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A Mathematical Model Analysis of a Super infection Control Strategy for the Hepatitis B-Hepatitis D Viruses in Highly Epidemic Areas of the World

Tesfaye Tefera Mamo[1], Samuel T. Tefera[2]

[1]Departement of Mathematics, college of natural and computational science, Debre Berhan University, Post code 445, Debre Berhan, Ethiopia
[2]Department of ICU, Cambridge medical and rehabilitation center, Abu Dhabi, UAE

Abstract

In this work we considered nonlinear ordinary differential equations to study the super infection of hepatitis B virus (HBV)-hepatitis D virus (HDV) epidemics in highly epidemic areas of the world. We proved the posetivity 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 point. We found that the diseases free equilibrium point exist for some conditions. We proved that the disease free equilibrium point is locally asymptotically stable and also globally asymptotically stable. Using second generation matrix, we obtained that the effective reproduction number for the dynamical system is $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}]$, which depends on nine parameters; and basic reproduction number is $R_0 = \frac{1}{\alpha+\mu}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right]$.Using standard parameter estimation we found that the numerical value of effective reproduction number is $R_{eff} = 1.46$ and the basic reproduction number is$R_0 = 4.02$. From this numerical value it is possible to conclude that vaccination intervention strategy is effective to control the spread of the diseases. Out of nine parameters, the most sensitive parameter is π; the proportion of vaccinated new bourns. We also conduct numerical simulations which support the finding in the sensitivity analysis.

Keywords: Super infection, Epidemic, Chronic, Equilibrium Point, Stability, Simulation.

1. Introduction

Hepatitis is an infection of the liver that frequently results in irreversible liver tissue damage and swelling (cirrhosis) [1].Hepatitis can be caused by viruses, bacteria, microorganisms, toxic chemicals, alcohol, and other drugs; but viral hepatitis is the most common cause of hepatitis. When a virus infects the liver cells, it results in biochemical and cellular changes that impair liver function, resulting in viral hepatitis, a systemic illness [2]. The discovery of viral hepatitis led to the development of a very effective hepatitis vaccination, the first vaccine to successfully prevent liver cancer and introducing a novel method of protecting people from infectious diseases [3].

The Hepadnaviridae (hepatotropic DNA virus) family includes the prototype member, the Hepatitis B virus (HBV). Although kidney, pancreatic, and mononuclear cells can also contain trace amounts of

hepadnaviral DNA, hepadna viruses prefer to infect liver cells [4].Hepatitis B interferes with the function of the liver by replicating in the liver cells called hepatocytes. Contact with biological fluids that are infected, such as blood, semen, cervical fluid, and vertical transmission, spreads hepatitis B. Although the virus is found in every bodily secretion, it is not transferred through casual contact [5, 6].The infectious HBV circulates in the blood in concentrations as high as 10^8 Virions per ml [7].Hepatitis B virus can be either acute or chronic stage. The acute form is a short-term illness that occurs within the first 6 months after a person is exposed to HBV. The diseases can become chronic stage when the hepatitis B virus occurs more than 6 months. The quantity of virus replication and the strength of the host immune response determine the chronicity of HBV.

HBV infection is a silent killer. Many acutely and chronically infected people are unaware of their infection until indications of severe liver disease occur due to a lack of screening for infection[8, 9, 11].Most newborns with HBV infection at birth and many kids with infection between one and six years old develop chronic infection [13]. People with severe HBV infection make up about two thirds of carriers. These people do not develop symptoms, even though they harbor the virus and can transmit it to other people. The remaining one-third experience active hepatitis, a liver disorder that can be extremely dangerous. About 25% of HBV-induced liver cancer victims will pass away[10].

High mortality and morbidity are caused by viral hepatitis, one of the top 10 killer diseases. Humans are the only known natural host for HBV. About 2 billion people are infected with HBV globally from which over 378 million are chronically infected and at high risk of developing liver cirrhosis and hepatocellular carcinoma (HCC)**.** About 4.5 million people are newly infected every year. According to the global disease burden, about 1.34 million people die each year from HBV infections caused by acute infections, hepatic cancer and cirrhosis [25].

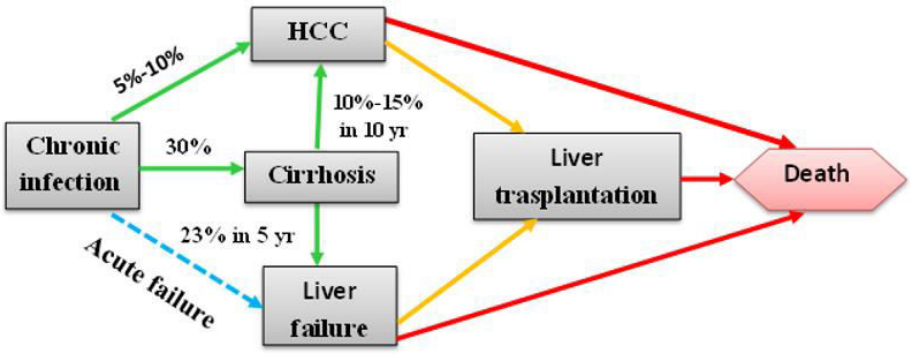

Figure 1 Chronic hepatitis B virus disease progression

Areas with a high endemicity include areas of the Middle East, South-east Asia, the Pacific Basin (with the exception of Japan, Australia, and New Zealand), sub-Saharan Africa, the Amazon Basin, the central Asian states, and a few nations in Eastern Europe. In these areas, about 70% to 90%of the population becomes HBV infected before the age of 40, and 8% to 20% of the people are HBV carriers [28].

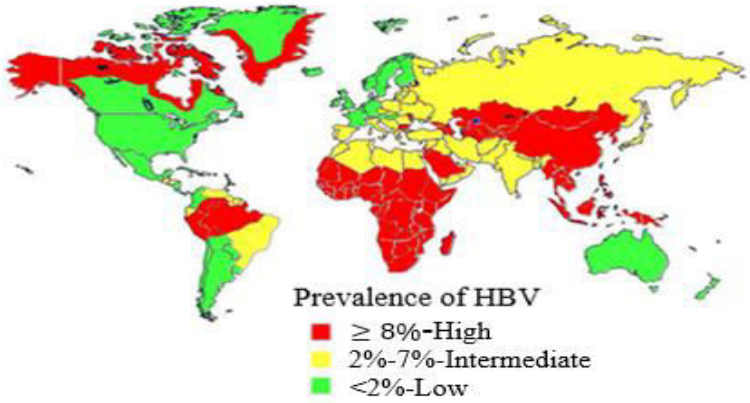

Figure 2 Geographic distribution of chronic HBV, (Source:Hepatitis B virus infection… virology-online.com)

In 1992, the World Health Assembly passed a resolution recommending global vaccination against hepatitis B. There are now about 179 countries offering hepatitis vaccine as part of their neonatal immunization program [27]. Hepatitis B vaccines are very effective, resulting in immunity in about 95% of people [26]. Immunity provided by vaccination often lasts a lifetime and lasts for 20 years.

