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Recognizing the impact of endemic hepatitis D virus on hepatitis B virus eradication

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ABSTRACT

Background:

Hepatitis delta virus (HDV) in conjunction with hepatitis B virus (HBV) increases adult morbidity and mortality. A number of studies have performed cost-benefit analyses for HBV interventions, but they have ignored the impact of HDV on these outcomes.

Methods:

Using a mathematical model of HBV–HDV epidemiology, we compare health benefits and cost outcomes of four interventions: testing with HBV adult vaccination (diagnosis), diagnosis with antiviral treatment for HBV infections (mono-infections), diagnosis with antiviral treatment for HBV–HDV infections (dual-infections), and awareness programs. The relationship between optimal levels and outcomes of each of these interventions and HDV prevalence in HBV infected individuals ranging from 0 to 50% is determined.

Results:

Over a 50 year period under no intervention, HBV prevalence, per capita total cost and death toll increase by 2.25%, -$11 and 2.6-fold respectively in moderate HDV endemic regions compared to mono-infected regions; the corresponding values for high HDV endemic regions are 4.2%, -$21 and 3.9-fold. Optimal interventions can be strategized similarly in mono and dually endemic regions. Only implementation of all four interventions achieves a very low HBV prevalence of around 1.5% in a moderate HDV endemic region such as China, with 2.8 million fewer deaths compared to no intervention. Although the policy of implementation of all four interventions costs additional $382 billion compared to no intervention, it still remains cost-effective with an incremental cost-effectiveness ratio of $1400/QALY. Very high efficacy awareness programs achieve less prevalence with fewer deaths at a lower cost compared to treatment and/or vaccination programs.

Conclusion:

HDV substantially affects the performance of any HBV-related intervention. Its exclusion results in over-estimation of the effectiveness of HBV interventions.

1. Introduction

Hepatitis B virus (HBV) is the leading cause of liver infection and liver failure around the globe. The current infection pool is approximately 350 million worldwide causing 1 million deaths per year (Elgouhari et al., 2008). China alone contributes 300,000 HBV related deaths annually from a population of 120 million carriers (Bureau of Democracy, 2010; Lu et al., 2013b). Infection with HBV is necessary for HDV replication within and transmission from an individual and 5%–10% of HBV mono-infected individuals are also infected with HDV (Hughes et al., 2011; WHO, 2001). Despite the comparably lower numbers, the high progression rates to the chronic phase, cirrhosis, liver failure, and ten times higher risk of mortality makes HDV a significant concern in a number of regions (WHO, 2001).

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The main routes of HBV transmission are: (i) from a mother to child at birth (vertical transmission), (ii) through sexual contact with an infected person (horizontal transmission), and (iii) among intravenous drug users (Elgouhari et al., 2008). HDV transmission modes are similar to HBV except for the absence of vertical transmission (Bonino and Rizzetto, 1989; Purcell and Gerin, 1996; WHO, 2001).

There are a few antiviral therapies available for HBV, but none specifically for HDV (Buti et al., 2011; Di Bisceglie, 2002; Hutton et al., 2010). The success of HBV antiviral therapies is also uncertain and highly dependent upon the infection stage in which therapy is administrated (Di Bisceglie, 2002; WHO, 2001; Yi et al., 2011). The World Health Organization (WHO) has recommended HBV vaccination to newborns in order to eliminate both HBV and HDV in highly endemic regions. However total elimination would require an unreasonably long time even in the absence of HBV vertical transmission (Goyal and Murray, 2014). In the meantime, HBV and HDV continue to result in new infections and subsequent deaths from horizontal transmission of these diseases. The resulting increased adult morbidity and mortality pose a significant drain on the development of the economies affected by both diseases (Lorentzen et al., 2008).

Mathematical models and numerical simulations have been widely used to identify effective interventions for several infectious diseases (Lee et al., 2010; Martin et al., 2011; Piratvisuth, 2013; Zhou et al., 2013). Mathematical models are time and cost effective ways to study a disease and find effective means for their management. Numerous studies have captured the transmission dynamics of HBV in a population (Pang et al., 2010; Zhao et al., 2000; Zhou et al., 2009; Zou et al., 2010a,b). They have considered age structured modeling, spatial effects, and the effectiveness of long term vaccination programs. In particular, Armbruster et al. studied the optimal control of HBV in a population through different policies such as optimal screening and contact tracing (Armbruster and Brandeau, 2010). Several studies report cost-effectiveness analyses for HBV (He et al., 2012; Lu et al., 2013a,b; Tu et al., 2012; Wu et al., 2012). Focusing mostly on China, these studies did not consider the additional complications of the 10% of individuals who are also infected with HDV (Lee et al., 2010; Martin et al., 2011; Piratvisuth, 2013; Zhou et al., 2013). HDV inclusion may significantly alter the outcome of any intervention as there is no vaccination or effective therapy for this virus (Xiridou et al., 2009). Therefore the focus of this article is to determine the impact HDV can have on policies for regions endemic with both HBV and HDV.

In this paper, we develop a mathematical model which captures the dynamics of the spread of HBV and HDV in a population. In the process of determining HDV impact, we also derive (i) optimal interventions achieving the minimum prevalence of both viruses, and (ii) conduct a cost-benefit analysis. We consider four interventions: testing and HBV adult vaccination (diagnosis), diagnosis and antiviral treatment for HBV mono-infected individuals, diagnosis and antiviral treatment for dually (HBV–HDV) infected individuals and awareness programs (Anderson et al., 2009; Di Bisceglie, 2002; Kiss et al., 2010; Shepard et al., 2006). Finally, the model is applied to two different HDV endemic environments, moderate (China) and high (Amazon Basin).

2. Methods

2.1. Disease transmission and natural course

Our model is the extended version of the model proposed by Goyal and Murray (2014) and Xiridou et al. (2009). We divide the population into the following classes: R_u vaccinated children; X_u unvaccinated and uninfected children; Y_u unvaccinated and infected children; X susceptible adults; R_v adults vaccinated as children; Y_{a2u} undiagnosed chronic HBV infections developed from unvaccinated and infected children; Y_{b1u} acute undiagnosed HBV adults; Y_{b2u} chronic diagnosed HBV adults; Y_{b1} acute diagnosed HBV adults; Y_{b2} chronic diagnosed HBV adults; Y_{bd1u} acute undiagnosed HBV–HDV adults; Y_{bd2u} chronic undiagnosed HBV–HDV adults; Y_{bd1} acute diagnosed HBV–HDV adults; Y_{bd2} chronic diagnosed HBV–HDV adults; Y_{bT} HBV mono-infected adults with failed treatment; Y_{bdT} HBV–HDV dually infected adults with failed treatment. The R and R_T classes are both recovered adults (via natural recovery, recovery due to treatment, or adult vaccination). The only difference between the two is that individuals in the R_T class are aware of their status while those in R are not.

