Hepatitis B and D: A Forecast on Actions Needed to Reduce Incidence and Achieve Elimination

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Hepatitis B and D: A Forecast on Actions Needed to Reduce Incidence and Achieve Elimination

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1Introduction

Hepatitis viruses are estimated to infect 2.3 billion individuals worldwide [11]. Of these individuals, the 12.4 million [15, 33] who are chronically co-infected with the hepatitis B (HBV) and hepatitis D (HDV) viruses face the worst prognosis, as the odds of liver cancer are more likely, and the progression towards liver-related death occurs much more rapidly [33]. Fortunately, two key facts offer hope against these negative outcomes. First, HDV infection is uncommon, as it requires infection with HBV to infect and transmit [33]. Second, the annual incidence of HBV continues to plummet in many regions due to the successful rollout of highly efficacious HBV vaccines. In fact, the HBV vaccine has been so successful that it has been adopted into 184 government immunization programs [15], which have been a driving force in its continued ability to reduce the global prevalence of HBV.

While the effect of the HBV vaccine on HBV incidence and prevalence are well-studied [2, 13, 16], far less is known about its impact on the transmission of HDV. In part, this lack of information is because some do not consider HDV to be a relevant medical problem [18]. It is this stance that once led to a decline in screening for HDV infection [5, 10], and its subsequent rebound in parts of Europe [16]. Even with the rebound of HDV, some public health officials continue to only control HDV indirectly through sustained efforts to reduce HBV, such as HBV vaccination, the use of harm reduction services, and education on both blood and injection safety [33], instead of investing time and resources into developing HDV-specific health interventions. Regardless of whether specific health interventions should be developed for HDV, there are still important questions that remain unanswered concerning HDV’s status in the world. For instance, it is unknown what level of HBV vaccination is required so the decline in current HDV incidence reaches the reductions called for by the Global Health Sector Strategy on Viral Hepatitis 2016–2021 [30]. Similarly, it is also unknown whether the current HBV vaccination levels are sufficiently high to cause the elimination of HDV, as ongoing surveillance illustrates a marked decline of HDV in the Western world, among other regions [15].

To inform on the potential for HBV vaccination to aid in meeting the targets of the Global Health Sector Strategy on Viral Hepatitis 2016–2021 [30], and its potential to cause HDV elimination, we developed a mathematical model of HBV and HDV transmission. Our mathematical model considers the most common transmission routes for both HBV and HDV infection, namely person-to-person transmission, with acute and chronic stages of infection. To calibrate our mathematical model, we used freely available data on HBV and HDV [4, 18, 36], along with effective HBV vaccination levels of 10.72%, 22.23%, and 62.1% coverage, which are based on a meta-analysis of HBV vaccination in Africa [1], along with data on the efficacy of the HBV vaccine [5]. Using our model, we esti-
mate the vaccination levels required to reduce HBV and HDV incidence by 90% (one of the primary objectives of the Global Health Sector Strategy on Viral Hepatitis 2016–2021 [20]), and the levels required to cause both HBV and HDV elimination.

2 Materials and Methods

To evaluate the effect of the HBV vaccination on inhibiting the spread of HDV, we created a mathematical model of HBV and HDV transmission (see Figure 1 and the Appendix). Through the mathematical model, we estimate the effect that HBV vaccination has on HDV transmission by reducing the number of individuals who are susceptible to HDV infection. We consider scenarios where the effective HBV vaccination level achieves 10.72%, 22.23%, and 62.1% coverage, based on the results of a recent meta-analysis of HBV vaccination in Africa [1, 8]. Under the scenarios, we measure the associated decline in HDV incidence, identify the vaccination required to reduce hepatitis incidence by 90%, and determine the thresholds that cause hepatitis B and D elimination.

2.1 Mathematical model

For our mathematical model, we consider a population divided into classes based on disease status. For HBV, this amounts to individuals susceptible to infection (S), acute HBV infected individuals (A), chronic HBV infected individuals (C), individuals recovered from HBV infection (R), and HBV vaccinated individuals (V). For HDV, due to the requirement of HBV infection, we have acute HBV and HDV infected individuals ([A, A, D]), chronic HBV and acute HDV infected individuals ([C, A, D]), chronic HBV and HDV infected individuals ([C, C, D]) and individuals with chronic HBV infection that have recovered from HDV ([C, R, D]). Note, we do not consider a compartment where individuals have recovered from HBV infection and are infected with HDV, as HDV requires the simultaneous presence of HBV to complete its life cycle [14].

