International Journal of Public Health and Pharmacology
Volume 4, Issue 1, 2024 (pp. 74-93)
www.abjournals.org

MODELLING THE IMPACT OF RELAPSE AND WEANING OFF IMMUNITY ON HEPATITIS B VIRUS TRANSMISSION DYNAMICS

Nwaokolo M. A.[1*], Oguche A. J.[2], Umaru R.[3], and Nwaokolo B.[4]

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

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

[4]Department of Science Educations, Federal University Wukari, Taraba State. Nigeria.

[*]Corresponding Author's Email: nwaokoloafam2@yahoo.com; Tel.: +2347068663805

Cite this article:

Nwaokolo M. A., Oguche A. J., Umaru R., Nwaokolo B. (2024), Modelling the Impact of Relapse and Weaning Off Immunity on Hepatitis B Virus Transmission Dynamics. International Journal of Public Health and Pharmacology 4(1), 74-93. DOI: 10.52589/IJPHP-RRT1W4KI

Manuscript History

Received: 13 Apr 2024

Accepted: 4 Jun 2024

Published: 7 Jul 2024

ABSTRACT: *In this study, we present a numerical simulation of the impact of relapse in patients with chronic HBV infection and weaning off immunity on vaccinated individuals within the transmission dynamics of Hepatitis B. The sensitivity analysis result establishes that relapse rate and weaning off immunity increase the value of the effective reproduction number when it is increased. Similarly, the result of the numerical simulation reveals that the combined effect of relapse and weaning off immunity increases the number of infected persons and thus, increases the spread of the Hepatitis B Virus. Also, relapse delays the quick response to the treatment regimen which consequently slows down the potential of recovery from the infection, whereas, weaning off immunity reduces the number of vaccinated individuals.*

KEYWORDS: Hepatitis B Virus, treatment, relapse.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

INTRODUCTION

In recent years, the study of infectious diseases has gained considerable attention due to their widespread impact on global health. Among these diseases, Hepatitis B remains a significant public health concern, affecting millions of individuals worldwide (Visvanathan *et al.,* 2016; Yi *et al.,* 2016). A nuanced understanding of its transmission dynamics is crucial for designing effective control strategies. This project aims to delve into two key aspects of Hepatitis B dynamics: the impact of relapse in patients with chronic HBV infection and the phenomenon of weaning off immunity in vaccinated individuals.

Chronic carriers of HBV represent a unique subset of the population whose viral loads fluctuate over time, sometimes leading to relapses in disease activity. Relapse could result from the exposure to suboptimal treatment regimens (types of immunosuppression), an elevation in viral load (virologic factors), and modifications in immune function (patient factors) (Tseng et al., 2012). These often lead to a pronounced exacerbation of the disease, which can culminate in liver failure (Hoofnagle et al., 2009) and contributing to a relatively high incidence of HBV infections (Moore and Chang, 2010). The implication of such relapses on the spread of the virus and long-term health outcomes remains underexplored. This thesis seeks to bridge this knowledge gap by employing numerical simulations to explore the influence of relapse on disease transmission within populations with varying levels of immunity and vaccination coverage.

Additionally, the success of vaccination campaigns in mitigating Hepatitis B has been substantial, resulting in the establishment of immunity in a significant proportion of the population. However, immunity developed through vaccination can be influenced by factors such as timing of administration, level of immunity conferred and the existing prevalence of the virus within the population which may potentially render individuals susceptible to infection once again. The phenomenon of weaning off immunity poses challenges to maintaining control over the disease and requires careful analysis to assess its contribution to transmission dynamics. This thesis aims to provide insights into the potential consequences of weaning off immunity, taking into account factors such as age, duration since vaccination, and population-wide immunity levels. By employing advanced numerical simulation techniques, this research seeks to provide a more comprehensive understanding of how relapse in chronic carriers and the weaning off immunity in vaccinated individuals collectively shape the transmission dynamics of Hepatitis B. The findings of this study will contribute to refining strategies for disease control and vaccination efforts, ultimately assisting in the formulation of more effective public health policies aimed at reducing the burden of Hepatitis B on a global scale.

In order to improve understanding on the dynamics of HBV infection, several mathematical models have been formulated (Zou *et al.,* 2009; Pang *et al.,* 2010; Kimbir *et al.,* 2014; Khan *et al.,* 2016). This study is motivated by the work of Khan *et al. (2016*) which is centered on the transmission model of Hepatitis B virus with the migration effect. Against this background, the present study intends to extend their work by incorporating treatment and its relapse rate, which was not considered in their model, in other to study the impact of relapse and weaning off immunity on the transmission dynamics.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Statement of the problem

Hepatitis B is a potentially life-threatening liver disease with high mortality rate (0.5-1.2 million deaths per year). Because vaccination does not eliminate infectivity nor block the route of transplacental (vertical) transmission, the need for vaccination in conjunction with treatment becomes necessary. Beside, not all treated individuals' recovers, some relapse if drug resistant mutants are present, which has posed a global health threat for many. This thesis aim to investigate the intricate transmission dynamics of Hepatitis B by numerically simulating the influence of relapse in patients with chronic HBV infection and Weaning off Immunity on vaccinated individuals, thus addressing the complex interplay between viral resurgence and loss of vaccine-induced protection in the context of Hepatitis B transmission. To this end, the work by Khan *et al.* (2016) is extended to include the relapse rate on the treated individual as a robust way to get more understanding on HBV transmission with infective migrants.

Aim of the Study

The aim of this study is to model the impact of relapse in patients with chronic HBV infection and the weaning off immunity on HBV transmission dynamics.

Objective of the study

The objectives are:

i. Extend the model of Khan *et al.* (2016) by incorporating treatment class and its relapse effect.
ii. Compute the effective reproduction number R_e for the modified model using next generation method.
iii. Carry out sensitivity analysis on the effective reproduction number in order to determine the parameters of the model that are most sensitive.
iv. Carry out numerical simulation of the extended model.
v. Interpret results in (i)-(iv).

