

Scheckelhoff, Kristen; Ejaz, Ayesha; Erovenko, Igor V.; Rychtář, Jan; Taylor, Dewey

## Article

# Optimal voluntary vaccination of adults and adolescents can help eradicate Hepatitis B in China

Games

## Provided in Cooperation with:

MDPI – Multidisciplinary Digital Publishing Institute, Basel

*Suggested Citation:* Scheckelhoff, Kristen; Ejaz, Ayesha; Erovenko, Igor V.; Rychtář, Jan; Taylor, Dewey (2021) : Optimal voluntary vaccination of adults and adolescents can help eradicate Hepatitis B in China, Games, ISSN 2073-4336, MDPI, Basel, Vol. 12, Iss. 4, pp. 1-13, <https://doi.org/10.3390/g12040082>

This Version is available at:

<https://hdl.handle.net/10419/257564>

### Standard-Nutzungsbedingungen:

Die Dokumente auf EconStor dürfen zu eigenen wissenschaftlichen Zwecken und zum Privatgebrauch gespeichert und kopiert werden.

Sie dürfen die Dokumente nicht für öffentliche oder kommerzielle Zwecke vervielfältigen, öffentlich ausstellen, öffentlich zugänglich machen, vertreiben oder anderweitig nutzen.

Sofern die Verfasser die Dokumente unter Open-Content-Lizenzen (insbesondere CC-Lizenzen) zur Verfügung gestellt haben sollten, gelten abweichend von diesen Nutzungsbedingungen die in der dort genannten Lizenz gewährten Nutzungsrechte.

### Terms of use:

*Documents in EconStor may be saved and copied for your personal and scholarly purposes.*

*You are not to copy documents for public or commercial purposes, to exhibit the documents publicly, to make them publicly available on the internet, or to distribute or otherwise use the documents in public.*



*If the documents have been made available under an Open Content Licence (especially Creative Commons Licences), you may exercise further usage rights as specified in the indicated licence.*



<https://creativecommons.org/licenses/by/4.0/>

## Article

# Optimal Voluntary Vaccination of Adults and Adolescents Can Help Eradicate Hepatitis B in China

Kristen Scheckelhoff <sup>1</sup>, Ayesha Ejaz <sup>2</sup>, Igor V. Erovenko <sup>1,\*</sup> , Jan Rychtář <sup>3</sup>  and Dewey Taylor <sup>3</sup>

<sup>1</sup> Department of Mathematics and Statistics, University of North Carolina at Greensboro, Greensboro, NC 27402, USA; kmscheck@uncg.edu

<sup>2</sup> Department of Chemistry and Biochemistry, University of North Carolina at Greensboro, Greensboro, NC 27402, USA; a\_ejaz@uncg.edu

<sup>3</sup> Department of Mathematics and Applied Mathematics, Virginia Commonwealth University, Richmond, VA 23284, USA; rycharj@vcu.edu (J.R.); dttaylor2@vcu.edu (D.T.)

\* Correspondence: igor@uncg.edu

**Abstract:** Hepatitis B (HBV) is one of the most common infectious diseases, with a worldwide annual incidence of over 250 million people. About one-third of the cases are in China. While China made significant efforts to implement a nationwide HBV vaccination program for newborns, a significant number of susceptible adults and teens remain. In this paper, we analyze a game-theoretical model of HBV dynamics that incorporates government-provided vaccination at birth coupled with voluntary vaccinations of susceptible adults and teens. We show that the optimal voluntary vaccination brings the disease incidence to very low levels. This result is robust and, in particular, due to a high HBV treatment cost, essentially independent from the vaccine cost.

**Keywords:** hepatitis B; epidemiology; vaccination; public health; game theory; Nash equilibrium



**Citation:** Scheckelhoff, K.; Ejaz, A.; Erovenko, I.V.; Rychtář, J.; Taylor, D. Optimal Voluntary Vaccination of Adults and Adolescents Can Help Eradicate Hepatitis B in China. *Games* **2021**, *12*, 82. <https://doi.org/10.3390/g12040082>

Academic Editors: Ulrich Berger and Anna Conte

Received: 8 September 2021

Accepted: 22 October 2021

Published: 26 October 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Worldwide, an estimated 250 to 350 million people are infected with hepatitis B virus (HBV), and 600 to 800 thousand will die from complications of the disease each year [1–3]. This statistic persists despite the availability of highly effective HBV vaccines and the implementation of widespread vaccination programs beginning in the 1980s [4]. The prevalence of HBV infection varies throughout the world and is endemic in many of the most populous regions, including China, Southeast Asia, and parts of Africa and the Middle East, where between 8% and 15% of the population is chronically infected [5,6]. More than three-quarters of those infected with HBV live in the Asia-Pacific region, including 93 million people in China alone [4,7]. Infection with hepatitis B leads to chronic and severe liver disease, particularly cirrhosis and hepatocellular carcinoma (HCC), which account for the vast majority of HBV-related deaths [8,9].

Hepatitis B virus replicates in the liver and is spread by infected bodily fluids, primarily blood [6]. Replication is rapid and typically colonizes 70% of human liver cells within a few weeks of infection [2]. If an individual has an immune response and is able to clear the acute infection, such a response typically occurs after the liver is largely colonized; this delayed immune response presents a challenge for the timely diagnosis of HBV and may contribute to its propensity to spread. If the immune response fails to fully suppress the virus, the disease will progress to a chronic carrier state [2]. The likelihood of progression from acute to chronic infection is inversely related to the age of the individual at exposure. In about 95% of cases, adults' immune systems are able to clear the virus, while children are far more likely to develop chronic infection [2]. Children under the age of 5 develop chronic infection at a rate of 25–30%, and newborns with carrier mothers have a 90% risk of chronic infection [10].

Transmissions of HBV between humans can be classified as either perinatal, sexual, or parenteral [8]. Perinatal transmission is of particular importance to the global hepatitis

B problem, due to the extremely high risk of chronic infection in infants born to carrier mothers [6,8]. Mother-to-child represents the primary mode of transmission in highly endemic regions—those with a population seroprevalence of at least 8% [6]. In low-endemic regions—those with population seroprevalence below 2%—sexual transmission and parenteral transmission (for example, from intravenous drug use) are more significant [6], though these modes of transmission carry a relatively low risk of chronicity [8].

In China, vaccination of newborns against HBV has been recommended since 1992, and government-funded vaccination was implemented in 2002 [3,11]. The first dose of the vaccine is typically administered 24 h after birth, with follow-up doses at 1 and 3 months of age [11]. Long-term studies of the vaccination program in China have indicated that timely administration of HBV vaccines in newborns is 88% effective [11]. These programs have succeeded in reducing the infection prevalence among young children; vaccine coverage, however, varies between provinces and locations of birth (hospital vs. home birth) [3,4,12]. This may be due to rural communities typically having lower access to healthcare and other government services than urban regions. The income status is the main barrier for HBV vaccination by adults in rural China [13], where the HBV prevalence is 5.86% as opposed to 3.29% in urban areas [14].

While vaccination of newborns has been explicitly prioritized, reducing the prevalence of infection among adults has thus far not seen significant investment. Recent studies of HBV prevalence among Chinese adults indicate that vaccine coverage is higher in more economically prosperous regions [15]. Furthermore, the nationwide prevalence of HBV infection in adults remains high and represents a significant risk of virus transmission to unvaccinated individuals, both children and adults [14]. The sheer size of the human population in China and the high endemicity justifies further study into strategies to reduce disease prevalence in the adult population, as China continues to contribute significantly to the global burden of HBV.

Possible strategies to target HBV infection in adults include antiviral therapies for infected individuals and vaccination for susceptible individuals. While antiviral therapies used to impose a significant financial burden on patients, and the drugs were priced out of reach of the average Chinese adult [16,17], the costs of generic drugs have decreased dramatically, which made chronic HBV treatment with highly efficacious drugs much more cost-effective and affordable [18].