In the model, we assume that a fraction of newborns (β) receive HBV vaccination after birth and move to the X_u group. The remaining fraction will become part of Y_u. Almost 95% of HBV infected and unvaccinated children (Y_u) fail to clear acute infection and develop chronic infection and move to Y_{a2u} (D'Souza and Foster, 2004). The parameters G_b and F_b represent rates of HBV horizontal transmission from HBV mono-infected individuals and dually infected individuals respectively to susceptible individuals. Similarly F_d represents the rate of HDV horizontal transmission from dually infected individuals to HBV mono-infected individuals. Furthermore, F_{bd} represents the simultaneous transmission rate of HBV and HDV from dually infected individuals to susceptible individuals. We also include age group specific (α) and disease specific (ν_{b2}, ν_{bd2}) mortality in the model (The World Bank, 2013). Relapse is not included in the model as a person recovered from these infections is considered to be immune forever due to the development of disease specific antibodies (Prevention, 2009; Wedemeyer and Manns, 2010). A detailed description of model parameters is provided in Table 1.

The acute phase in our model is representative of all acute and severe acute infections while the chronic phase includes chronic HBV, compensated cirrhosis, decompensated cirrhosis and primary liver cancer infections. Per person per year cost in the acute and chronic phases were reported as average values which are calculated after employing costs and proportions of patients in the different sub-classes of the acute and chronic phases. In a study by Lu et al. in Shandong (China), the number of patients with acute HBV, severe HBV, chronic HBV, compensated cirrhosis, decompensated cirrhosis and primary liver cancer were 29, 28, 449, 121, 202 and 65 respectively. The associated nonmedical per year per person cost in these different stages of HBV infection were \$199, \$1426, \$831, \$1237, \$1069 and \$1490 respectively (Lu et al., 2013a). In their study, the nonmedical cost accounted for expenditures on nutritional supplements, transportation, and patient accompaniers' costs as a result of the disease, and were calculated based on patients hospitalized, and the costs were reported for the last month and year before their hospitalization. After including the cost of several stages of HBV (Wu et al., 2012), we determine per person per year cost in the acute and chronic phases as \$1431 and \$1783 respectively based on the proportion of patients and associated costs (Lu et al., 2013a). Costs in the acute and chronic phases of HDV are assumed the same as for HBV since current treatment guidelines for HBV and HDV are similar.

2.2. Interventions

We consider four interventions,

1. HBV antiviral therapy provided to a fraction of mono-infected individuals represented by $u_1(t)$.
2. HBV antiviral therapy provided to a fraction of dually infected individuals represented by $u_2(t)$.

Table 1
Parameter description and their values. All costs are in US$.

Parameter	Interpretation	Value (Range)	Reference
γ_b	Rate of progression from acute to chronic HBV infection	0.4/person/year	Xiridou et al. (2009) and Zhao et al. (2000)
ϕ	Rate of partner change	1.64 partners/year	Goyal and Murray (2014), Hertog (2007), Huang et al. (2014), Xiridou et al. (2009) and Zou et al. (2015)
μ_r	Birth rate	0.013/year	The World Bank (2013)
μ	Death rate	0.007/year	Goyal and Murray (2014)
β	HBV vaccination coverage in newborns	90%	Goyal and Murray (2014)
θ_{b1}	Rate of adult recovery from acute HBV infection	3.6/person/year	Goyal and Murray (2014), Xiridou et al. (2009) and Zhao et al. (2000)
θ_{b2}	Rate of adult recovery from chronic HBV infection	0.02/person/year	Goyal and Murray (2014) and Xiridou et al. (2009)
p_{b1}	Probability of HBV sexual transmission from an individual in the HBV acute phase	0.46	Constantin (2015), Goyal and Murray (2014), Williams et al. (1996) and Xiridou et al. (2009)
p_{b2}	Probability of HBV sexual transmission from an individual in the HBV chronic phase	$0.65p_{b1}$	Goyal and Murray (2014) and Xiridou et al. (2009)
γ_{bd}	Rate of progression from acute to chronic in dually infected	2/person/year	Goyal and Murray (2014) and Xiridou et al. (2009)
θ_{bd1}	Rate of recovery from acute dual infection	2/person/year	Goyal and Murray (2014) and Xiridou et al. (2009)
θ_{bd2}	Rate of recovery from chronic dual infection	0.02/person/year	Goyal and Murray (2014) and Xiridou et al. (2009)
q_{bj}	Probability of HBV sexual transmission from dually infected individual at stage $j = 1, 2$ corresponding to acute and chronic phase respectively	$0.71p_{bj}$	Goyal and Murray (2014) and Xiridou et al. (2009)
q_{dj}	Probability of HDV sexual transmission from dually infected individual at stage $j = 1, 2$ corresponding to acute and chronic phase respectively	q_{bj}	Goyal and Murray (2014) and Xiridou et al. (2009)
δ_X	Rate of maturation of children to adulthood	1/14/year	Bureau of Democracy (2010) and Goyal and Murray (2014)
ν_{b2}	Disease induced mortality rate in chronically HBV infected individuals	0.0013/year	Bonino and Rizzetto (1989), Buti et al. (2011) and Purcell and Gerin (1996)
ν_{bd2}	Disease induced mortality rate in chronically dually infected individuals	0.013/year	Bonino and Rizzetto (1989), Buti et al. (2011) and Purcell and Gerin (1996)
α	Extra-mortality rate during childhood	0.01/year	Goyal and Murray (2014) and The World Bank (2013)
W_{11}	Cost associated with $\rho(t)$ (HBV testing)	$92.75/person[a]	Liu et al. (2012)
W_{12}	Cost associated with $\rho(t)$ (HBV vaccination)	$17.75/person[a]	Liu et al. (2012)
W_2	Cost associated with $u_1(t)$ or $u_2(t)$ (HBV testing and treatment cost)	$13 375/person/year[b]	He et al. (2012) and Lu et al. (2013a)
W_3	Cost associated with $u_3(t)$	$0.58/person/year	Anderson et al. (2009)
ϵ_1	HBV antiviral therapy efficacy for HBV mono-infected	0.7 (0.5–0.7)	Yi et al. (2011)
ϵ_2	HBV antiviral therapy efficacy for dually infected	0.25 (0.17–0.43)	Hughes et al. (2011) and Wedemeyer and Manns (2010)
ϵ_3	Social distancing control function efficacy	0.2 (0–1)	Assumed
T	Time interval	50 years[c]	
C_1	Cost associated with acute HBV	$1431/person/year	Lu et al. (2013a)
C_2	Cost associated with chronic HBV	$1783/person/year	Lu et al. (2013a)
C_3	Cost associated with acute HBV–HDV	$1431/person/year	
C_4	Cost associated with chronic HBV–HDV	$1783/person/year	
r	Annual discount rate	3% (1%–5%)	He et al. (2012)
ρ_0	Maximum threshold of testing rate	2% per year[d]	
ν	Reduction in sexual contact rate after positive diagnosis for HBV or HDV	0.5 (0–1)	Assumed

[a] Interleukin-28B (IL-28B) test is used to determine HBV positivity in an individual. The cost of this test is $371 while the cost of a HBV adult vaccination course is around $70 per person in the US. We also assume the testing cost of HDV to be the same as for the IL-28B test for HBV. The cost estimates of vaccination and testing are derived by assuming that medical costs in China are approximately 4 times lower than in the US (detailed explanation provided in Procedure).

[b] Treatment cost includes drug, medical and nonmedical care with peginterferon/ribavirin (PEG-IFN+Rb) for 48 weeks (similar for HCV and HBV) or in extreme cases, liver transplantation (Hutton et al., 2010). We determined per person cost in either the acute or chronic phase based on the proportion of patients and associated costs in different stages of either acute or chronic phase (Lu et al., 2013a).