Our model considers the rate that susceptible individuals become infected with HBV to be

\[ \lambda_B = \frac{\beta_B}{N} \left( A_B + C_B + [A_B A_D] + [C_B A_D] + [C_B C_D] + [C_B R_D] \right), \]

where \( \beta_B \) is the transmission rate of HBV and \( N \) is the total population. In addition, the rate that HBV infected individuals become co-infected with HDV is

\[ \lambda_D = \frac{\beta_D}{N} \left( [A_B A_D] + [C_B A_D] + [C_B C_D] \right), \]

where \( \beta_D \) is the transmission rate of HDV. Also considered in our model, is the birth rate \( b \), the proportion of newborns with hepatitis \( \sigma \), the rate acute hepatitis infection clears or becomes chronic \( \gamma \), the proportion of acute hepatitis infections that lead to chronic disease \( \rho \), the recovery rate from hepatitis infection \( \delta \), death rate \( \mu \), and the vaccination rate for HBV of susceptible individuals \( \nu \). Note, parameter subscripts of B and D correspond to the parameters associated directly with HBV infection and HDV infection, respectively. Further details of parameters, including values and sources, are available in Table 1.

2.2 The reproductive numbers of HBV and HDV

To provide insight on the potential for the HBV vaccine to eliminate both HBV and HDV we estimated the basic [9, 25], control [24], and effective [24] reproductive numbers. The reproductive numbers of HBV are estimated using the next-generation method (Appendix). Using this approach, we have that the effective reproductive number is calculated as

\[ R^B_{eff} = \frac{\delta_B + \mu + \mu_B + \rho B \gamma B^2}{(\gamma_B + \mu)(\delta_B + \mu + \mu_B)} \left( \beta_B \frac{S}{N} + b \sigma B \right). \]

Evaluating the effective reproductive number at the disease-free equilibrium, we obtain the control reproductive number for HBV:

\[ R^B_0 = \frac{\delta_B + \mu + \mu_B + \rho B \gamma B^2}{(\gamma_B + \mu)(\delta_B + \mu + \mu_B)} \left( \beta_B \frac{b}{\mu + \nu} + b \sigma B \right). \]

Further imposing that \( \nu = 0 \), we obtain the basic reproductive number for HBV:

\[ R^B_0 = R^B_0 |_{\nu=0}. \]

From the control reproductive number, we determine the critical HBV vaccination level to cause elimination by solving \( R^B_0 \leq 1 \) for \( \nu \).

With regards to HDV, we also use the next-generation method to estimate the reproductive numbers (see the Appendix). Using this approach, we have that the control reproductive number for HDV is

\[ R^D_0 = \frac{1}{(\gamma_D + \mu)(\gamma_D + \mu + \mu_D + \delta_D)(\mu + \mu_D + \delta_D) \cdot \left( (\mu + \mu_D + \rho D \gamma D + \mu_D + \delta_D) \mu + (\mu + \gamma_D + \delta_D + \rho D \gamma B)(\mu_D + \delta_D) + \rho B \gamma B \rho D \gamma D \right) (\beta_D \frac{A_D}{N} + b \sigma D) + \beta_D (\gamma_B + \mu)(\rho D \gamma D + \mu + \mu_D + \delta_D) \frac{C_B}{N}}, \]
Figure 1: Compartmental diagram of HBV and HDV co-infection. The diagram details the HBV and HDV transmission structure. Note, for ease of presentation, demographic rates are excluded.