There are now many mathematical models of HBV dynamics, see, for example, [19–21] for recent reviews. ODE models typically include a version of susceptible, latent, acutely infected, chronic, recovered and/or vaccinated compartments, see for example [3,12,22–26]. Age has also been incorporated into the models, and many age-dependent models have been developed [27–31].

Game theory [32] is now increasingly applied to help model disease prevention, including HBV [33], Hepatitis C [34], polio [35], chikungunya [36], meningitis [37], monkeypox [38], cholera [39], Ebola [40], dengue [41], malaria [42], toxoplasmosis [43], African trypanosomiasis [44], visceral leishmaniasis [45] and many others. While [46–48] studied the cost-effectiveness of vaccination against Hepatitis A from a population perspective, the key factors in determining the level of vaccination within a community are the risk perception and vaccination costs from the individual's perspective [49]. The game-theoretic models can make accurate predictions about vaccination coverage. For example, a high relative typhoid vaccine cost can be linked to a low vaccine coverage in Ghana [50] and a variance of relative costs can explain the variances of Chagas disease incidence rates across countries in Latin America [51]. Many recent studies such as [52–59] used multi-agent-simulation (MAS) methodology, thus allowing considerable flexibility and realism in the modeling approach. Moreover, vaccine imperfection was considered in [60], and [61] studied vaccination games on social networks. A cost efficiency analysis of voluntary vaccination was performed in [62].

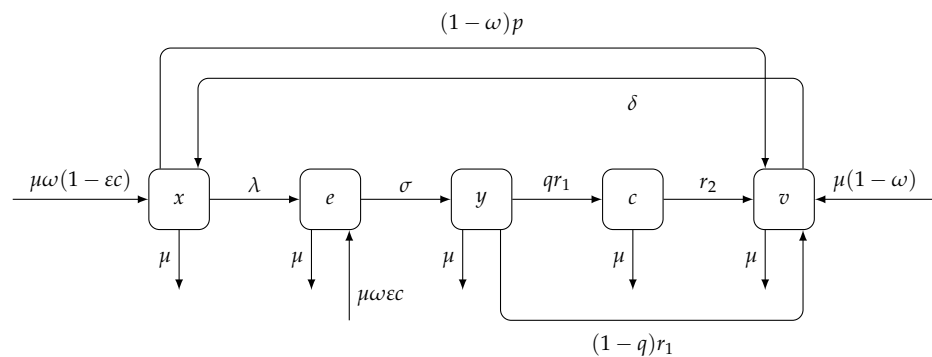
Here we add a game-theoretic component to a model of [12] to assess the effectiveness of the vaccination strategy among the population of adults and adolescents. Our aim is

to see whether voluntary vaccination can help eliminate HBV infections. We introduce the ODE model, provide its equilibrium solution and effective reproduction number in Section 2. We add the game-theoretic component in Section 3. Our main results, the optimal voluntary vaccination strategies, are shown in Section 4.1. We perform the sensitivity analysis in Section 4.2 and conclude the paper with a discussion in Section 5.

### 2. Model of HBV Dynamics

We adopt an epidemiological model for HBV from [12]. The model incorporates all key aspects of HBV dynamics, including imperfect vaccination, waning immunity, and vertical disease transmission.

The compartmental model is shown in Figure 1. The population is normalized to one and divided into five homogeneous compartments: susceptible ( $x$ ); exposed ( $e$ ); acute infections ( $y$ ); carrier ( $c$ ); and individuals with temporary immunity that was gained either naturally or through vaccination ( $v$ ).



**Figure 1.** Compartmental model of Hepatitis B. The population is divided into five compartments: susceptible ( $x$ ), exposed ( $e$ ), acutely infected ( $y$ ), chronically infected ( $c$ ), and temporarily immune ( $v$ ) individuals. Descriptions of parameters are given in Table 1.

Individuals are born at the rate  $\mu$ , and we assume that all newborns are now vaccinated. The vaccine efficacy is assumed to be  $(1 - \omega)$ ; only a fraction of  $(1 - \omega)$  of vaccinated individuals enter the compartment  $v$ . If the vaccine failed and a child is born to a carrier mother, it can become exposed with probability  $\epsilon$ , that is, individuals enter the compartment  $e$  at the rate  $\mu\omega\epsilon c$ . The rest of the newborns enter the susceptible compartment  $x$  at the rate  $\mu\omega(1 - \epsilon c)$ .

The immunity wanes and the individuals become susceptible at the rate  $\delta$ . A susceptible individual becomes exposed either through the contact with an acutely infected individual (at the rate  $\beta y$ ) or the carrier (at the rate  $\beta\alpha c$ ). The force of infection is thus

$$\lambda = \beta(y + \alpha c). \tag{1}$$

To avoid the infection, susceptible individuals vaccinate at the rate  $p$ . As with the newborn vaccination, we assume that the vaccine efficacy is  $(1 - \omega)$ .

The exposed individuals cannot infect others but slowly acquire acute infection at the rate  $\sigma$ . The acute stage lasts for the time  $1/r_1$ . A fraction  $(1 - q)$  of acutely infected individuals recover and gain immunity; they move to  $v$ . However, a fraction  $q$  progresses to a chronic carrier stage,  $c$ . The recovery rate from the chronic stage is very slow,  $r_2$ .

To keep the population size constant, we assume no disease-induced mortality and that the death rate is the same as the birth rate.

Since  $v = 1 - (x + e + y + c)$ , the model yields the following set of equations.

$$\begin{aligned}
 \frac{dx}{dt} &= \mu\omega(1 - \epsilon c) - \lambda x - (1 - \omega)px + \delta[1 - (x + e + y + c)] - \mu x \\
 \frac{de}{dt} &= \lambda x + \mu\omega\epsilon c - \sigma e - \mu e \\
 \frac{dy}{dt} &= \sigma e - r_1 y - \mu y \\
 \frac{dc}{dt} &= qr_1 y - r_2 c - \mu c.
 \end{aligned}
 \tag{2}$$

**Table 1.** Description of the symbols and parameters used in the model. The rates are per capita per year. The costs are in US dollars.

Symbol	Description	Base Value	Range	Source
$\mu$	Death rate and birth rate	1/76	[0.01, 0.015]	[63]
$\omega$	Proportion of failed immunization	0.12	[0, 0.2]	[11]
$\sigma$	Incubation rate	3	[1, 6]	[64]
$\delta$	Rate of loss of immunity	0.033	[0.01, 0.067]	[65]
$r_1$	Recovery rate from acute infections	4	[3, 5]	[19]
$r_2$	Recovery rate of carriers	0.025	[0.005, 0.025]	[27]
$\epsilon$	Probability of transmission from carrier mothers	0.78	[0.7, 0.9]	[66]
$q$	Probability of an acute infection becoming chronic	0.04	[0.02, 0.06]	[67]
$p$	Vaccination rate	varies	[0, 0.3]	assumed
$\beta$	Transmission rate	10	[5, 15]	[27]
$\alpha$	Reduction factor for transmission from carriers	0.16	[0.1, 0.2]	[27]
$K_v$	Cost of vaccination	\$3	[1, 5]	[68]
$K_y$	Cost of acute infection	\$300	[100, 500]	[69]
$K_c$	Cost of chronic infection	\$1000	[100, 2000]	[18]
$K_{HBV}$	Expected cost of infection	\$1895		Equation (11)
$K$	Relative cost of infection	0.0016		$K_v/K_{HBV}$
$p_{NE}$	Optimal vaccination rate	varies		Equation (16)
$p_{HI}$	Vaccination rate needed for herd immunity	varies		Equation (15)
$K_m$	Minimal $K$ for which $p_{NE} = 0$	varies		Equation (20)
$\lambda$	Force of infection	varies		Equation (1)
$\pi_{nv}$	Probability of infection if unvaccinated	varies		Equation (12)
$\pi_v$	Probability of infection if vaccinated	varies		Equation (13)

The effective reproduction number  $R_0$  is the average number of secondary infections caused by a single infectious individual in a wholly susceptible population [70]. Following [12] and using the next-generation matrix method [71], we obtain

$$R_0 = \frac{\beta\sigma x_0(r_2 + \mu + \alpha qr_1)}{(\sigma + \mu)(r_1 + \mu)(r_2 + \mu) - \sigma\mu\omega\epsilon qr_1}
 \tag{3}$$

where

$$x_0 = \frac{\mu\omega + \delta}{(1 - \omega)p + \delta + \mu}
 \tag{4}$$

is the value of  $x$  at the disease-free equilibrium.