Scope of the Study

This study extends the model of Khan *et al.* (2016) by including treated class, its relapse effect. Next, the effective reproduction number is computed using the next generation method. Sensitivity analysis is applied to some key parameters of the extended model; in addition, numerical simulation of the model is carried out using the fourth order Runge-kutta method embedded in MATLAB to study the impact of relapse in patients with chronic HBV infection and the weaning off immunity on HBV transmission dynamics.

Significance of the study

This study holds significant implications for both Hepatitis B control strategies and broader infectious disease modeling. By elucidating the effects of Relapse and Weaning off Immunity through numerical simulation, the research contributes to a deeper understanding of transmission dynamics. The findings could inform tailored interventions for chronic carriers and enhance vaccination policies, potentially leading to more effective disease management and reduced public health burden. Additionally, the study's methodology can serve as a model

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

for investigating similar phenomena in other infectious diseases, advancing the field of epidemiological research.

DEFINITION OF TERMS

Numerical Simulation: Numerical simulation is a computational technique used to model and analyze real-world processes or systems using mathematical equations and algorithms.

Relapse: Relapse pertains to the resurgence of infection due to the development of drug resistance.

Weaning off Immunity on Vaccinated Individual: Weaning off immunity in vaccinated individual refers to the gradual reduction of the protective immune response generated by a vaccine over time.

Hepatitis B: Hepatitis B is a viral infection that primarily affects the liver. It is caused by the hepatitis B virus (HBV).

LITERATURE REVIEW

"The term 'relapse' pertains to the resurgence of infection due to the development of drug resistance. Primarily, drug resistance entails a decrease in the efficacy of medication for treating diseases such as Hepatitis B (HBV) (Zoulim, 2009). Relapse presents a particularly formidable challenge within the realm of antiviral therapy and can result from prior exposure to suboptimal treatment regimens (types of immunosuppression), an elevation in viral load (virologic factors), and modifications in immune function (patient factors) (Tseng et al., 2012). This often leads to a pronounced exacerbation of the disease, which can culminate in liver failure (Hoofnagle et al., 2009).

The prevalence of relapse in patients with Hepatitis B is influenced by factors including drug-resistant strains, co-infection with HIV, re-infection, cultural factors, and disruptions in public health programs (Athena et al., 2012; Charan and Paramita, 2016). This global escalation is primarily attributed to inadequate patient adherence to healthcare services. Risk stratification categorizes incidence rates as low when they are less than 1%, moderate when falling between 1% and 10%, and high when surpassing 10% (Wu et al., 2019).

The challenge of relapse in patients is a substantial concern within antiviral therapy. When patients undergo immunosuppressive treatment, the reactivation of HBV becomes a distinct possibility, potentially leading to acute hepatic failure (Karajibani et al., 2018; Tseng et al., 2012). Presently, the predictive factors for relapse following discontinuation of nucleotide analogs remain unclear (Yao et al., 2017). Relapse can emerge either intrinsically within liver cells or be acquired due to drug exposure, chemical misuse, cellular stress, or other triggering conditions that awaken dormant HBV.

Additionally, specific drugs (such as anti-CD20 monoclonal antibodies, rituximab, ibrutinib, glucocorticoids, cisplatin, and imatinib) can directly induce relapse, provoking B-cell depletion and a robust immune-mediated response (Buti, 2014). These factors can render standard

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

therapies ineffective, leading to treatment delays and contributing to a relatively high incidence of HBV infections (Moore and Chang, 2010). However, the intricacy lies in identifying individuals necessitating antiviral therapy and determining the optimal timing, dosage, and duration of treatment. Hence, a comprehensive understanding of the impact of relapse is imperative to prevent harm."

Also, carriers may also experience a reactivation (10%-40%) of disease following HBeAg seroconversion, progressing into HBeAg-negative chronic hepatitis B (Guo, *et al.*, 2018; Tseng, *et al.*, 2012). This is marked by a reappearance of HBV DNA replication and ALT levels in serum and is associated with progression of disease and necro-inflammation on histology (Fattovich, 2003; Pan, *et al.*, 2013). Reactivation can happen directly from the immune active state in a small proportion (1-5%) of patients, after which it occurs at a rate of 3% annually, such that up to 30% of inactive carriers will subsequently experience reactivated infection (Shepherd *et al.*, 2006; Chu and Liaw, 2009). The reactivated state is a later and more advanced stage in disease progression, occurs in patients of older age, and occurs more frequently in males (Fattovich, 2003). About 0.5% of chronically infected persons will spontaneously resolve their illness annually (by loss of hepatitis B surface antigen and development of antibodies to HBsAg), which has a benign prognosis unless cirrhosis has already developed (Weinbaum *et al.*, 2008; Fattovich, 2003). All of these stages tend to be clinically asymptomatic and have minimal impact on quality of life (Shepherd *et al.*, 2006).

Hepatitis B Virus Reactivation/ Relapse

Recent advances in HBV reactivation (relapse) research shows that it generally occurs in occult HBV infection patients who suffered chemotherapy or immunosuppressive therapy have a higher risk of HBV reactivation (Guo *et al,.2018*; Tseng *et al.2012*)which range from 10%-40%. This is because HBV in a resting (inactive) state or low replicative state (cured) is likely to be activated or increased which would lead to severe liver function demage or even liver failure (Liu *et al.*2013; Masarone *et al.2014; Ho et al.*2015).

At present, there are no absolute unified diagnostic criteria for HBV relapse: it is usually based on clinical experience (EASL 2017; Perrillo *et al,.2015;* Yao *et al,.2017*). Clinical and virological relapse occurs when ALT > 2 times the upper limit of normal and HBVDNA >2,000IU/ml after stopping nucleosides analogue for 3-6 months (Liaw *et al,.2013;Jeng et al,.2013;*Pan *et al,.2013*; *Seto et al,.2013;*Chang *et al,.2015*). However, when HBVDNA increases at least 10 times relative to baseline level; and ALT increases at least 3 times normal it is known as HBV reactivation.

HBV relapse could occur spontaneously, clinically and virologically (HBVDNA $> 10^3$ copies/ml) according to the state of the body or mostly after immunosuppressive therapy which could lead to acute hepatitis or acute liver failure. However, a large number of HBV reactivation occur in subclinical cases, such as occult infections due to sexual, family contact, drug induce or alcoholic hepatitis. HBV reactivation can occur in some patient with autoimmune diseases, organ transplants and most serious case are often with bone marrow or liver transplant (Evens *et al.*, 2011; Lok *et al.,2012;* Hsu *et al.*,2015)

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

METHODOLOGY

The Existing Model

Khan *et al.* (2016) presented a transmission model of Hepatitis B virus with migration effect. We state the assumptions, parameters and the equations of their model below.

