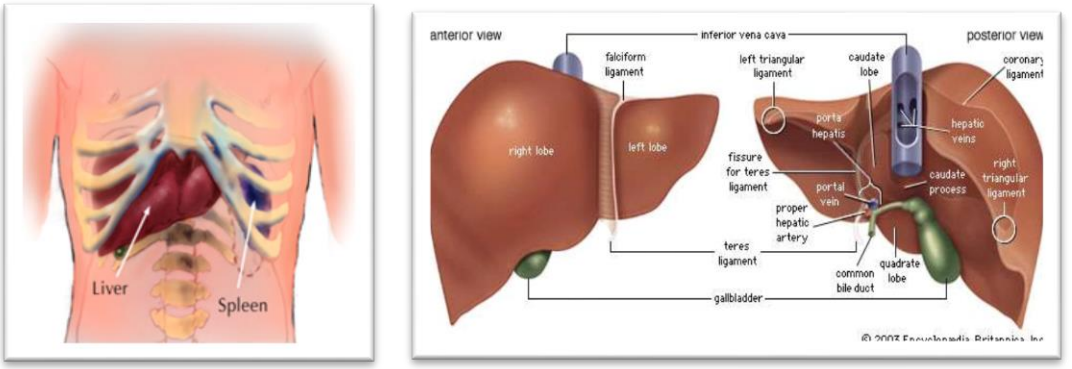

Figure 1: Human Liver (Collected from standard websites which shows Human Liver Stock Photos and Images)

The liver is the largest solid organ, the largest gland and one of the most vital organs that functions as a center for metabolism of nutrients and excretion of waste metabolites [30]. Its primary functions are acting as a gatekeeper between the digestive system and the circulatory system, Processing toxic substances before they enter general circulation, Storing and converting nutrients for future use, Synthesizing most plasma proteins and Secreting bile into small intestine to break down fats [4]. A total loss of liver function could leads to death within minutes, demonstrating the liver‘s great importance [31]. Hepatitis has been known since ancient times. The Greek philosopher Hippocrates characterized its signs; including jaundice (also known as icterus, is a yellowish or greenish pigmentation of the skin and whites of the eyes due to high bilirubin levels). It was recognized as a disease affecting the liver, causing the skin and eye to turn yellow. By the eighth century some cases were found

to be infectious [40]. The WHO has reported that more than 2 billion people worldwide have been infected by HBV. There are over 350 million people who are chronically infected with HBV [41]. 25-40% of these chronic infection carriers will die from liver cirrhosis or primary hepatocellular carcinoma (HCC) [23]. Hepatitis B can cause a short-term illness (acute) or a lifelong (chronic) infection. Chronic infection may go on to cause life-threatening cirrhosis (scaring of the liver), liver failure, or liver cancer. After acute HBV infection, the risk of developing chronic infection varies with age. Infants infected at birth have about a 90% chance of chronic illness, compared to 1-10% for older children and adults.

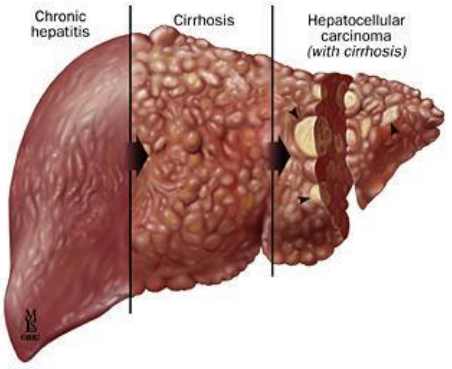

Figure 2: Progress of hepatitis B infection (Collected from standard websites which shows Human Liver Stock Photos and Images).

HBV, which can be transmitted through parenteral, perinatal, or sexual contact, is a serious infectious disease of the liver. Parenteral and sexual transmission predominates in industrialized countries, whereas horizontal and perinatal transmission predominates in developing countries. HBV infection during pregnancy is associated with a high risk of maternal complications, high rate of vertical transmission causing fetal and neonatal hepatitis, and higher maternal mortality [34]. In the presence of an acute maternal HBV infection, up to 90% of newborn infants and 30% of children under the age of 5 years develop chronic HBV infection, compared with only 1–5% of adults with an intact immune system [18]. Although data on the prevalence of HBV in pregnant women in Ethiopia are limited, a study done in Northwest Ethiopia reported intermediate endemicity (5.3%) of HBV among pregnant women. According to the recent studies conducted in different geographical locations in Ethiopia, the prevalence of HBV ranges from 4.7% to 9.5% [16]. Since 1982 a vaccine against HBV infection has been available [1]. Today the group that vaccination focuses on is the one with highest risk of developing chronic infection; children less than 6 years old [46]. According to Trepo and his colleagues [10], 40% of men and 15% of women with HBV infection acquired at birth die of liver cirrhosis or hepatocellular carcinoma. The optimal vaccination strategy is for newborns to receive the first dose within the first 24hr after birth and two boosters during their childhood. In 95% of the cases, the children will be protected from infection for at least 20 years, and they may be immune for life [46]. As a consequence, the number of liver cancer cases has diminished [6]. To reduce the number of HBV infections even more, it is recommended to vaccinate other high risk groups such as patients who require transplantations or dialysis, health-care workers, travelers before visiting an endemic area, people in prisons, or people with multiple sexual partners [46]. Ethiopian national hepatitis study showed that 10.8% of young males from all regions of the country were positive for HBsAg [21]. A community

based sero-epidemiological survey of Addis Ababa, Ethiopia has shown a 7% seroprevalence for HBsAg, higher in males than females [2]. Another study done in Ethiopia has shown an overall HBsAg prevalence of 6.2% and infection occurring early in life and continuing to increase gradually without leveling off [39]. Published information's on the sero-epidemiological of HBV infection among pregnant women are sparse and these reports were mainly from Addis Ababa (5%) and Jimma (3.7%, range 1.4-6.4%) [7,36]. HBsAg carrier pregnant mother transmit infection to neonates usually during birth or soon after birth following close contact. Neonates who contract HBV will have an almost 85-90% risk of developing chronic HBsAg carriage and chronic liver disease [24]. In Ethiopia, an old clinical study showed that liver disease accounted for 12% hospital admissions and 31% hospital mortality [37]. Moreover, in Ethiopia and neighboring Kenya more than 60% of chronic liver disease and up to 80% of hepatocellular carcinoma (HCC) are due to chronic HBV and HCV infections [8, 37]. Cross-sectional community studies of serological markers of HBV infection have an important role in identifying population endemicity, possible routes of transmission and associated risk factors [9, 15, 29, 33,35]. Such data help in the development of appropriate control measures, for example, estimating the optimal age for vaccine delivery, the level of vaccine coverage required for elimination, and possible high-risk target groups [5, 12]. They support predictive mathematical models by which to explore the merits of different control options [12, 43], to assess cost-effectiveness of intervention programs [42], and to predict the risk of evolution of escape mutants [44]. In Ethiopia, HCC is the eighth most common cancer with 100% fatality rate among males [45]. Most of the HCC cases in low income countries like Ethiopia die within few months (<2.5 months) following diagnosis. This might be due to lack of facility for cancer screening, lack of skill to differentially diagnose HCC from other diseases and late arrival of cases in seeking medical care [19, 45]. Mathematical analysis of the HBV dynamics not only provide important quantitative insights into the pathogenesis, but also lead to design treatment strategies which would more effectively bring the infection under control [34]. One of the primary reasons for studying hepatitis B virus (HBV) infection is to improve control and finally to put down the infection from the population. Mathematical models can help us to gain insights into the disease transmission, assess the effectiveness of various preventive strategies, and then control of it eventually. More advanced population models add some structure to the population such as specification of spatial location or age. Age is one of the most important characteristics in the modeling of populations and infectious diseases. Individuals with different ages may have different reproduction and survival capacities. Diseases may have different infection rates and mortality rates for different age groups [25]. The purpose of this paper is to develop a mathematical model to study the transmission dynamics and control of HBV in Ethiopia based on age group, taking accounts the character of the virus infection in the country. After analyzing the existence and stability of the disease-free and disease- endemic equilibria of the model, we shall use the model to simulate the HBV data reported by the Ministry of Health of Ethiopia. By carrying out sensitivity analysis of the basic reproduction number on various parameters, we shall suggest some optimal strategies for control of HBV infection in Ethiopia. One of the primary reasons for studying hepatitis B virus (HBV) infection is to improve control and finally to put down the infection from the population. Mathematical models can help us to gain insights into the disease transmission, assess the effectiveness of various preventive strategies, and then control of it eventually.

2. The Initial model

A treatment model in a constant population where birth rate equal death rate is considered in a mixing

homogeneous population: The total population is categorized into four compartments namely susceptible S (t), infective, I(t), treated class, T(t), and removed class, R (t). Here, there is an influx of newly recruited to the susceptible class at a rate of μ. Infection invades the susceptible class at a rate of β. It is assumed that only a fraction of the population seeks medical attention, and hence represents the treated class. Treatment here is defined as the process of offering the Hepatitis of type B infected person with a life prolonging medicine known as antiretroviral (ARV) drug or treatment (ART). Recruitment into the treated class occurs at a rate of λ. Again, infected individuals are recruited into the removed class at a rate of γ, while treated individuals also move to the removed class at a rate of δ. At the same time, natural death occurs at the different compartments.

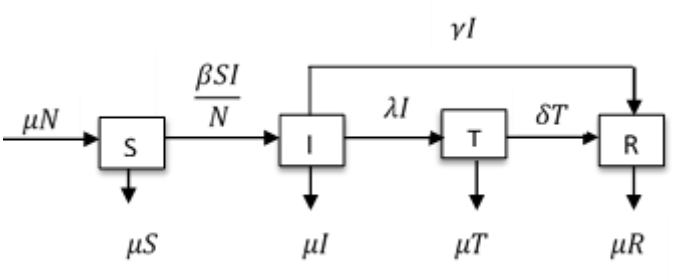

Figure 3: Schematics of the susceptible –Infected-Treated-Removed (SITR) model

The dynamics of the model is:

$$\frac{ds}{dt} = \mu N - \mu S - \frac{\beta SI}{N} \quad (1)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \mu I - \gamma I - \lambda I \quad (2)$$

$$\frac{dT}{dt} = \lambda I - \mu T - \delta T \quad (3)$$

$$\frac{dR}{dt} = \gamma I + \delta T - \mu R \quad (4)$$

3. The extended model

3.1 Basic assumptions of the model

Let $S(t)$ is susceptible individuals, $V(t)$ is Vaccinated class, E(t)is infected but not yet infectious individuals (exposed), $A_1(t)$ is acutely infected class with age below or equal to 5 years, $A_2(t)$ is acutely infected class with age above 5 years, C is chronically infected class and R is the recovered class. The following are basic assumptions of the $SVEA_1A_2CR$ HBV model. The populations under this study are homogenously mixing (every person has the same chance to be coming in contact with an infected person), the disease spreads in a closed environment; that is there is no emigration or immigration, age, sex, social status, and race do not affect the probability of being infected, the population is divided in to seven non-intersecting compartments, the efficacy of the vaccines wanes out at the rate ψ, vaccination against HBV leads to permanent immunity, patients

with either acute or chronic infections are capable of transmitting the disease, and chronically infected individuals are immunized by treatment or transplantation of liver; or died by the diseases.