When  $R_0 < 1$ , there is no HBV in the population and when  $R_0 \geq 1$ , there is a unique endemic equilibrium given in [12] as follows.

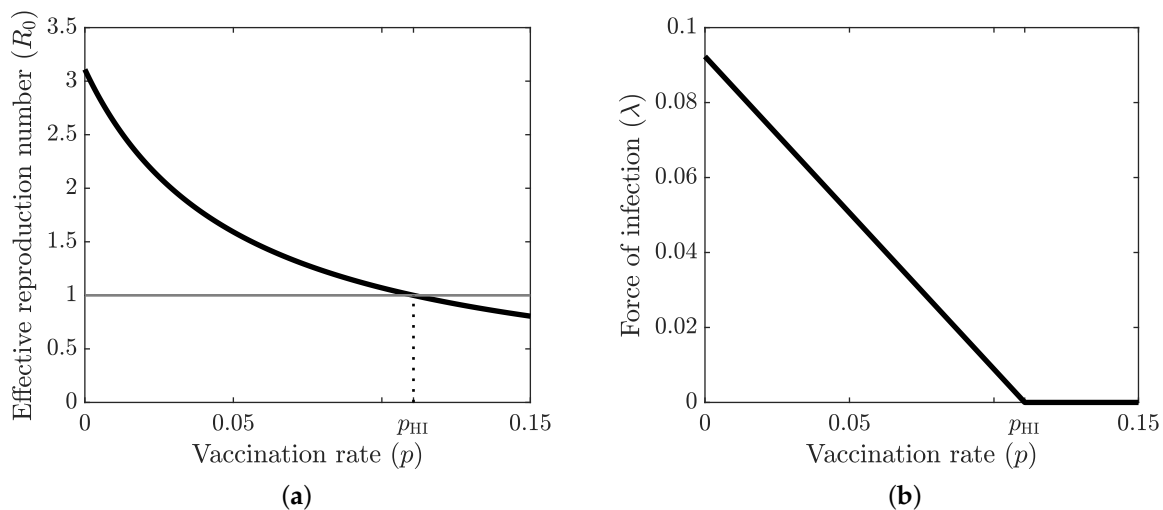
$$x^* = \frac{(\sigma + \mu)(r_1 + \mu)(r_2 + \mu) - \mu\omega\epsilon qr_1\sigma}{\beta\sigma(r_2 + \mu + \alpha qr_1)} \tag{5}$$

$$y^* = -\frac{((1 - \omega)p + \delta + \mu)x^* - (\mu\omega + \delta)}{\beta x^* \left(1 + \frac{\alpha qr_1}{r_2 + \mu}\right) + \delta \left(\frac{r_1 + \mu}{\sigma} + 1 + \frac{qr_1}{r_2 + \mu}\right) + \frac{\mu\omega\epsilon qr_1}{r_2 + \mu}} \tag{6}$$

$$e^* = \frac{r_1 + \mu}{\sigma} y^* \tag{7}$$

$$c^* = \frac{qr_1}{r_2 + \mu} y^*. \tag{8}$$

The effective reproduction number changes with the population vaccination rate  $p$ . There is a threshold herd immunity vaccination rate  $p_{HI}$  such that  $R_0 < 1$  when  $p > p_{HI}$  and  $R_0 > 1$  when  $p < p_{HI}$ . Figure 2a shows how the effective reproduction number  $R_0$  depends on  $p$ , and Figure 2b shows how the force of infection  $\lambda$  depends on  $p$ .



**Figure 2.** (a) Dependence of the effective reproduction number  $R_0$  on the vaccination rate  $p$  of susceptible individuals. (b) Dependence of the force of infection  $\lambda$  at equilibrium on the vaccination rate  $p$ . When  $p < p_{HI}$  the equilibrium is endemic, and when  $p > p_{HI}$  the equilibrium is disease-free. Parameter values as specified in Table 1.

### 3. Game-Theoretical Model of Vaccination Decisions

Here we follow the framework introduced in [32] and add a game-theoretical component to the model of [12] discussed in the previous section.

The players of the game are adult and teen individuals who chose whether to (re)vaccinate or not. We note that due to vaccine failures and vaccine waning, even if 100% are vaccinated at birth, all individuals are eventually at risk of HBV infection. The payoffs  $E_s$  to a player using strategy  $s \in \{v, nv\}$  for vaccinate and not vaccinate are given by

$$E_v = -K_v - \pi_v K_{HBV} \tag{9}$$

$$E_{nv} = -\pi_{nv} K_{HBV} \tag{10}$$

where  $K_v$  is the cost of vaccination,  $K_{HBV}$  is the expected cost of HBV infection. Here  $\pi_{nv}$  is the lifetime probability of becoming infected if not vaccinated, while  $\pi_v$  is the lifetime probability of HBV infection after receiving a vaccine.

The solution of the game, called the Nash equilibrium, is the population-level vaccination strategy at which no individual can increase their own payoff by deviating from the population strategy.

The cost of vaccination,  $K_v$ , includes direct costs associated with obtaining the vaccine, indirect costs such as negative side effects, the time loss and the travel cost, and perceived costs such as the fear of vaccines [72]. The expected cost of HBV infection,  $K_{HBV}$ , similarly includes direct, indirect, and perceived costs. We can evaluate

$$K_{HBV} = K_y + \frac{qr_1}{r_1 + \mu} K_c \tag{11}$$

which reflects the cost of acute infection  $K_y$  and the cost of chronic infection  $K_c$ . The cost of the chronic infection is adjusted by the probability of developing the chronic infection; this probability is calculated as the probability of transitioning from the acute state  $y$  to the chronic state  $c$ . Many costs associated with vaccination and infection cannot be quantified, but it can be assumed in the short term that these costs are constant. The estimates for the direct costs are given in Table 1. The direct costs may be paid by the government or insurance companies. However, the individuals still have to consider the indirect costs (such as lower quality of life), and we assume that the indirect costs are correlated with the direct costs.

The probabilities  $\pi_{nv}$  and  $\pi_v$  are determined as follows. If an individual does not vaccinate, they become exposed with probability  $\frac{\lambda}{\lambda + \mu}$  and then progress to acute infection with probability  $\frac{\sigma}{\sigma + \mu}$ :

$$\pi_{nv} = \frac{\lambda}{\lambda + \mu} \cdot \frac{\sigma}{\sigma + \mu}. \tag{12}$$

Note that, by (1), the force of infection  $\lambda$  depends on  $y$  and  $c$ , and hence by Equations (6) and (8) on the population’s vaccination rate  $p$ .