Table 1: Parameters and sources.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Variable</th>
<th>Value</th>
<th>Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa population</td>
<td>N</td>
<td>1.08 billion</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>Birth rate</td>
<td>b</td>
<td>0.046 year(^{-1})</td>
<td></td>
<td>[7]</td>
</tr>
<tr>
<td>Death rates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Natural</td>
<td>μ</td>
<td>1/61.3 year(^{-1})</td>
<td>Exp(1/61.3)</td>
<td>[28]</td>
</tr>
<tr>
<td>HBV</td>
<td>μ(_B)</td>
<td>0.00086 year(^{-1})</td>
<td>Exp(0.00086)</td>
<td>Appendix</td>
</tr>
<tr>
<td>HDV</td>
<td>μ(_D)</td>
<td>0.0030 year(^{-1})</td>
<td>Exp(0.0030)</td>
<td>Appendix</td>
</tr>
<tr>
<td>Proportion of newborns (from infected parents) with chronic HBV</td>
<td>σ(_B)</td>
<td>0.2</td>
<td>U[0.0, 0.4]</td>
<td>[35]</td>
</tr>
<tr>
<td>chronic HDV</td>
<td></td>
<td>0.05 (\cdot) σ(_B)</td>
<td></td>
<td>[31]</td>
</tr>
<tr>
<td>Transmission rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>β(_B)</td>
<td>0.288 year(^{-1})</td>
<td></td>
<td>Appendix</td>
</tr>
<tr>
<td>HDV</td>
<td>β(_D)</td>
<td>6.79 year(^{-1})</td>
<td></td>
<td>Appendix</td>
</tr>
<tr>
<td>Incubation period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1/γ(_B)</td>
<td>91.25 days</td>
<td>Tri[45, 68.75, 160]</td>
<td>[6]</td>
</tr>
<tr>
<td>HDV</td>
<td>1/γ(_D)</td>
<td>91.25 days</td>
<td>Tri[45, 68.75, 160]</td>
<td>[6]</td>
</tr>
<tr>
<td>Proportion that develops active disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>ρ(_B)</td>
<td>0.1</td>
<td></td>
<td>Appendix</td>
</tr>
<tr>
<td>HDV</td>
<td>ρ(_D)</td>
<td>0.1</td>
<td></td>
<td>Appendix</td>
</tr>
<tr>
<td>Average duration of chronic infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>1/δ(_B)</td>
<td>50 years</td>
<td>δ (\sim) Exp(1/50)</td>
<td>[34]</td>
</tr>
<tr>
<td>HDV</td>
<td>1/δ(_D)</td>
<td>50 years</td>
<td>δ (\sim) Exp(1/50)</td>
<td>[34]</td>
</tr>
<tr>
<td>Vaccination rate for HBV</td>
<td>ν</td>
<td></td>
<td>U[0, 0.026]</td>
<td>Appendix</td>
</tr>
</tbody>
</table>
where \( \hat{A}_B \) and \( \hat{C}_B \) correspond to the HBV endemic and HDV free equilibrium values (Appendix). It naturally follows that the basic reproductive number is

\[
R_0^D = R_0^D|_{\nu=0}.
\]

From \( R_0^D \), the critical HBV vaccination level to cause the elimination of HDV is determined by solving \( R_0^D \leq 1 \) for \( \nu \).

### 2.3 HBV and HDV scenarios

To illustrate the effect of HBV vaccination on HBV and HDV incidence, we base model demographics on the population of Sub-Saharan Africa [28]. Specifically, we use life expectancy, birth rates, and baseline HBV vaccination rates from the literature on Sub-Saharan Africa [1, 27, 29].

#### 2.3.1 HBV vaccination

We consider effective vaccination rates of 10.72%, 22.23%, and 62.1% to encapsulate the variety of vaccination coverages that occur in Sub-Saharan Africa [1, 8]. Specifically, we assume the HBV vaccination rates achieve a coverage of 13.4%, 24.7%, and 62.1% [1] with vaccine efficacies of 80%, 90%, and 100%, respectively [8]. We classify these as high, intermediate, and low HBV endemic scenarios, respectively. For these scenarios, we obtain two estimates of the required increase in HBV vaccination rates needed to achieve a 90% reduction in HBV incidence. The first estimate uses the HBV endemic and HDV free equilibrium to determine the baseline vaccination rate to reach each coverage level, and the required increase in HBV vaccination rate to reduce HBV incidence by 90%. The second estimate follows the same procedure using the HBV and HDV co-endemic equilibrium. We also use the HBV and HDV co-endemic equilibrium to estimate the increase in HBV vaccination required to reduce HDV incidence by 90%.

#### 2.3.2 HBV and HDV transmission

To calibrate HBV vaccination rates, we use estimates of the basic reproductive number for HBV [35], along with estimates of HBV recovery and mortality rates (see Table 1 and the Appendix). Similarly, to determine the transmission rate of HDV, we use estimates of its reproductive number from the literature [34] (Appendix).

#### 2.3.3 HBV and HDV incidence averted

In addition to using the endemic equilibria to inform on the vaccination levels required to reduce incidence by 90%, we also provide an estimate on the incidence averted over a 8-year time horizon (the timeframe of the goals set by health officials in the Global Health Sector Strategy on Viral Hepatitis 2016–2021 [30]). For the base case, we perturb the HBV endemic and HDV free equilibrium so that 4.5% of HBV incidences are co-infected with HDV [21] as the initial condition, with baseline vaccination rates. We then subtract the predicted incidence when the model features a vaccination rate from the baseline up to 0.05 per year from the base case to obtain incidence averted, where the initial conditions are assumed the same, for each equilibrium, respectively.