3.2 Model Descriptions

We use a mathematical model analysis to study the transmission of hepatitis B virus in Ethiopia. The total population is divided into seven non intersecting classes. The following table shows Compartments, Parameters and their description of the extended model:

Table 1: Compartments, Parameters and their description of the model

N0	Compartments	Parameters	Descriptions
1	S(t)		Susceptible individuals
2	V(t)		Vaccinated class
3	E(t)		Exposed group
4	$A_1(t)$		Acutely infected class with age below or equal to 5 years
5	$A_2(t)$		Acutely infected class with age above 5 years
6	C(t)		Chronically infected class
7	R(t)		Immunized group (recovered class)
8	N(t)		Total population
9		ρ	Proportions of vaccinated newborns
10		Φ	Recruitment of the population
11		β_1	Transmission coefficients of acutely infectious individuals A_1
12		β_2	Transmission coefficients of acutely infectious individuals A_2
13		β_3	Transmission coefficients of chronically infectious individuals C
14		ψ	Rate of waning vaccine induced immunity
15		ϵ	The proportion of individuals which loose the efficacy of vaccine.
16		θ	Rate of moving from exposed to acutely infected class with age below or equal to 5 years
17		λ	Rate of moving from exposed to acutely infected class with age above 5 years
18		α	Rate of moving from acutely infected class with age below or equal to 5 years to chronically infected class.
19		π	The proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class.
20		δ	Rate of moving from acutely infected class with age above 5 years to chronically infected class.
21		ω	The proportion of leaving acutely infected class with age above 5 years and progressing to chronically infected class.
22		γ	Recovery rate
23		η	Chronic HBV related mortality rate
24		μ	Natural mortality rate

3.3 The flow chart of the model

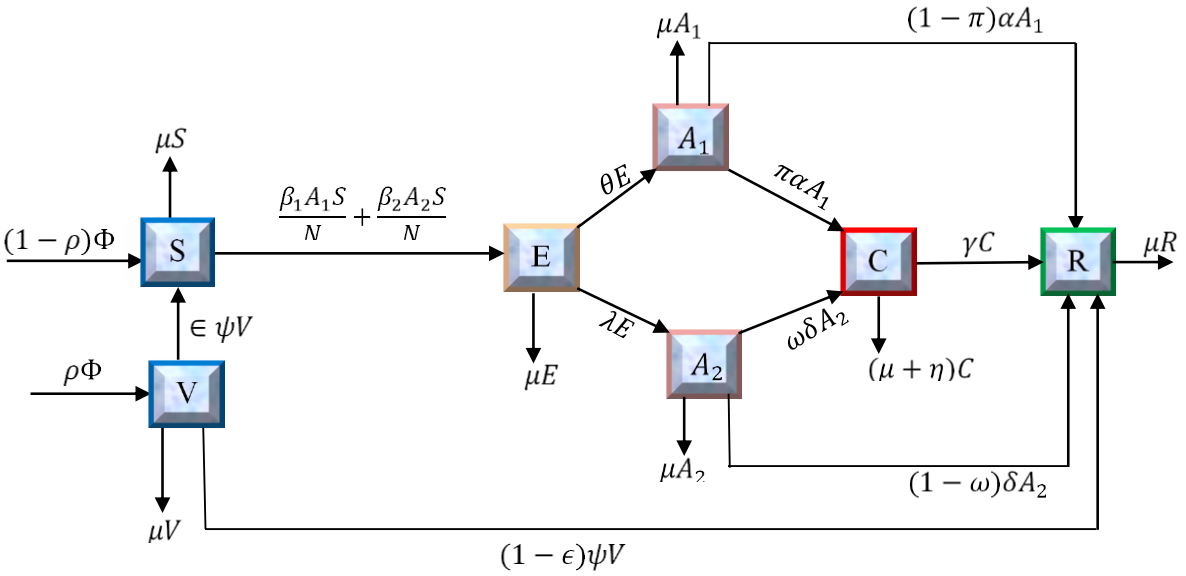

Figure 4: Flowchart of HBV transmission in population

3.4 The dynamics of the model

Let $S = S(t), V = V(t), E = E(t),\ A_1 = A_1(t), A_2 = A_2(t), C = C(t) and\ R = R(t)$. Then

$$\frac{dS}{dt} = (1-\rho)\Phi + \epsilon\psi V - \frac{\beta_1 A_1 S}{N} - \frac{\beta_2 A_2 S}{N} - \frac{\beta_3 CS}{N} - \mu S \quad [1]$$

$$\frac{dV}{dt} = \rho\Phi - (\psi+\mu)V \quad [2]$$

$$\frac{dE}{dt} = \frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N} + \frac{\beta_3 CS}{N} - (\theta+\lambda+\mu)E \quad [3]$$

$$\frac{dA_1}{dt} = \theta E - (\alpha+\mu)A_1 \quad [4]$$

$$\frac{dA_2}{dt} = \lambda E - (\delta+\mu)A_2 \quad [5]$$

$$\frac{dC}{dt} = \pi\alpha A_1 + \omega\delta A_2 - (\eta+\gamma+\mu)C \quad [6]$$

$$\frac{dR}{dt} = (1-\epsilon)\psi V + (1-\pi)\alpha A_1 + (1-\omega)\delta A_2 + \gamma C - \mu R \quad [7]$$

Here, the total population is compartmentalized in to seven none intersecting classes. That is,

$$N(t) = S(t) + V(t) + E(t) + A_1(t) + A_2(t) + C(t) + R(t)$$

3.5 Positivity of Solutions

For the human population of model [1-7] to be epidemiologically meaningful, all solution of the model with positive initial value must remain positive for all time $t > 0$. Therefore, we have to discuss under which the model we are studied has non-negative solutions. The derivative of a function at a point is one property that shows the behavior of that function. It is known that if the derivative at a point is positive, then the function is increasing there; if it is negative, the function is decreasing and if it is zero, the function is constant.

THEOREM 1:

Let the initial data for the model be $S(0) > 0, V(0) > 0, E(0) > 0, A_1(0) > 0, A_2(0) > 0,$

$C(0) > 0 \; and \; R(0) > 0$. Then, the solutions $S(t), V(t), E(t), A_1(t), A_2(t), C(t) \; and \; R(t)$ of the model will be remaining positive for all time $t > 0$.

Proof:

Let $S(0) > 0, V(0) > 0, E(0) > 0, A_1(0) > 0, A_2(0) > 0 \; and \; R(0) > 0$.

Also, we assume that all parameters are positive.

By considering the seven ordinary differential equations and after taking steps on finding their solution, we do have:

i) From equation [1] we have:

$\frac{dS}{dt} = (1-\rho)\Phi + \epsilon\psi V - \frac{\beta_1 A_1 S}{N} - \frac{\beta_2 A_2 S}{N} - \frac{\beta_3 CS}{N} - \mu S$, whose solution is:

$S(t) = \frac{[(1-\rho)\Phi + \epsilon\psi V]}{(\frac{\beta_1 A_1}{N} + \frac{\beta_2 A_2}{N} + \frac{\beta_3 C}{N} + \mu)} + ke^{-\left(\frac{\beta_1 A_1}{N} + \frac{\beta_2 A_2}{N} + \frac{\beta_3 C}{N} + \mu\right)t} > 0.$ Because, $\frac{[(1-\rho)\Phi + \epsilon\psi V]}{(\frac{\beta_1 A_1}{N} + \frac{\beta_2 A_2}{N} + \frac{\beta_3 C}{N} + \mu)} > 0, k > 0$ $and \; e^{-\left(\frac{\beta_1 A_1}{N} + \frac{\beta_2 A_2}{N} + \frac{\beta_3 C}{N} + \mu\right)t} > 0 \; for \; all \; t.$

ii) From equation [2], we have:

$\frac{dV}{dt} = \rho\Phi - (\psi + \mu)V$, whose solution is:

$V(t) = \frac{\rho\Phi}{(\psi+\mu)} + ke^{-(\psi+\mu)t} > 0.$ Because $\frac{\rho\Phi}{(\psi+\mu)} > 0, k > 0 \; and e^{-(\psi+\mu)t} > 0.$

iii) From equation [3], we have;

$\frac{dE}{dt} = \frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N} + \frac{\beta_3 CS}{N} - (\theta + \lambda + \mu)E$, whose solution is:

$E(t) = \frac{\frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N} + \frac{\beta_3 CS}{N}}{(\theta+\lambda+\mu)} + Ke^{-(\theta+\lambda+\mu)t} > 0$. Because $\frac{\frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N} + \frac{\beta_3 CS}{N}}{(\theta+\lambda+\mu)} > 0, k > 0 \; and \;\; e^{-(\theta+\lambda+\mu)t} > 0.$

iv) From equation [4], we have the following:

$\frac{dA_1}{dt} = \theta E - (\alpha + \mu)A_1$, whose solution is; $A_1(t) = \frac{\theta E}{(\alpha+\mu)} + ke^{-(\alpha+\mu)t} > 0$. Since $\frac{\theta E}{(\alpha+\mu)}, k > 0 \; and \; e^{-(\alpha+\mu)t}$.

v) From equation [5], we have ;

$\frac{dA_2}{dt} = \lambda E - (\delta + \mu)A_2$, whose solution is:

$A_2(t) = \frac{\lambda e}{(\delta+\mu)} + ke^{-(\delta+\mu)t} > 0$. Because $\frac{\lambda e}{(\delta+\mu)} > 0, k > 0 \; and \; e^{-(\delta+\mu)t} > 0.$

vi) From equation [6] we have:

$\frac{dC}{dt} = \pi\alpha A_1 + \omega\delta A_2 - (\eta + \gamma + \mu)C$, whose solution is:

$C(t) = \frac{\pi\alpha A_1 + \omega\delta A_2}{(\eta+\gamma+\mu)} + Ke^{-(\eta+\gamma+\mu)t} > 0$. Because $\frac{\pi\alpha A_1 + \omega\delta A_2}{(\eta+\gamma+\mu)} > 0, k > 0 \; and \; e^{-(\eta+\gamma+\mu)t} > 0.$

vii) From equation [7], we have:

$\frac{dR}{dt} = (1-\epsilon)\psi V + (1-\pi)\alpha A_1 + (1-\omega)\delta A_2 + \gamma C - \mu R$, whose solution is:

$R(t) = \frac{[(1-\epsilon)\psi V + (1-\pi)\alpha A_1 + (1-\omega)\delta A_2 + \gamma C]}{\mu} + ke^{-\mu t} > 0.$

Since $\frac{[(1-\epsilon)\psi V + (1-\pi)\alpha A_1 + (1-\omega)\delta A_2 + \gamma C]}{\mu} > 0, k > 0 \; and \; e^{-\mu t} > 0.$

3.6 Invariant Region

THEOREM 2:

The feasible region Ω of the model [1]-[7] is defined as:

$\Omega = \{\big(S(t), V(t), E(t), A_1(t), A_2(t), C(t), R(t)\big) \epsilon \Re_+^7 \cup (0,0,0,0,0,0,0)$:

$0 \le S(t) \le \frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1 + \beta_2 A_2 + \beta_3 C}{N} + \mu\right)}, 0 \le V(t) \le \frac{\Phi}{(\psi+\mu)}, 0 \le E(t) \le \frac{\left[\frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N}\right]}{(\theta+\lambda+\mu)}, 0 \le A_1(t) \le \frac{E}{\alpha+\mu},$

$0 \le A_2(t) \le \frac{E}{\delta+\mu}, 0 \le C(t) \le \frac{\pi\alpha A_1}{(\eta+\gamma+\mu)}, 0 \le R(t) \le \frac{\gamma C}{\mu}\}.$

If $(s(0), v(0), e(0), i_1(0), i_2(0), c(0),\ r(0)) \in \Omega$, then the solution of $\big(s(t), v(t), e(t), i_1(t), i_2(t), c(t), r(t)\big) \in \Omega$, for all time t. That is, as time goes on, the given dynamical system is bounded in the regionΩ.