A vaccinated individual can become infected if the vaccine fails (with probability  $\omega$ ) or vaccine did not fail (with probability  $(1 - \omega)$ ) but the vaccine-induced immunity wanes over time (with probability  $\frac{\delta}{\delta + \mu}$ ). Thus,

$$\pi_v = \left( \omega + \frac{(1 - \omega)\delta}{\delta + \mu} \right) \cdot \pi_{nv}. \tag{13}$$

To find the Nash equilibrium, we solve  $E_{nv} = E_v$  for  $p \in [0, 1]$ , that is,

$$\pi_{nv} = K - \pi_v \tag{14}$$

where  $K = K_v / K_{HBV}$  is the relative cost of the HBV infection. If  $E_v < E_{nv}$  for all  $p \in [0, \infty)$ , then  $p_{NE} = 0$ .

### 4. Results

#### 4.1. Optimal Vaccination Strategies

When  $R_0 < 1$ , there is no disease in the population. Thus, the optimal vaccination rate is  $p_{NE} = 0$  and the vaccination rate needed for the herd immunity is  $p_{HI} = 0$ . When  $R_0 \geq 1$ , the herd immunity rate is given by

$$p_{HI} = \left( \frac{\mu\omega + \delta}{x^*} - \mu - \delta \right) (1 - \omega)^{-1}, \tag{15}$$

see [12], and the Nash equilibrium (i.e., the solution of Equation (14)) for small enough  $K$  is given by

$$p_{NE} = p_{HI} - \frac{\mu Kb}{d(a - K)(1 - \omega)}, \tag{16}$$

where

$$a = (1 - \omega) \left( \frac{\sigma}{\sigma + \mu} \right) \left( \frac{\mu}{\delta + \mu} \right) \tag{17}$$

$$b = \beta \left( 1 + \frac{\alpha q r_1}{r_2 + \mu} \right) + \delta \left( \frac{r_1 + \mu}{\sigma} + 1 + \frac{q r_1}{r_2 + \mu} \right) + \frac{\mu \omega \epsilon q r_1}{r_2 + \mu} \tag{18}$$

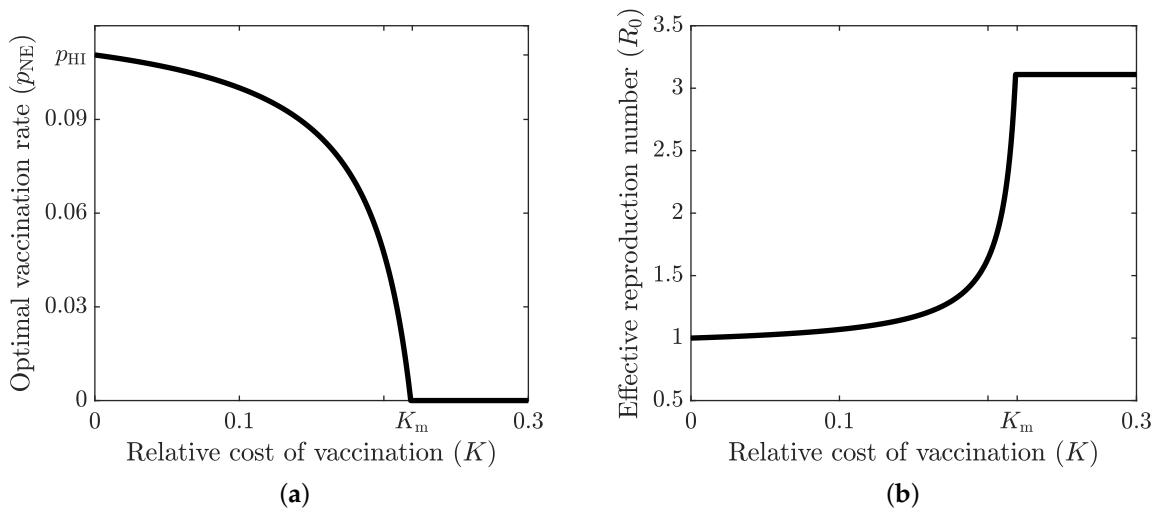
$$d = \beta \left( 1 + \frac{\alpha q r_1}{r_2 + \mu} \right). \tag{19}$$

For the parameter values as in Table 1,  $p_{HI} = 0.11065$  and  $p_{NE} = 0.11055$ . This means that the optimal vaccination rate is very close to the rate needed to eradicate the disease and if slightly over 11% of susceptible individuals vaccinate every year, the herd immunity should be achieved.

We note that  $p_{NE} = 0$  whenever  $K \geq K_m$  where

$$K_m = \frac{p_{HI}(1 - \omega)ad}{\mu b + p_{HI}(1 - \omega)d}. \tag{20}$$

As shown in Figure 3,  $p_{NE}$  decreases as the relative cost of vaccination increases. Furthermore, when  $K > 0$ ,  $p_{NE} < p_{HI}$ . The effective reproduction number  $R_0$  remains close to the threshold value of 1 for small values of relative cost, then increases sharply as  $K$  approaches a critical threshold  $K_m$  at which no vaccination is optimal.



**Figure 3.** (a) The graph of optimal population vaccination rate  $p_{NE}$  as a function of relative cost  $K$ . Note that  $p_{NE} = p_{HI}$  only when  $K = 0$ . (b) Variation in  $R_0$  at the optimal vaccination rate as a function of relative cost  $K$ .

#### 4.2. Sensitivity and Uncertainty Analysis

We performed uncertainty and sensitivity analysis using the LHS-PRCC scheme [73,74]. LHS stands for the Latin Hyper-cube Sampling, also called a stratified sampling without replacement technique. The random parameter distributions are divided into equal probability intervals, which are then sampled. The sampling is performed independently for each parameter. It gives an unbiased estimate of the average model output and requires fewer samples than simple random sampling to achieve the same accuracy [75]. PRCC, partial rank correlation coefficient, between model parameter  $P$  and model output  $O$  is a correlation coefficient

$$r_{R_P, R_O} = \frac{\text{Cov}(R_P, R_O)}{\sqrt{\text{Var}(R_P)\text{Var}(R_O)}} \tag{21}$$

between  $R_P$  and  $R_O$ , which are residuals of the rank-transformed linear regression models for  $P$  and  $O$ . PRCC is a robust sensitivity measure for nonlinear but monotonic relationships



between inputs and the output, as long as little to no correlation exists between the inputs [76]. A PRCC value of  $\pm 1$  means a perfectly linear relationship while a PRCC value of 0 means no linear relationship. The LHS-PRCC scheme is described in detail in [76] and the MATLAB and R implementation can be found in [77].