Assumptions of the model by Khan *et al.* (2016)

The following are the assumptions of the existing model by Khan *et al.* (2016):

i. The population is compartmentalized into six groups namely: Susceptible individuals, S(t), Exposed individuals E(t), Acutely infected individuals, A(t), Chronic carriers, C(t), Immunised individuals, V(t), and Migrated individuals, M(t), all at time t.
ii. The population is mixed homogeneously, that is, all people are equally likely to be infected by the infectious individuals in case of contact.
iii. The newborns to carrier mothers infected at birth are latently infected individual.
iv. A proportion of susceptible is vaccinated per unit time and the vaccinated individuals do not acquire permanent immunity.
v. By vaccination coverage we assumed the complete three dose of HBV vaccine.
vi. Migrants are adults hence; the natural birth rate of the migrated class is neglected.
vii. There is a transmission rate from exposed to migrated class and vice–versa.
viii. There is a transmission rate from migrated class to susceptible class and migrated class to acutely infected class.
ix. There is a stable population with equal percapita birth and death rate δ (as disease-induced death rate is not considered in the system).

Variables and parameters of the existing model.

The existing model has the following variables and parameters as given in Table 1.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Table 1: The Variables and Parameters of the Existing Model by Khan *et al.* (2016).

Parameters	Description
$S(t)$	Number of Susceptible individuals at time t
$E(t$	Number of Exposed individuals at time t
$A(t)$	Number of Acute infectives at time t
$C(t)$	Number of Chronic carriers at time t
$V(t)$	Number of Immunized individuals at time t
$M(t)$	Number of Migrated individuals at time t
δ	Equal per capita birth and death rate (as disease-induced death rate is not considered in the system)
π	The Proportion without immunization
γ_1	Rate at which exposed individuals become infectious and move to the Acute infected class
γ_2	Rate at which acutely infected individuals move to the chronic carrier class
γ_3	Rate at which chronic carriers acquire immunity and move to the immunized class
β	The transmission coefficient
κ	The infectiousness of carriers relative to acute infections
q	Proportion of acute infected individuals that become carriers
$1-q$	Proportion of acute infected individuals that move to the immunity class.
δ_0	The loss of immunity from the immunized class to susceptible class
ρ	Proportion of vaccinated susceptible per unit time
ξ	The rate of flow from exposed to migrated class.
α	The flow from migrated to susceptible class.
μ_1	The transmission rate from migrated class to exposed class.
μ_2	The transmission rate from migrated class to acute infected class
η	Proportion of the unimmunized children born to carrier mothers
$\delta(1-\pi)$	The newborns that are successfully immunized
$\delta\pi(1-\eta C(t))$	Births flux into the susceptible class

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

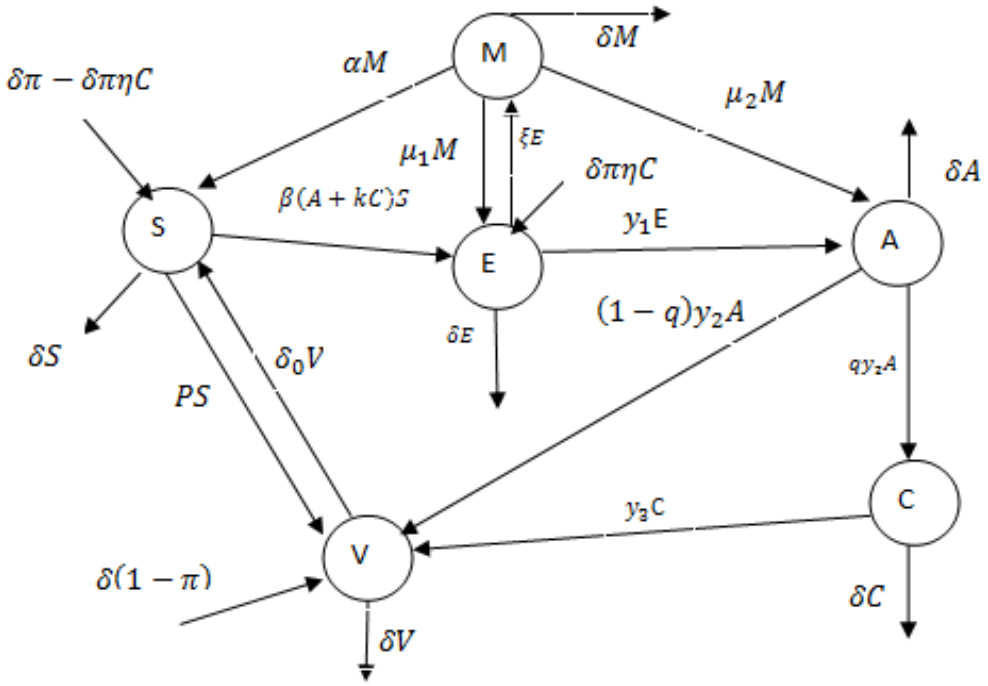


Figure 1: Flow Diagram of HBV transmission Dynamics for the Existing Model

The existing model equations

With the above assumptions, parameters and flow diagram in khan *et al*. (2016), the following existing model equations were derived.

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A+kC)S + \delta_0 V - pS + \alpha M, \quad (3.1)$$

$$\frac{dE}{dt} = \beta(A+KC)S - \delta E + \delta\pi\eta C - \gamma_1 E + \mu_1 M - \xi E, \quad (3.2)$$

$$\frac{dA}{dt} = \gamma_1 E - (\delta+\gamma_2)A + \mu_2 M, \quad (3.3)$$

$$\frac{dC}{dt} = q\gamma_2 A - \delta C - \gamma_3 C, \quad (3.4)$$

$$\frac{dV}{dt} = \gamma_3 C + (1-q)\gamma_2 A - \delta_0 V - \delta V + \delta(1-\pi) + pS, \quad (3.5)$$

$$\frac{dM}{dt} = \xi E - (\mu_1+\mu_2)M - \delta M - \alpha M. \quad (3.6)$$

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

The Extended Model

In addition to the assumptions of the existing model we present the new assumptions, parameters and the model flow diagram thereafter.