Proof:-

We assume that all state variables $S(t), V(t), E(t), A_1(t), A_2(t), C(t), R(t)$ and parameters are positive. Also, let $S(0) \geq 0, V(0) \geq 0, E(0) \geq 0, A_1(0) \geq 0, A_2(0) \geq 0, C(0) \geq 0,\ R(0) \geq 0$.

i) From equation [1], we have:

$\frac{dS}{dt} = (1-\rho)\Phi + \epsilon\psi V - \frac{\beta_1 A_1 S}{N} - \frac{\beta_2 A_2 S}{N} - \frac{\beta_3 CS}{N} - \mu S$, and after some simplifications we have:

$S(t) \leq \frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)} + [S(0) - \frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)}]e^{-\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)t}$

Thus, $\lim_{t\to\infty} \sup S(t) \leq \lim_{t\to\infty} \sup\{\frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)} + [S(0) - \frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)}]e^{-\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)t}\}$

$\leq \frac{(1-\rho)\Phi}{\left(\frac{\beta_1 A_1+\beta_2 A_2+\beta_3 C}{N}+\mu\right)}$, and $S(t)$ is bounded.

ii) From equation [2], we have:

$\frac{dV}{dt} = \rho\Phi - (\psi+\mu)V$, and after some simplifications we have; $V(t) \leq \frac{\Phi}{(\psi+\mu)} + [V(0) - \frac{\Phi}{(\psi+\mu)}]e^{-(\psi+\mu)}$

Therefore, $\lim_{t\to\infty} \sup V(t) \leq \lim_{t\to\infty}\{\frac{\Phi}{(\psi+\mu)} + [V(0) - \frac{\Phi}{(\psi+\mu)}]e^{-(\psi+\mu)}\} \leq \frac{\Phi}{(\psi+\mu)}$, and $V(t)$ is bounded.

iii) From equation [3], we have:

$\frac{dE}{dt} = \frac{\beta_1 A_1 S}{N} + \frac{\beta_2 A_2 S}{N} + \frac{\beta_3 CS}{N} - (\theta+\lambda+\mu)E$, and after some simplifications we have:

$E(t) \leq \frac{\left[\frac{\beta_1 A_1 S}{N}+\frac{\beta_2 A_2 S}{N}\right]}{(\theta+\lambda+\mu)} + \left\{E(0) - \frac{[\beta_1 i_1 s+\beta_2 i_2 s+\beta_3 cs]}{(\theta+\lambda+\mu)}\right\} e^{-(\theta+\lambda+\mu)t}$

Hence, $\lim_{t\to\infty} \sup E(t) \leq \lim_{t\to\infty} \sup\{\frac{\left[\frac{\beta_1 A_1 S}{N}+\frac{\beta_2 A_2 S}{N}\right]}{(\theta+\lambda+\mu)} + \left\{E(0) - \frac{[\beta_1 i_1 s+\beta_2 i_2 s+\beta_3 cs]}{(\theta+\lambda+\mu)}\right\} e^{-(\theta+\lambda+\mu)t}\} \leq$

$\frac{\left[\frac{\beta_1 A_1 S}{N}+\frac{\beta_2 A_2 S}{N}\right]}{(\theta+\lambda+\mu)}$, and E is bounded.

iv) From [4] we have:

$\frac{dA_1}{dt} = \theta E - (\alpha+\mu)A_1$, and after some simplifications we have; $A_1(t) \leq \frac{E}{\alpha+\mu} + [A_1(0) - \frac{E}{\alpha+\mu}]e^{-(\alpha+\mu)t}$

Hence, $\lim_{t\to\infty} \sup A_1(t) \leq \lim_{t\to\infty} \sup \{\frac{E}{\alpha+\mu} + [A_1(0) - \frac{E}{\alpha+\mu}]e^{-(\alpha+\mu)t}\} \leq \frac{E}{\alpha+\mu}$ and A_1 is bounded.

v) From [5], we have:

$\frac{dA_2}{dt} = \lambda E - (\delta+\mu)A_2$, and after some simplifications we have; $A_2(t) \leq \frac{E}{(\delta+\mu)} + [A_2(o) - \frac{E}{(\delta+\mu)}]e^{-(\delta+\mu)t}$

Hence, $\lim_{t\to\infty} \sup A_2(t) \leq \lim_{t\to\infty} \sup \{\frac{E}{(\delta+\mu)} + [A_2(o) - \frac{E}{(\delta+\mu)}]e^{-(\delta+\mu)t}\} \leq \frac{E}{\delta+\mu}$ and A_2 is bounded.

vi) From [6], we have:

$\frac{dC}{dt} = \pi\alpha A_1 + \omega\delta A_2 - (\eta+\gamma+\mu)C$, and after some simplifications we have:

$C(t) \leq \frac{\pi\alpha A_1}{(\eta+\gamma+\mu)} + [C(0) - \frac{\pi\alpha A_1}{(\eta+\gamma+\mu)}]e^{-(\eta+\gamma+\mu)t}$

Thus, $\lim_{t\to\infty} \sup C(t) \leq \lim_{t\to\infty} \sup \{\frac{\pi\alpha A_1}{(\eta+\gamma+\mu)} + [C(0) - \frac{\pi\alpha A_1}{(\eta+\gamma+\mu)}]e^{-(\eta+\gamma+\mu)t}\} \leq \frac{\pi\alpha A_1}{(\eta+\gamma+\mu)}$ and C is bounded.

vii) From [7], we have:

$\frac{dR}{dt} = (1-\epsilon)\psi V + (1-\pi)\alpha A_1 + (1-\omega)\delta A_2 + \gamma C - \mu R$, and after some simplifications we have:

$R(t) \leq \frac{\gamma C}{\mu} + [R(0) - \frac{\gamma C}{\mu}]e^{-\mu t}$

Therefore, $\lim_{t\to\infty} \sup R(t) \leq \lim_{t\to\infty} \sup \{\frac{\gamma C}{\mu} + [R(0) - \frac{\gamma C}{\mu}]e^{-\mu t}\} \leq \frac{\gamma C}{\mu}$ and R is bounded.

Thus, all feasible solutions of the model with initial conditions in $\Omega = \{\big(S(t), V(t), E(t), A_1(t), A_2(t), C(t), R(t)\big)\epsilon\Re_+^7 \cup (0,0,0,0,0,0,0)\}$ do remain in Ω for all $t > 0$. That is, the set Ω is positively invariant and attracting. Therefore, the model is mathematically and epidemiologically well posed.

3.7 Scaling of $SVEA_1A_2CR$ model

We consider the equations for the normalized quantities because it is easier to analyze our model in terms of proportions of quantities than of actual populations. This can be done by scaling the population of each class by the total population.

Hence, $N(t) = S(t) + V(t) + E(t) + A_1(t) + A_2(t) + C(t) + R(t)$

$\Longrightarrow 1 = \frac{S}{N} + \frac{V}{N} + \frac{E}{N} + \frac{A_1}{N} + \frac{A_2}{N} + \frac{C}{N} + \frac{R}{N}$. Also, $\frac{dN}{dt} = (\Phi - \mu N - \eta C)$

Let $s = \frac{S}{N}, v = \frac{V}{N}, e = \frac{E}{N}, i_1 = \frac{A_1}{N}, i_2 = \frac{A_2}{N}, c = \frac{C}{N}, r = \frac{R}{N}$ and $\frac{\Phi}{\mathrm{N}} = H.$

Then, the model [1-7] is transformed to:

$$\frac{ds}{dt} = (1-\rho)H + \epsilon\psi v - (\beta_1 i_1 + \beta_2 i_2 + (\beta_3 - \eta)c + H)s \quad [8]$$

$$\frac{dv}{dt} = \rho\mathrm{H} - (\psi + H - \eta c)v \quad [9]$$

$$\frac{de}{dt} = \beta_1 i_1 s + \beta_2 i_2 s + \beta_3 cs - (\theta + \lambda + \mathrm{H} - \eta c)e \quad [10]$$

$$\frac{di_1}{dt} = \theta e - (\alpha + \mathrm{H} - \eta c)i_1 \quad [11]$$

$$\frac{di_2}{dt} = \lambda e - (\delta + \mathrm{H} - \eta c)i_2 \quad [12]$$

$$\frac{dc}{dt} = \pi\alpha i_1 + \omega\delta i_2 - (\eta + \gamma + \mathrm{H} - \eta c)c \quad [13]$$

$$\frac{dr}{dt} = (1-\epsilon)\psi v + (1-\pi)\alpha i_1 + (1-\omega)\delta i_2 + \gamma c - (\mathrm{H} - \eta c)r \quad [14]$$

4. Analysis of the model at equilibrium points

The model [8-14] is analyzed qualitatively to get insights into its dynamical features that give better understanding of the HBV transmission in the population.

4.1 Existence of Disease Free Equilibrium (DFE), E^0

The disease free equilibrium point of the model [8]-[14] is obtained by setting:

$\frac{ds}{dt} = \frac{dv}{dt} = \frac{de}{dt} = \frac{di_1}{dt} = \frac{di_2}{dt} = \frac{dc}{dt} = \frac{dr}{dt} = 0$. That is:

$$\frac{ds}{dt} = (1-\rho)H + \epsilon\psi v - (\beta_1 i_1 + \beta_2 i_2 + (\beta_3 - \eta)c + H)s = 0$$

$$\frac{dv}{dt} = \rho\mathrm{H} - (\psi + H - \eta c)v = 0$$

$$\frac{de}{dt} = \beta_1 i_1 s + \beta_2 i_2 s + \beta_3 cs - (\theta + \lambda + \mathrm{H} - \eta c)e = 0$$

$$\frac{di_1}{dt} = \theta e - (\alpha + \mathrm{H} - \eta c)i_1 = 0$$

$$\frac{di_2}{dt} = \lambda e - (\delta + \mathrm{H} - \eta c)i_2 = 0$$

$\frac{dc}{dt} = \pi\alpha i_1 + \omega\delta i_2 - (\eta + \gamma + \mathrm{H} - \eta c)c = 0$

$\frac{dr}{dt} = (1-\epsilon)\psi v + (1-\pi)\alpha i_1 + (1-\omega)\delta i_2 + \gamma c - (\mathrm{H} - \eta c)r = 0$

During the diseases free, $e = i_1 = i_2 = c = r = 0$; and after some algebraic manipulation,

DFE point of the model is:

$E^0 = (s^0, v^0, e^0, i_1^0, i_2^0, c^0, r^0) = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho\mathrm{H}}{\psi+H}, 0,0,0,0,0)$. In the case of no disease

$e^0 = i_1^0 = i_2^0 = c^0 = r^0 = 0, \epsilon = 1$. The sum of susceptible and vaccinated populations equals to the total population; that is, $s^0 + v^0 = \frac{\psi+H-\rho H}{\psi+H} + \frac{\rho\mathrm{H}}{\psi+H} = 1$.

4.1.1 The Basic reproduction number R_0 and Effective Reproduction Number R_{eff}

The reproduction number (basic reproduction number R_0 or effective reproduction number R_{eff}) is defined as the average number of secondary infections caused by typical infected individual during his/her entire period of infectiousness. This definition is given for the models that represent spread of infection in a population, given an intervention and naturally acquired immunity at that time.