[c] Model only achieves HBV prevalence of less than 1.5% under any policy with a low 2% diagnosis rate and $T = 50$. Therefore, we choose $T = 50$ for the investigation of the model.

[d] There are 65,838 hospitals and clinics in China. Assuming all of these have the capability to test for HBV and HDV and each of them can easily test one person per day, we get a maximum coverage rate of 2% per year in China.

3. Intensity of the awareness programs including educating adolescents and promoting safer sex to reduce horizontal transmission represented by $u_3(t)$. This represents the percentage of the population receiving this intervention.
4. Intensity of diagnosis represented by $\rho\,(t) = \rho_0 u_4(t)$. Here, ρ_0 is the maximum feasible annual diagnosis rate.

Efficacies ϵ_1 and ϵ_2 represent the fraction of HBV mono-infected and dually infected individuals respectively receiving antiviral treatment and successfully treated (moved to class R_T of recovered). The remaining fractions $(1-\epsilon_1)$ and $(1-\epsilon_2)$ move to class Y_{bT} and Y_{bdT} of failed treatment respectively. The efficacy ϵ_3 represents the % reduction in infectivity due to awareness programs. We omit treatment for children because of the very low efficacy and side-effects at young age (Maria Elzbieta and Marek, 2005).

All infected individuals are first assumed to be untested, and after testing classified as diagnosed. Furthermore, we assume that diagnosed infected individuals become aware of their transmission risk and hence their transmission probability reduces by a factor of ν.

2.3. Mathematical model

Combining all the elements presented above, the mathematical model is given by

$$
\begin{aligned}
dR_u/dt &= \mu_r\beta(N - R_u - X_u - Y_u) - \delta_X R_u - \alpha R_u - \mu R_u\\
dX_u/dt &= \mu_r\,(1-\beta)\,(X + R_v + R + R_T) - \delta_X X_u - \alpha X_u - \mu X_u\\
dY_u/dt &= \mu_r\,(1-\beta)\,(N - (R_u + X_u + Y_u + X + R_v\\
&\qquad + R + R_T)) - \delta_X Y_u - \alpha Y_u - \mu Y_u\\
dX/dt &= \delta_X X_u - X\,(G_b + F_b + F_{bd}) - \mu X - \rho(t)X\\
dR_v/dt &= \delta_X\,R_u - \mu R_v
\end{aligned}
$$

$$dY_{a2u}/dt = 0.95\delta_X Y_u - Y_{a2u}F_d - (\mu + \rho(t) + \theta_{b2} + \nu_{b2})Y_{a2u}$$
$$dY_{b1u}/dt = X\,(G_b + F_b) - Y_{b1u}F_d - (\mu + \rho(t) + \theta_{b1} + \gamma_b)Y_{b1u}$$
$$dY_{b2u}/dt = \gamma_b Y_{b1u} - Y_{b2u}F_d - (\mu + \rho(t) + \theta_{b2})Y_{b2u} - \nu_{b2}Y_{b2u}$$
$$dY_{b1}/dt = \rho(t)Y_{b1u} - \nu Y_{b1}F_d - (\mu + \theta_{b1} + \gamma_b)\,Y_{b1}$$
$$\begin{aligned} dY_{b2}/dt \;=\; & \rho\,(t)\,(Y_{b2u} + Y_{a2u}) + \gamma_b Y_{b1} - \nu Y_{b2}F_d \\ & - (\mu + \theta_{b2})\,Y_{b2} - \nu_{b2}Y_{b2} - u_1\,(t)\,Y_{b2} \end{aligned}$$
$$\begin{aligned} dY_{bd1u}/dt \;=\; & XF_{bd} + (Y_{a2u} + Y_{b1u} + Y_{b2u} + \nu Y_{b1} \\ & + \nu Y_{b2})\,F_d - (\mu + \rho(t) + \theta_{bd1} + \gamma_{bd})Y_{bd1u} \end{aligned}$$
$$dY_{bd2u}/dt = \gamma_{bd}Y_{bd1u} - (\mu + \rho(t) + \theta_{bd2})Y_{b2u} - \nu_{bd2}Y_{bd2u}$$
$$dY_{bd1}/dt = \rho(t)Y_{bd1u} - (\mu + \theta_{bd1} + \gamma_{bd})\,Y_{bd1} - u_2\,(t)\,Y_{bd1}$$
$$\begin{aligned} dY_{bd2}/dt \;=\; & \rho(t)Y_{bd2u} + \gamma_{bd}Y_{bd1} - (\mu + \theta_{bd2})\,Y_{bd2} \\ & - u_2\,(t)\,Y_{bd2} - \nu_{bd2}Y_{bd2} \end{aligned}$$
$$dY_{bT}/dt = (1 - \epsilon_1)u_1\,(t)\,Y_{b2} - \mu Y_{bT}$$
$$dY_{bdT}/dt = (1 - \epsilon_2)u_2\,(t)\,(Y_{bd1} + Y_{bd2}) - \mu Y_{bdT}$$
$$\begin{aligned} dR/dt \;=\; & 0.05\delta_X Y_u + \theta_{b1}\,(Y_{b1} + Y_{b1u}) + \theta_{b2}(Y_{b2} + Y_{b2u} + Y_{a2u}) \\ & + \theta_{bd1}(Y_{bd1} + Y_{bd1u}) \\ & + \theta_{bd2}(Y_{bd2} + Y_{bd2u}) - \rho(t)R - \mu R \end{aligned}$$
$$\begin{aligned} dR_T/dt \;=\; & u_1\,(t)\,\epsilon_1 Y_{b2} + u_2\,(t)\,\epsilon_2(Y_{bd1} + Y_{bd2}) \\ & + \rho(t)X + \rho(t)R - \mu R_T \end{aligned}$$

where,

$$G_b = \phi\,(1 - \epsilon_3 u_3\,(t))\sum_{j=1,2}(p_{bj}Y_{bju} + p_{b2}Y_{a2u} + \nu p_{bj}Y_{bj})/N$$
$$\begin{aligned} F_b \;=\; & \phi\,(1 - \epsilon_3 u_3\,(t))\sum_{j=1,2}\left(q_{bj}\left(1 - q_{dj}\right)Y_{bdju}\right. \\ & \left. + \nu q_{bj}\left(1 - \nu q_{dj}\right)Y_{bdj}\right)/N \end{aligned}$$
$$F_d = \phi\,(1 - \epsilon_3 u_3\,(t))\sum_{j=1,2}(q_{dj}Y_{bdju} + \nu q_{dj}Y_{bdj})/N$$
$$F_{bd} = \phi\,(1 - \epsilon_3 u_3\,(t))\sum_{j=1,2}(q_{bj}q_{dj}Y_{bdju} + \nu^2 q_{bj}q_{dj}Y_{bdj})/N$$
$$\rho(t) = \rho_0 u_4(t).$$

Here,

$$\begin{aligned} N \;=\; & R_u + X_u + Y_u + R_v + X + Y_{b1u} + Y_{b2u} + Y_{a2u} \\ & + Y_{b1} + Y_{b2} + Y_{bd1u} + Y_{bd2u} + Y_{bd1} \\ & + Y_{bd2} + Y_{bT} + Y_{bdT} + R + R_T. \end{aligned}$$

2.4. Policies and associated cost functions

Five different policies and their cost functions are formulated as follows,

1. Policy 0: No intervention applied.

   $G\,(0, 0, 0, 0) = I_0$.
2. Policy 1: Four interventions applied together.