Assumptions of the extended model

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

Table 2: Parameters of the Extended Model.

Parameters	Description
$T(t)$	Number of treated individuals at time t
$R(t)$	Number of recovered individuals at time t
δ_0	The loss of immunity from the vaccinated class to susceptible class
α_o	Proportion of chronic carriers that are treated per unit time.
γ_3	Rate of recovery of the treated individuals
φ	Rate at which treated individual relapse and proceed to the chronic class
$1-q$	Proportion of acute infected individual that move to the recovered class

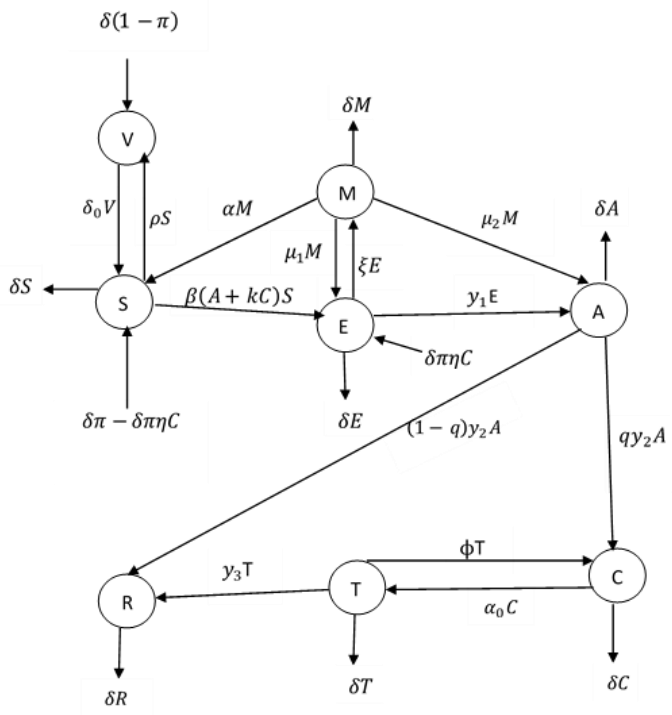


Figure 2: Flow Diagram of HBV transmission Dynamics for the Extended Model

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

The equations of the extended model.

The extended model equations are derived based on the above assumptions, parameters and flow diagram:

$$\frac{dS}{dt} = \delta\pi(1-\eta C) - \delta S - \beta(A + kC) - pS + \delta_0 V + \alpha M \quad (3.7)$$

$$\frac{dE}{dt} = \beta(A + kC)S - (\delta + \xi + \gamma_1)E + \delta\pi\eta C + \mu_1 M \quad (3.8)$$

$$\frac{dA}{dt} = \gamma_1 E - (\delta + \gamma_2)A + \mu_2 M \quad (3.9)$$

$$\frac{dC}{dt} = q\gamma_2 A + \varphi T - (\delta + \alpha_0)C \quad (3.10)$$

$$\frac{dT}{dt} = \alpha_0 C - (\delta + \varphi + \gamma_3)T \quad (3.11)$$

$$\frac{dR}{dt} = (1-q)\gamma_2 A + \gamma_3 T - \delta R \quad (3.12)$$

$$\frac{dM}{dt} = \xi E - (\mu_1 + \mu_2 + \delta + \alpha)M \quad (3.13)$$

$$\frac{dV}{dt} = \delta(1-\pi) + pS - (\delta + \delta_0)V, \quad (3.14)$$

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

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

Where,

$$R = 1 - S - E - A - C - T - M - V \quad (3.15)$$

The effective reproduction number, R_{r^c}

The effective reproduction number is defined as the average number of new infection generated by a typical infectious individual in the presence of a control (Gumel *et al.*, 2004). Effective reproduction number is the useful threshold for predicting outbreaks and evaluating control strategies that would reduce the spread of the disease in the population. If $R_{r^c} < 1$, the disease can be eliminated, however, when $R_{r^c} > 1$ it will persist or become endemic in the population.

The effective reproduction number for the model (3.17) – (3.23) is calculated using the next generation operator approach as described by Driessche and Watmough (2002) .

Applying this approach, we rearrange our model in equation (3.17) – (3.23) in order of infected compartments followed by uninfected compartment. This gives

$$\frac{dE}{dt} = \beta(A + kC)S - \delta E + \delta\pi\eta C - \gamma_1 E - \xi E + \mu_1 M, \quad (3.17)$$

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

$$\frac{dA}{dt} = \gamma_1 E - (\delta + \gamma_2)A + \mu_2 M, \tag{3.18}$$

$$\frac{dC}{dt} = q\gamma_2 A + \varphi T - (\delta + \alpha_0)C, \tag{3.19}$$

$$\frac{dM}{dt} = \xi E - (\mu_1 + \mu_2 + \delta + \alpha)M. \tag{3.20}$$

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

$$\frac{dS}{dt} = \delta\pi(1 - \eta C) - \delta S - \beta(A + kC)S + \delta_0 V \ - pS + \alpha M, \tag{3.22}$$

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

From equation (3.17) – (3.21), we have the new infective and transfer terms from one compartment to another given as

$$f = \left(\frac{\beta(A + KC)S\ 0}{0\ 0\ \ 0}\right) \tag{3.24}$$

and

$$v = \big((\delta + \xi + \gamma_1)E - \delta\pi\eta C - \mu_1 M\ (\delta + \gamma_2)A - \mu_2 M - \gamma_1 E\ (\delta + \alpha_0)C - q\gamma_2 A - \varphi T \quad (\delta + \varphi + \gamma_3)T - \alpha_0 C\ (\mu_1 + \mu_2 + \alpha + \delta)M - \xi E\ \big) \tag{3.25}$$

Therefore, taking the partial derivatives of (3.24) with respect to (E, A, C, T, M) at disease free equilibrium $\varepsilon_0 = S^0$, we obtain

$$F = Df(\varepsilon_0) = (0\ \beta S^0\ \beta K S^0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ ) \tag{3.26}$$