We calculate the effective reproduction number R_{eff} by using the next generation operator method on the system as described by Van den Driessche and Watmough (2002) and obtain:

$$R_{eff} = \frac{\boldsymbol{\theta\beta_1}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\beta_2}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})(\boldsymbol{\delta}+\boldsymbol{H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}$$

On the other hand, the basic reproduction number without intervention is that initially the entire population is susceptible. That is, when there is no vaccination (ψ=$\rho = \epsilon$ =0), then the basic reproduction number R_0 of the model system [8]-[14] is:

$$R_0 = \frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\delta}+\boldsymbol{H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}$$

4.1.2 Local Stability Analysis of the Disease Free Equilibrium (DFE) point

THEOREM 3:

The disease free equilibrium point $E^0 = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho\mathrm{H}}{\psi+H}, 0,0,0,0,0)$ of the model [8]-[14] is locally asymptotically stable if the effective reproduction number $R_{eff} < 1$ and is unstable if $R_{eff} > 1$.

Proof: Let

The Jacobean matrix, $J(E^0)$ of model [8]-[14] with respect to $(s, v, e, i_1, i_2, c, r)$ at the disease free equilibrium point $E^0 = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho H}{\psi+H}, 0,0,0,0,0)$ is:

$$J(E^0) =$$

$$\begin{bmatrix} -H & \epsilon\psi & 0 & \frac{-\beta_1\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & \frac{-\beta_2\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & \frac{-(\beta_3-\eta)\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & 0 \\ 0 & -(\psi+H) & 0 & 0 & 0 & \frac{-\eta\rho H}{\psi+H} & 0 \\ 0 & 0 & -(\theta+\lambda+H) & \frac{\beta_1\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & \frac{\beta_2\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & \frac{\beta_3\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H} & 0 \\ 0 & 0 & \theta & -(\alpha+H) & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & -(\delta+H) & 0 & 0 \\ 0 & 0 & 0 & \pi\alpha & \omega\delta & -(\eta+\gamma+H) & 0 \\ 0 & (1-\epsilon)\psi & 0 & (1-\pi)\alpha & (1-\omega)\delta & \gamma & -H \end{bmatrix}$$

The corresponding characteristic equation for the eigenvalue τ is:

$$\begin{vmatrix} -(H+\tau) & \epsilon\psi & 0 & -p & -q & -x & 0 \\ 0 & -(a+\tau) & 0 & 0 & 0 & -y & 0 \\ 0 & 0 & -(b+\tau) & p & q & z & 0 \\ 0 & 0 & \theta & -(d+\tau) & 0 & 0 & 0 \\ 0 & 0 & \lambda & 0 & -(f+\tau) & 0 & 0 \\ 0 & 0 & 0 & \pi\alpha & \omega\delta & -(g+\tau) & 0 \\ 0 & (1-\epsilon)\psi & 0 & (1-\pi)\alpha & (1-\omega)\delta & \gamma & -(H+\tau) \end{vmatrix} = 0$$

Letting $a = (\psi + H) > 0, b = (\theta + \lambda + H) > 0, d = (\alpha + H) > 0, f = (\delta + H) > 0,$

$$g = (\eta + \gamma + H) > 0, p = \frac{\beta_1\{\psi + H - \rho[(1-\epsilon)\psi + H]\}}{\psi + H} > 0, q = \frac{\beta_2\{\psi + H - \rho[(1-\epsilon)\psi + H]\}}{\psi + H} > 0,$$

$$x = \frac{(\beta_3-\eta)\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H}, y = \frac{\eta\rho H}{\psi+H} > 0, z = \frac{\beta_3\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{\psi+H},$$

$$\Longrightarrow \tau = -H \; or \; \tau = -(\psi + H) \; or \; \tau^4 + c_1\tau^3 + c_2\tau^2 + c_3\tau + c_4 = 0.$$

Here, for the polynomial equation $\tau^4 + c_1\tau^3 + c_2\tau^2 + c_3\tau + c_4 = 0$; all $c_1, c_2, c_3 \; and \; c_4$ are positive. Let $b_1, c_1, d_1 \; and \; g_1$ be the first column of Routh Hurwitz Array . After some steps, we have got that all coefficients $b_1, c_1, d_1, and \; g_1$are positive and hence the dynamical system is locally asymptotically stable at disease free equilibrium point.

4.1.3 Global Stability Analysis of the Disease Free Equilibrium (DFE) point

THEOREM 4:

If the effective reproduction number $R_{eff} < 1$, then the disease free equilibrium point $E^0 = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho H}{\psi+H}, 0,0,0,0,0)$ of the model $[8-14]$ is globally asymptotically stable (G.A.S).

Proof:- Suppose $R_{eff} < 1$, and $E^0 = (s^0, v^0, e^0, i_1^0, i_2^0, c^0, r^0) = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho \mathrm{H}}{\psi+H}, 0,0,0,0,0)$ is the disease free equilibrium point. Let the Lyapunov function $W: R_+^7 \longrightarrow R_+$ is defined by:

$W(s,v,e,i_1,i_2,c,r) = A[s - s^0 - s^0 \ln\left(\frac{s}{s^0}\right)] + B[v - v^0 - v^0 \ln\left(\frac{v}{v^0}\right)] + De + Ei_1 + Fi_2 + Gc$, where

A, B, D, E, F and G are positive constants.

W is continuous function for all $(s,v,e,i_1,i_2,c,r) \in \Re_+^7 \cup (0,0,0,0,0,0,0)$ and has 1st order partial derivatives. W has minimum at $(s,v,e,i_1,i_2,c,r) = (\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho \mathrm{H}}{\psi+H}, 0,0,0,0,0)$, which is $W(\frac{\psi+H-\rho[(1-\epsilon)\psi+H]}{\psi+H}, \frac{\rho \mathrm{H}}{\psi+H}, 0,0,0,0,0) = 0$

Then, $\dot{W} = -\left[A(\varphi+k)\left(1-\frac{s^0}{s}\right)^2 - D\varphi\right]s - [B(\psi+k)\left(1-\frac{v^0}{v}\right)^2 - A\psi\left(1-\frac{s^0}{s}\right)\left(1-\frac{v^0}{v}\right)]v \quad -G(\eta+\gamma+\mathrm{k})c < 0$.

For $(\varphi+k)\left(1-\frac{s^0}{s}\right)^2 > D\varphi$, $B(\psi+k)\left(1-\frac{v^0}{v}\right)^2 > A\psi\left(1-\frac{s^0}{s}\right)\left(1-\frac{v^0}{v}\right)$, $F = \frac{G\delta}{(\delta+k)}, E = \frac{G\alpha}{(\alpha+\mathrm{k})}$ and

$D = \frac{G[\alpha\theta(\delta+k)+\delta\lambda(\alpha+k)]}{(\alpha+k)(\delta+k)(\theta+\lambda+k)}$

.Thus, the disease free equilibrium point of the model is globally asymptotically stable for $R_{eff} < 1$.

4.2 Existence of Endemic Equilibrium Points (EEP), E^*

Let the endemic equilibrium of our normalized model system [8-14] be denoted by E^*. It is obtained by $E^* = (s^*, v^*, e^*, i_1^*, i_2^*, c^*, r^*)$ setting the right hand side of each equation of the normalized model system [8-14] equal to zero and solving for the state variables in terms of the force of infection $\varphi = \beta_1 i_1^* + \beta_2 i_2^* + \beta_3 c^*$. That is:

$$\frac{ds}{dt} = (1-\rho)H + \epsilon\psi v - (\beta_1 i_1 + \beta_2 i_2 + (\beta_3 - \eta)c + H)s = 0 \quad [8]$$

$$\frac{dv}{dt} = \rho \mathrm{H} - (\psi + H - \eta c)v = 0 \quad [9]$$

$$\frac{de}{dt} = \beta_1 i_1 s + \beta_2 i_2 s + \beta_3 cs - (\theta + \lambda + \mathrm{H} - \eta c)e = 0 \quad [10]$$

$$\frac{di_1}{dt} = \theta e - (\alpha + \mathrm{H} - \eta c)i_1 = 0 \quad [11]$$

$$\frac{di_2}{dt} = \lambda e - (\delta + \mathrm{H} - \eta c)i_2 = 0 \quad [12]$$

$$\frac{dc}{dt} = \pi\alpha i_1 + \omega\delta i_2 - (\eta + \gamma + \mathrm{H} - \eta c)c = 0 \quad [13]$$

$$\frac{dr}{dt} = (1-\epsilon)\psi v + (1-\pi)\alpha i_1 + (1-\omega)\delta i_2 + \gamma c - (\mathrm{H} - \eta c)r = 0 \qquad [14]$$

Thus after some calculation we get the endemic equilibrium point is:

$$E^* = (s^*, v^*, e^*, i_1^*, i_2^*, c^*, r^*) =$$

$$\left(\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho\mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*\right)$$

Where,

$$r^* = \frac{(1-\epsilon)\psi\rho\mathrm{H}[(\alpha+\xi)(\theta+\lambda+\xi)(\varphi+\xi)(\delta+\xi)] + (1-\pi)\alpha\varphi H\theta(\delta+\xi)[(1-\rho)(\psi+\xi)+\rho\epsilon\psi] + \gamma c^*[(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)]}{\xi(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)(\delta+\xi)}$$

Now, we can show the existence of endemic equilibrium points using the force of infection

$$\varphi = \beta_1 i_1^* + \beta_2 i_2^* + \beta_3 c^*$$

$$\Longrightarrow \varphi = \frac{\varphi H\theta\beta_1[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)} + \frac{\varphi H\lambda\beta_2[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)} + \beta_3 c^*$$

$$\Longrightarrow \varphi = \frac{\varphi}{(\varphi+\xi)}\left[\frac{H\theta\beta_1[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)} + \frac{H\lambda\beta_2[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)}\right] + \beta_3 c^*$$

$\Longrightarrow \varphi = \frac{\varphi}{(\varphi+\xi)}[A] + \beta_3 c^*$. By letting $A = \frac{H\theta\beta_1[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)} + \frac{H\lambda\beta_2[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)}$

$$\Longrightarrow \varphi^2 - (A + \beta_3 c^* - \xi)\varphi - \beta_3\xi c^* = 0. \qquad [18]$$

This is the quadratic polynomial and has at most two solutions.

Let $\alpha_1 = (A + \beta_3 c^* - \xi)$ and $\alpha_2 = \beta_3\xi c^*$. Then,

$$\varphi^2 - \alpha_1\varphi - \alpha_2 = 0$$

$\Longrightarrow \varphi = \frac{1}{2}[\alpha_1 \pm \sqrt{\alpha_1^2 + 4\alpha_2}]$. Here, we consider the following cases:

CASE-1: If $\alpha_2 = 0$, then $\varphi = 0$ or $\varphi = \alpha_1$. Here, $\varphi = 0$ shows the existence of disease free equilibrium point.

If $\alpha_1 > 0$, then $\varphi = \alpha_1$, shows the existence of unique endemic equilibrium point. This means that, $\alpha_2 = 0$

$$\Leftrightarrow \beta_3\xi c^* = 0$$

$$\Leftrightarrow \beta_3(\mathrm{H} - \eta c^*)c^* = 0$$

$$\Leftrightarrow \mathrm{H} = \eta c^*$$

$\Leftrightarrow \frac{\Phi}{\mathrm{N}} = \eta \frac{C}{N}$

$\Leftrightarrow \Phi = \eta C$. From the model, this implies that the newborn is equal to the product of disease induced death rate and chronically infected population. Epidemiologically this means, unique endemic equilibrium point exists whenever children below or equal to 5 years old have a 95% probability of infected chronically.