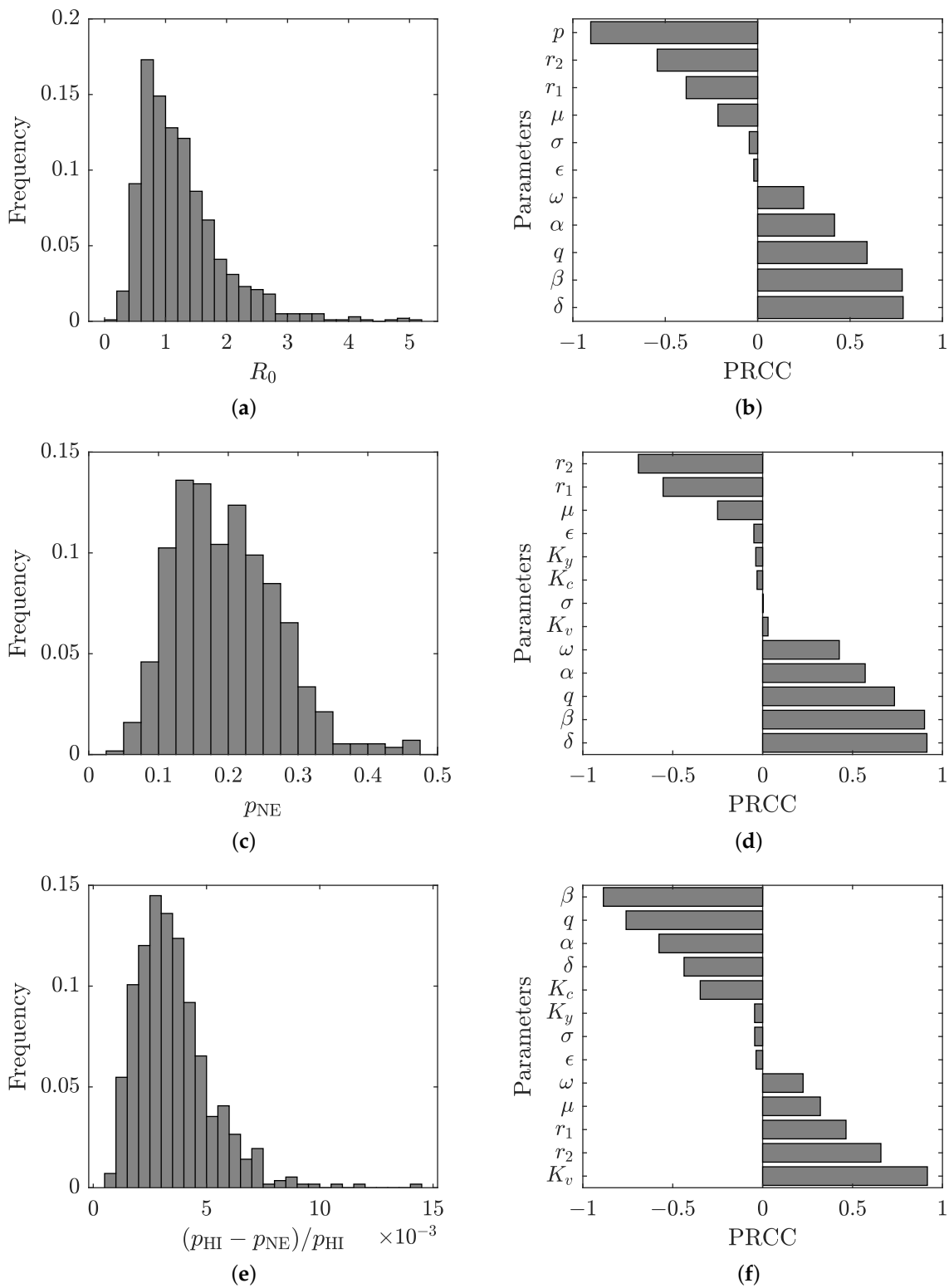
Three response functions were selected for the LHS-PRCC analysis: (1) the effective reproduction number  $R_0$  given by (3); (2) the optimal vaccination rate  $p_{NE}$  given by (16); and (3) the relative difference between the optimal vaccination rate and the herd immunity vaccination rate,  $|p_{HI} - p_{NE}|/p_{HI}$ . The results are shown in Figure 4.

There is a strong negative correlation between the vaccination rate in susceptibles ( $p$ ) and the effective reproduction number ( $R_0$ ). The effective reproduction number also shows negative correlation with recovery rate of carriers ( $r_2$ ) and acute cases ( $r_1$ ), and the death and birth rate ( $\mu$ ). There is a strong positive correlation between  $R_0$  and the loss of immunity ( $\delta$ ), probability of chronic infection ( $q$ ), transmission rate ( $\beta$ ), and relative infectiousness of carriers ( $\alpha$ ). The proportion of failed immunizations ( $\omega$ ) also positively correlates with  $R_0$ . There is essentially no dependence on the proportion of unimmunized children born to infectious mothers ( $\varepsilon$ ) or the incubation rate ( $\sigma$ ), which is expected because these parameters do not significantly affect the total number of infections in a population.

The PRCCs for the optimal vaccination are very similar to the PRCCs for  $R_0$  for all parameters that  $p_{NE}$  and  $R_0$  have in common. With the exception of the incubation rate  $\sigma$  (which does not have any significant effect), the parameters which increase (or decrease) the effective reproduction number also increase (or decrease) the optimal vaccination rate. This is because  $R_0$  and the herd immunity vaccination level  $p_{HI}$  are highly correlated and, as seen from Figure 4e,  $p_{NE}$  is essentially identical to  $p_{HI}$ . Note that  $p_{NE}$  is not overly sensitive to changes in the vaccination cost or the cost of the infection. This is caused by an already low relative cost  $K$ . Note that when  $R_0 < 1$ , the optimal response is  $p_{NE} = 0$ , so the Figure 4c–f focus only on parameters for which  $R_0 \geq 1$ .

The relative difference between the optimal vaccination rate and herd immunity vaccination rate is always very small, typically less than  $10^{-2}$  and the distribution peaks around at  $3 \times 10^{-3}$ . This means that  $p_{NE}$  is very close to  $p_{HI}$  regardless of the variation of model parameters, and the prediction that the optimal voluntary vaccination can help to eradicate HBV is very robust. There is a strong negative correlation with the probability of chronic infection ( $q$ ) and the transmission rate ( $\beta$ ). An increase in any of these parameters means that  $p_{NE}$  would follow  $p_{HI}$  even closer. There is also a strong positive correlation with the cost of the vaccine ( $K_v$ ) and the recovery rates ( $r_2$  and  $r_1$ ). An increase in any of these parameters would mean that the optimal voluntary vaccination levels would differ more from the level needed to achieve herd immunity.

We note that there is quite a large uncertainty about the true values of vaccine effectiveness  $\omega$  [11] and vaccine waning  $\delta$  [65]. However, our analysis, specifically Figure 4f, indicates that none of these parameters have a significant effect on the qualitative results. The optimal voluntary vaccination helps with the HBV elimination regardless of the exact values of  $\omega$  and  $\delta$ .



**Figure 4.** Results of the uncertainty (left-hand side panels) and sensitivity (right-hand side panels) analysis. Three response functions were considered: (1) the effective reproduction number  $R_0$  (panels (a,b)); (2) the optimal vaccination rate  $p_{NE}$  when  $R_0 > 1$  (panels (c,d)); and (3) the relative difference between the herd immunity vaccination rate and the optimal vaccination rate  $|p_{HI} - p_{NE}|/p_{HI}$  when  $R_0 > 1$  (panels (e,f)). The parameter ranges are as in Table 1.

## 5. Conclusions and Discussion

We investigated the impact of individual decisions for or against vaccination by applying the game-theoretic approach [32] to an epidemiological model of [12]. The model parameters were selected from data specific to the current HBV epidemic in China, which accounts for a significant portion of HBV infections and HBV-related deaths worldwide. Our results show that given the success of current efforts to inoculate children [11], population-level herd immunity against HBV can be obtained through annual vaccination of approximately 11% of adults and teens who are susceptible. The model also predicts that optimal voluntary vaccination levels closely match the levels needed for the herd immunity. This prediction is very robust and essentially independent on relatively large variances in model parameters. Consequently, the voluntary vaccination program can significantly help to reduce HBV prevalence in China and contribute to its eventual eradication.

The HBV voluntary vaccination was also recently studied by [33], who based their model on [3]. They separated vaccine-induced immunity from the natural immunity, considered a much faster loss of the vaccine-induced protection but assumed no loss of the natural immunity. They also assumed 100% vaccine efficacy. In the light of recent data that the vaccine-induced immunity can last 30 or more years [78], the model presented here is more realistic. However, despite the differences, both models qualitatively agree that the voluntary vaccination of adults and teens can significantly lower the disease incidence levels. The predictions are also in agreement with [79], who demonstrated that when the relative cost of the vaccine is sufficiently low, the optimal voluntary vaccination can yield to disease elimination even for an imperfect vaccine.