Similarly, the partial derivatives of (3.25) with respect to (E, A, C, T, M) at disease free equilibrium ε_0 gives

$$V = (m_1\ 0\ \ -m_2\ 0\ \ -\mu_1\ \ -\gamma_1\ m_3\ 0\ 0\ \ -\mu_2\ 0\ \ -m_4\ m_5\ \ -\varphi\ 0\ 0\ 0\ \ -\alpha_0\ m_6\ 0\ -\xi\ 0\ 0\ 0\ m_7\ ) \tag{3.27}$$

where , $m_1 = (\delta + \xi + \gamma_1)$, $m_2 = \ \delta\pi\eta, m_3 = (\delta + \gamma_2), m_4 = q\gamma_2, m_5 = (\delta + \alpha_0)$,

$m_6 = (\delta + \varphi + \gamma_3), m_7 = (\alpha + \delta + \mu_1 + \mu_2)$

Therefore, by taking the transpose of the matrix of co factors and dividing by its

determinant,

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

We have,

$$V^{-1} = (B_1\ B_2\ B_3\ B_4\ B_5\ C_1\ C_2\ C_3\ C_4\ C_5\ D_1\ D_2\ D_3\ D_4\ D_5\ E_1\ E_2\ E_3\ E_4\ E_5\ F_1\ F_2\ F_3\ F_4\ F_5\ )$$

such that

$$FV^{-1} = (N_1\ N_2\ ), \tag{3.29}$$

where

$$N_1 = \big((\beta S^0 C_1 + \beta K S^0 D_1)\ (\beta S^0 C_2 + \beta K S^0 D_2)\ (\beta S^0 C_3 + \beta K S^0 D_3)\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ \big) \tag{3.30}$$

$$N_2 = \big((\beta S^0 C_4 + \beta K S^0 D_4)\ (\beta S^0 C_5 + \beta K S^0 D_5)\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ 0\ \big) \tag{3.31}$$

From which we obtain

$$R_{r^c} = \rho(FV^{-1}) = \beta S^0 C_1 + \beta K S^0 D_1\ \ , \tag{3.32}$$

where

$$D_1 = \left(\frac{m_4 m_6(\gamma_1 m_7 + \xi\mu_2)}{\theta}\right)$$

$$C_1 = \left(\frac{(m_5 m_6 - \varphi\alpha_0)(\gamma_1 m_7 + \xi\mu_2)}{\theta}\right)$$

and

$$\theta = \varphi\alpha_0 m_3(m_1 m_7 + \xi\mu_1) - \xi m_6(m_2 m_4 \mu_2 + m_3 m_5 \mu_1) - m_6 m_7(m_2 m_4 \gamma_1 - m_1 m_3 m_5)$$

Thus, the effective reproduction number with relapse in (3.32) can be rewritten as

$$R_{r^c} = \frac{\big[\beta S^O\big(c + Kq\gamma_2(\delta + \varphi + \gamma_3)\big) + e(\delta + \varphi + \gamma_3)\big](\mu_2\xi + \gamma_1 a) + \xi\mu_1 bc}{dbca} \tag{3.33}$$

Numerical Simulation

Numerical Simulations is used to illustrate some of the analytical results and verify theoretical predictions of the model (1)-(7) using a set of parameter values (Table 2). These parameter values are gotten from the epidemiology of HBV and the demographic profile of the population which is obtained from the literature (Khan *et al.*, 2016; Pan *et al*., (2013)).

In this section, we indeed demonstrate numerically using the fourth-order Runge-Kutta method coded by the aid of MATLAB program in Appendix A to simulate the model (1)-(7).

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Table 2: Parameters Values used in Numerical Simulation

Parameters	*Range*	Value	Source
β		0.8	Khan *et al.*(2016)
δ		0.0143	Khan *et al.*(2016)
δ_0	0.03-0.06	0.03	Khan *et al.*(2016)
γ_1		6 per year	Khan *et al.*(2016)
γ_2		4 per year	Khan *et al.*(2016)
γ_3		0.34	Khan *et al.*(2016)
k		0.1	Khan *et al.*(2016)
π		0.8	Khan *et al.*(2016)
η		0.7	Khan *et al.*(2016)
μ_1		0.1	Khan *et al.*(2016)
μ_2		0.1	Khan *et al.*(2016)
α	0-1	0.1	Khan *et al.*(2016)
ξ	0-1	0.1	Khan *et al.*(2016)
q	0.05-0.9	0.05	WHO (2002)
φ		0.393	Pan *et al* .(2013)
S_O		0.493	Medley *et al* . (2001)
E_O		0.0035	Medley *et al* . (2001)
A_O		0.0035	Medley *et al* . (2001)
C_O		0.25	Assumed
M_O		0.003	Assumed
P		0.8	Assumed
α_o		0.8	Assumed

The results of the numerical experiments are meant to study the following cases (a)-(d).

a) The behaviour of chronic carriers in the absence of relapse. This is shown in Figure 2.

b) The impact of different relapse rates on the chronic carriers. This is shown in Figure 3.

c) The impact of different relapse rates on Acute infection. This is shown in Figure 4.

d) The impact of reproduction number against relapse. This is shown in Figure 5.

Sensitivity Analysis

We perform sensitivity analysis to determine the relative importance of model parameters responsible for disease transmission. The analysis will enable us to find out parameters that have a high impact on the effective reproduction number and which should be targeted by

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

intervention strategies. We perform sensitivity analysis by calculating the sensitivity indices of the effective reproduction number with relapse R_r^c to determine whether HBV can be eradicated in the population or not. These indices tell us how vital each parameter is to hepatitis B transmission and prevalence.

Sensitivity analysis is commonly used to determine the robustness of model predictions to parameter values because there are usually errors in data collection and presumed parameter values (Chitnis *et al.*, 2008). To investigate which parameters in the model system have a high impact on the R_r^c and should be targeted by intervention strategies, we apply the approach presented by Chitnis *et al.* (2008). The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives as follows.