CASE-2: If $\alpha_1 > 0, \alpha_2 < 0 \; and \; \alpha_1^2 + 4\alpha_2 > 0,$ then there are two distinct endemic equilibrium points. That is, $\varphi_1 = \frac{\alpha_1 + \sqrt{\alpha_1^2 + 4\alpha_2}}{2} \; and \; \varphi_2 = \frac{\alpha_1 - \sqrt{\alpha_1^2 + 4\alpha_2}}{2}$.

THEOREM 5:

The HBV model [8–14] has a unique endemic equilibrium point if $\alpha_1 = \xi A + \beta_3 c^* - \xi > 0 \; and$

$\alpha_2 = \beta_3 \xi c^* = 0$ or $\alpha_1^2 + 4\alpha_2 = 0$.

4.2.1 Local stability analysis of the endemic equilibrium point

Endemic equilibrium points are steady state solutions where the disease persists in the population (all state variables are positive). We use the Jacobean matrix and Routh-Hurwitz criterion to prove the existence of at least one locally stable endemic equilibrium point for$R_{eff} > 1$. When $R_{eff} > 1$, it is expected that the disease would be able to invade in the population.

THEOREM 6:

The endemic equilibrium point $E^* = (s^*, v^*, e^*, i_1^*, i_2^*, c^*, r^*) =$

$$\left(\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho \mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*\right),$$

Where

$$r^* = \frac{(1-\epsilon)\psi\rho \mathrm{H}[(\alpha+\xi)(\theta+\lambda+\xi)(\varphi+\xi)(\delta+\xi)] + (1-\pi)\alpha\varphi H\theta(\delta+\xi)[(1-\rho)(\psi+\xi)+\rho\epsilon\psi] + \gamma c^*[(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)]}{\xi(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)(\delta+\xi)}$$

of the HBV model [8-14] is locally asymptotically stable (LAS) if $R_{eff} > 1$.

Proof:

The Jacobean matrix, $J(E^*)$ of model [8-14] with respect to $(s^*, v^*, e^*, i_1^*, i_2^*, c^*, r^*)$ at the endemic equilibrium point is:

$$J(E^*) = \begin{bmatrix} -(\varphi+\xi) & \epsilon\psi & 0 & -\beta_1 S^* & -\beta_2 S^* & -(\beta_1-\eta)S^* & 0 \\ 0 & -(\psi+\xi) & 0 & 0 & 0 & \eta V^* & 0 \\ \varphi & 0 & -(\theta+\lambda+\xi) & \beta_1 S^* & \beta_2 S^* & \beta_3 S^* - \eta e^* & 0 \\ 0 & 0 & \theta & -(\alpha+\xi) & 0 & \eta i_1^* & 0 \\ 0 & 0 & \lambda & 0 & -(\delta+\xi) & \eta i_2^* & 0 \\ 0 & 0 & 0 & \pi\alpha & \omega\delta & -((1-c^*)\eta+\gamma+\xi) & 0 \\ 0 & (1-\epsilon)\psi & 0 & (1-\pi)\alpha & (1-\omega)\delta & \gamma+\eta r^* & -\xi \end{bmatrix}$$

Let τ be eigenvalue of $J(E^*)$. Then,

$$\begin{vmatrix} -(\varphi+\xi+\tau) & \epsilon\psi & 0 & -\beta_1 S^* & -\beta_2 S^* & -(\beta_1-\eta)S^* & 0 \\ 0 & -(\psi+\xi+\tau) & 0 & 0 & 0 & \eta V^* & 0 \\ \varphi & 0 & -(\theta+\lambda+\xi+\tau) & \beta_1 S^* & \beta_2 S^* & \beta_3 S^* - \eta e^* & 0 \\ 0 & 0 & \theta & -(\alpha+\xi+\tau) & 0 & \eta i_1^* & 0 \\ 0 & 0 & \lambda & 0 & -(\delta+\xi+\tau) & \eta i_2^* & 0 \\ 0 & 0 & 0 & \pi\alpha & \omega\delta & -((1-c^*)\eta+\gamma+\xi+\tau) & 0 \\ 0 & (1-\epsilon)\psi & 0 & (1-\pi)\alpha & (1-\omega)\delta & \gamma+\eta r^* & -\xi-\tau \end{vmatrix}$$

$= 0$

After some steps we have:

$\tau = -\xi \; or \; \tau^6 + a_1\tau^5 + a_2\tau^4 + a_3\tau^3 + a_4\tau^2 + a_5\tau + a_6 = 0.$

Let $a_1, b_1, c_1, d_1, e_1 \; and \; f_1$ be the first column of Routh-Hurwitz array. After some steps we arrived on all coefficients $a_1, b_1, c_1, d_1, e_1 and \; f_1$of Routh Hurwitz first array are positive, and hence the dynamical system is locally asymptotically stable at the endemic equilibrium point.

4.2.2 Global stability of endemic equilibrium point

We will analyze the global stability of the endemic equilibrium points applying the approach in [32].

$$V = \sum_{i=1}^{8} A_i \left(x_i - x_i^* - x_i^* ln \frac{x_i}{x_i^*} \right) \qquad [20]$$

where A_i is properly selected positive constant, x_i is the population of i^{th}compartment and x_i^* is the equilibrium point. This approach has been found to be useful for more complex compartmental epidemic models.

THEOREM 7

The endemic equilibrium point

$E^* = (\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho \mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*)$ of the dynamical system of HBV model of [8] – [14] is globally asymptotically stable (GAS) if $R_{eff} > 1$.

Proof:- Let the Lyapunov function $W: R_+^7 \longrightarrow R_+$ is defined by:

$W(s,v,e,i_1,i_2,c,r) = A(s - s^* - s^* \ln\left(\frac{S}{S^*}\right)) + B(v - v^* - v^* \ln\left(\frac{v}{v^*}\right)) +$

$D\left(e - e^* - e^* \ln\left(\frac{\mathrm{e}}{e^*}\right)\right) + E\left(i_1 - i_1^* - \ln\left(\frac{i_1}{i_1^*}\right)\right) + F\left(i_2 - i_2^* - \ln\left(\frac{i_2}{i_2^*}\right)\right) +$

$G\left(c - c^* - \ln\left(\frac{c}{c^*}\right)\right) + M\left(r - r^* - \ln\left(\frac{r}{r^*}\right)\right)$. Where, $E^* = (s^*, v^*, e^*, {i_1}^*, {i_2}^*, c^*, r^*)$ is the endemic equilibrium point; and A, B, D, E, F, G, M are positive constants.

The function W is positive definite with respect to the endemic equilibrium point $(s,v,e,i_1,i_2,c,r) = E^*$and W is continuous function for all $(s,v,e,i_1,i_2,c,r) \in \Re_+^7$and has 1st order partial derivatives; W has minimum at $(s,v,e,i_1,i_2,c,r) =$

$(\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho \mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*)$, which is

$W\left(\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho \mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*\right) = 0$

$and\ \frac{\partial \mathrm{W}}{\partial \mathrm{t}} = \frac{\partial \mathrm{W}}{\partial \mathrm{s}}\frac{ds}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{v}}\frac{dv}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{e}}\frac{de}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{i}_1}\frac{di_1}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{i}_2}\frac{di_2}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{c}}\frac{dc}{dt} + \frac{\partial \mathrm{W}}{\partial \mathrm{r}}\frac{dr}{dt}$.

$\Leftrightarrow \frac{\partial \mathrm{W}}{\partial \mathrm{t}} = A\left(1 - \frac{s^*}{s}\right)\frac{ds}{dt} + \mathrm{B}\left(1 - \frac{\mathrm{v}^*}{v}\right)\frac{dv}{dt} + \mathrm{D}\left(1 - \frac{\mathrm{e}^*}{\mathrm{e}}\right)\frac{de}{dt} + \mathrm{E}\left(1 - \frac{\mathrm{i}_1^*}{\mathrm{i}_1}\right)\frac{di_1}{dt} + \mathrm{F}(1 - \frac{\mathrm{i}_2^*}{\mathrm{i}_2})\frac{di_2}{dt} +$

$\mathrm{G}(1 - \frac{\mathrm{c}^*}{\mathrm{c}})\frac{dc}{dt} + \mathrm{M}(1 - \frac{\mathrm{r}^*}{\mathrm{r}})\frac{dr}{dt}$. After some steps, we have:

$\Longrightarrow \dot{W} = -\{\left[A(\varphi + k)\left(1 - \frac{s^*}{s}\right)^2 - D\varphi(1-u)\right]s + \left[B(\psi + k)\left(1 - \frac{\mathrm{v}^*}{v}\right)^2 - [A\epsilon\psi(1-p)(1-q) +$

$\mathrm{M}(1-\epsilon)\psi(1-z)]\right]v + Mk\left(1 - \frac{H}{k}z\right)r\}$.

$\Longrightarrow \dot{W} < 0, for\ A(\varphi + k)\left(1 - \frac{S^*}{s}\right)^2 > D\varphi(1-u),$

$B(\psi + k)\left(1 - \frac{\mathrm{v}^*}{v}\right)^2 > [A\epsilon\psi(1-p)(1-q) + \mathrm{M}(1-\epsilon)\psi(1-z)]\ and\ 1 > \frac{H}{k}z.$

Therefore, The endemic equilibrium point

$E^* = (\frac{H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\psi+\xi)(\varphi+\xi)}, \frac{\rho \mathrm{H}}{(\psi+\xi)}, \frac{\varphi H[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\theta[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\alpha+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, \frac{\varphi H\lambda[(1-\rho)(\psi+\xi)+\rho\epsilon\psi]}{(\delta+\xi)(\theta+\lambda+\xi)(\psi+\xi)(\varphi+\xi)}, c^*, r^*)$ of the

model is globally asymptotically stable for $R_{eff} > 1$.

5. Real parametric estimation, sensitivity analysis and numerical simulations

5.1 Parameter estimation

Estimation theory is a branch of statistics that deals with estimating the values of parameters based on measured empirical data that has a random component. The parameters describe an underlying physical setting in such a way that their value affects the distribution of the measured data. The term parameter estimation refers to the process of using sample data to estimate the parameters of the selected distribution. In this paper, we analyzed a non-linear mathematical $SVEA_1A_2CR$ model of Hepatitis B virus with horizontal, vertical, sexual and blood donation transmission using the secondary data from Ministry of Health of Federal Republic of Ethiopia. Ethiopia is the tenth largest country in Africa, covering 1,104,300 square kilometers and the major constituent of the land marks known as Horn of Africa. The total population of Ethiopia is 107,534,882 [13]. Ethiopia is a federal republic with nine regional states (Amhara, Afar, Benishangul-Gumuz, Gambella, Harari, Oromia, Somali, Tigray and Southern Nations Nationalities and Peoples (SNNPR)) and two administration cities, Addis Ababa and Dire Dawa. The regional states are divided into 85 zones and are further divided in to about eight hundred woredas/districts/ and around 15,000 kebeles (wards) [11].