   $G\,(u_1, u_2, u_3, \rho) = I_0 + I_1 + I_2 + I_3 + I_4$.
3. Policy 2: Diagnosis with antiviral treatment for HBV mono-infected individuals.

   $G\,(u_1, 0, 0, \rho) = I_0 + I_1 + I_2$.
4. Policy 3: Diagnosis with antiviral treatment for dually infected individuals.

   $G\,(0, u_2, 0, \rho) = I_0 + I_1 + I_3$.
5. Policy 4: Awareness programs alone.

   $G\,(0, 0, u_3, 0) = I_0 + I_4$.

Here, $I_0(t)$ represents the cost incurred due to diagnosed and untreated infected individuals while $I_1(t)$ to $I_4(t)$ represent the cost of diagnosis, the treatment cost of mono-infected individuals, the treatment cost of dually infected individuals and the cost of awareness programs respectively incurred on state on the time interval $[t, t + 1)$. In our model, controls (u_1 to u_4) are calculated at discrete times (yearly) while all variables in the model are continuous which makes the calculation of costs on the time interval $[t, t + 1)$ complex. In order to simplify it, we employ the population structure at the start of the year (time, t). In this process, these population compartments at the start of the year represent the approximate average number of individuals over the entire year. For example, an individual stays in the HBV acute phase for about 6 months accommodated through the progression rate $\gamma_b = 0.4$/year. Therefore $Y_{b1}(t)$ in the definition of costs (I_0 to I_4) represents the approximate average number of individuals with diagnosed acute HBV infection over the entire year $[t, t + 1)$ (although any single individual will only be acute for 6 months).

Cost of diagnosis includes the cost of interleukin-28B (IL-28B) test conducted to determine HBV positivity in an individual as well as the cost of HBV adult vaccination course (Liu et al., 2012). The testing cost of HDV is assumed to be similar as IL-28B test for HBV. HBV antiviral treatment cost includes drug, medical and nonmedical care with peginterferon/ribavirin (PEG+IFN +Rb) for 48 weeks or in extreme cases, liver transplantation (Hutton et al., 2010). We estimate per person cost in acute and chronic phase based on the proportion of patients and associated costs in different stages of acute and chronic phase determined by Lu et al. (2013a). Since current treatment guidelines are similar for HBV and HDV, therefore we assume same cost for both diseases in acute and chronic phase. Detailed information on the per capita yearly costs of infections (C_1 to C_4) and interventions (W_1 to W_3) is provided in Table 1. These costs are calculated over a finite time interval of T years with a discount rate 'r',

$$\begin{aligned} I_0 \;=\; & \sum_{t=0}^{T}(1 + r)^{-t}\,\{C_1 Y_{b1}\,(t) + C_2 Y_{bT}\,(t) + (1 - u_1\,(t)) \\ & C_2 Y_{b2} + C_2 Y_{bdT}(t) + (1 - u_2\,(t))\,[C_3 Y_{bd1}(t) + C_4 Y_{bd2}(t)]\} \end{aligned}$$
$$\begin{aligned} I_1 \;=\; & \sum_{t=0}^{T}(1 + r)^{-t}\,\rho(t)\,[W_{11}\,(X\,(t) + 4Y_{b1u}\,(t) \\ & + 4Y_{b2u}\,(t) + 4Y_{a2u}(t) + 2Y_{bd1u}\,(t) \\ & + 2Y_{bd2u}\,(t) + R\,(t)) + W_{12}X\,(t)] \end{aligned}$$
$$I_2 = \sum_{t=0}^{T}W_2\,(1 + r)^{-t}\,[u_1\,(t)\,Y_{b2}\,(t)]$$
$$I_3 = \sum_{t=0}^{T}W_2\,(1 + r)^{-t}\,[u_2(t)(Y_{bd1}(t) + Y_{bd2}(t))]$$
$$I_4 = \sum_{t=0}^{T}W_3\,(1 + r)^{-t}\,u_3(t)(N(t) - R_u(t) - R_v(t) - R_T(t))$$
$$u_i\,(t) = \sum_{\tau=0}^{T}u_{i\tau}\,\chi_\tau(t), \quad i = 1, \ldots, 4$$

where $\chi_\tau\,(t) = 1$, for $t \in [\tau, \tau + 1)\,, 0$ else.

Each diagnosed HBV infection is first assumed to be in the acute phase and is confirmed within 6 months to verify that an individual has not spontaneously cleared the infection but is in the chronic phase. They are then enrolled on treatment (Liu et al., 2012). If HDV is present in the population, an individual diagnosed with HBV is also tested for HDV (Prevention, 2009). The testing cost (I_1) includes the testing of HBV mono-infected individuals four times (twice in 6 months duration each for both HBV and HDV) and dually infected individuals twice (once each for HBV and HDV). For I_1, I_2 and I_3, associated costs depend on target groups such as susceptible individuals and infected individuals. For I_4, the cost

is dependent on the total size of the susceptible group and the infected population which is given by $(N - R_u - R_v - R_T)$.

At the end of the time interval $T = 50$ years (or, year 2064), a certain number of people may still be infected with HBV and HDV (residual infections). The lifetime cost of residual infections at time T (I_5) is calculated as follows,

$$\begin{aligned} I_5(T) = {} & 15\,000\,(1+r)^{-T}\,[Y_u\,(T) + Y_{b1u}\,(T) + Y_{b1}\,(T) \\ & + Y_{b2u}\,(T) + Y_{b2}\,(T) + Y_{a2u}(T) + Y_{bT}\,(T) \\ & + Y_{bd1u}\,(T) + Y_{bd1}\,(T) + Y_{bd2u}\,(T) \\ & + Y_{bd2}\,(T) + Y_{bdT}\,(T)]. \end{aligned}$$

For I_5, we employ the lifetime health care cost per HBV infected person of \$15,000 in China (Foundation, 2014). We assume a similar lifetime cost for HDV. All costs are estimated in US\$.