Definition 1: The normalized forward sensitivity index of a variable, τ that depends differentiable on the index of a parameter p is defined as

$$r_\tau^\rho = \frac{\partial \rho}{\partial \tau} \times \frac{\tau}{\rho} \tag{3.34}$$

From the formula of effective reproduction, R_r^c in equation (3.34), we derive an analytical expression for the sensitivity of R_r^c as

$$r_\tau^{R_r^c} = \frac{\partial R_r^c}{\partial \tau} \times \frac{\tau}{R_r^c} \tag{3.35}$$

where τ denotes the parameter. We compute the sensitive indices of the model system for some parameters involved in R_r^c. For example the sensitivity index of R_r^c with respect to β is given by

$$r_\beta^{R_r^c} = \frac{\partial R_r^c}{\partial \beta} \times \frac{\beta}{R_r^c} \tag{3.36}$$

Also, the sensitivity index of R_r^c with respect to α_0 is given by

$$r_{\alpha_0}^{R_r^c} = \frac{\partial R_r^c}{\partial \alpha_0} \times \frac{\alpha_0}{R_r^c} \tag{3.37}$$

Furthermore, the sensitivity index of R_r^c with respect to φ is given by

$$r_\varphi^{R_r^c} = \frac{\partial R_r^c}{\partial \varphi} \times \frac{\varphi}{R_r^c} \tag{3.38}$$

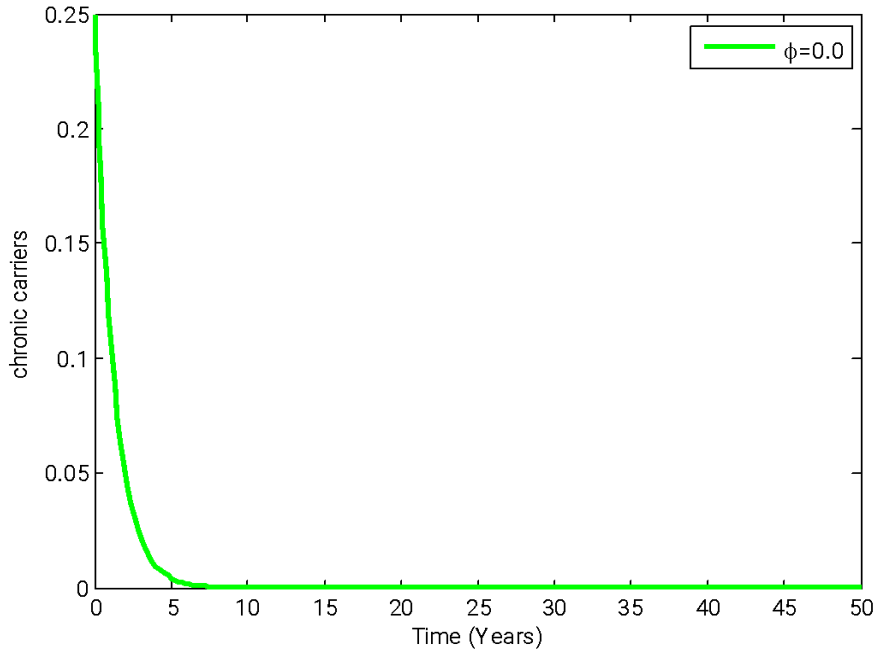
RESULTS AND DISCUSSION

In this section, we present the main findings of the study under the following sub-headings.

Numerical Results

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

We begin this sub-section by presenting the numerical results of the above experiments (a-d).



Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Figure 2: A situation where there is no relapse on Chronic Carriers$(\varphi = 0, 0)$.

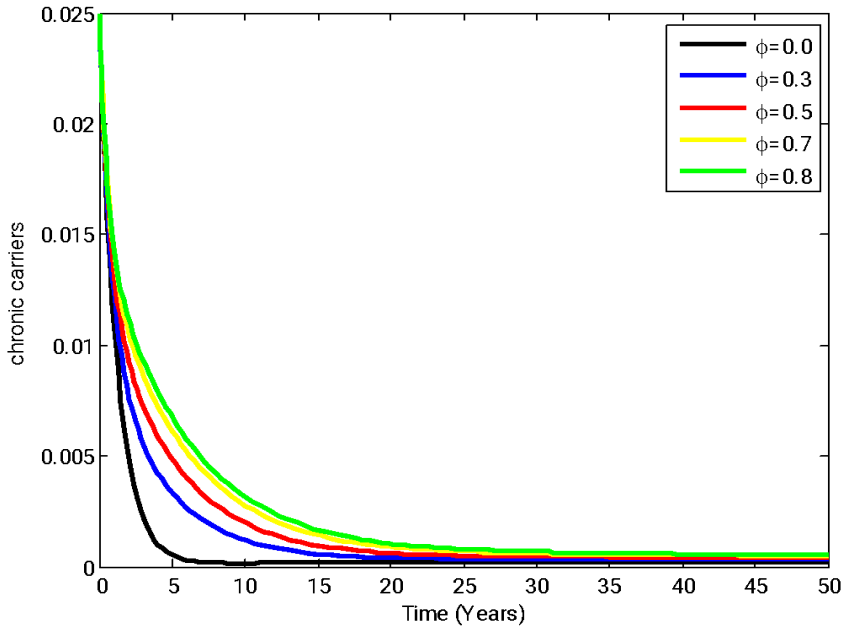


Figure 3:Impact of increasing Relapse Rate on Chronic Carriers$(\varphi = 0, 0.3, 0.5, 0.7, 0.8)$