#### 2.4 Sensitivity analysis

To quantify how each parameters’ uncertainty contributes to the variability in predictions of control reproductive numbers, we calculated variance-based first-order sensitivity indices [20, 22]. Details of the probability distributions used in the calculation of indices are available in Table 1.

### 3 Results

By evaluating and comparing endemic equilibria at different HBV vaccination rates, we showed the upscale of vaccination required to decrease HBV incidence, and HDV incidence by 90%, respectively. We considered three baseline scenarios of effective HBV vaccination rates based on the literature, which achieve vaccination coverages of 10.72%, 22.23%, and 62.1% [1]. In addition to our results based on equilibria, we also estimated HBV and HDV incidence averted over an 8-year time horizon caused by increasing HBV vaccination rates.

#### 3.1 HBV endemic and HDV free scenario

In the absence of HDV, we found that the vaccination rates required to achieve the effective vaccination coverages of 10.72%, 22.23%, and 62.1% are 0.00423 year\(^{-1}\), 0.00886 year\(^{-1}\), and 0.0248 year\(^{-1}\) for high, intermediate, and low HBV endemic scenarios, respectively, at the HBV endemic and HDV free equilibrium. For the low endemic scenario, the vaccination rate of 0.0248 year\(^{-1}\) causes \( R_0^B < 1 \) (Figure 3), thereby rendering any comparison of the endemic equilibrium at higher vaccination rates infeasible. For the high and intermediate scenarios, a 90% reduction in HBV incidence requires increasing the vaccination rates to 0.0216 year\(^{-1}\), and 0.0221 year\(^{-1}\), from the baseline rates, respectively (Figure 3).

#### 3.2 HBV and HDV co-endemic scenario

We found that the vaccination rates required to achieve HBV vaccination coverages at the HBV and HDV co-endemic equilibrium were similar to those of the HBV endemic and HDV free equilibrium, namely 0.00427 year\(^{-1}\),
Figure 2: Percent reduction in incidence for given vaccination rate. (a) Reduction at HBV endemic and HDV free equilibrium [Appendix equation 2] for high (red dashed line) and intermediate (blue dash-dot curve) transmission at the given vaccination rate, and (b) Reduction at HBV and HDV co-endemic equilibrium [Appendix equation 3] for high (red dashed curve), and intermediate (blue dash-dot curve) transmission at the given vaccination rate.

Figure 3: Control reproductive number for HBV and HDV versus the annual vaccination rate. The critical value for disease elimination (red dash-dot line), \( R^B_{\nu} \) (black solid curve) and \( R^D_{\nu} \) (blue dashed curve).

0.00892 year\(^{-1}\), and 0.0248 year\(^{-1}\), respectively. However, achieving a 90% reduction in HBV incidence required higher HBV vaccination rates of 0.0281 year\(^{-1}\), and 0.0315 year\(^{-1}\) (Figure 2), respectively. When considering HDV, achieving a 90% reduction for the high endemic setting required an increase in the HBV vaccination rate to 0.00643 year\(^{-1}\). For the intermediate HBV endemic scenario, the increase in vaccination required to reduce HDV incidence by 90% was negligible, as \( R^D_{\nu} = 1 \). Finally, for the low endemic scenario, the HBV vaccination rate causes \( R^D_{\nu} < 1 \) (Figure 3), therefore the HDV-related states are infeasible for determining the reduction.

3.3 HBV and HDV incidence averted

For our high HBV endemic scenario, our model predicts increasing HBV vaccination rates from 0.00427 per year to 0.0216 per year averts 13167 (95% CI 13018, 13317) incidence of HBV over 8 years, and 61.6 (95% CI 60.2, 62.9) incidence of HDV (Figure 4). In addition, when we consider increasing the vaccination rate for our intermediate HBV endemic scenario from 0.00886 to 0.0221 per year, a total of 9870 (95% CI 9758, 9982) incidence of HBV, and 46.2 (95% CI 45.2, 47.2) incidence of HDV are averted (Figure 4). Finally, for our low HBV endemic scenario, increasing the vaccination rate from 0.0248 to 0.05 per year averted 16375 (95% CI 16194, 16555) incidence of HBV, and 77.7 (95% CI 76.1, 79.4) incidences of HDV (Figure 4).