2.5. Procedure

Our aim is to determine interventions $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$ that minimize the cost of each of the programs G with constraints $0 \le u_{it} \le 1,\ i = 1, \ldots, 4,\ t = 0, \ldots, T$. Here, $u_{it} = 1$ represents the intervention applied at its full intensity on the time interval $[t, t+1)$. The solutions to these optimal intervention problems are determined after discretizing the time interval into yearly time steps, where the interventions are held constant on each time step and where the optimal levels of the interventions over each year u_{it} are calculated through the optimization routine fmincon [Matlab R2012a]. We assume 10% and 50% initial HDV prevalence in HBV infected individuals for moderate and high HDV endemic regions respectively (Castilho et al., 2012; Wedemeyer and Manns, 2010). Model parameters related to population structure and demographics are derived for the Chinese population in Table 1. Since costs of these interventions are not easily available for China (moderately HDV endemic) or highly HDV endemic regions (such as the Amazon Basin), they are calculated based on the medical and health care cost in the US (Table 1). Further, these estimates can be translated to a particular economy such as China based on the ratio of cost of interventions for other viruses in the same category. For example, high end HBV newborn vaccination costs \$8 in China; however, the same vaccination costs \$29 in the US (Hutton et al., 2010; Prevention, 2016). Similarly HCV treatment costs \$80,000 (with administration costs) and \$18,000 (without administration costs) in the US and China respectively (Sisters et al., 2010). Based on these numbers, we assume HBV and HDV related costs in China are approximately 4 times lower than in the US. Therefore all the medical costs are calculated for the US economy and then all results are converted for China using a 4:1 ratio of medical cost between the US and China (and then reported in Table 1). We are unable to obtain similar figures for high HDV endemic regions. Therefore, we use the same conversion for both regions. The conversion procedure only impacts cost and has no effect on the structure of the optimal controls. Our model also includes 90% vaccination in newborns which holds true for China (a moderate HDV endemic region) but its level is unknown for high HDV endemic regions. Maintaining equivalent costs between regions as well as assuming 90% vaccination levels in newborns for high HDV endemic regions allows us to test the impact of different levels of HDV endemicity on policies, which is our main aim. The results for high HDV endemic regions may not be as accurate as desired because of the underlying assumptions and data restrictions; however, these assumptions enable us to fulfill our aim. Additionally we did not include the program cost of 90% vaccination in newborns because they have already been proven cost-effective and serves as a base case for additional interventions (Hutton et al., 2010; Lu et al., 2013b). We also found that newborn vaccination only adds \$0.64 to per capita total cost (PCTC) and therefore can be omitted. We define PCTC as the sum of the cumulative cost of implementation of any policy over the next 50 years and the lifetime cost of residual infections at 50 years divided by the total population.

3. Results

3.1. Performance of optimal policies

HBV and HDV prevalence decrease from 6.2% and 1.19% in 2014 to 3.2% and 0.37% in 2064 respectively in China, a moderately HDV endemic country, in the absence of any intervention as a result of 90% HBV vaccination in newborns (Fig. 1). Model simulations of the HBV–HDV-related death toll are 244,500 for China in 2014, a reasonable estimate compared to the 300,000 annual deaths (WHO, 2001). Minor discrepancies are due to ignoring the disease-induced deaths in the acute phase of both viruses. With no intervention, a total of 10.01 million disease related deaths will be recorded over the 50 year duration in China despite the significant decrease observed in HBV and HDV prevalence (Fig. 2).

The optimal HBV antiviral treatment policy for mono-infected individuals treats no-one in the last 15 years (Fig. 3, simulated for $T = 50$ years). The same effect is also observed when simulations are conducted for $T = 20$, 30 and 70 years. Therefore, this is an artifact caused by the constraint on the time period T. Due to this constraint, infections that are diagnosed in the period $[T - 15, T]$ have lower accumulated non-medical costs (I_0 for 15 years) compared to providing high cost antiviral treatment for one year (I_2 for one year). However there are no such constraints on the time period T in the real world. Therefore we remove this artifact in optimal interventions and assume the presence of all interventions at full intensity for the duration $[0, T]$ except for antiviral treatment for dually infected individuals. Antiviral treatment for dually infected individuals has low efficacy and very high cost which results in no monetary benefit of treating these infections. As a result dually infected individuals are not treated in any policy at any time. Awareness programs are implemented for almost as long as the duration T while HBV adult vaccination is applied until all of the susceptible population is vaccinated. These results hold for all policies (Fig. 3).

Understandably any additional intervention performs better than no intervention in terms of death-toll and new infections. For example, policies 1, 2, 3 and 4 would prevent 21.1, 19.1, 13.3 and 4.2 million new HBV infections, and 1.9, 1.5, 1.4 and 0.6 million new HDV infections respectively compared to policy 0 over the next 50 years in China. Any additional intervention also causes a minimum decrease of 8.4% in the death toll of policy 0. In particular, policy 1, 2, 3 and 4 would bring down the death toll of policy 0 by 2.8, 2.3, 1.3 and 0.8 million in China over the next 50 years. Policies 0 to 4 are slightly less effective in highly HDV endemic regions (Table 2).

PCTC of policy 0 increases due to implementation of the interventions, where the degree of increase is independent of HDV endemicity. For example, PCTC are \$294, \$311, \$339 and \$2 higher than policy 0 under policies 1, 2, 3 and 4 respectively for moderately HDV endemic regions. Even for highly HDV endemic regions, all interventions make a similar impact as PCTC are \$294, \$313, \$338 and \$1 higher respectively than policy 0. Despite this similar increase, highly HDV endemic regions still exhibit lower PCTC under all polices compared to moderately HDV endemic regions (Table 2). Additionally policies 1–4 are cost-effective compared to policy 0 (see supplementary text for more details, Appendix A).

3.2. Impact of initial HDV prevalence on the performance of optimal policies

Increasing initial HDV prevalence decreases the performance of these policies except for PCTC. For example, PCTC of a highly HDV endemic region would be \$10, \$10, \$8, \$11 and \$11 lower than PCTC of a moderately HDV endemic region under policy 0, 1, 2, 3 and 4

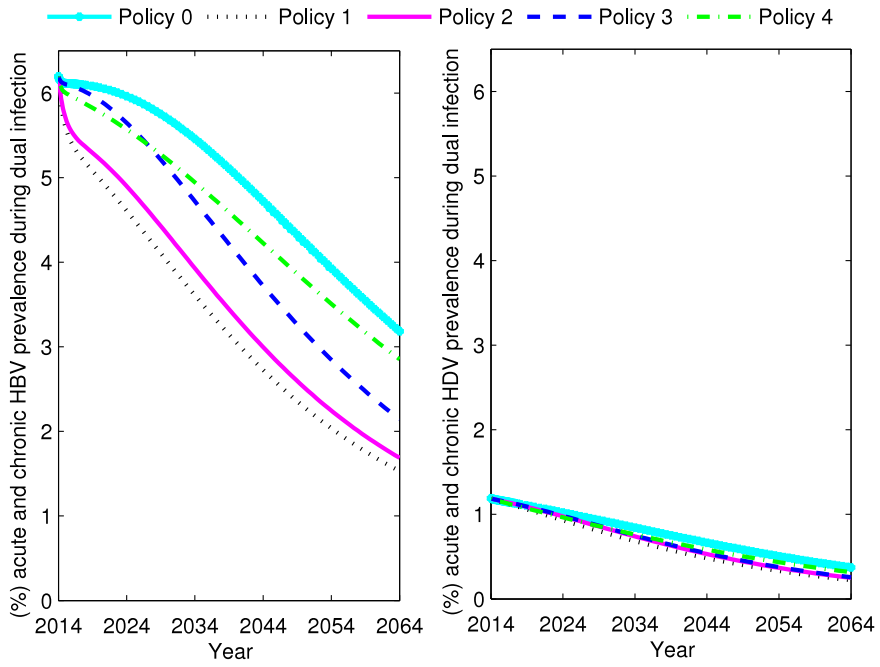

Fig. 1. (%) HBV and (%) HDV prevalence in the total population over the next 50 years under five optimal policies in a moderately HDV endemic region (China). Parameter values are given in Table 1.