In 1977, Rizzetto discovered the Hepatitis D virus (HDV), also known as the Hepatitis Delta Virus, in people who had a severe variant of the Hepatitis B virus infection [19]. Hepatitis D virus is a dysfunctional virus that depends on hepatitis B virus for helper functions for virions construction and spread [14]. Therefore, infection with hepatitis D can occur only with an associated HBV infection. This can happen as co-infection (infection with both viruses at the same time) or superinfection (where an already HBV chronically infected individual can be infected with hepatitis D virus); individuals co-infected or superinfected transmit both viruses [15]. Hepatitis D transmission pathways include blood borne and sexual, percutaneous, per mucosa, and perinatal contact. Hepatitis D virus superinfection is linked to a higher likelihood of chronic disease progression and catastrophic consequences [15, 16]. Compared to individuals with HBV infection only, people with both HDV and HBV infection appear to have drastically accelerated development of cirrhosis and hepatocellular cancer[17, 18].

Globally, it is believed that 2.3 billion people have hepatitis viruses[20]. The prognosis of these people is likely the poorest for the 12.4 million [21, 22] people who have chronic HBV and HDV infections because they are more likely to develop liver cancer and experience liver-related death considerably more quickly [22]. It is believed that the reductions in hepatitis D are largelydue to the reductions in HBV [23], as result of the introduction of HBV vaccination. The reduced prevalence of HBV reduces the reservoir required for the spread of hepatitis D, preventing the faulty virus from infecting vulnerable hosts.

Investigating the superinfection of the two fatal illnesses is essential due to the complication of the health issues produced by HBV infection and HDV infection. The primary goal of this research is to create a mathematical model to investigate the dynamics of super-infection of HBV with HDV. We will utilize the model to simulate the super infection of HBV with HDV based on the standard data of highly endemic locations after examining the existence and stability of the disease-free equilibria of the model. We suggest some effective ways for preventing superinfection of HBV with HDV by performing sensitivity analysis of the reproduction number on various parameters. One of the primary reasons for the study of super infection of HBV with HDV infection is to improve control strategy 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. Materials and methods

2.1. Basic assumptions of the model

Let$N(t)$ is the total number of population;$S(t)$ is susceptible individuals, $V(t)$ is vaccinated individuals, $B_A(t)$ is acutely infected individuals with HBV, $B_C(t)$ is chronically infected individuals with HBV, $I_1(t)$ is individual infected by chronic HBV and acute HDV, $I_2(t)$ is individual infected by chronic HBV and chronic HDV and $R(t)$ is recovered individuals. The basic assumptions of $SVB_AB_CI_1I_2R$ model of super infection of HBV with HDV are the following. 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 ϕ; vaccination against HBV leads to permanent immunity; individual only chronically infected by HBV is infected by HDV acutely; acutely infected individuals are either chronically infected or permanently immunized; chronically infected individuals are immunized by treatment or transplantation of liver; the natural death rate is assumed to be the same for all compartments

2.2. Flow chart of the model

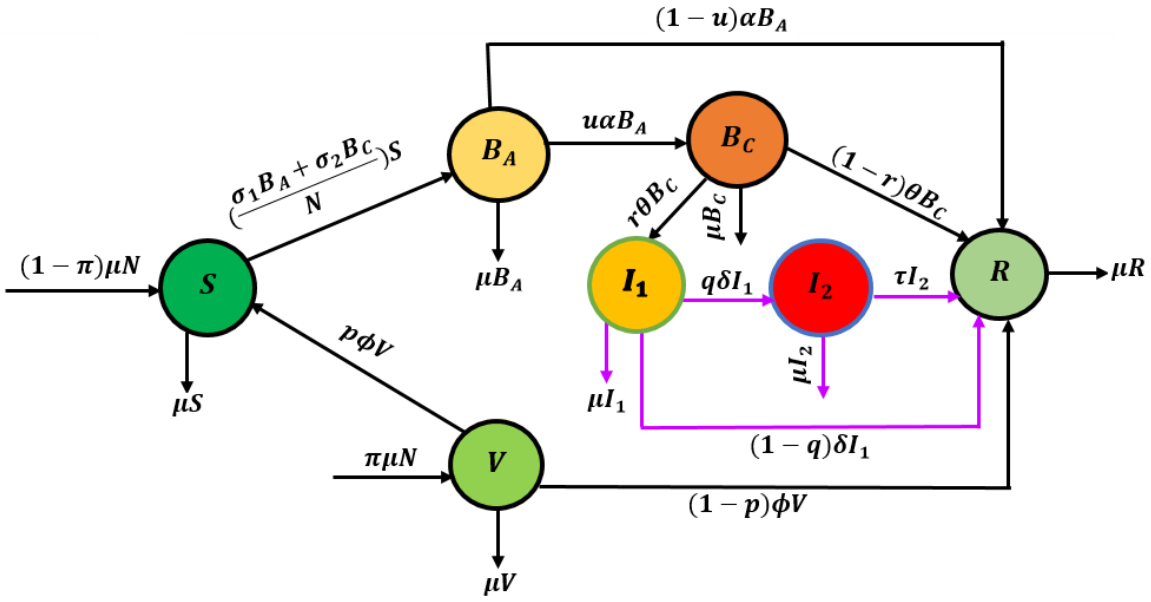

Figure 3 The flow chart of the model

Table 1 Meaning of parameters in the super infection of HBV with HDV model

Parameters	Meaning of parameters
π	Proportions of vaccinated newborns
μ	The natural death rate
σ_1	Transmission coefficients of acutely infectious individuals of HBV
σ_2	Transmission coefficients of chronically infectious individuals of HBV
u	Proportions of individuals moving from acutely infected by HBV to chronically infected by HBV
α	Rate of moving from acutely infected class to chronically infected class of HBV
r	Proportion of rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV class
θ	Rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV class
q	Proportion of rate of moving from acutely infected by HDV and chronically infected by HBV class to chronically infected by HBV and chronically infected by HDV
δ	Rate of moving from chronically infected by HBV and acutely infected by HDV to chronically infected by HBV and chronically infected by HDV
p	The proportion of individuals which loose the efficacy of vaccine.
ϕ	Rate of waning vaccine induced immunity
τ	Recovery rate of individuals infected by chronic HBV and chronic HDV

*2.3. **Dynamics of the model***

Let $\lambda = \frac{\sigma_1 B_A + \sigma_2 B_C}{N}$ be force of infection. Then, the dynamics of the model is:

$$\frac{dS}{dt} = (1-\pi)\mu N + p\phi V - (\lambda + \mu)S \quad (1)$$

$$\frac{dV}{dt} = \mu\pi N - (\phi + \mu)V \quad (2)$$

$$\frac{dB_A}{dt} = \lambda S - (\alpha + \mu)B_A \quad (3)$$

$$\frac{dB_C}{dt} = u\alpha B_A - (\theta + \mu)B_C \quad (4)$$

$$\frac{dI_1}{dt} = r\theta B_C - (\delta + \mu)I_1 \quad (5)$$

$$\frac{dI_2}{dt} = q\delta I_1 - (\tau + \mu)I_2 \quad (6)$$

$$\frac{dR}{dt} = (1-p)\phi V + (1-u)\alpha B_A + (1-r)\theta B_C + (1-q)\delta I_1 + \tau I_2 - \mu R \quad (7)$$