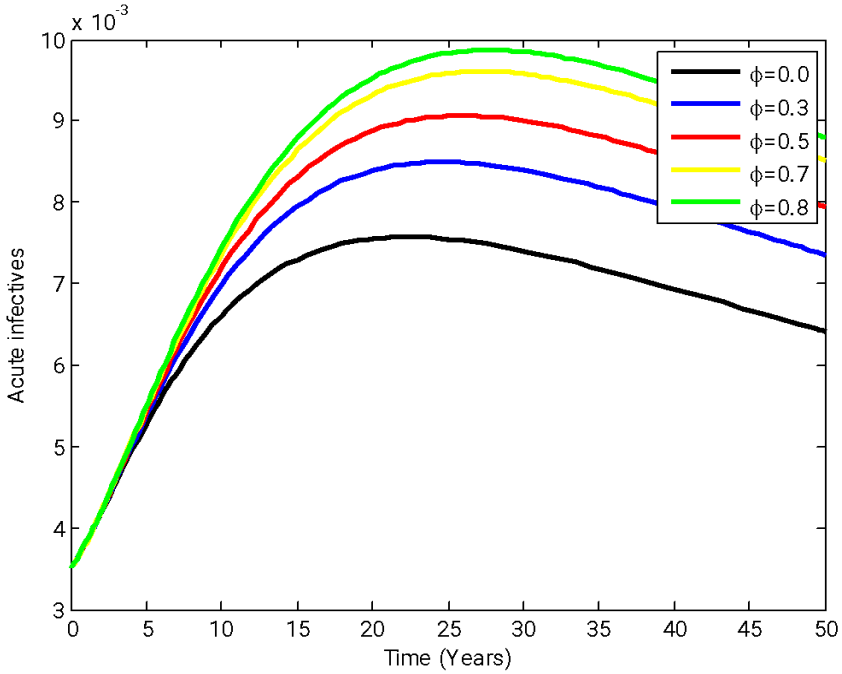


Figure 4: Impact of Relapse Rates on Acute Infectives $(\varphi = 0, 0.3, 0.5, 0.7, 0.8)$.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

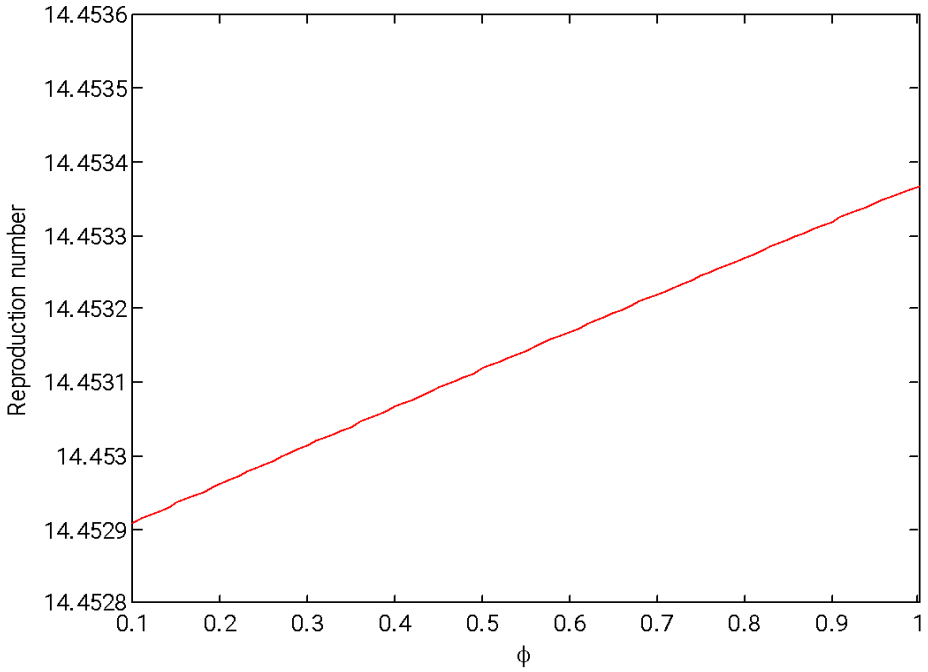


Figure 5: Impact of reproduction number against relapse rate

Sensitivity Results

We use the parameter values displayed in Table 1 to obtain the numerical value, therefore, the sensitivity index of R_r^c with respect to β is given by

$$r_{\beta}^{R_r^c} = 1$$

the sensitivity index of R_r^c with respect to α_0 is given by

$$r_{\alpha_0}^{R_r^c} = -0.0000342508$$

Furthermore, the sensitivity index of R_r^c with respect to φ is given by

$$r^{R_r^c} = 0.00001801218$$

The sensitivity indices results of R_r^c are given in Table 3 and are arranged from the highest sensitivity value to the lowest value. The indices with positive signs show that the value of R_r^c increases when the corresponding parameters are increased and those having negative signs indicate that the value of R_r^c decreases when the parameters are increased.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Table 3: Sensitivity Indices of R_r^c with respect to some Parameters

S/N	Parameter	Sensitivity Index	Sign
1	β	1.000000000	+
2	p	0.9475304984	−
3	δ_0	0.6884058306	+
4	γ_2	0.434756444	−
5	μ_2	0.3475541027	+
6	α	0.3123292643	−
7	π	0.2760833440	+
8	γ_1	0.1742824945	+
9	ξ	0.0296644089	−
10	μ_1	0.0094382464	+
11	q	0.00003554198	+
12	α_0	0.00003425081	−
13	η	0.00002156809	+
14	φ	0.00001801218	+
15	k	0.0000139739	+
16	γ_3	0.000001728521	−

Numerical Simulation Results

The behaviour of the model is shown in Figure 2 - 6 where we plot the prevalence of the population with time. The parameter values used in the numerical experiment are in Table 2.

Figure 2 shows clearly that when there is no relapse rate, the chronic carriers' declines over a short period. The medical implication is that the result in Figure 1 agrees with the report of Weinbaum *et al.* (2008) that HBeAg will clear in a short time, which leads to a marked reduction in disease activity, viral load, and histological improvement in the population. This agrees with the requirement for the global elimination of hepatitis B (WHO, 2015; Nayagam *et al.*, 2016).

Figure 3 demonstrates clearly that when the relapse rate is increased (0%, 30%, 50%, 70%, 80%), it takes a longer time for the infection (chronic carrier) to be curtailed. That is relapse slows down the potential of recovery from the infection. On the other hand, when the relapse rate is reduced by adhering to treatment it takes a short time for the infection to be curtailed as seen in figure 3. Therefore, for the infection to be put under control relapse in patients, need to be checked.

Figure 4 demonstrates clearly that when the relapse rate is increased, the number of acute infective increases.