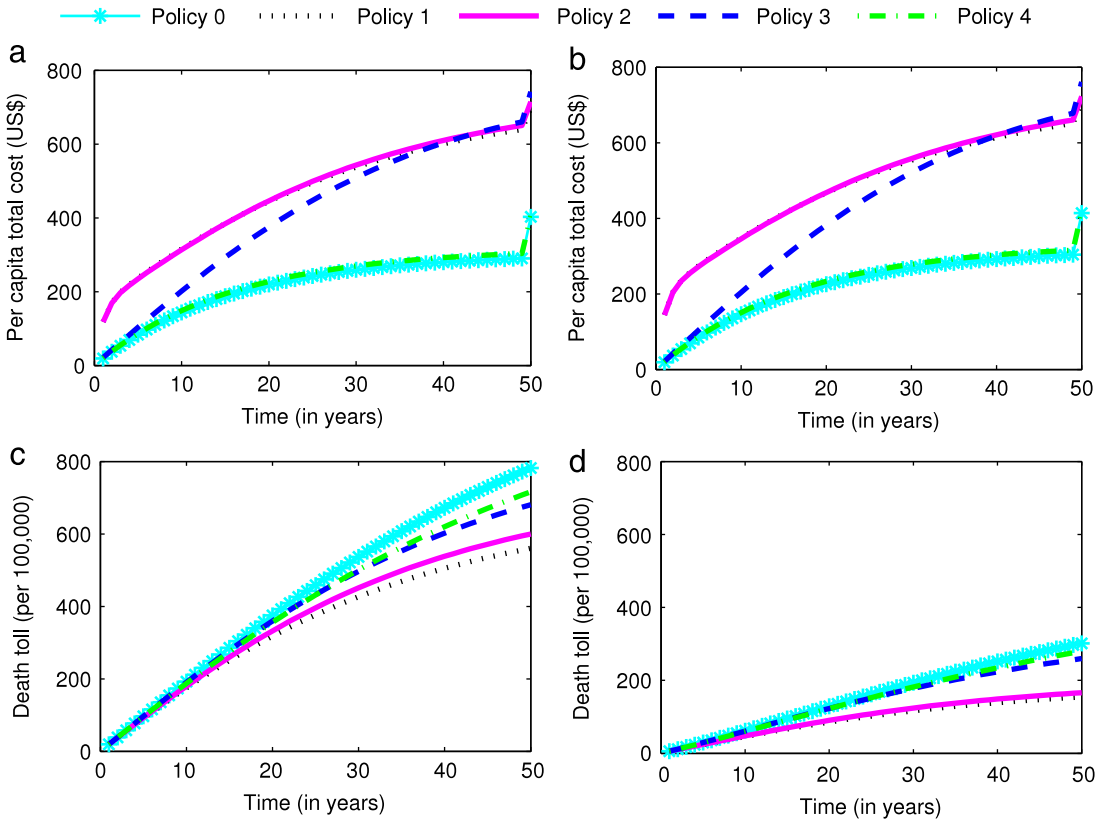

Fig. 2. Per capita total cost (in US$) and death toll (per 100,000) over the next 50 years (2014–2064) under five optimal policies in a moderately HDV endemic region (China). (a) and (c) represent the case of HBV–HDV infection in the population (dual infection), (b) and (d) represent the case of HBV mono-infection in the population. Parameter values are given in Table 1 and the results were obtained using the optimal values of the four interventions (u_1 to $\boldsymbol{u_4}$).

respectively. This is simply because an increase of more than 50% in the death toll over the next 50 years is recorded under policies 0–4 when HDV endemicity switches from a moderate to high level. In a similar manner, HBV and HDV prevalence in the total population at 50 years also increase by at least 0.7% and 75% respectively when the initial HDV prevalence in HBV infected individuals increases from 10% to 50% (with an exception for HBV prevalence under policy 3).

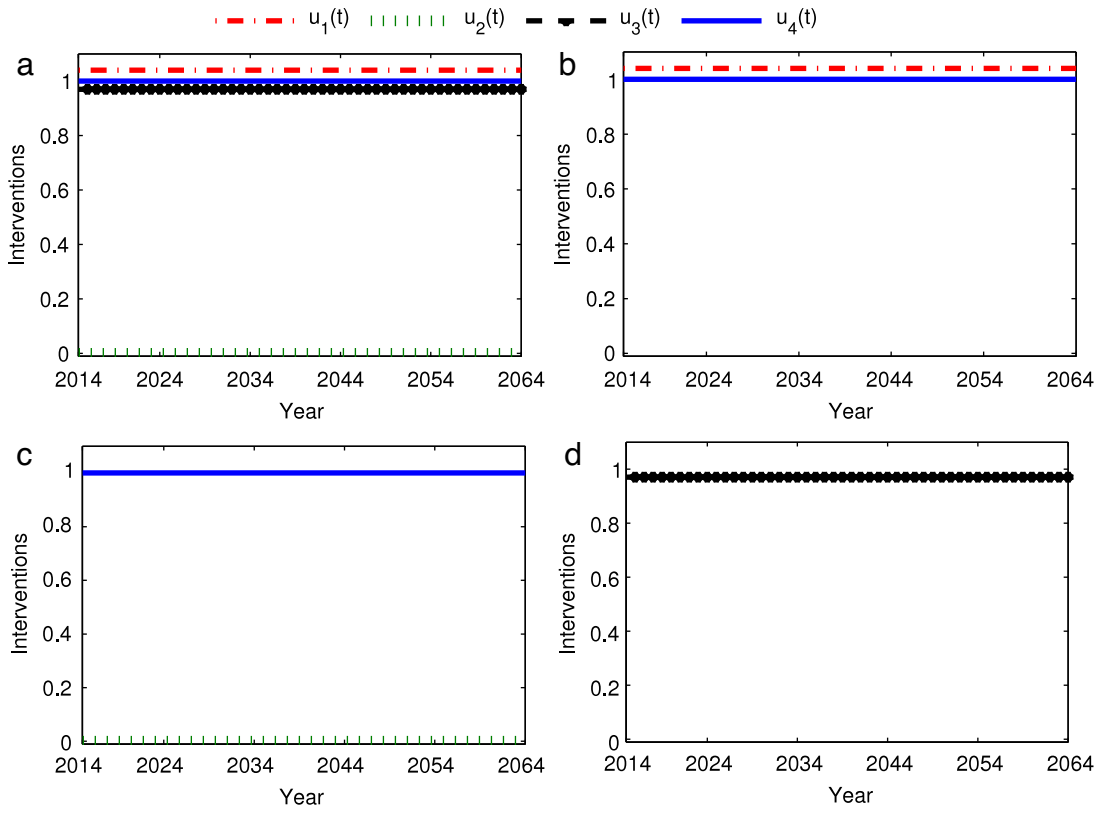

Fig. 3. Structure of optimal policies for a timeframe of 50 years (2014–2064) considering HBV–HDV dual-infection in a moderately HDV endemic region (China). (a), (b), (c) and (d) represent policy 1, policy 2, policy 3 and policy 4 respectively. Parameter values are given in Table 1 and the results were obtained using the optimal values of the four interventions ($\boldsymbol{u_1}$ to $\boldsymbol{u_4}$).

3.3. Impact of HDV presence on the performance of optimal policies

Model simulations show that the dynamics of interventions under optimal policies 1–4 remain unaffected by HDV status (Figs. 3 and 4). However HDV prevalence has an impact on outcomes of these policies. For example, HBV prevalence in moderately HDV endemic regions is higher compared to HBV prevalence in mono-infected regions under policies 0, 1, 2 and 4. Similarly HBV prevalence in moderately HDV endemic regions is lower compared to HBV prevalence in mono-infected regions under policy 3 (Table 2).