An individual's age is an important factor for the risk of HBV infection becoming chronic [10]. Our model should thus be further extended by explicitly including age-dependency as performed, for example, in [27–31]. We expect that such an extension will not qualitatively alter the results, and the voluntary vaccination will still be a crucial tool helping to eliminate HBV. However, the exact quantitative results may change, and it is thus worthwhile to consider further research in this direction.

For the voluntary vaccination program to work, the relative cost of the vaccine needs to be low and the population needs to be made aware of the disease. In agreement with [72], our sensitivity analysis demonstrated that the actual vaccines should be as cheap and accessible as possible to minimize the patient's direct cost, time loss, and travel costs. At the same time, note that the costs of curative HBV treatments are more expensive than the average Chinese adult can afford, and in many cases, the perceived cost of infection is inordinately high, leading to fear and discrimination [80]. Our sensitivity analysis also shows that this high cost of the treatment (and the high risk of becoming a chronic carrier) is one of the main reasons why the optimal voluntary vaccination levels closely track the level needed for herd immunity. The high cost of HBV infections means that the relative vaccination cost is very low even if the vaccine is not provided for free. The actual access to vaccination, rather than the direct vaccine cost, is thus a more important limiting factor to achieving the desired vaccination coverage. At the same time, the lack of HBV awareness is one of the main barriers for the vaccination in rural China [13].

Nationwide efforts are needed to eradicate HBV in China. The efforts in rural areas could be especially cost-effective and could help reduce regional disparities in the burden of disease caused by HBV [68]. The eradication efforts should include not only providing access to vaccination in rural regions but also providing proper education and increasing the awareness of the general population. The education campaign should stress the existence and availability of a vaccine to adults and teens.

**Author Contributions:** Conceptualization, K.S., A.E. and I.V.E.; methodology I.V.E., J.R. and D.T.; formal analysis, K.S., A.E., I.V.E., J.R. and D.T.; writing—original draft preparation, K.S., A.E., I.V.E., J.R. and D.T.; writing—review and editing, I.V.E., J.R. and D.T.; funding acquisition, I.V.E. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Center for Undergraduate Research in Mathematics (CURM) mini-grant with I.V.E. as a faculty advisor and K.S. and A.E. as undergraduate student researchers.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

- MacLachlan, J.; Locarnini, S.; Cowie, B. Estimating the global prevalence of hepatitis B. *Lancet* **2015**, *386*, 1515–1517. [[CrossRef](#)]
- Seeger, C.; Litwin, S.; Mason, W. Hepatitis B virus: Persistence and clearance. In *Hepatitis B Virus in Human Diseases*; Liaw, Y., Zoulim, F., Eds.; Humana Press: Cham, Switzerland, 2016; Chapter 6, pp. 123–145. [[CrossRef](#)]
- Zou, L.; Zhang, W.; Ruan, S. Modeling the transmission dynamics and control of Hepatitis B virus in China. *J. Theor. Biol.* **2010**, *262*, 330–338. [[CrossRef](#)] [[PubMed](#)]
- Chu, C.; Liaw, Y. Natural history of hepatitis B infection. In *Hepatitis B Virus in Human Diseases*; Liaw, Y., Zoulim, F., Eds.; Humana Press: Cham, Switzerland, 2016; Chapter 11, pp. 217–248. [[CrossRef](#)]
- Margolis, H.S.; Alter, M.J.; Hadler, S.C. Hepatitis B: Evolving epidemiology and implications for control. In *Seminars in Liver Disease*; Thieme Medical Publishers, Inc.: Stuttgart, Germany, 1991; Volume 11, pp. 84–92.
- Shepard, C.; Simard, E.; Finelli, L.; Fiore, A.; Bell, B. Hepatitis B virus infection: Epidemiology and vaccination. *Epidemiol. Rev.* **2006**, *28*, 112–125. [[CrossRef](#)]
- Khan, T.; Zaman, G.; Chohan, M. The transmission dynamic and optimal control of acute and chronic hepatitis B. *J. Biol. Dyn.* **2017**, *11*, 172–189. [[CrossRef](#)] [[PubMed](#)]
- Hou, J.; Liu, Z.; Gu, F. Epidemiology and prevention of hepatitis B virus infection. *Int. J. Med. Sci.* **2005**, *2*, 50–57. [[CrossRef](#)] [[PubMed](#)]
- Abubakar, I.I.; Tillmann, T.; Banerjee, A. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **2015**, *385*, 117–171. [[CrossRef](#)]
- Lok, A.S.; McMahon, B.J. Chronic hepatitis B. *Hepatology* **2007**, *45*, 507–539. [[CrossRef](#)] [[PubMed](#)]
- Liang, X.; Bi, S.; Yang, W.; Wang, L.; Cui, G.; Cui, F.; Zhang, Y.; Liu, J.; Gong, X.; Chen, Y.; et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992–2005 in China. *J. Infect. Dis.* **2009**, *200*, 39–47. [[CrossRef](#)] [[PubMed](#)]
- Pang, J.; Cui, J.; Zhou, X. Dynamical behavior of a hepatitis B virus transmission model with vaccination. *J. Theor. Biol.* **2010**, *265*, 572–578. [[CrossRef](#)]
- Zhu, D.; Guo, N.; Wang, J.; Nicholas, S.; Wang, Z.; Zhang, G.; Shi, L.; Wangen, K.R. Socioeconomic inequality in hepatitis B vaccination of rural adults in China. *Hum. Vaccines Immunother.* **2018**, *14*, 464–470. [[CrossRef](#)]
- Wang, H.; Men, P.; Xiao, Y.; Gao, P.; Lv, M.; Yuan, Q.; Chen, W.; Bai, S.; Wu, J. Hepatitis B infection in the general population of China: A systematic review and meta-analysis. *BMC Infect. Dis.* **2019**, *19*, 811. [[CrossRef](#)] [[PubMed](#)]
- Liu, J.; Zhang, S.; Wang, Q.; Shen, H.; Zhang, M.; Zhang, Y.; Yan, D.; Liu, M. Seroepidemiology of hepatitis B virus infection in 2 million men aged 21–49 years in rural China: A population-based, cross-sectional study. *Lancet Infect. Dis.* **2016**, *16*, 80–86. [[CrossRef](#)]
- Zhang, C.; Ke, W.; Gao, Y.; Zhou, S.; Liu, L.; Ye, X.; Yao, Z.; Yang, Y. Cost-effectiveness analysis of antiviral therapies for hepatitis B e antigen-positive chronic hepatitis B patients in China. *Clin. Drug Investig.* **2015**, *35*, 197–209. [[CrossRef](#)]
- Zheng, X.; Wang, J.; Yang, D. Antiviral therapy for chronic hepatitis B in China. *Med. Microbiol. Immunol.* **2015**, *204*, 115–120. [[CrossRef](#)] [[PubMed](#)]
- Toy, M.; Hutton, D.; McCulloch, K.; Romero, N.; Revill, P.A.; Penicaud, M.C.; So, S.; Cowie, B.C. The price tag of a potential cure for chronic hepatitis B infection: A cost threshold analysis for USA, China and Australia. In *Liver International*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2021.
- Liang, P.; Zu, J.; Zhuang, G. A literature review of mathematical models of hepatitis B virus transmission applied to immunization strategies from 1994 to 2015. *J. Epidemiol.* **2018**, *28*, 221–229.
- Goyal, A.; Liao, L.E.; Perelson, A.S. Within-host mathematical models of hepatitis B virus infection: Past, present, and future. *Curr. Opin. Syst. Biol.* **2019**, *18*, 27–35. [[CrossRef](#)] [[PubMed](#)]
- Li, M.; Zu, J. The review of differential equation models of HBV infection dynamics. *J. Virol. Methods* **2019**, *266*, 103–113. [[CrossRef](#)] [[PubMed](#)]
- Kamyad, A.V.; Akbari, R.; Heydari, A.A.; Heydari, A. Mathematical modeling of transmission dynamics and optimal control of vaccination and treatment for hepatitis B virus. *Comput. Math. Methods Med.* **2014**, *2014*, 475451. [[CrossRef](#)]
- Zhang, S.; Zhou, Y. The analysis and application of an HBV model. *Appl. Math. Model.* **2012**, *36*, 1302–1312. [[CrossRef](#)]
- O’Leary, C.; Hong, Z.; Zhang, F.; Dawood, M.; Smart, G.; Kaita, K.; Wu, J. A mathematical model to study the effect of hepatitis B virus vaccine and antiviral treatment among the Canadian Inuit population. *Eur. J. Clin. Microbiol. Infect. Dis.* **2010**, *29*, 63. [[CrossRef](#)] [[PubMed](#)]