3.4 Sensitivity analysis

The variance-based sensitivity analysis of model parameters shows that \( R^B_{\nu} \) and \( R^D_{\nu} \) were most sensitive to life expectancy (i.e., the natural death rate) and the duration of chronic infection with HBV (Figure 5). Beyond these parameters, \( R^B_{\nu} \) was also sensitive to the HBV vaccination rate, although this had little effect on \( R^D_{\nu} \) (Figure 5). In a similar fashion, \( R^D_{\nu} \) was sensitive to the duration of chronic infection with HDV, but this parameter had a negligible impact on \( R^B_{\nu} \) (Figure 5). Other model parameters had a minimal impact on any variability of both \( R^B_{\nu} \) and \( R^D_{\nu} \) (Figure 5).

4 Discussion

The analysis of our mathematical model of HBV and HDV co-infection predicts that HBV vaccination levels beyond 0.0221 year\(^{-1}\) are required to reduce both HBV and HDV incidence by 90%. Furthermore, if this vaccination level is reached, our results on the control repro-
Figure 4: HBV and HDV incidence averted. (a) HBV incidence averted and (b) HDV incidence averted were calculated by subtracting the total incidence over an 8-year time horizon, for the given vaccination rate, from baseline incidence predictions of HBV and HDV, respectively, in high (red dashed curve), intermediate (blue dash-dot solid curve), and low (black solid curve) HBV endemicity.

Productive numbers for both diseases show that their elimination would be well within the realm of possibilities, as an annual vaccination rate of 0.025 causes $R^B_{\nu} < 1$.

The findings of our work reaffirm theoretical studies that show HDV has an impact on the spread and control of HBV [34]. Specifically, our results indicate that the presence of HDV requires a higher HBV vaccination rate to cause the elimination of both diseases. A potential workaround of this issue is to first focus on HDV elimination, given the relatively low HBV vaccination rate required to accomplish this feat, and then focus on HBV elimination. While such an endeavor would likely take a longer period to complete, it would entail less upscaling of HBV vaccination and therefore may be more feasible in regions where health resources are scarce.

As our work considers HBV and HDV transmission among a general population, an important direction for future work is to include demographic structure to reflect the role that at-risk communities, such as drug injectors and sex workers, play in enabling the persistence of both HBV and HDV. Similarly, modifications to our model to reflect individuals’ knowledge of HBV and HDV infection status and stratification by age would also likely prove to be fruitful avenues for further investigation.

To obtain our results, we made several simplifying assumptions. To begin, our model only accounts for stages of acute and chronic infection for both HBV and HDV. Therefore, our model does not reflect other disease stages, such as superinfection, latent infection, or the difference between chronically infected individuals that receive or do not receive drug treatment, such as entecavir for HBV [32], or in-development drug treatments for HDV [12]. In addition, we did not account for the difference in transmission potential between acute and chronically infected individuals, which has been shown to affect critical vaccination thresholds [19], nor do we account for the impact of co-infection with other types of viral hepatitis that commonly occur, such as hepatitis C [34]. In addition, our model is calibrated to describe HBV and HDV transmission in Sub-Saharan Africa, although with modest modifications it could be used to evaluate the HBV and HDV interventions under different demographic settings.

5 Conclusion

In summary, our results indicate that HDV elimination is likely underway in the vast majority of low HBV transmission settings. Our results also suggest that modest increases in HBV vaccination rates in intermediate and high HBV endemic settings could lead to the elimination of HBV and HDV. As such, these findings reinforce the idea that the elimination of HBV and HDV are feasible endeavors. Thus, with sufficient investments to scale up global hepatitis prevention, testing, and treatment services, both HBV and HDV could be eliminated in time for the WHO’s 2030 target date.

Author Contributions

SG came up with the study design, AK and SG contributed to model development and analysis. All authors participated in the drafting and editing of the manuscript.
6 Appendix

This appendix provides further details on the hepatitis B and D co-infection model. We outline the differential equations used in model simulations, and the methods for estimating the reproductive numbers [9, 24] of both hepatitis B and D.

6.1 Model equations

6.1.1 Hepatitis B and D system

For our mathematical model, we consider a population that divides the population-based on susceptibility to infection, acute infection, chronic infection and immunity from infection. For hepatitis B, this amounts to susceptible individuals (\(S\)), acute hepatitis B infected individuals (\(A_B\)), chronic hepatitis B infected individuals (\(C_B\)), the recovered individuals from hepatitis B (\(R_B\)), and the hepatitis B vaccinated individuals (\(V\)). The population infected with hepatitis B is further subdivided based on hepatitis D infection status, namely acute hepatitis B and D infected individuals (\([A_B A_D]\)), chronic hepatitis B and acute hepatitis D infected individuals (\([C_B A_D]\)), chronic hepatitis B and D infected individuals (\([C_B C_D]\)), and chronic hepatitis B infected individuals that have recovered from hepatitis D (\([C_B R_D]\)). To describe the transition between compartments for hepatitis B and D, we consider the system of differential equations,