Here, the total population is compartmentalized in to seven none intersecting classes. That is$N(t) = S(t) + V(t) + B_A(t) + B_C(t) + I_1(t) + I_2(t) + R(t)$

$$\Rightarrow \frac{dN(t)}{dt} = \frac{dS(t)}{dt} + \frac{dV(t)}{dt} + \frac{dB_A(t)}{dt} + \frac{dB_C(t)}{dt} + \frac{dI_1(t)}{dt} + \frac{dI_2(t)}{dt} + \frac{dr(t)}{dt} = 0$$

Thus, total population is constant.

2.4. Positivity and bounded ness of solution

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 $t > 0$. The visible of invariant region is a region where the solution of the given dynamical system is bounded as time is goes on.

THEOREM 1: (Positivity of solution)

Let the initial data for the model be $S(0) > 0, V(0) > 0, B_A(0) > 0, B_C(0) > 0, I_1(0) > 0,$ $I_2(0) > 0$ *and* $R(0) > 0$. Then, the solutions $S(t), V(t), B_A(t), B_C(t), I_1(t), I_2(t)$ *and* $R(t)$ of the model will be remain positive for all time $t > 0$.

Proof: Assume that all parameters are positive, $S(0) > 0, V(0) > 0, B_A(0) > 0, B_C(0) > 0,$ $I_1(0) > 0, I_2(0) > 0, R(0) > 0$ and the total population N(t) positive. Also let the force of infection $\lambda = \frac{\sigma_1 B_A + \sigma_2 B_C}{N}$is positive.

From differential equation of the dynamical system (1)-(7), we get the following

I) From equation (2), we have:

$$\frac{dV}{dt} = \mu\pi N - (\phi + \mu)V$$

$\Rightarrow \int_0^t de^{(\phi+\mu)t}V(t) = \mu\pi N \int_0^t e^{(\phi+\mu)t}dt$, $e^{(\phi+\mu)t}$ is integration factor.

$\Rightarrow V(t) = V(0) + \mu\pi N \int_0^t e^{(\phi+\mu)t}dt > 0, for\ t > 0$ .Here, $V(0) > 0,$ $\mu\pi N \int_0^t e^{(\phi+\mu)t}dt > 0$. Thus, $V(t)$ is positive.

II) From equation (1), we get that;

$$\frac{dS}{dt} = (1-\pi)\mu N + p\phi V - (\lambda + \mu)S$$

$$\Rightarrow \int_0^t de^{(\lambda+\mu)t}S(t) = \int_0^t [(1-\pi)\mu N + p\phi V(t)]e^{(\lambda+\mu)t}dt$$

$\Rightarrow S(t) = s(0) + \int_0^t [(1-\pi)\mu N + p\phi V(t)]e^{(\lambda+\mu)t}dt > 0$.

Therefore $S(t)$ is positive.

III) From equation (3), $\frac{dB_A}{dt} = \lambda S - (\alpha + \mu)B_A$, we get:

$$\int_0^t de^{(\alpha+\mu)t}B_A(t) = \lambda \int_0^t S(t)e^{(\alpha+\mu)t}dt$$

$\Rightarrow B_A(t) = B_A(0) + \lambda \int_0^t S(t)e^{(\alpha+\mu)t}dt > 0, for\ t > 0$. Thus, $B_A(t)$is positive.

IV) From equation (4), $\frac{dB_C}{dt} = u\alpha B_A - (\theta + \mu)B_C$, we have;

$$\int_0^t de^{(\theta+\mu)t}B_C(t) = u\alpha \int_0^t B_A(t)e^{(\theta+\mu)t}dt$$

$\Rightarrow B_C(t) = B_C(0) + u\alpha \int_0^t B_A(t)e^{(\theta+\mu)t}dt > 0$. Hence, $B_C(t)$ is positive.

V) From equation (5), $\frac{dI_1}{dt} = r\theta B_C - (\delta + \mu)I_1$, we get:

$$\int_0^t de^{(\delta+\mu)t} I_1(t) = r\theta \int_0^t B_C(t) e^{(\delta+\mu)t} dt$$

$\Rightarrow I_1(t) = I_1(0) + r\theta \int_0^t B_C(t) e^{(\delta+\mu)t} dt > 0$.Hence, $I_1(t)$ is positive.

VI) From equation (6), $\frac{dI_2}{dt} = q\delta I_1 - (\tau + \mu)I_2$, we get:

$$\int_0^t de^{(\tau+\mu)t} I_2(t) = q\delta \int_0^t I_1(t) e^{(\tau+\mu)t} dt$$

$\Rightarrow I_2(t) = I_2(0) + q\delta \int_0^t I_1(t) e^{(\tau+\mu)t} dt$. Therefore, $I_2(t)$ is positive.

VII) From equation (7) we get:

$$\frac{dR}{dt} = (1-p)\phi V + (1-u)\alpha B_A + (1-r)\theta B_C + (1-q)\delta I_1 + \tau I_2 - \mu R$$

$\Rightarrow \int_0^t de^{\mu t} R(t) = \int_0^t [(1-p)\phi V + (1-u)\alpha B_A + (1-r)\theta B_C + (1-q)\delta I_1 + \tau I_2] e^{(\mu)t} dt > 0$

. Thus, $R(t)$ is positive.

THEREM 2: (Bounded ness of solution)

The feasible region Ω of the model (1) – (7) is defined as:

$\Omega = \{(S(t), V(t), B_A(t), B_C(t), I_1(t), I_2(t), R(t)) \epsilon \Re_+^7 \cup (0,0,0,0,0,0,0)$:

$$0 \le S(t) \le \frac{N[(1-q)(\phi+\mu)\mu + \rho\phi q]}{(\lambda+\mu)(\phi+\mu)}, 0 \le V(t) \le \frac{\pi N}{\phi+\mu}, 0 \le B_A(t) \le \frac{\lambda N[(1-\pi)(\phi+\mu) + p\pi\phi]}{(\alpha+\mu)(\lambda+\mu)(\phi+\mu)},$$

$$0 \le B_C(t) \le \frac{u\alpha\lambda N[(1-\pi)(\phi+\mu) + p\pi\phi]}{(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}, 0 \le I_1(t) \le \frac{ru\theta\alpha\lambda N[(1-\pi)(\phi+\mu) + p\pi\phi]}{(\delta+\mu)(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)},$$

$$0 \le I_2(t) \le \frac{qru\delta\theta\alpha\lambda N[(1-\pi)(\phi+\mu) + p\pi\phi]}{(\tau+\mu)(\delta+\mu)(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}, 0 \le R(t)$$

$$\le \frac{1}{\mu(\phi+\mu)} \{(1-p)\phi\pi N + \frac{\alpha\lambda N[(1-\pi)(\phi+\mu) + p\pi\phi]}{(\alpha+\mu)(\lambda+\mu)} [1 - u + \frac{(1-r)u\theta}{\theta+\mu}$$

$$+ \frac{(1-q)ru\delta\theta}{(\delta+\mu\mu)(\theta+\mu)} + \frac{qru\tau\delta\theta}{(\tau+\mu)(\delta+\mu)(\theta+\mu)}]\}$$

If$(S(0), V(0), B_A(0), B_C(0), I_1(0), I_2(0), R(0)) \in \Omega$, then the solution of $(S(t), V(t), B_A(t), B_C(t), I_1(t), I_2(t), R(t)) \in \Omega$, for all time t.