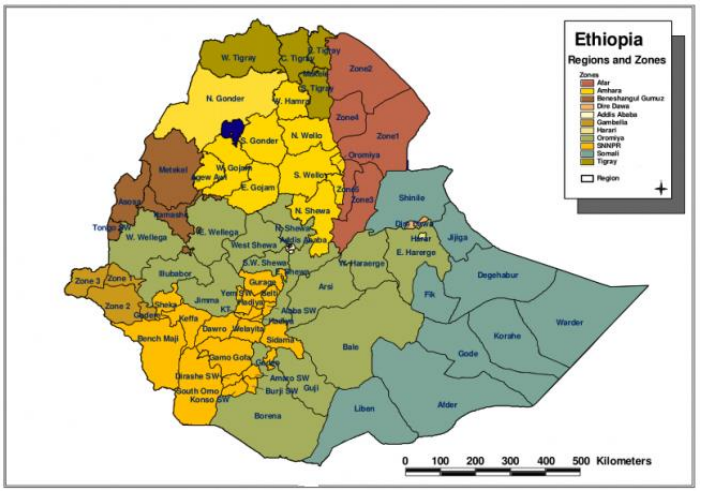

Figure 4: Ethiopia: Regions and Zones- Ethiopia| Relief Web.int

5.1.2 Method of data collection

Data collection is the process of gathering and measuring information on targeted variables in an established system, which then enables one to answer relevant questions and evaluate outcomes. It is useful to distinguish between two broad types of variables: qualitative and quantitative. For our research we are collecting numerical secondary data. The secondary data has an important role in terms of increasing the level of research validity, accuracy and reliability.

5.1.3 Collection of secondary data

The required secondary data collected from demographic of Ethiopia about the population is given in the table

below:

Table 2: population of Ethiopia [13]

Description	Notation	Values
Total number of Female in Ethiopia	F	54,590,362
Total number of Male in Ethiopia	M	54,634,052
Total number of population in Ethiopia	T	109,224,414

In this paper the total population is $N = S + V + E + A_1 + A_2 + C + R$. The fraction of population and parameter values of the HBV model of $SVEA_1A_2CR$ is given in the table below:

Table 3: summery of fraction of population and parameter values

Descriptions	Symbol	Values	Data source
Rate of waning vaccine induced immunity	ψ	0.1	[25]
Transmission coefficients of acutely infectious individuals with age below or equal to 5 years	β_1	0.8729	[14]
Transmission coefficients of acutely infectious individuals with age above 5 years	β_2	0.8511	[14]
Transmission coefficients of chronically infectious individuals	β_3	0.8823	[14]
Rate of moving from exposed to acutely infected class with age below or equal to 5 years	θ	0.0164	[25]
Rate of moving from exposed to acutely infected class with age above 5 years	λ	0.0164	[25]
Rate of moving from acutely infected class with age below or equal to 5 years to chronically infected class.	α	0.08	[25]
Rate of moving from acutely infected class with age above 5 years to chronically infected class.	δ	0.08	[25]
Recovery rate	γ	0.007	[25]
Natural death rate	μ	0.00653	[22]
Mortality rate by chronic infection	η	0.002	[25]
Proportions of vaccinated newborns	ρ	0.883	[17]
The proportion of individuals which loose the efficacy of vaccine.	ϵ	0.05	[25]
The proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class.	π	0.523	[25]
The proportion of leaving acutely infected class with age above 5 years and progressing to chronically infected class.	ω	0.03	[25]
Ratio of vaccinated newborn to total population	H	0.006	[25]

In our research, the data collection instruments will design for a standard record review format containing study variables. Secondary data is collected from already recorded document in the two administrative Cities and the nine regional states Health Bureau. The model on HBV will include the following information: age, number of acutely and chronically infected population, the number of acutely infected population with age less than or equal to 5 year which are recovered, the number of acutely infected population with age greater than 5 year which are recovered, the number of acutely infected population with age below or equal to 5 year which are chronically infected, the number of acutely infected population with age above 5 year which are chronically infected, the number of population recovered from chronic infection, the number of vaccinated population. We

obtained secondary data from the reports of world Health Organization (WHO), Federal Democratic Republic of Ethiopia Ministry of Health and related literatures.

5.2 Sensitivity Analysis

The sensitivity analysis reveals how imperative every parameter is to illness transmission. It is regularly used to decide the robustness of model expectations to parameter values since there are errors in data collection and assumed parameter values [27]. The perturbation of fixed point estimation of model parameters and the uncertainty in the model parameter estimation are the two most commonly used techniques for sensitivity analysis. The sensitivity of a variable with respect to system parameters is usually measured by sensitivity index. Sensitivity indices enable us to quantify the relative change in a variable when a parameter changes. The normalized forward sensitivity index of a variable regarding a parameter is the proportion of the relative change in the variable to the relative change in the parameter. When the variable is a differentiable function of the parameter, the sensitivity index might be on the other hand defined utilizing partial derivatives.

Definition: The normalized forward sensitivity index of R_{eff} that depends differentiably on a

Parameter p is defined by:

$$SI(P) = \frac{\partial R_{eff}}{\partial p} \times \frac{p}{R_{eff}}$$

The parameter with higher magnitude is/are more influential. The sign of the sensitivity indices of R_{eff} with respect to the parameters show the positive or negative impact of the parameter onR_{eff} . That is, if the sign of the sensitivity indices is positive then the value of R_{eff} increase whenever the value of the parameter increases and if the sign of the sensitivity indices is negative then the value of R_{eff} decrease whenever the value of the parameter increase [28].

The effective reproduction number of the model is:

$$R_{eff} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta}+\boldsymbol{H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right]$$

$$SI(\theta) = \frac{\partial R_{eff}}{\partial \theta} \times \frac{\theta}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi}+\boldsymbol{H})(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})^2}\left[\frac{\boldsymbol{\beta_1}}{(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\pi\alpha\beta_3}}{(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right] \times \frac{\theta}{R_{eff}}$$

$$SI(\beta_1) = \frac{\partial R_{eff}}{\partial \beta_1} \times \frac{\beta_1}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\theta}{(\alpha+H)}\right] \times \frac{\beta_1}{R_{eff}}$$

$$SI(\beta_2) = \frac{\partial R_{eff}}{\partial \beta_2} \times \frac{\beta_2}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\lambda}{(\delta+H)}\right] \times \frac{\beta_2}{R_{eff}}$$

$$SI(\beta_3) = \frac{\partial R_{eff}}{\partial \beta_3} \times \frac{\beta_3}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\theta\pi\alpha}{(\delta+H)(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\lambda\omega\delta}{(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right] \times \frac{\beta_3}{R_{eff}}$$

$$SI(\lambda) = \frac{\partial R_{eff}}{\partial \lambda} \times \frac{\lambda}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi+H})(\boldsymbol{\theta+\lambda+H})^2}\left[\frac{\boldsymbol{\beta_2}}{(\boldsymbol{\delta+H})} + \frac{\boldsymbol{\omega\delta\beta_3}}{(\boldsymbol{\delta+H})(\boldsymbol{\eta+\gamma+H})}\right] \times \frac{\lambda}{R_{eff}}$$

$$SI(\pi) = \frac{\partial R_{eff}}{\partial \pi} \times \frac{\pi}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi+H})(\theta+\lambda+H)}\left[\frac{\boldsymbol{\theta\alpha\beta_3}}{(\boldsymbol{\alpha+H})(\boldsymbol{\eta+\gamma+H})}\right] \times \frac{\pi}{R_{eff}}$$

$$SI(\omega) = \frac{\partial R_{eff}}{\partial \omega} \times \frac{\omega}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi+H})(\theta+\lambda+H)}\left[\frac{\boldsymbol{\lambda\delta\beta_3}}{(\boldsymbol{\delta+H})(\boldsymbol{\eta+\gamma+H})}\right] \times \frac{\omega}{R_{eff}}$$

$$SI(\alpha) = \frac{\partial R_{eff}}{\partial \alpha} \times \frac{\alpha}{R_{eff}} = -\frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi+H})(\theta+\lambda+H)}\left[\frac{\theta\beta_1}{(\alpha+H)^2} - \frac{\theta\pi\beta_3}{(\boldsymbol{\eta+\gamma+H})(\alpha+H)^2}\right] \times \frac{\alpha}{R_{eff}}$$

$$SI(\delta) = \frac{\partial R_{eff}}{\partial \delta} \times \frac{\delta}{R_{eff}} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\psi+H})(\theta+\lambda+H)}\left[\frac{-\lambda\beta_2}{(\delta+H)^2} + \frac{\lambda\omega H\beta_3}{(\boldsymbol{\eta+\gamma+H})(\delta+H)^2}\right] \times \frac{\delta}{R_{eff}}$$

$$SI(\psi) = \frac{\partial R_{eff}}{\partial \psi} \times \frac{\psi}{R_{eff}} = \frac{[1-\rho(1-\epsilon)](\psi+H)-\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\psi+H)} \frac{1}{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}} \times \psi$$

$$SI(\rho) = \frac{\partial R_{eff}}{\partial \rho} \times \frac{\rho}{R_{eff}} = \frac{-[(1-\epsilon)\psi+H]}{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}} \times \rho$$

$$SI(\gamma) = \frac{\partial R_{eff}}{\partial \gamma} \times \frac{\gamma}{R_{eff}} = -\left[\frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha+H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta+H})}\right] \frac{1}{(\boldsymbol{\eta+\gamma+H})^2}\left[\frac{1}{\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha+H})}+\frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta+H})}+\frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha+H})(\boldsymbol{\eta+\gamma+H})}+\frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta+H})(\boldsymbol{\eta+\gamma+H})}}\right] \times \gamma$$

$$SI(\epsilon) = \frac{\partial R_{eff}}{\partial \epsilon} \times \frac{\epsilon}{R_{eff}} = \frac{\rho\psi}{\{\psi + H - \rho[(1-\epsilon)\psi + H]\}} \times \epsilon$$

$$SI(\eta) = \frac{\partial R_{eff}}{\partial \eta} \times \frac{\eta}{R_{eff}} = -\left[\frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha+H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta+H})}\right] \frac{1}{(\boldsymbol{\eta+\gamma+H})^2}\left[\frac{1}{\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha+H})}+\frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta+H})}+\frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha+H})(\boldsymbol{\eta+\gamma+H})}+\frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta+H})(\boldsymbol{\eta+\gamma+H})}}\right] \times \eta$$

$$SI(H) = \frac{\partial R_{eff}}{\partial H} \times \frac{H}{R_{eff}}$$

The resulting sensitivity indices of R_{eff} to the fifteen different parameters in the model are shown in the following table in the order from most sensitive to least.

From the sensitivity index of the model we consider that the most sensitive parameter is ρ, which is proportions of vaccinated newborns. The least sensitive parameter is β_3, which the transmission coefficients of chronically infectious individuals.

Table 4: The sensitivity index of the parameters

Order	Parameter	Sensitivity index
1	ρ	-5.30314562
2	λ	0.89737403
3	π	0.57104767
4	H	-0.48105592
5	θ	0.35091160
6	γ	-0.28177508
7	ϵ	0.26253196
8	β_1	0.20254436
9	β_2	0.19748597
10	α	-0.18436455
11	δ	-0.18367360
12	η	-0.08050716
13	ω	0.03275608
14	ψ	0.01486029
15	β_3	0.00905705

5.3 Numerical simulation

The underlying purpose of simulation is to shed light on the underlying mechanisms that control the behavior of a system. More practically, simulation can be used to predict (forecast) the future behavior of a system, and determine what you can do to influence that future behavior. It also uses to study the behavior of a system without building it.