\[
\begin{align*}
\frac{dA_B}{dt} &= b\sigma_B(A_B + C_B) + \lambda_B S - \gamma_B A_B - \mu A_B - \lambda_D A_B, \\
\frac{dC_B}{dt} &= \rho_B \gamma_B A_B - (\mu + \mu_B + \delta_B) C_B - \lambda_D C_B, \\
\frac{dR_B}{dt} &= (1 - \rho_B) \gamma_B A_B + (1 - \rho_B) \gamma_B [A_B A_D] + \delta_B (C_B + [C_B R_D] + [C_B A_D]) - \mu R_B + \delta_D [C_B C_D], \\
\frac{d[C_B A_D]}{dt} &= \rho_B \gamma_B [A_B A_D] - \gamma_D [C_B A_D] - (\mu + \mu_B + \delta_B) [C_B A_D] + \lambda_D C_B, \\
\frac{d[C_B C_D]}{dt} &= \rho_D \gamma_D [C_B A_D] - (\mu + \mu_D + \delta_D) [C_B C_D], \\
\frac{d[C_B R_D]}{dt} &= (1 - \rho_D) \gamma_D [C_B A_D] - (\mu + \mu_D + \delta_D) [C_B R_D], \\
\frac{dV}{dt} &= \nu S - \mu V, \quad (1)
\end{align*}
\]

where the force of infection for hepatitis B is given by,

\[
\lambda_B = \frac{\beta_B}{N} \left( A_B + C_B + [A_B A_D] + [C_B A_D] + [C_B C_D] + [C_B R_D] \right),
\]

and the force of infection for hepatitis D is given by,

\[
\lambda_D = \frac{\beta_D}{N} \left( [A_B A_D] + [C_B A_D] + [C_B C_D] \right).
\]

6.2 Model equilibria

6.2.1 Hepatitis B and D equilibria

The model has 3 valid equilibria: a disease-free equilibrium, a hepatitis B endemic and hepatitis D free equi-
librium, and a hepatitis B and D co-endemic equilibrium.

The disease-free equilibrium is

\[ S^{DFE} = \frac{b}{\mu + \nu} N, \quad V^{DFE} = \frac{b}{\mu \mu + \nu} N, \]

and

\[ A_B^{DFE} = C_B^{DFE} = R_B^{DFE} = [A_B\tilde{A}_D]^{DFE}_B = [C_B\tilde{C}_D]^{DFE} = [C_B\tilde{C}_D]^{DFE}_B = 0. \]

When hepatitis B is endemic and hepatitis D free, the equilibrium is

\[
\tilde{S} = \frac{N}{\beta_B (\mu + \mu_B + \delta_B + \rho_B \sigma_B)} \cdot \left( \mu^2 + (\mu_B + \delta_B + \gamma_B - b \sigma_B) \mu \right.
\]

\[
\left. + (\mu_B + \delta_B - b \rho_B \sigma_B) \gamma_B - b \sigma_B (\mu_B + \delta_B) \right),
\]

\[
\tilde{A}_B = \frac{N}{\beta_B (\gamma_B + \mu) (\mu + \mu_B + \delta_B + \rho_B \sigma_B)} \cdot \left( \mu^2 - (\mu + \nu + b \sigma_B + \gamma_B + \delta_B) \mu^2 \right.
\]

\[
\left. + \left((\nu + \mu + \delta_B + \rho_B \gamma_B) \sigma_B + \beta_B \right) \right)
\]

\[
\left. + (\mu_B + \delta_B - b \rho_B \sigma_B) (\nu \sigma_B + \beta_B) \mu \right)
\]

\[
\left. - \gamma_B \nu (\mu_B + \delta_B) \right),
\]

\[
\tilde{C}_B = \frac{\rho_B \gamma_B}{\mu + \mu_B + \delta_B},
\]

\[
\tilde{R}_B = \frac{(1 - \rho_B)(\mu + \mu_B) + \delta_B}{\rho_B \mu} \tilde{C}_B,
\]

\[
\tilde{V} = \frac{\nu}{\mu} \tilde{S},
\]

and

\[
[A_B\tilde{A}_D] = [\tilde{C}_B\tilde{A}_D] = [\tilde{C}_B\tilde{C}_D] = [\tilde{C}_B\tilde{R}_D] = 0. \quad (2)
\]