Proof:

Assume that all state variables $S(t), V(t), B_A(t), B_C(t), I_!(t), I_2(t), R(t)$ and parameters are positive. Also, let $S(0) \ge 0, V(0) \ge 0, B_A(0) \ge 0, B_C(0) \ge 0, I_1(0) \ge 0, I_2(0) \ge 0$, $R(0) \ge 0$ and the force of infection $\lambda = (\sigma_1 B_A + \sigma_2 B_C) \epsilon (0,1)$

I) From equation (2), $\frac{dV}{dt} = \mu\pi N - (\phi + \mu)V$,we have:

$\frac{dV}{dt} + (\phi + \mu)V = \mu\pi N \le \pi N$ … Since $\mu \epsilon (0,1)$

$$\Rightarrow \int_0^t de^{(\phi+\mu)t} V(t) \le \pi N \int_0^t e^{(\phi+\mu)t} dt$$

$$\Rightarrow V(t) \le \frac{\pi N}{\phi+\mu} + \left[V(0) - \frac{\pi N}{\phi+\mu}\right] e^{-(\phi+\mu)t}$$

$$\Rightarrow \lim_{t\to\infty} \sup V(t) \le \lim_{t\to\infty} \left\{\frac{\pi N}{\phi+\mu} + \left[V(0) - \frac{\pi N}{\phi+\mu}\right] e^{-(\phi+\mu)t}\right\} \le \frac{\pi N}{\phi+\mu}.$$

Thus, $0 \leq V(t) \leq \frac{\pi N}{\phi+\mu}$and $V(t)$ is bounded.

II) From equation (1), we get:

$0 \leq S(t) \leq \frac{N[(1-\pi)(\phi+\mu)\mu+p\pi\phi]}{(\lambda+\mu)(\phi+\mu)}$. Hence, $S(t)$ is bounded.

III) From equation (3), we have:

$$0 \leq B_A(t) \leq \frac{\lambda N[(1-\pi)(\phi+\mu)\mu+p\pi\phi]}{(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}$$

IV) From equation (4), we get:

$$0 \leq B_C(t) \leq \frac{u\alpha\lambda N[(1-\pi)(\phi+\mu)\mu+p\pi\phi]}{(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}$$

V) From equation (5), we have:

$$0 \leq I_1(t) \leq \frac{ru\theta\alpha\lambda N[(1-\pi)(\phi+\mu)\mu\mu+p\pi\phi]}{(\delta+\mu)(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}$$

VI) From equation (6), we get:

$$0 \leq I_2(t) \leq \frac{qru\delta\theta\alpha\lambda N[(1-\pi)(\phi+\mu)\mu+p\pi\phi]}{(\tau+\mu)(\delta+\mu)(\theta+\mu)(\alpha+\mu)(\lambda+\mu)(\phi+\mu)}$$

VII) From equation (7), we have:

$$0 \leq R(t) \leq \frac{1}{\mu(\phi+\mu)}\{(1-p)\phi\pi N + \frac{\alpha\lambda N[(1-\pi)(\phi+\mu)\mu+p\pi\phi]}{(\alpha+\mu)(\lambda+\mu)}[1-u+\frac{(1-r)u\theta}{\theta+\mu} + \frac{(1-q)ru\delta\theta}{(\delta+\mu\mu)(\theta+\mu)} + \frac{qru\tau\delta\theta}{(\tau+\mu)(\delta+\mu)(\theta+\mu)}]\}$$

2.5. Scaling of the 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. Here,$N(t) = S(t) + V(t) + B_A(t) + B_C(t) + I_1(t) + I_2(t) + R(t)$ and $\frac{dN}{dt} = 0$.

$\Longrightarrow 1 = \frac{S(t)}{N} + \frac{V(t)}{N} + \frac{B_A(t)}{N} + \frac{B_C(t)}{N} + \frac{I_1(t)}{N} + \frac{I_2(t)}{N} + \frac{R(t)}{N}$ .Let

$$s(t) = \frac{S(t)}{N}, v(t) = \frac{V(t)}{N}, b_a(t) = \frac{B_A(t)}{N}, b_c(t) = \frac{B_C(t)}{N}, i_1(t) = \frac{I_1(t)}{N}, \quad i_2(t) = \frac{I_2(t)}{N}, f(t) = \frac{R(t)}{N}$$

$$\Longrightarrow \frac{ds(t)}{dt} = \frac{dS(t)}{Ndt}, \frac{dv(t)}{dt} = \frac{dV(t)}{Ndt}, \frac{db_a(t)}{dt} = \frac{dB_A(t)}{Ndt}, \frac{db_c(t)}{dt} = \frac{dB_C(t)}{Ndt}, \frac{di_1(t)}{dt} = \frac{dI_1(t)}{Ndt}, \frac{di_2(t)}{dt} = \frac{dI_2(t)}{Ndt},$$

$\frac{df(t)}{dt} = \frac{dR(t)}{Ndt}$. Thus, the transformed dynamical system is:

$$\frac{ds}{dt} = (1-\pi)\mu + p\phi v - (\beta+\mu)s \quad (8)$$

$$\frac{dv}{dt} = \mu\pi - (\phi+\mu)v \quad (9)$$

$$\frac{db_a}{dt} = \beta s - (\alpha+\mu)b_a \quad (10)$$

$$\frac{db_c}{dt} = u\alpha b_a - (\theta + \mu)b_c \quad (11)$$

$$\frac{di_1}{dt} = r\theta b_c - (\delta + \mu)i_1 \quad (12)$$

$$\frac{di_2}{dt} = q\delta i_1 - (\tau + \mu)i_2 \quad (13)$$

$$\frac{df}{dt} = (1-p)\phi v + (1-u)\alpha b_a + (1-r)\theta b_c + (1-q)\delta i_1 + \tau i_2 - \mu f \quad (14)$$

Where $\beta = \sigma_1 b_a + \sigma_2 b_c$

2.6. ***Equilibrium point***

At disease free equilibrium point, $b_a = b_C = i_1 = i_2 = 0$ since there is no diseases at this point. Thus, the disease free equilibrium point of the dynamical system (8)-(14) is:

$(s, v, b_a, b_c, i_1, i_2, f) = (\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu})$.