Figure 5 shows clearly that R_r^c increases in the presence of relapse (treatment failure). Therefore, φ increases the spread of the disease in the population. Hence, it will be profitable if the impact of treatment failure is checked.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

Sensitivity Analysis Result

In interpreting the sensitivity indices, we keep all other factors constant. Table 3 shows that parameters $\beta, \delta_0, \pi, q, \gamma_{1,}\varphi$ and η increase the value of R_r^c when they are increased. This implies that the HBV infection will grow up in the population when these parameters are increased. On the contrary, $\gamma_{2\,,}p, \alpha_0$ $and\ \gamma_3$ decrease the value of R_r^c when they are increased. This implies that the disease cannot grow in the population when these parameters are increasing.

The most, sensitive parameter is the transmission coefficient β. Increasing or decreasing the value of β leads to the increase or decrease of the value of R_r^c with the same proportion since the sensitivity index is equal to one. Therefore, as β increases, many persons become infected, so HBV transmission increases in the population. Treatment rate α_0 is also sensitive, showing that as α_0 increases R_r^c decreases. This implies that treatment as a control strategy helps to reduce viral loads in most treated persons.

Furthermore, when relapse rate, φ increases then R_r^c increases, this implies that many treated individuals move to the chronic carrier-class after undergoing relapse. Therefore, to minimize HBV transmission in a population, this study recommends that relapse should be curtailed because it increases the livelihood of reoccurrences of the infection.

CONCLUSION AND RECOMMENDATION

Conclusion

In this study, we simulate a deterministic compartmental model on the impact of relapse on HBV transmission dynamics. The sensitivity analysis is carried out to show some important parameters that may cause an increase in the effective reproduction number, which could be checked by way of reoccurrences of the infection. The result of the numerical simulation reveals that relapse (reoccurrences of the infection) delays the quick response to a treatment regimen which consequently slows down the potential of recovery from the infection. Also, it increases the number of infected persons in the population and hence increases the spread of HBV.

Recommendations

Based on the findings of this research, to reduce the development of relapse as much as possible and to increase recovery, the study recommends that new drugs with low resistance should be provided, which will help to minimize the risk of relapse in controlling the spread of HBV.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI

REFERENCES

Athena, P., Kourtis, M.D., Bulterys, M.D., Dale, J., Hu, M.D. and Denise J.J.(2012). HIV-HBV co-infection- A Global challenge. *New England Journal of Medicine*.366:1749-1752.

Buti, M. (2014). HBeAg-positive chronic hepatitis B: Why do I treat my patients with nucleos(t)ide analogs.

Charan, M.S., Paramita, S.(2016). Health Programs in a Developing Country-Why do we fail? Health system policy press. 2254-9137. 100046.

Chitnis, N., Hyman, J. M. and Cushing, J. M. (2008). Determining important Parameters in the Spread of Malaria through the Sensitivity Analysis of a Mathematical model. *Bulletin of Mathematical Biology*, 70 (5): 1272-1296.

Hoofnagle, J. H. (2009). Reactivation of hepatitis B. *Journal of Hepatology*. 49(5): 156-165. Khan, A. M., Saeed, I., Muhammad, A., and Zahoor, U. H. (2016). Transmission Model of Hepatitis B Virus with the Migration Effect. *Journal of Biomedical Research International*, 2016 (2).

Kumar, M., Chauhan, R., Gupta, N. ET *et. al.,* (2009). Spontaneous increases in alanine aminotransferase levels in asymptomatic chronic hepatitis B virus-infected patients. *Journal of Gastroenterology*. 136: 1272-1280.

Karajibani, M., Hasanjan, M.*et., al.* (2018). Spontaneous relapse in patients with inactive chronic hepatitis B virus infection. *Caspian Journal of international medicine*. 9(4): 393-396.

Moore, P. S., and Chang, Y. (2010). Why do viruses cause cancer Highlights of the first century of human tumor virology. *Nature reviews Cancer*. 10(12): 878-889.

Nayagam, S., Thursz, M., Sicuri, E., Conteh, L., Wiktor, S., Low-Beer, D., and Hallett, T. B. (2016). A Modeling Study on the Requirements for Global Elimination of Hepatitis B. *Journal of The Lancet Infectious Diseases*, 16(12): 1399-1408.

Nwaokolo, M.A., Kimbir, A. R., Onah, E. S. Aboiyar, T. (2020). Global stability analysis of the effect of vaccination and treatment in controlling the spread of HBV with infective immigrants. *Journal of the Nigerian Association of mathematical physics. 54:21-35.*

Nowak. H. (2005). The natural history and treatment of chronic hepatitis B: the critical evaluation of standard treatment and endpoints. *Annals of internal medicine*. 147:58-61.

Tseng, T. C., Liu, C. I., Su, T. H., *et al.* (2012). Young chronic hepatitis B patients with nucleos(t)ide analogue induced hepatitis b e antigen seroconversion to have a higher risk of HBV reactivation. *Journal of Infectious Disease*. 206(10): 1521-1531.

Weinbaum, C. M., Williams, I., Mast, E. E., Wang, S. A., Finelli, L., Wasley, A., Neitzel, S. M. and Ward, J. W. (2008). Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection. *Journal of Morbidity and Mortality Weekly* Report, 57(8): 1-20.

Wu, C. C. H. (2019). Hepatitis B reactivation in patients with previous hepatitis B exposure to immunosuppressants. *World journal metaphysical- analysis*. 7(5): 209-217.

World Health Organization, (2015) Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization, www. who.int/HIV/pub/hepatitis/ hepatitis-b-guidelines/en/ (accessed Jan 8, 2021).

Yao, C. C.,Hung, C. H., Hu, T. H., Lu, S. N., Wang, J. H., Lee, C. M. and Chen, C. H. (2017).Incidence and Predictors of Hepatitis B Virus Relapse after Cessation of Nucleoside Analogues in Hepatitis B enveloped Antigen-Negative Patients with Hepatitis B Surface Antigen. *Natural Research Journal*, 1839(7): 2045-2322.

Zoulim, F. and Locarnini, S. (2009). Hepatitis B Virus Resistance to Nucleos(t)ide Analogues. *Journal of Gastroenterology*, 137(2): 1593– 1608.

Article DOI: 10.52589/IJPHP-RRT1W4KI
DOI URL: https://doi.org/10.52589/IJPHP-RRT1W4KI