Finally, when both hepatitis B and hepatitis D are endemic, we have the co-endemic equilibrium, which is defined implicitly for the ease of presentation, is

\[
\tilde{S} = \frac{1}{\lambda_B + \nu + \mu} \left( bN + b \sigma_B (\tilde{A}_B + \tilde{C}_B) \right.
\]

\[
\left. + b \sigma_D ([A_B\tilde{A}_D] + [\tilde{C}_B\tilde{A}_D] + [\tilde{C}_B\tilde{C}_D]) \right),
\]

\[
\tilde{A}_B = \lambda_B (\mu + \mu_B + \delta_B + \lambda_D)
\]

\[
\cdot \left( \lambda_D^2 + (2 \mu + \mu_B + \delta_B + \gamma_B - b \sigma_B) \lambda_D \right.
\]

\[
\left. + \mu^2 + (\mu_B + \delta_B + \gamma_B - b \sigma_B) \mu \right)
\]

\[
\left. + \gamma_B (\mu_B + \delta_B) \right)
\]

\[
\left. - b (\mu_B + \delta_B + \rho_B \gamma_B) \sigma_B \right) \right) \right)
\]

\[
\left. \right)^{-1} \tilde{S},
\]

\[
\tilde{C}_B = \frac{\rho_B \gamma_B}{\mu + \mu_B + \delta_B + \lambda_D} \tilde{A}_B,
\]

\[
\tilde{R}_B = \frac{1}{\mu} \left( (1 - \rho_B) \gamma_B \tilde{A}_B + (\tilde{A}_B \tilde{A}_D) \right.
\]

\[
\left. + \delta_B (\tilde{C}_B + [\tilde{C}_B \tilde{A}_D] + [\tilde{C}_B \tilde{C}_D]) \right)
\]

\[
\left. + \delta_D [\tilde{C}_B \tilde{C}_D] \right),
\]

\[
\tilde{A}_B \tilde{A}_D = \lambda_D \psi_1 + \psi_0
\]

\[
\tilde{C}_B \tilde{A}_D = \mu + \mu_B + \delta_B + \gamma_D,
\]

\[
\tilde{C}_B \tilde{C}_D = (1 - \rho_D) \gamma_D \tilde{C}_D = \tilde{C}_B R_D = \frac{(1 - \rho_D) \gamma_D \tilde{C}_D}{\mu + \mu_B + \delta_D},
\]

(3)

where

\[
\phi_1 = 1,
\]

\[
\phi_2 = \mu_D + \delta_B - b \sigma_D + \delta_D + \gamma_D + \mu_B \gamma_B
\]

\[
\phi_1 = - (\delta_D + \gamma_D + \rho_B \gamma_B + \mu_D + \mu_B + \delta_B) b \sigma_D
\]

\[
+ (\mu_B + \gamma_B + \delta_B + \gamma_D) \mu_D
\]

\[
+ (\mu_B + \gamma_B + \delta_B + \gamma_D) \delta_D
\]

\[
+ \gamma_B (\delta_B + \gamma_D + \mu_B)
\]

\[
\phi_0 = \left( - (\delta_B + \gamma_D + \rho_B \gamma_B + \mu_B) \mu_D
\right.
\]

\[
- (\delta_B + \gamma_D + \rho_B \gamma_B + \mu_B) \delta_D
\]

\[
- \rho_B \rho_D \gamma_D \tilde{B}_D
\]

\[
+ \gamma_B (\mu_D + \delta_B) (\tilde{B}_D + \gamma_D + \mu_B)
\]

\[
\psi_1 = b \sigma_D \tilde{C}_B + (\gamma_D + \delta_B + \delta_D + \mu_B + \mu_D) \tilde{A}_B
\]

\[
\psi_0 = (\mu_D + \delta_D) (\tilde{B}_D + \mu_B) \tilde{A}_B
\]

\[
+ b \tilde{C}_B (\rho_D \gamma_D + \delta_D + \mu_D) \sigma_D
\]

\[
6.3 \quad \text{The reproductive numbers}
\]

\[
6.3.1 \quad \text{The reproductive numbers for hepatitis B}
\]