2.7. ***The basic reproduction number*** $(\boldsymbol{R_0})$ ***and effectivereproduction number*** $(\boldsymbol{R_{eff}})$.

The reproduction number (basic reproduction numberR_0or effective reproduction numberR_{eff}) is defined as the average number of secondary infections caused by typical infected individual during his/her entire period of infectiousness. I 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[11].

Using next generation method, the effective reproduction number (reproduction number with vaccination intervention) of this model is: $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}]$

The basic reproduction number (reproduction number without vaccinationintervention in which $\phi = 0\ and\ \pi = 0$) is:$R_0 = \frac{1}{\alpha+\mu}[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}]$.

2.8. ***Local and global stability of disease free equilibrium point.***

THEOREM 3 (local stability)

The disease free equilibrium point

$E^0 = (s, v, b_a, b_c, i_1, i_2, f) = (\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu})$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: The Jacobean matrix, $J(E^0)$of model [8]-[14] with respect to $(s, v, b_a, b_c, i_1, i_2, f)$at the disease free equilibrium point$E^0 = (\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu})$ is:

$$J(E^0) = \begin{bmatrix} -\mu & p\phi & 0 & 0 & 0 & 0 & 0 \\ 0 & -(\phi+\mu) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\alpha+\mu) & 0 & 0 & 0 & 0 \\ 0 & 0 & u\alpha & -(\theta+\mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & r\theta & -(\delta+\mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & q\delta & -(\tau+\mu) & 0 \\ 0 & (1-p)\phi & (1-u)\alpha & (1-r)\theta & (1-q)\delta & \tau & -\mu \end{bmatrix}$$

. Let x be eigenvalue of the $J(E^0)$. Then;

$$\begin{vmatrix} -(\mu+x) & p\phi & 0 & 0 & 0 & 0 & 0 \\ 0 & -(\phi+\mu+x) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -(\alpha+\mu+x) & 0 & 0 & 0 & 0 \\ 0 & 0 & u\alpha & -(\theta+\mu+x) & 0 & 0 & 0 \\ 0 & 0 & 0 & r\theta & -(\delta+\mu+x) & 0 & 0 \\ 0 & 0 & 0 & 0 & q\delta & -(\tau+\mu+x) & 0 \\ 0 & (1-p)\phi & (1-u)\alpha & (1-r)\theta & (1-q)\delta & \tau & -(\mu+x) \end{vmatrix} = 0$$ is characteristics equation.

$$\Longrightarrow (\mu+x)^2(\phi+\mu+x)(\alpha+\mu+x)(\theta+\mu+x)(\delta+\mu+x)(\tau+\mu+x) = 0$$

$$\Longrightarrow x = -\mu, x = -(\phi+\mu), x = -(\alpha+\mu), x = -(\theta+\mu), x = -(\delta+\mu), x = -(\tau+\mu)$$

Here, all eigenvalues are negative and hence the disease free equilibrium point $E^0 = (s, v, b_a, b_c, i_1, i_2, f) = (\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu})$ of the model is locally asymptotically stable for $R_{eff} < 1$.

THEOREM 4: (Global stability)

If the effective reproduction number $R_{eff} < 1$, then the disease free equilibrium point $E^0 = (s, v, b_a, b_c, i_1, i_2, f) = \left(\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu}\right)$ of the model [8] − [14] is globally asymptotically stable (G.A.S).

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

$W(s, v, b_a, b_c, i_1, i_2, f) = A[s - s^0 - s^0 \ln\left(\frac{s}{s^0}\right)] + B[v - v^0 - v^0 \ln\left(\frac{v}{v^0}\right)] + Db_a + EB_c + Fi_1 + Gi_2 + H[f - f^0 - f^0 \ln(\frac{f}{f^0})]$, where A, B, D, E, F, G and H are positive constants; and

$E^0 = (s^0, v^0, b_a^0, b_c^0, i_1^0, i_2^0, f^0) = \left(\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu}\right)$ be DFE point.

i) W is continuous function for all $(s, v, b_a, b_c, i_1, i_2, f) \in \Re_+^7 \cup (0,0,0,0,0,0,0)$ and has 1st order partial derivatives.

ii) W has minimum at $(s, v, b_a, b_c, i_1, i_2, f) = (\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu})$, which is $W(\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu}) = 0$

iii) $\frac{dW}{dt} = A\frac{\partial W}{\partial s}\frac{ds}{dt} + B\frac{\partial W}{\partial v}\frac{dv}{dt} + D\frac{\partial W}{\partial b_a}\frac{db_a}{dt} + E\frac{\partial W}{\partial b_c}\frac{db_c}{dt} + F\frac{\partial W}{\partial i_1}\frac{di_1}{dt} + G\frac{\partial W}{\partial i_2}\frac{di_2}{dt} + H\frac{\partial W}{\partial f}\frac{df}{dt}$

Assuming the coefficient of b_a, b_c, i_1 and i_2 are all zero, we have:

$$\frac{dW}{dt} = -A(\beta+\mu)\left(1 - \frac{s^0}{s}\right)^2 s - B(\phi+\mu)\left(1 - \frac{v^0}{v}\right)^2 v - H\mu\left(1 - \frac{f^0}{f}\right)^2 f < 0$$

Thus, the disease free equilibrium point $E^0 = (s^0, v^0, b_a^0, b_c^0, i_1^0, i_2^0, f^0) = \left(\frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{\phi+\mu}, \frac{\pi\mu}{\phi+\mu}, 0,0,0,0, \frac{(1-p)\phi\pi}{\phi+\mu}\right)$ of the model is globally asymptotically stable for $R_{eff} < 1$.

2.9. Sensitivity analysis

Sensitivity analysis tells us how important each parameter is to disease transmission. Such information is crucial not only for experimental design, but also to data assimilation and reduction of complex nonlinear models [12]. Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values, since there are usually errors in data collection and presumed parameter values. It is used to discover parameters that have a high impact on reproduction number and should be targeted by intervention strategies.

In my model, effective reproduction number $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right]$ is depending on nine parameters. The value of these parameters is taken from standard data.