We also observe that the presence of HDV decreases PCTC and escalates the death toll. For example, PCTC (death toll) of a mono-infected region increases by -$11 (2.6-fold), -$12 (3.6-fold), -$9 (3.6-fold), -$19 (2.6 fold) and -$12 (2.5-fold) under policy 0, 1, 2, 3 and 4 respectively in a moderately HDV endemic region. The corresponding values for a highly HDV endemic region are -$21 (3.9-fold), -$22 (6.0-fold), -$17 (5.8-fold), -$30 (3.9 fold) and -$23 (3.8-fold) (Table 2). We also notice that the introduction of any intervention leads to an increase in the ratio of the death toll of dually infected region and HBV mono-infected region (with an exception under policy 4). This increase is caused by the absence of antiviral treatment for HDV in the structure of any policy and thus, reflects the necessity of an effective antiviral treatment for HDV.

3.4. Sensitivity analysis

HDV infectivity, the efficacy of awareness programs, the reduction in transmission probabilities due to diagnosis and the sexual contact rate are important parameters but their values are subject to uncertainty. Therefore, we determine the sensitivity of optimal policies to these parameters (Supplementary Information, eTable 2–5, Appendix A).

Table 2
HBV and HDV prevalence along with per-capita total cost (PCTC) and death-toll (DT) under policy 0 to 4. Here, DIR and MIR represent dually and mono infected region respectively. All results were obtained using the optimal values of the four interventions ($\boldsymbol{u_1}$ to $\boldsymbol{u_4}$).

Policy	(%) Prevalence at 50 years in the total population		PCTC[b] (US $), DT[c] (per 100,000)	
Initial HDV prevalence	DIR[a] HBV, HDV	MIR[a] HBV	DIR[a]	MIR[a]
Policy 0				
Moderate	3.18, 0.37	3.11	$403, 782	$414, 301
High	3.24, 0.66	3.11	$393, 1168	$414, 301
Policy 1				
Moderate	1.53, 0.22	1.52	$697, 560	$709, 154
High	1.55, 0.40	1.52	$687, 900	$709, 154
Policy 2				
Moderate	1.69, 0.25	1.65	$714, 600	$723, 166
High	1.73, 0.46	1.65	$706, 960	$723, 166
Policy 3				
Moderate	2.13, 0.26	2.17	$742, 681	$761, 260
High	2.13, 0.46	2.17	$731, 1025	$761, 260
Policy 4				
Moderate	2.85, 0.32	2.84	$405, 716	$417, 280
High	2.87, 0.56	2.84	$394, 1072	$417, 280

[a] DIR and MIR represent dually and mono infected region respectively.
[b] Per capita total cost (PCTC) over 50 years. PCTC is defined as the sum of the cumulative cost of implementation of any policy over the next 50 years and the lifetime cost of residual infections at 50 years divided by the total population.
[c] Death-toll (DT) is defined as the mortality caused by both diseases in the time interval $[0, T]$ per 100,000 population.

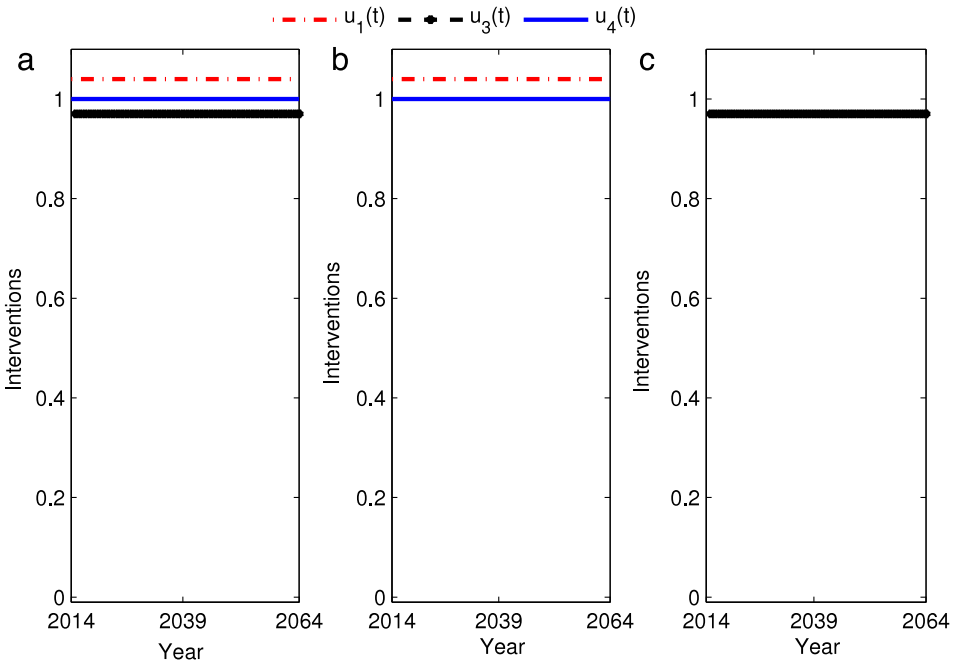

Fig. 4. Structure of optimal policies for a timeframe of 50 years (2014–2064) considering a moderately HDV endemic region (China) as a HBV mono-infected endemic region. (a), (b) and (c) represent policy 1, policy 2 and policy 4 respectively. Parameter values are given in Table 1 and the results were obtained using the optimal values of the three interventions ($\boldsymbol{u_1}$, $\boldsymbol{u_3}$ and $\boldsymbol{u_4}$).

The sexual contact rate and HDV infectivity are major players in deciding several outcomes of these policies (eTable 2 and 5). As a result of an increase in HDV infectivity from a low ($q_{d1} = 0.06$ with $q_{d2} = 0.65q_{d1}$) to a high value ($q_{d1} = 0.6$ with $q_{d2} = 0.65q_{d1}$), PCTC increases by 4.3% under policy 1, highest among all policies. However, the death toll under policy 1 increases much higher by 40.5%. Similarly HBV prevalence also increases by 12.9%, 10.9%, 13.7%, −2.7% and 10.0% under policies 0, 1, 2, 3 and 4 respectively as a result of an increase in HDV infectivity. Policy 3 exhibits a negative increase because of the lower HBV transmission risk and higher mortality of dually infected individuals in the presence of low efficacy awareness programs. In contrast when the efficacy of awareness programs is increased to 50%, an increase in HDV infectivity resulted in an increase of HBV prevalence under all policies including policy 3. The increase in HDV prevalence is sharper compared to HBV prevalence because an elevation in HDV infectivity leads to a rapid rise in the number of dually infected individuals who do not receive treatment (Goyal and Murray, 2014). The sexual contact rate (ϕ) also influences policies (eTable 5). It behaves similar to HDV infectivity but more strongly on several outputs such as HBV prevalence, HDV prevalence, death toll, interventions cost and total cost.

The efficacy of awareness programs is also identified as a strong driver in moderating outcomes of these policies (eTable 4). As only policies 1 and 4 are inclusive of awareness programs, only their performance is affected by this change in efficacy. While HBV prevalence, HDV prevalence and death toll under policy 4 remain higher than other policies, PCTC is considerably lower than policies 2 and 3 for awareness programs with all efficacies. Further increasing this efficacy ($e_3 = 0.9$) results in lower HBV and HDV prevalence, death toll and PCTC under policy 4 compared to policy 2 and 3. Similarly the performance gap between policy 1 and 4 narrows down as the efficacy of awareness programs increases, however, policy 1 performs best at all times (except for PCTC). The reduction in transmission probabilities due to diagnosis (ν) is the least influential parameter (eTable 3).