25. Thornley, S.; Bullen, C.; Roberts, M. Hepatitis B in a high prevalence New Zealand population: A mathematical model applied to infection control policy. *J. Theor. Biol.* **2008**, *254*, 599–603. [[CrossRef](#)]
26. Medley, G.F.; Lindop, N.A.; Edmunds, W.J.; Nokes, D.J. Hepatitis-B virus endemicity: Heterogeneity, catastrophic dynamics and control. *Nat. Med.* **2001**, *7*, 619. [[CrossRef](#)] [[PubMed](#)]
27. Edmunds, W.; Medley, G.; Nokes, D. The transmission dynamics and control of Hepatitis B virus in The Gambia. *Stat. Med.* **1996**, *15*, 2215–2233. [[CrossRef](#)]
28. Williams, J.; Nokes, D.; Medley, G.; Anderson, R. The transmission dynamics of hepatitis B in the UK: A mathematical model for evaluating costs and effectiveness of immunization programmes. *Epidemiol. Infect.* **1996**, *116*, 71–89. [[CrossRef](#)] [[PubMed](#)]
29. Zhao, S.; Xu, Z.; Lu, Y. A mathematical model of hepatitis B virus transmission and its application for vaccination strategy in China. *Int. J. Epidemiol.* **2000**, *29*, 744–752. [[CrossRef](#)]
30. Kretzschmar, M.; Mangen, M.J.; van de Laar, M.; de Wit, A. Model based analysis of hepatitis B vaccination strategies in the Netherlands. *Vaccine* **2009**, *27*, 1254–1260. [[CrossRef](#)] [[PubMed](#)]
31. Zou, L.; Ruan, S.; Zhang, W. An age-structured model for the transmission dynamics of hepatitis B. *SIAM J. Appl. Math.* **2010**, *70*, 3121–3139. [[CrossRef](#)]
32. Bauch, C.; Earn, D. Vaccination and the theory of games. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 13391–13394. [[CrossRef](#)] [[PubMed](#)]
33. Chouhan, A.; Maiwand, S.; Ngo, M.; Putalapattu, V.; Rychtář, J.; Taylor, D. Game-theoretical model of retroactive Hepatitis B vaccination in China. *Bull. Math. Biol.* **2020**, *82*, 80. [[CrossRef](#)] [[PubMed](#)]
34. Scheckelhoff, K.; Ejaz, A.; Erovenko, I.V. A game-theoretic model of optimal clean equipment usage to prevent hepatitis C among injecting drug users. *Preprint* **2019**.
35. Cheng, E.; Gambhirrao, N.; Patel, R.; Zhouandai, A.; Rychtář, J.; Taylor, D. A game-theoretical analysis of Poliomyelitis vaccination. *J. Theor. Biol.* **2020**, *499*, 110298. [[CrossRef](#)] [[PubMed](#)]
36. Klein, S.R.; Foster, A.O.; Feagins, D.A.; Rowell, J.T.; Erovenko, I.V. Optimal voluntary and mandatory insect repellent usage and emigration strategies to control the chikungunya outbreak on Reunion Island. *PeerJ* **2020**, *8*, e10151. [[CrossRef](#)] [[PubMed](#)]
37. Martinez, A.; Machado, J.; Sanchez, E.; Erovenko, I.V. Optimal vaccination strategies to reduce endemic levels of meningitis in Africa. *Preprint* **2019**.
38. Bankuru, S.V.; Kossol, S.; Hou, W.; Mahmoudi, P.; Rychtář, J.; Taylor, D. A Game-theoretic Model of Monkeypox to Assess Vaccination Strategies. *PeerJ* **2020**, *8*, e9272. [[CrossRef](#)] [[PubMed](#)]
39. Kobe, J.; Pritchard, N.; Short, Z.; Erovenko, I.V.; Rychtář, J.; Rowell, J.T. A Game-Theoretic Model of Cholera with Optimal Personal Protection Strategies. *Bull. Math. Biol.* **2018**, *80*, 2580–2599. [[CrossRef](#)] [[PubMed](#)]
40. Brettin, A.; Rossi-Goldthorpe, R.; Weishaar, K.; Erovenko, I.V. Ebola could be eradicated through voluntary vaccination. *R. Soc. Open Sci.* **2018**, *5*, 171591. [[CrossRef](#)]
41. Dorsett, C.; Oh, H.; Paulemond, M.L.; Rychtář, J. Optimal repellent usage to combat Dengue Fever. *Bull. Math. Biol.* **2016**, *78*, 916–922. [[CrossRef](#)] [[PubMed](#)]
42. Broom, M.; Rychtář, J.; Spears-Gill, T. The game-theoretical model of using insecticide-treated bed-nets to fight Malaria. *Appl. Math.* **2016**, *7*, 852–860. [[CrossRef](#)]
43. Sykes, D.; Rychtář, J. A game-theoretic approach to valuating Toxoplasmosis vaccination strategies. *Theor. Popul. Biol.* **2015**, *105*, 33–38. [[CrossRef](#)] [[PubMed](#)]
44. Crawford, K.; Lancaster, A.; Oh, H.; Rychtář, J. A voluntary use of insecticide-treated cattle can eliminate African Sleeping Sickness. *Lett. Biomath.* **2015**, *2*, 91–101. [[CrossRef](#)]
45. Fortunato, A.; Glasser, C.; Watson, J.; Lu, Y.; Rychtář, J.; Taylor, D. Mathematical modeling of the use of insecticide treated nets for elimination of visceral leishmaniasis in Bihar, India. *R. Soc. Open Sci.* **2021**, *8*, 201960. [[CrossRef](#)] [[PubMed](#)]
46. Bauch, C.; Anonychuk, A.; Pham, B.; Gilca, V.; Duval, B.; Krahn, M. Cost-utility of universal hepatitis A vaccination in Canada. *Vaccine* **2007**, *25*, 8536–8548. [[CrossRef](#)] [[PubMed](#)]
47. Bauch, C.; Rao, A.S.S.; Pham, B.; Krahn, M.; Gilca, V.; Duval, B.; Chen, M.; Tricco, A. A dynamic model for assessing universal Hepatitis A vaccination in Canada. *Vaccine* **2007**, *25*, 1719–1726. [[CrossRef](#)] [[PubMed](#)]
48. Anonychuk, A.M.; Tricco, A.C.; Bauch, C.T.; Ba'Pham; Gilca, V.; Duval, B.; John-Baptiste, A.; Woo, G.; Krahn, M. Cost-effectiveness analyses of hepatitis A vaccine. *Pharmacoeconomics* **2008**, *26*, 17–32. [[CrossRef](#)] [[PubMed](#)]
49. Chang, S.L.; Piraveenan, M.; Pattison, P.; Prokopenko, M. Game theoretic modelling of infectious disease dynamics and intervention methods: A review. *J. Biol. Dyn.* **2020**, *14*, 57–89. [[CrossRef](#)]
50. Acosta-Alonzo, C.B.; Erovenko, I.V.; Lancaster, A.; Oh, H.; Rychtář, J.; Taylor, D. High endemic levels of typhoid fever in rural areas of Ghana may stem from optimal voluntary vaccination behavior. *Proc. R. Soc. A* **2020**, *476*, 20200354,
51. Han, C.Y.; Issa, H.; Rychtář, J.; Taylor, D.; Umana, N. A voluntary use of insecticide treated nets can stop the vector transmission of Chagas disease. *PLoS Neglected Trop. Dis.* **2020**, *14*, e0008833. [[CrossRef](#)] [[PubMed](#)]
52. Iwamura, Y.; Tanimoto, J. Realistic decision-making processes in a vaccination game. *Phys. A Stat. Mech. Its Appl.* **2018**, *494*, 236–241. [[CrossRef](#)]
53. Kabir, K.A.; Jusup, M.; Tanimoto, J. Behavioral incentives in a vaccination-dilemma setting with optional treatment. *Phys. Rev. E* **2019**, *100*, 062402. [[CrossRef](#)] [[PubMed](#)]
54. Kabir, K.A.; Tanimoto, J. Modelling and analysing the coexistence of dual dilemmas in the proactive vaccination game and retroactive treatment game in epidemic viral dynamics. *Proc. R. Soc. A* **2019**, *475*, 20190484. [[CrossRef](#)]