Table 2 Parameter description and their values

Parameters	Meaning of parameters	Value (range)	Reference
π	Proportions of vaccinated newborns	0.883	[29]
μ	The natural death rate	0.007	[28]
σ_1	Transmission coefficients of acutely infectious individuals of HBV	0.851	[29]
σ_2	Transmission coefficients of chronically infectious individuals of HBV	0.882	[29]
u	Proportions of individuals moving from acutely infected by HBV to chronically infected by HBV	0.46	[28]
α	Rate of moving from acutely infected class to chronically infected class of HBV	0.4	[28]
θ	Rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV class	0.2	[28]
p	The proportion of individuals which loose the efficacy of vaccine.	0.3	[28]
ϕ	Rate of waning vaccine induced immunity	0.1	[29]
τ	Recovery rate of individuals infected by chronic HBV and chronic HDV	0.028	[30]
r	Proportion of rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV class	0.038	[30]
q	Proportion of rate of moving from acutely infected by HDV and chronically infected by HBV class to chronically infected by HBV and chronically infected by HDV	0.038	[30]
δ	Rate of moving from chronically infected by HBV and acutely infected by HDV to chronically infected by HBV and chronically infected by HDV	0.5	[31]

Based on numerical values of parameters in table 2, the value of effective reproduction number $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right] = 1.46$ and basic reproduction number

$R_0 = \frac{1}{\alpha+\mu}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right] = 4.02$. This shows that vaccination intervention reduces the number of infected individuals from 4.02 persons to 1.46 persons which is infected by one infectious individualthroughout his infectious time. From the data we see that$R_{eff} = 1.46 > 1$, which shows us that the prevalence of super infection of HBV-HDV still persists in the community

Definition:

The normalized forward sensitivity index ofR_{eff}, which depends differentiably on a parameter ψ, is defined by: $\Upsilon_{\psi}^{R_{eff}} = \frac{\partial R_{eff}}{\partial \psi} \times \frac{\psi}{R_{eff}}$[24].

Based on the effective reproduction number $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right]$, the sensitivity indices of each parameters is as follows:

1. $\Upsilon_{R_{eff}}^{\pi} = \frac{\partial R_{eff}}{\partial \pi} \times \frac{\pi}{R_{eff}} = -\frac{[(1-p)\phi+\mu]\pi}{[(1-\pi)(\phi+\mu)+p\pi\phi]} = -1.74$
2. $\Upsilon_{R_{eff}}^{\phi} = \frac{\partial R_{eff}}{\partial \phi} \times \frac{\phi}{R_{eff}} = \frac{p\pi\mu\phi[\sigma_1(\theta+\mu)+u\alpha\sigma_2]}{(\phi+\mu)[(1-\pi)(\phi+\mu)+p\pi\phi]} = 0.01$
3. $\Upsilon_{R_{eff}}^{p} = \frac{\partial R_{eff}}{\partial p} \times \frac{p}{R_{eff}} = \frac{p\pi\phi}{[(1-\pi)(\phi+\mu)+p\pi\phi]} = 0.68$
4. $\Upsilon_{R_{eff}}^{\sigma_1} = \frac{\partial R_{eff}}{\partial \sigma_1} \times \frac{\sigma_1}{R_{eff}} = \frac{\sigma_1(\theta+\mu)}{\sigma_1(\theta+\mu)+u\alpha\sigma_2} = 0.52$
5. $\Upsilon_{R_{eff}}^{\sigma_2} = \frac{\partial R_{eff}}{\partial \sigma_2} \times \frac{\sigma_2}{R_{eff}} = \frac{u\alpha\sigma_2}{\sigma_1(\theta+\mu)+u\alpha\sigma_2} = 0.48$
6. $\Upsilon_{R_{eff}}^{\theta} = \frac{\partial R_{eff}}{\partial \theta} \times \frac{\theta}{R_{eff}} = -\frac{u\alpha\sigma_2\theta}{(\theta+\mu)[\sigma_1(\theta+\mu)+u\alpha\sigma_2]} = -0.46$
7. $\Upsilon_{R_{eff}}^{u} = \frac{\partial R_{eff}}{\partial u} \times \frac{u}{R_{eff}} = \frac{u\alpha\sigma_2}{\sigma_1(\theta+\mu)+u\alpha\sigma_2} = 0.48$
8. $\Upsilon_{R_{eff}}^{\alpha} = \frac{\partial R_{eff}}{\partial \alpha} \times \frac{\alpha}{R_{eff}} = \frac{[u\mu\sigma_2-\sigma_1(\theta+\mu)]\alpha}{(\alpha+\mu)(\sigma_1(\theta+\mu)+u\alpha\sigma_2)} = -0.49$
9. $\Upsilon_{R_{eff}}^{\mu} = \frac{\partial R_{eff}}{\partial \mu} \times \frac{\mu}{R_{eff}} =$

$$\left\{(1-\pi)[\sigma_1(\theta+\mu)+u\alpha\sigma_2] + \sigma_1[(1-\pi)(\phi+\mu)+p\pi\phi] - \frac{[(1-\pi)(\phi+\mu)+p\pi\phi][\sigma_1(\theta+\mu)+u\alpha\sigma_2][(\phi+\mu)(\theta+\mu)+(\alpha+\mu)(\phi+\theta+2\mu)]}{(\alpha+\mu)(\phi+\mu)(\theta+m)}\right\} \times \frac{\mu}{[(1-\pi)(\phi+\mu)+p\pi\phi][\sigma_1(\theta+\mu)+u\alpha\sigma_2]}$$

$$\Upsilon_{R_{eff}}^{\mu} = -0.01$$

Table 3 Sensitivity index of parameters

Order	parameter	value
1	π	-1.74
2	p	0.68
3	σ_1	0.52
4	σ_2	0.48
5	u	0.48
6	α	-0.49
7	θ	-0.46
8	ϕ	0.01
9	μ	-0.02

Here, we see that the most sensitive parameterthat influences the effective reproduction numberis π, that isthe proportion of vaccinated newborns. It influences the effective reproduction number negatively. That is,

when the proportion of vaccinated newbornsπ increases, the effective reproduction number decreases and in the long time the disease will eradicate.

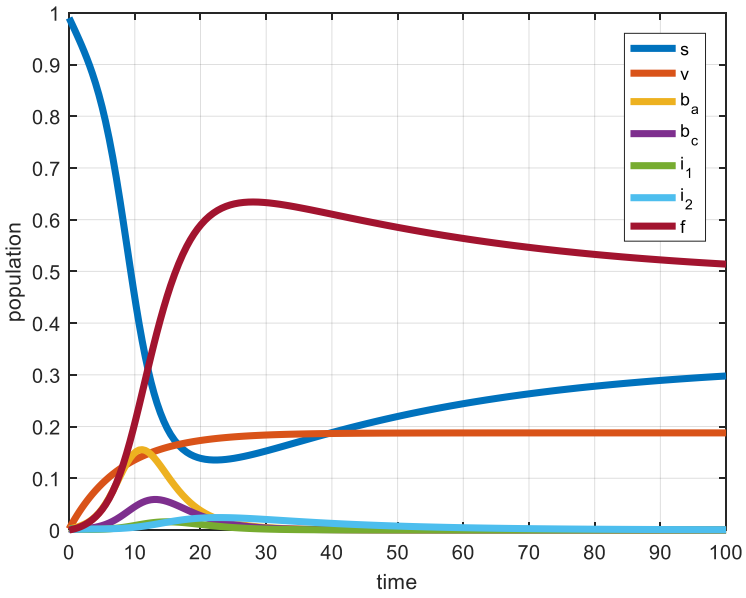

Figure 4 Local stability of endemic equilibrium point of the super infection of HBV-HDV model when $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right] = 1.46$ at $\sigma_1 = 0.851$ *and* $\sigma_2 = 0.882$