The sensitivity analyses demonstrate some of the main results of the model. For example, high efficacy awareness programs can replace HBV adult vaccination or antiviral treatment in countries with limited resources. However achieving such a high level of efficacy for awareness programs will be a daunting task as it demands a continued reduction in risky behavior over an extended duration.

4. Discussion

Implementation of universal newborn hepatitis B vaccination in a moderate HDV endemic region such as China would reduce new HBV infections by about 76% (Lu et al., 2013b). Modeling also showed that the implementation of newborn vaccination programs costs very little (Hutton et al., 2010; Lu et al., 2013b) and it is possible to eradicate both viruses in the long term using high HBV vaccination coverage in newborns (Goyal and Murray, 2014). Studies determining policies aimed at the reduction in horizontal transmission in the presence of HDV are essential for two reasons. The first reason is that there exists no antiviral treatment or vaccination for HDV and therefore it is essential to prevent new HDV infections. Secondly, despite effective universal newborn hepatitis B vaccination, a total of 10.01 million related deaths could be recorded in China over the next 50 years. Therefore, it is of considerable interest to public health policymakers to determine economically viable solutions that reduce the horizontal spread of both diseases. They also need to be informed on how to construct these policies, in order to obtain the greatest social benefits.

Incorporating HDV when it is present in the community is important and policymakers need to be considerate about HDV endemicity for better accuracy and results (Xiridou et al., 2009). Its inclusion does not affect the dynamics of the interventions under optimal policies but exacerbates the level of HBV and HDV prevalence, PCTC and death toll. In particular, the impact of HDV on estimating HBV prevalence in the community is small under any intervention(s) and can be ignored for a small population, but not for a population the size of China. The dynamics of optimal interventions obtained here are consistent with results by Armbruster and Brandeau (2010) who suggested enrolling infected individuals onto treatment at the maximal rate until the incremental health benefits balance the incremental cost of

controlling the disease. In a theoretical study by Kamyad et al. (2014) the optimal level of interventions to control HBV alone in a population were derived. Their sensitivity analysis revealed that high and low intensity of interventions result in lower and higher levels of HBV prevalence respectively at the end of the time period 'T'. Our simulations show that HBV infections are untreated in the last 15 years in China due to the fixed time period (Figs. 3 and 4). In a hypothetical age-structured model for China, life expectancy (75 years) could itself behave as a time period T. Thus, another interpretation of the absence of HBV treatment in the last 15 years could be that HBV antiviral treatment to older age groups (>60 years) has less of an impact compared to 30–60 year olds (Hulstaert et al., 2013; Toy et al., 2013). This additionally suggests the importance of early detection and initiation of antiviral treatment to maximize monetary benefits (Hulstaert et al., 2013).

Only implementation of all four interventions achieved HBV prevalence close to 1.5% (and can lead to eradication in the longer time-frame), prevented the maximum number of new HBV and HDV infections, generated maximum savings and pushed death toll to a minimum. As expected taking no action will produce the worst results in terms of HBV and HDV prevalence, PCTC and death toll. In a study of hepatitis C virus (HCV), it was found that investing in new costly therapies could generate savings estimated at more than $3.2 billion annually in the US and five European countries (Zobair et al., 2015). In our study, investing in four interventions altogether would also prevent 21.1, 1.9 and 2.8 million new HBV infections, new HDV infections and deaths respectively compared to no intervention in China over the next 50 years. Our model suggested that although all policies cost more than policy with no intervention at all times, it is still beneficial to invest earlier as it will pay-off later in terms of fewer infections. In addition, benefits associated with awareness programs could be higher compared to the one estimated here as they may also reduce the transmission of other sexually transmitted diseases (STDs) such as HIV and HCV. Treatment programs along with adult vaccination achieve lower HBV prevalence and death toll, at a slightly higher cost compared to adult vaccination alone. This shows the capability of treatment programs as a prevention measure. Similar benefits in terms of prevention of HIV and other STDs have been estimated for HIV antiretroviral therapy (Bavinton et al., 2015).

In another related study by Xiridou et al. it was suggested that HDV may hinder the control of a HBV epidemic and may modulate the interventions controlling it (Xiridou et al., 2009). Our results are consistent with these hypotheses. Sensitivity simulations also reveal that as HDV infectivity switches from a low level to a high level, the percentage increase in HDV prevalence under any combination of interventions is much smaller compared to no intervention. This is further accompanied by a smaller increase in HBV prevalence (with an exception under adult vaccination programs alone). As a result the number of HDV infections among HBV infected individuals and the death toll rise faster as HDV infectivity increases and this suggests the necessity of antiviral treatment for HDV. Awareness programs alone achieve higher HBV and HDV prevalence but are less costly and generate fewer death tolls than adult vaccination when HDV transmission probability is 90% or higher. Higher rates of HBV adult vaccination could speed up the eradication process; however, it could be a daunting and time-consuming task requiring high expenditure on improving existing infrastructure related to medical services. In another simulation, high efficacy awareness programs outperform the combination of adult vaccination and antiviral treatment, reinforcing the importance of awareness programs. High efficacy awareness programs (90% or higher) achieve lower cost and death toll compared to the combination of antiviral treatment and adult vaccination even for very high probabilities of HDV transmission. This shows the importance of the inclusion of awareness programs in policies and the failure of antiviral treatment for HBV mono-infected individuals when there is a high risk of HDV infection. Therefore, HDV endemic regions with few resources can resort to low cost and high efficacy awareness programs instead of high cost antiviral treatment and/or adult vaccination. However achieving such a high level of efficacy for awareness programs will be a daunting task as it demands a continued reduction in risky behavior over an extended duration. The reduction in transmission probabilities due to diagnosis (ν) has the least effect on the outputs of any policy.

Despite its usefulness, there are several limitations to our model. We assume homogeneous mixing, ignore reduction of transmission probabilities during treatment, and do not specifically include high risk groups such as injecting drug users or female sex workers. In the current model, new HBV infections arising through household transmission are ignored as the two major transmission routes of HBV include mother-to-child and sexual transmission in China (Hou et al., 2005; Yan et al., 2014). This can also be included in future models. Incorporating diverse ethnic groups living in vast and remote jungle areas such as the Amazon Basin would be a difficult task but relevant to proper assessment of HBV and HDV interventions in this highly HDV endemic region. Another limitation of our model is the overestimation of the cost of awareness programs as we assume that they also target infants and some of the early age groups of the children class which might not be the case. In addition, the implementation of all four interventions required an average yearly budget of $14 billion which is almost one third of the healthcare budget of $47 billion in 2015 in China (Ministry of Finance, 2015).

In conclusion, mathematical modeling suggests that the best way to control HBV and HDV prevalence is to apply interventions together. While this approach will be initially costly, in the long term it will perform best in every criterion tested here. In poor countries, low cost awareness programs are recommended.

Appendix A. Supplementary data

Supplementary material related to this article can be found online at http://dx.doi.org/10.1016/j.tpb.2016.08.004.

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