55. Kuga, K.; Tanimoto, J.; Jusup, M. To vaccinate or not to vaccinate: A comprehensive study of vaccination-subsidizing policies with multi-agent simulations and mean-field modeling. *J. Theor. Biol.* **2019**, *469*, 107–126. [CrossRef] [PubMed]
56. Arefin, M.R.; Masaki, T.; Kabir, K.A.; Tanimoto, J. Interplay between cost and effectiveness in influenza vaccine uptake: A vaccination game approach. *Proc. R. Soc. A* **2019**, *475*, 20190608. [CrossRef] [PubMed]
57. Arefin, M.R.; Kabir, K.A.; Tanimoto, J. A mean-field vaccination game scheme to analyze the effect of a single vaccination strategy on a two-strain epidemic spreading. *J. Stat. Mech. Theory Exp.* **2020**, *2020*, 033501. [CrossRef]
58. Huang, J.; Wang, J.; Xia, C. Role of vaccine efficacy in the vaccination behavior under myopic update rule on complex networks. *Chaos Solitons Fractals* **2020**, *130*, 109425. [CrossRef]
59. Kabir, K.A.; Tanimoto, J. Evolutionary game theory modelling to represent the behavioural dynamics of economic shutdowns and shield immunity in the COVID-19 pandemic. *R. Soc. Open Sci.* **2020**, *7*, 201095. [CrossRef] [PubMed]
60. Kabir, K.A.; Tanimoto, J. Analysis of individual strategies for artificial and natural immunity with imperfectness and durability of protection. *J. Theor. Biol.* **2021**, *509*, 110531. [CrossRef] [PubMed]
61. Kuga, K.; Tanaka, M.; Tanimoto, J. Pair approximation model for the vaccination game: Predicting the dynamic process of epidemic spread and individual actions against contagion. *Proc. R. Soc. A* **2021**, *477*, 20200769. [CrossRef]
62. Kabir, K.A.; Tanimoto, J. Cost-efficiency analysis of voluntary vaccination against n-serovar diseases using antibody-dependent enhancement: A game approach. *J. Theor. Biol.* **2020**, *503*, 110379. [CrossRef] [PubMed]
63. World Bank. Life Expectancy at Birth. 2019. Available online: <https://data.worldbank.org/indicator/SP.DYN.LE00.IN?locations=CN> (accessed on 18 December 2019).
64. Alter, M.J. Epidemiology and prevention of Hepatitis B. *Semin. Liver Dis.* **2003**, *23*, 39–46. [CrossRef] [PubMed]
65. van Damme, P. Long-term protection after hepatitis B vaccine. *J. Infect. Dis.* **2016**, *214*, 1–3. [CrossRef]
66. Lo, K.J.; Tsai, Y.T.; Lee, S.D.; Wu, T.C.; Wang, J.Y.; Chen, G.H.; Yeh, C.L.; Chiang, B.N.; Yeh, S.H.; Goudeau, A. Immunoprophylaxis of infection with hepatitis B virus in infants born to hepatitis B surface antigen-positive carrier mothers. *J. Infect. Dis.* **1985**, *152*, 817–822. [CrossRef] [PubMed]
67. Hyams, K.C. Risks of chronicity following acute hepatitis B virus infection: A review. *Clin. Infect. Dis.* **1995**, *20*, 992–1000. [CrossRef]
68. Hutton, D.W.; So, S.K.; Brandeau, M.L. Cost-effectiveness of nationwide Hepatitis B catch-up vaccination among children and adolescents in China. *Hepatology* **2010**, *51*, 405–414. [CrossRef]
69. Toy, M.; Hutton, D.W.; So, S.K. Cost-effectiveness and cost thresholds of generic and brand drugs in a national chronic Hepatitis B treatment program in China. *PLoS ONE* **2015**, *10*, e0139876. [CrossRef] [PubMed]
70. Hethcote, H. The Mathematics of Infectious Diseases. *SIAM Rev.* **2000**, *42*, 599–653. [CrossRef]
71. van den Driessche, P.; Watmough, J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math. Biosci.* **2002**, *180*, 29–48. [CrossRef]
72. Zhu, D.; Wang, J.; Wangen, K.R. Hepatitis B vaccination coverage rates among adults in rural China: Are economic barriers relevant? *Vaccine* **2014**, *32*, 6705–6710. [CrossRef] [PubMed]
73. Blower, S.; Dowlatabadi, H. Sensitivity and uncertainty analysis of complex models of disease transmission: An HIV model, as an example. *Int. Stat. Rev.* **1994**, *62*, 229–243. [CrossRef]
74. Saltelli, A.; Tarantola, S.; Campolongo, F.; Ratto, M. *Sensitivity Analysis in Practice: A Guide to Assessing Scientific Models*; Wiley Online Library: Hoboken, NJ, USA, 2004; Volume 1.
75. McKay, M.D.; Beckman, R.J.; Conover, W.J. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics* **2000**, *42*, 55–61. [CrossRef]
76. Marino, S.; Hogue, I.B.; Ray, C.J.; Kirschner, D.E. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *J. Theor. Biol.* **2008**, *254*, 178–196. [CrossRef] [PubMed]
77. Kirschner, D. Uncertainty and Sensitivity Functions and Implementation. 2020. Available online: <http://malthus.micro.med.umich.edu/lab/usanalysis.html> (accessed on 9 January 2021).
78. Bruce, M.G.; Bruden, D.; Hurlburt, D.; Zanis, C.; Thompson, G.; Rea, L.; Toomey, M.; Townshend-Bulson, L.; Rudolph, K.; Bulkow, L.; et al. Antibody levels and protection after hepatitis B vaccine: Results of a 30-year follow-up study and response to a booster dose. *J. Infect. Dis.* **2016**, *214*, 16–22. [CrossRef] [PubMed]
79. Jijón, S.; Supervie, V.; Breban, R. Prevention of treatable infectious diseases: A game-theoretic approach. *Vaccine* **2017**, *35*, 5339–5345. [CrossRef] [PubMed]
80. Yu, L.; Wang, J.; Zhu, D.; Leng, A.; Wangen, K. Hepatitis B-related knowledge and vaccination in association with discrimination against hepatitis B in rural China. *Hum. Vaccines Immunother.* **2016**, *12*, 70–76. [CrossRef] [PubMed]