2.10. *Simulation*

The 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 we can do to influence that future behavior. It also uses to study the behavior of a system without building it. The effective reproduction number of the model $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right]$depends on nine parameters. The effect of these parameters on effective reproduction number is represented by Graphs as follows:

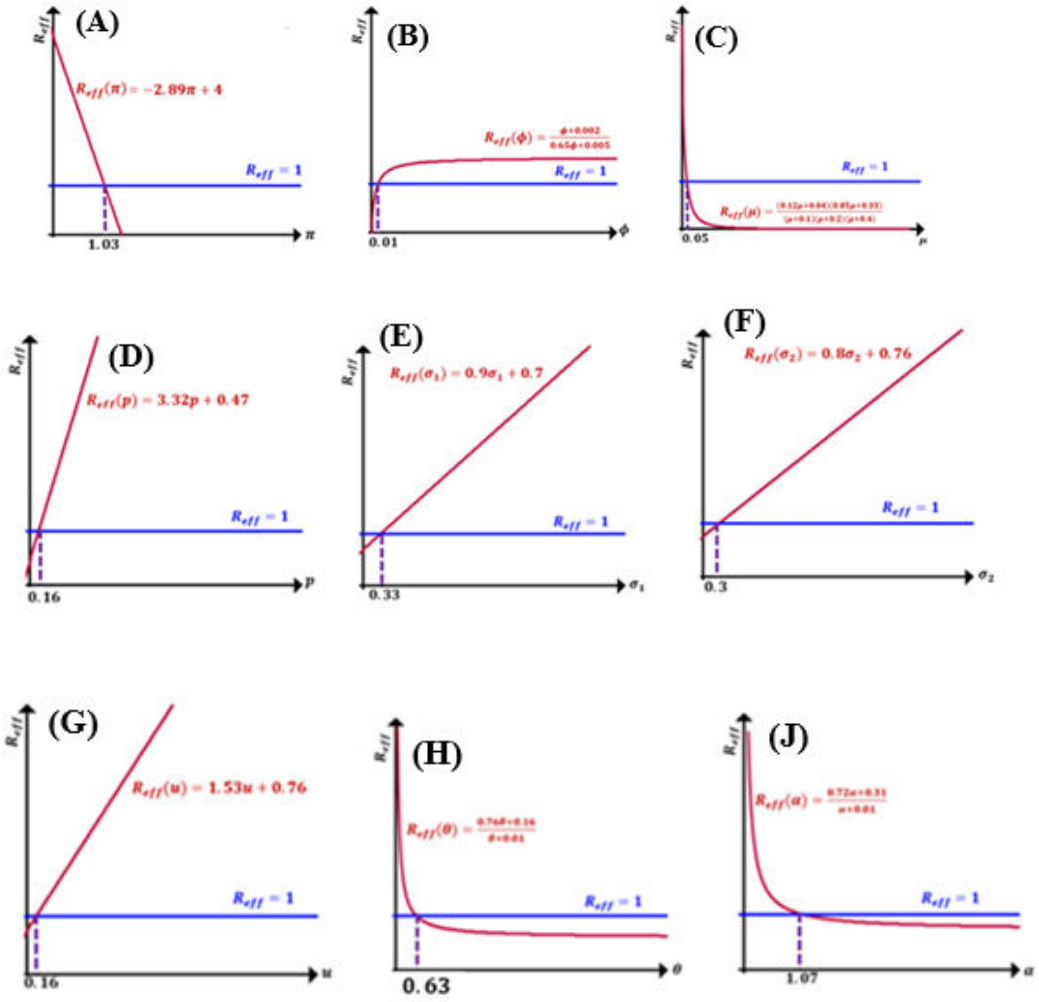

Figure 5 Graphs of effective reproduction number verses influential parameters

From (A) to (J) ofFigure5, all parameters up on which effective reproduction number depends are control parameters.

The graphs in Figure (A), (C), (H) and (J) tell us that proportions of vaccinated newborns π, the natural death rate μ,rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV classθ and rate of moving from acutely infected class to chronically infected class of HBVα influences the effective reproduction number R_{eff} negatively.This means, whenever$\pi > 1.03, \mu > 0.05, \theta > 0.16\ and\ \alpha > 1.07$, then correspondingly the value of$R_{eff} < 1$. That is,disease dies out. When ever $\pi < 1.03, \mu < 0.05, \theta < 0.16\ and\ \alpha < 1.07$, then the value of $R_{eff} > 1$ and hence disease spreads in the community. Thus, for super infection of HBV-HDV disease dies out of the community, the values of $\pi > 1.03, \mu > 0.05, \theta > 0.16\ and\ \alpha > 1.07$.

From the graphs of (B), (D), (E), (F)and (G), the effective reproduction number R_{eff} is positively influenced by rate of waning vaccine induced immunityϕ,the proportion of individuals which loose the efficacy of vaccine p, transmission coefficients of acutely infectious individuals of HBV σ_1,transmission coefficients of chronically infectious individuals of HBV σ_2 and proportions of individuals moving from acutely infected by HBV to chronically infected by HBV u. That is, when $\phi > 0.01, p > 0.16, \sigma_1 > 0.33, \sigma_2 > 0.3$ and
$u > 0.16$, then the effective reproduction number $R_{eff} > 1$ and the disease spreads in the community. If $\phi < 0.01, p < 0.16, \sigma_1 < 0.33, \sigma_2 < 0.3$ *and* $u < 0.16$,then the effective reproduction number $R_{eff} < 1$ and the disease dies out.

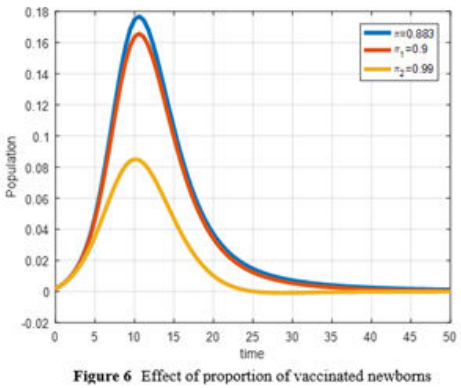

Figure 6 Effect of proportion of vaccinated newborns

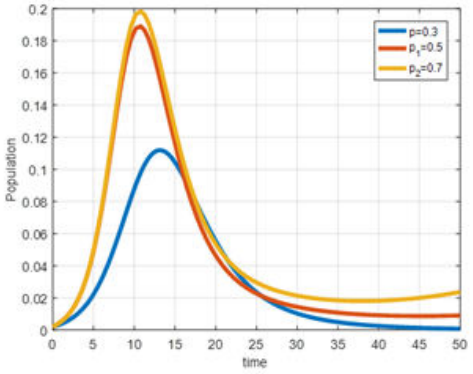

Figure 7 Effect of proportion of individuals which loose efficacy of vaccine

From Figure 6, we consider that proportion of vaccinated newborns has a great contribution in controlling the spread of superinfection of HBV-HDV. When proportion of vaccinated newborn is increasing, then the possibility of population infected by super infection of HBV-HDV is decreasing. Thus, attention should be given by policy maker for increment of vaccination for newborns. From Figure 7, we see that when proportion of individuals which loose efficacy of vaccine is increasing, the correspondingly the possibility of population fail under super infection of HBV-HDV is also increasing.