5.3.1 Evaluation of effective reproduction number and basic reproduction number

In our HBV model of $\mathrm{SVEA_1A_2CR}$,

$$R_{eff} = \frac{\boldsymbol{\theta\beta_1}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta+\lambda+\mathrm{H}})(\boldsymbol{\psi+H})(\boldsymbol{\alpha+H})} + \frac{\boldsymbol{\lambda\beta_2}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta+\lambda+\mathrm{H}})(\boldsymbol{\psi+H})(\boldsymbol{\delta+H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta+\lambda+\mathrm{H}})(\boldsymbol{\psi+H})(\boldsymbol{\alpha+H})(\boldsymbol{\eta+\gamma+H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta+\lambda+\mathrm{H}})(\boldsymbol{\psi+H})(\boldsymbol{\delta+H})(\boldsymbol{\eta+\gamma+H})}$$

and $R_0 = \frac{\theta\beta_1}{(\theta+\lambda+\mathrm{H})(\alpha+H)} + \frac{\lambda\beta_2}{(\theta+\lambda+\mathrm{H})(\delta+H)} + \frac{\theta\pi\alpha\beta_3}{(\theta+\lambda+\mathrm{H})(\alpha+H)(\eta+\gamma+H)} + \frac{\lambda\omega\delta\beta_3}{(\theta+\lambda+\mathrm{H})(\delta+H)(\eta+\gamma+H)}$.

After substitution of the above numerical values of the parameters we have: $R_{eff} = 3.37335245$ and $R_0 = 21.26273123$. From this data analysis, we consider that the basic reproduction number is $R_0 = 21.26273123$ which means one infectious individual infects 21 healthy individual in his/her infectious time. But the effective reproduction number is $R_{eff} = 3.37335245$ which means because of intervention by vaccination of HBV; one infectious individual can infect 3 healthy individuals in his/her infectious time. Since $R_{eff} = 3.37335245 > 0$, it indicates that HBV disease persists in a community. So, vaccination of HBV is effective to control the disease.

5.3.2 Effective reproduction numbers verses numerical parameter values

In this model, we have got the effective reproduction number

$R_{eff} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\theta+\lambda+\mathrm{H})(\psi+H)}[\frac{\theta\beta_1}{(\alpha+H)} + \frac{\lambda\beta_2}{(\delta+H)} + \frac{\theta\pi\alpha\beta_3}{(\alpha+H)(\eta+\gamma+H)} + \frac{\lambda\omega\delta\beta_3}{(\delta+H)(\eta+\gamma+H)}]$ of nonlinear HBV model which depends on fifteen parameters. In the analysis, we get only five parameters which influence the effective reproduction number. These are θ, which is the rate of moving from exposed to acutely infected class with age below or equal to 5 years; λ, which is the rate of moving from exposed to acutely infected class with age above 5 years; π, which is the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class; ρ, which is the proportions of vaccinated newborns and H, which is the ratio of vaccinated newborn to total population. The effect of these parameters on the effective reproduction number is graphically represented as follows using Win plot software, where the parameter values are taken from the table 4. Other parameters do not influence the effective reproduction number

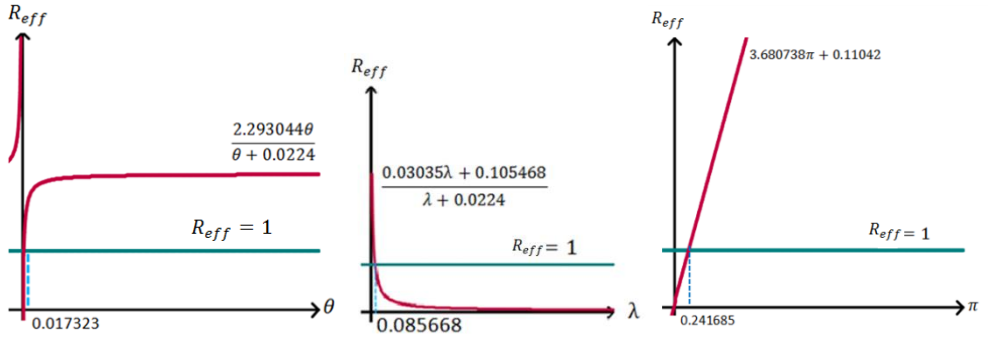

Fig. 5A Fig. 5B Fig.5C

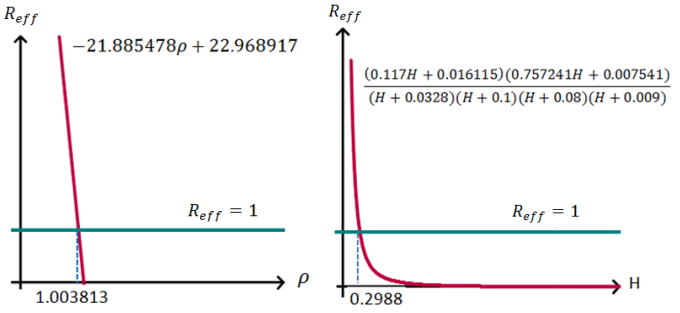

Fig.5D Fig.5E

Figure 5: Graphs of effective reproduction number verses the five parameters which influence the effective reproduction number

From the graph of Fig.5A, we see that there is intersection point $(0.017323, 1)$ between effective reproduction number R_{eff} and the rate of moving from exposed to acutely infected class with age below or equal to 5 years; θ, in the first quadrant. Here we observe that, when $R_{eff} < 1$, then $\theta < 0.017323$; this means that the spread of

HBV disease decreases when θ is less than 0.017323. If $R_{eff} > 1$, then $\theta > 0.017323$; this means the disease of HBV spreads in the community when θ is greater than 0.017323. Thus the parameter θ is our control parameter. From Fig.5B, we see that there is intersection point $(0.05668, 1)$ between effective reproduction number R_{eff} and the rate of moving from exposed to acutely infected class with age above 5 years; λ, in the first quadrant. Here we observe that, when $R_{eff} < 1$, then

$\lambda > 0.05668$; this means that the spread of HBV disease decreases when λ is greater than 0.05668. If $R_{eff} > 1$, then $\lambda < 0.05668$; this means the disease of HBV spreads in the community when λ is less than 0.05668. Thus the parameter λ is our control parameter. From the graph of Fig.5C, we see that there is intersection point $(0.241685, 1)$ between effective reproduction number R_{eff} and the rate of the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class; π, in the first quadrant. Here we observe that, when $R_{eff} < 1$, then $\pi < 0.241685$; this means that the spread of HBV disease decreases when π is less than 0.241685. If $R_{eff} > 1$, then

$\pi > 0.241685$; this means the disease of HBV spreads in the community when π is greater than 0.241685. Thus the parameter π is our control parameter. From Fig.5D, we see that there is intersection point $(1.003813, 1)$ between effective reproduction number R_{eff} and the proportions of vaccinated newborns; ρ, in the first quadrant. Here we observe that, when $R_{eff} < 1$, then $\rho > 1.003813$; this means that the spread of HBV disease decreases when ρ is greater than 1.003813. If $R_{eff} > 1$, then $\lambda < 1.003813$; this means the disease of HBV spreads in the community when ρ is less than 1.003813. Thus the parameter ρ is our control parameter. From Fig.5E, we see that there is intersection point $(0.2988, 1)$ between effective reproduction number R_{eff} and the ratio of vaccinated newborn to total population; H, in the first quadrant. Here we observe that, when $R_{eff} < 1$, then $H > 0.2988$; this means that the spread of HBV disease decreases when H is greater than 0.2988. If $R_{eff} > 1$, then $H < 0.2988$; this means the disease of HBV spreads in the community when H is less than 0.2988. Thus the parameter H is our control parameter.

6. Results and Discussions

The disease burden caused by HBV and other forms of hepatitis is undocumented in Ethiopia, although acute viral hepatitis, chronic hepatitis, cirrhosis of the liver and HCC accounted for significant hospital admissions and mortality rate [38]. In late 1990s, the most common tumor in medical units in Ethiopia was associated with a 50% carrier rate of HBsAg [8, 38]. In line to this, the overall HBsAg prevalence in the symptomatic liver disease patients estimated 20% and 21.2% from the Meta analysis and systematic review analysis, respectively. In Ethiopia, reports on HBsAg prevalence were also common from groups such as pregnant women, diabetic patients, street dwellers, HIV VCT clients and commercial sex workers. The HBsAg prevalence was hyper endemic among healthcare professionals [22] and medical waste handlers [17] in particular might be associated with occupational risk exposures since they deal with all sorts of the infected samples with no HBV vaccination, which is the simplest protection and standard practice elsewhere. A recent study showed that although knowledge about availability of HBV vaccine was 62% among healthcare workers, fully vaccinated professionals were only 5.4% [3]. We considered non-linear system of ordinary differential equation to study the

dynamics of HBV disease in Ethiopia. In this study we adopted and extended the appropriate mathematical model on the dynamics of HBV and we found that an important aspect of mathematical epidemiology which is known to be effective reproduction number R_{eff} which determines how HBV spreads in the country; and control it. To decide if the spread of HBV in Ethiopia is high or low, we used the standard measurement which is known as the effective reproduction number R_{eff}. In our modified model we have derived the effective reproduction number

$R_{eff} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha}+\boldsymbol{H})}+\frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta}+\boldsymbol{H})}+\frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}+\frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right]$ which depends on fifteen parameters. We also found that the numerical value of the effective reproduction number based on some collected data from Ministry of health of Ethiopia and standard data taken from different journals is $R_{eff} = 3.37335245 > 1$. This in principle implies that the disease spreads in the community and one infectious individual infects about three healthy individuals in his/her infectious time. We observe from the numerical simulation figures that we have five control parameters namely, the rate of moving from exposed to acutely infected class with age below or equal to 5 years θ, the rate of moving from exposed to acutely infected class with age above 5 years λ, the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class π,the proportions of vaccinated newborns ρ and the ratio of vaccinated newborn to total population H which influence the effective reproduction number. We discuss about these control parameters in detail as follows. The graph in figure 6 tell us that how effective reproduction number R_{eff} is affected by the rate θ of moving from exposed to acutely infected class with age below or equal to 5 years. From the graphical representation we have got that $\theta = 0.017323$ is our control parameter. If $\theta > 0.017323$, then the effective reproduction number is greater than one and HBV disease spreads in the community. If $\theta < 0.017323$ then the effective reproduction number is less than one and it is possible to reduce the spread of HBV in the community. The graph in figure 10 tells us that how effective reproduction number R_{eff} is affected by the rate λ of moving from exposed to acutely infected class with age above 5 years. From the graphical representation we have got that $\lambda = 0.05668$ is our control parameter. If $\lambda < 0.05668$ then the effective reproduction number is greater than one and HBV disease spreads in the community. If $\lambda > 0.05668$ then the effective reproduction number is less than one and the disease decrease its spread in the community. The graph in figure 11 shows that how effective reproduction number R_{eff} is affected by the rate π of the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class. From the graphical representation we have seen that $\pi = 0.241685$ is our control parameter. If $\pi < 0.241685$ then the effective reproduction number is less than one and the spreads of HBV in the community decreases. If $\pi > 0.241685$ then the effective reproduction number is greater than one and the HBV disease spreads in the community. The graph in figure 16 tells us that how effective reproduction number R_{eff} is strongly affected by the proportions of vaccinated newborns ρ. From the graphical representation we have got that $\rho = 1.003813$ is our control parameter. If $\rho < 1.003813$ then the effective reproduction number is greater than one and the HBV disease spreads in the community. If $\rho > 1.003813$ then the effective reproduction number is less than one and the disease dies out. Here, the parameter ρ is the most sensitive parameter which tell us that, increasing the number of vaccinated population decreases the spread of HBV and helps to control the transmission. From Figure 20, we have seen that how effective reproduction number R_{eff} is affected by the ratio

of vaccinated newborn to total population H. From the graphical representation we have got $H = 0.2988$ is our control parameter. If $H < 0.2988$ then the effective reproduction number is greater than one and the HBV disease spreads in the community. If $H > 0.2988$ then the effective reproduction number is less than one and the disease decreases its spread in the community.