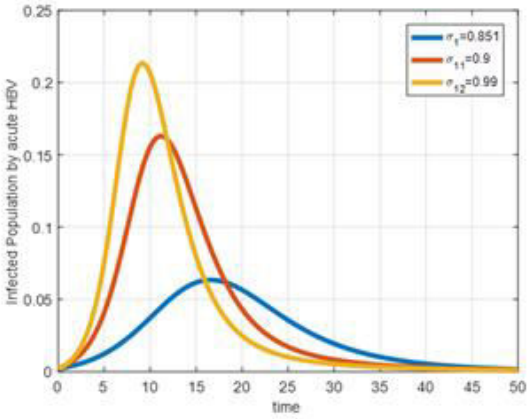

Figure 8 Effect of transmission coefficients of acutely infectious HBV

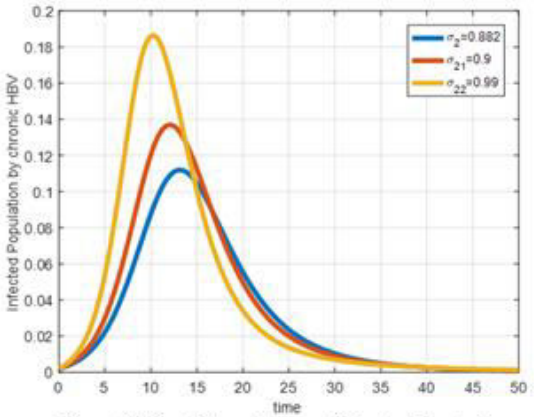

Figure 9 Effect of transmission coefficients of chronically infectious HBV

From Figure 8 and Figure 9, we see that increment of transmission coefficient of both acute and chronic HBV, also increases the number of population which is infected by HBV. Here, medical workers and policy makers must give attention for decrement of transmission coefficient of HBV.

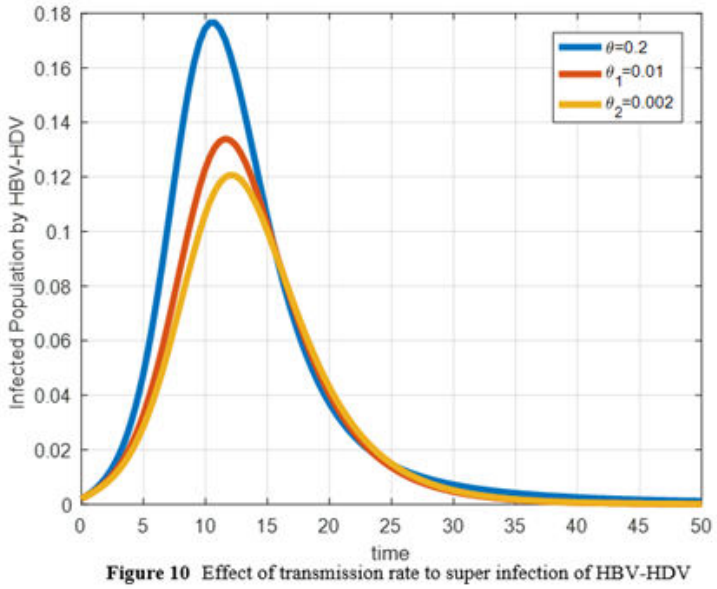

Figure 10 Effect of transmission rate to super infection of HBV-HDV

From Figure 10, we consider that decrement of rate of moving from chronically infected class of HBV to acutely infected by HDV and chronically infected by HBV class also decreases the infection of population by HBV-HDV.

3. Results and discussion

In the introduction section, I reviewed and introduced the epidemiology of Hepatitis B and Hepatitis D virus. Here, the cause roots, means of transmission, chronicity, prevalence of super infection of HBV-HDV are well discussed. In this section, it is seen that vaccination of HBV intervention helps for the control of HDV and as well for super infection of HBV-HDV prevalence. In Section 2, the compartmental super infection of HBV-HDV dynamical system using an ordinary differential equation is constructed; and partitioned it into seven distinct non intersecting compartments. Here, the qualitative behaviors of the model are discussed; that is, the positivity of future solutions of the models, boundedness of the dynamical system, disease-free equilibrium point, basic and effective reproduction numbers, stability analysis of disease-free equilibrium point, sensitivity analysis of reproduction numbers and simulation.

From the result it is obtained that increasing the proportion of vaccinated new bourns rate has a great contribution to decrease the prevalence of HBV-HDV super infection. Also, decreasing the proportion of individuals which loose the efficacy of vaccine can bring down the super infection of HBV-HDV disease. Controlling transmission coefficients of acutely infectious individuals of HBV and transmission coefficients of chronically infectious individuals of HBV is over all controlling the HBV-HDV super infection.

4. Conclusion

A realistic compartmental mathematical model on the spread and control of HBV-HDV super infection incorporating HBV vaccination and treatment for both infections are available at each stage of the infection in a population constructed and analyzed. I have shown the positivity and bounded ness of the complete HBV-HDV super infection model. The complete model has a disease free equilibrium point that is locally asymptotically stable for effective reproduction number less than one. For effective reproduction number less than one, the disease free equilibrium point of the model is globally asymptotically stable.

By analyzing the effective reproduction number, We have shown that the impact of some parameters changes on the associated reproduction numbers to give future recommendations for the stakeholders in the community. From the numerical result, I have got that the effective reproduction number for super infection of HBV-HDV is $R_{eff} = \frac{[(1-\pi)(\phi+\mu)+p\pi\phi]}{(\alpha+\mu)(\phi+\mu)}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right] = 1.46$ at $\sigma_1 = 0.851\ and\ \sigma_2 = 0.882$ and the basic reproduction is$R_0 = \frac{1}{\alpha+\mu}\left[\sigma_1 + \frac{u\alpha\sigma_2}{\theta+\mu}\right] = 4.02$. This shows that vaccination intervention of HBV reduces the number of infected individuals by both HBV-HDV from 4.02 persons to 1.46 persons which is infected by one infectious individual throughout his/her infectious time.

From this numerical result, increasing the proportion of vaccinated newborns has a great contribution in controlling the spread of super infection of HBV-HDV. I recommend that public policymakers must give value for vaccination of newborn. Finally, some of the main epidemiological findings of this study include HBV vaccination against HBV-HDV super infection has the effect of decreasing HBV-HDV disease expansion and prevalence.

Conflicts of interest

We declare that there is no conflict of interest regarding the publication of this article.

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