7. Conclusions

From the dynamical system of the HBV model, we obtain the effective reproduction number

$R_{eff} = \frac{\{\psi+H-\rho[(1-\epsilon)\psi+H]\}}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})(\boldsymbol{\psi}+\boldsymbol{H})}\left[\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta}+\boldsymbol{H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right]$. The basic reproduction number, where there is no intervention, is $R_0 = \frac{1}{(\boldsymbol{\theta}+\boldsymbol{\lambda}+\mathbf{H})}\left[\frac{\boldsymbol{\theta\beta_1}}{(\boldsymbol{\alpha}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\beta_2}}{(\boldsymbol{\delta}+\boldsymbol{H})} + \frac{\boldsymbol{\theta\pi\alpha\beta_3}}{(\boldsymbol{\alpha}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})} + \frac{\boldsymbol{\lambda\omega\delta\beta_3}}{(\boldsymbol{\delta}+\boldsymbol{H})(\boldsymbol{\eta}+\boldsymbol{\gamma}+\boldsymbol{H})}\right.$.

Based on the data collected from ministry of health of Ethiopia and standard data taken from different journals, the numerical value of reproduction number is $R_0 = 21.26273123$ which is greater than one. This tells us that; one infectious person can infect about 21 healthy individuals in his/her infectious time. Our new model shows that, the effective reproduction number $R_{eff} = 3.37335245 > 1$. This tells us that; one infectious person can infect about 3 healthy individuals in his/her infectious time. This reduction of infection is because of the vaccination intervention. However, still effective reproduction number is greater than one and the disease persists in the community. Hence further intervention must be investigated. We have observed that the disease free equilibrium point is locally asymptotically stable and globally asymptotically stable. Also the endemic equilibrium point is locally asymptotically stable and globally asymptotically stable. From the sensitivity index of the model we consider the most sensitive parameter is ρ, which is the proportions of vaccinated newborns. That is, increasing the proportion of vaccinated newborns can reduce the spread of HBV disease in the community. The list sensitive parameter is β_3; which is the transmission coefficient of chronically infectious individuals is. Therefore attention must be given to the proportions of vaccinated newborns to control the HBV disease.

8. Recommendations

In this study we observe that the effective reproduction number $R_{eff} = 3.37335245$ is greater than one and this implies that the disease spreads in the community. Therefore, we want to draw the following recommendations to make the effective reproduction number less than one:

The rate of moving from exposed to acutely infected class with age below or equal to 5 years θ should be less than 0.017323,the rate of moving from exposed to acutely infected class with age above 5 years λ should be greater than 0.05668, the rate of the proportion of leaving acutely infected class with age below or equal to 5 years and progressing to chronically infected class π should be less than 0.241685, the proportions of vaccinated newborns ρ should be greater than 1.003813 and the ratio of vaccinated newborn to total population H must be greater than 0.2988 .

References

[1]. A Bertoletti, L Rivino. Hepatitis B: future curative strategies. Curr Opin Infect Dis, 27(6):528{534, 2014.

[2]. Abebe A, Nokes DJ, Dejene A, et al. Seroepidemiology of hepatitis B virus in Addis Ababa, Ethiopia: transmission patterns and vaccine control. Epidemiol Infect, 2003; 131 (1):757-70.

[3]. Abeje G, Azage M. Hepatitis B vaccine knowledge and vaccination status among health care workers of Bahir Dar City Administration, Northwest Ethiopia: a cross sectional study. BMC Infect Dis. 2015;15:30.

[4]. Allen SE.The liver: Anatomy, Physiology, Disease and Treatment. 2002 North Eastern University Press, USA.

[5]. Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford: Oxford University Press, 1991.

[6]. AS Lok, BJ McMahon. Chronic hepatitis B: Update of recommendations. Hepatology, 39(3):857{861, 2004.

[7]. Awole M, Gebre-Selassie S. Seroprevalence of HBsAg and its risk factors among pregnant women in Jimma, Southwest Ethiopia. Ethiop J Health Dev, 2005; 19 (1): 45-50.

[8]. Bane A, Patil A, Khatib M. Healthcare cost and access to care for viral hepatitis in Ethiopia. IJIAS. 2014;9(4):1718–23.

[9]. Barin F, Perrin J, Chotard J, et al. Cross-sectional and ongitudinal epidemiology of hepatitis B in Senegal. Progress Med Virol 1981; 27: 148–162.

[10]. C Trepo, HLY Chan, A Lok. Hepatitis b virus infection. Lancet, 384(9959):2053{2063, 2014.[37

[11]. Country fact sheet Ethiopia, June 2014.

[12]. Edmunds WJ, Medley GF, Nokes DJ. The transmission dynamics and control of hepatitis B virus in The Gambia. Stat Med 1996; 15: 2215–2233.

[13]. Ethiopia population 2018 Demographic, maps, graphs.

[14]. Federal ministry of health of Ethiopia (FMOH) 2018.

[15]. Feret E, Larouze B, Diop B, Sow M, London WT, Blumberg BS. Epidemiology of hepatitis B virus infection in the rural community of Tip, Senegal. Am J Epidemiol 1987; 125: 140–149

[16]. Franciscus A. An overview of extra hepatic manifestations of hepatitis C. HCSP Fact Sheet. 2015 Jul;7:1-6.

[17]. Geberemicheal A, Gelaw G, Moges F, Dagnew M. Seroprevalence of hepatitis B virus infections among health care workers at the Bulle Hora Woreda Governmental Health Institutions, Southern Oromia, Ethiopia. J Environ Occup Sci. 2013;2(1):9–14.

[18]. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. The Lancet infectious diseases. 2007 Jun 1;7(6):402-9.

[19]. Jaka H, Mshana SE, Rambau PF, Masalu N, Chalya PL, Kalluvya SE. Hepatocellular carcinoma : clinicopathological profile and challenges of management in a resource-limited setting. 2014;12(1):1–9.

[20]. Kassa D, Gebremichael G, Tilahun T, Ayalkebet A, Abrha Y, Mesfin G, Belay Y, Demissie M, Gebrexiabher A, Assefa Y. Prevalence of sexually transmitted infections (HIV, hepatitis B virus, herpes simplex virus type 2, and syphilis) in pregnant women in Ethiopia: Trends over 10 years (2005–2014).

International Journal of Infectious Diseases. 2019 Feb 1;79:50-7.

[21]. Kefene H, Rapicetta M, Rossi GB, et al. Ethiopian national hepatitis B study. J Med Virol, 1988; 24(1): 75-84.

[22]. Kefenie H, Desta B, Abebe A, et al. Prevalence of hepatitis B infection among hospital personnel in Addis Ababa (Ethiopia). Eur J Epidemiol. 1989; 5(4):462–7. Lan Zou, Weinian Zhang , ShiguiRuan.

[23]. M.A. Nowak, R.M. May, Virus dynamics, Oxford University Press, Oxford, 2000.

[24]. McMahon BJ, Alberts SR, Wainwright RB, et al. Hepatitis B related sequalae: prospective study 1400 hepatitis B surface antigen positive Alaska native carriers. Arch Int Med 1990; 150 (5):1051–4.

[25]. Modeling the transmission dynamics and control of hepatitis B virus in China. Lan Zou, Weinian Zhang , ShiguiRuan

[26]. Moore KL, Dalley AF. Clinically Oriented Anatomy. 2006 5th Edition Lippincott Williams and Wilkins. 1209 pp.

[27]. N. Chitnis, J. M. Hyman, and J. M. Cushing, "Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model," Bulletin of Mathematical Biology, vol. 70, no. 5, pp. 1272–1296, 2008.

[28]. N. Nyerere, Modeling the Effect of Screening and Treatment on the Transmission of Tuberculosis Infections, Mathematical Theory and Modeling, 2014, Vol.4, No.7

[29]. Okoth FA, Kobayashi M, Kaptich DC, et al. Seroepidemiological study for HBV markers and anti-delta in Kenya. East Afr Med J 1991; 68: 515–523.

[30]. Ozougwu JC**,** Eyo JE. Hepatoprotective effects of Allium cepa extracts on paracetamol-induced liver damage in rat. African Journal of Biotechnology 2014, 13(26): 2679 -2688.

[31]. Ozougwu JC. Comparative hepatoprotective and antioxidant effects of Allium cepa, Allium sativum and Zingiber officinale methanolic extracts against paracetamol-induced liver damage in Rattus novergicus. 2014 Ph.D Research Thesis, Department Of Zoology and Environmental Biology, University of Nigeria, Nsukka. 222pp

[32]. S. Henshaw, C. C. Mccluskey, Global stability of a vaccination model with immigration, Electronic Journal of Differential Equations, 2015.

[33]. Tabor E, Bayley AC, Cairns J, Pelleu L, Gerety RJ. Horizontal transmission of hepatitis B virus among children and adults in five rural villages in Zambia. J Med Virol 1985; 15: 113–120.

[34]. Tanenbaum SJ. Pay for performance in Medicare: evidentiary irony and the politics of value. Journal of Health Politics, Policy and Law. 2009 Oct 1;34(5):717-46.

[35]. Tsega E, Mengesha B, Hansson BG, Lindberg J, Nordenfelt E. Hepatitis A, B, and delta infection in Ethiopia: a serological survey with demographic data. Am J Epidemiol 1986; 123: 344–350.

[36]. Tsega E, Tsega M, Mengesha B, et al. Transmission of hepatitis B virus infection in Ethiopia with emphasis on the importance of vertical transmission. Int J Epidemiol, 1988; 17 (4): 874-9.

[37]. Tsega E. Current views on liver diseases in Ethiopia. Ethiop Med J. 1977;15(2):75–82.

[38]. Tsega E. Hepatocellular carcinoma in Ethiopia. A prospective clinical study of 100 patients. East Afr Med J. 1977;54(5):281–92.

[39]. Tsega E. Viral hepatitis and chronic liver disease in Ethiopia, epidemiological and clinical aspects. 1991, PhD Thesis, University of Lund, Malmo, Sweden: 13-598.

[40]. W. KERMACK AND A. MCKENDRICK, A contribution to mathematical theory of epidemics, Proc. Roy. Soc. Lond. A, 115 (1927), pp. 700–721.

[41]. WHO, 2008. Fact sheet N204 Hepatitis B, available at http://www.who.int /media center/factsheets/fs204/en/index.html.

[42]. Williams JR, Nokes DJ, Anderson RM. Targeted hepatitis B vaccination – a cost effective immunization strategy for the UK? J Epidemiol Commun Health 1996; 50: 667–673

[43]. Williams JR, Nokes DJ, Medley GF, Anderson RM. The transmission dynamics of hepatitis B in the UK: a mathematical model for evaluating costs and effectiveness of immunization programs. Epidemiol Infect 1996; 116: 71–89.

[44]. Wilson JN, Nokes DJ, Carman WF. Predictions of the emergence of vaccine-resistant hepatitis B in The Gambia using a mathematical model. Epidemiol Infect 2000; 124: 295–307.

[45]. Woldeamanuel YW, Girma B, Teklu AM. Cancer in Ethiopia Ethiopia has a population of more than 84 million people and is expected to become the ninth. Lancet Oncol 2008;14(4):289–90.

[46]. World Health Organization. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO Library Cataloguing-in-Publication Data, 2015.

[47]. WJ E, GF M. Epidemiological patterns of hepatitis B virus (HBV) in highly endemic areas.