To compute the basic reproductive number for hepatitis B we apply the standard next-generation approach. The system [1] has two stages that contribute to hepatitis B: \( A_B \) and \( C_B \). By, decoupling the system into new hepatitis B infections and transitions between hepatitis B infection classes, it follows that

\[
F_B = \begin{pmatrix}
\beta_B S^{DFE}_N / N + b \sigma_B & \beta_B S^{DFE}_N / N + b \sigma_B \\
0 & 0
\end{pmatrix},
\]

and

\[
V_B = \begin{pmatrix}
\gamma_B + \mu & 0 \\
- \rho_B \gamma_B & \delta_B + \mu + \mu_B
\end{pmatrix}.
\]
Thus, the next-generation matrix is \( G_B = F_B V_B^{-1} \), which equates to
\[
\begin{pmatrix}
\frac{\beta_B S^{DFE} + b \sigma_B N (\mu + \mu_B + \delta_B + \rho B \gamma B)}{N (\gamma_B + \mu)} & \frac{\beta_B S^{DFE} + b \sigma_B N}{N (\delta_B + \mu + \mu_B)} \\
0 & 0
\end{pmatrix}
\]

From computing the spectral radius of \( G_B \), we obtain the basic reproductive number to be
\[
R^B_0 = \frac{\beta_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B)} \frac{S^{DFE}}{N} + \frac{b \sigma_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B)}, \tag{4}
\]
where \( S^{DFE} = \frac{\beta}{\mu} N \) in the absence of vaccination. From the calculation of \( R^B \), it follows that the effective reproductive number is
\[
R^B_{\text{eff}} = \frac{\beta_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B) \mu + \nu} \frac{S^{DFE}}{N} + \frac{b \sigma_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B) \mu + \nu},
\]
and the control reproductive number is
\[
R^v_0 = \frac{\beta_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B) \mu + \nu} + \frac{b \sigma_B (\mu + \mu_B + \delta_B + \rho_B \gamma_B)}{(\gamma_B + \mu) (\delta_B + \mu + \mu_B) \mu + \nu}.
\]

### 6.3.2 The reproductive numbers for hepatitis D

To compute the basic reproductive number for hepatitis D we once again apply the standard next-generation approach. The system has three stages that contribute to hepatitis D: \([A_B A_D], [C_B A_D], \text{and} [C_B C_D]\). By decoupling the system into new hepatitis D infections and transitions between hepatitis D infection classes, it follows that
\[
F_D = \begin{pmatrix}
\beta_D \frac{\bar{A}_B}{N} + b \sigma_D & \frac{\bar{A}_B}{N} + b \sigma_D & \frac{\bar{A}_B}{N} + b \sigma_D \\
\frac{\beta_D \bar{C}_B}{N} & 0 & 0 \\
0 & \frac{\beta_D \bar{C}_B}{N} & 0
\end{pmatrix},
\]
and
\[
V_D = \begin{pmatrix}
\gamma_B + \mu & 0 & 0 \\
-\rho_B \gamma_B & \gamma_D + \delta_B + \mu_B & 0 \\
0 & -\rho_D \gamma_D & \delta_D + \mu + \mu_D
\end{pmatrix}.
\]

Using \( F_D \) and \( V_D \), we take the spectral radius of \( F_D V_D^{-1} \) to estimate the control reproductive of hepatitis D as
\[
R^v_0 = \frac{1}{(\gamma_B + \mu) (\gamma_D + \mu + \mu_B + \delta_B) (\mu + \mu_D + \delta_D)} \cdot \left( \mu^2 + (\mu_B + \mu_D + \rho_B \gamma_B + \gamma_D + \delta_B + \delta_D) \mu + \rho_B \gamma_B \rho_D \gamma_D (\beta_D \frac{\bar{A}_B}{N} + b \sigma_D) + \beta_D (\gamma_B + \mu) (\rho_D \gamma_D + \mu + \mu_D + \delta_D) \frac{\bar{C}_B}{N} \right).
\]

Finally, the basic reproductive number is obtained by
\[
R^D_0 = R^v_0 |_{\nu = 0}. \tag{5}
\]

### 6.4 Hepatitis transmission rates

To estimate the transmission rate of hepatitis B we use estimates on the prevalence of hepatitis B, the proportion of chronic hepatitis B, the basic reproductive number of hepatitis B \([36]\) along with the endemic equilibrium for hepatitis B \([4]\). It follows for \( R^B_0 = 2.406 \) \([36]\) that
\[
\beta_B \approx 0.288 \text{ year}^{-1}.
\]

Chronic infection with hepatitis B reduces the average life span of 61.3 years by approximately 4.8 years \([26]\). Thus, on average, we have that
\[
\frac{1}{\mu + \mu_B} \approx 56.5 \text{ years}.
\]

It follows that \( \mu_B \approx 0.00139 \text{ year}^{-1} \). Similarly, chronic hepatitis D co-infection typically leads to death 10 years sooner than mono-infection with hepatitis \([14]\). Thus, we have that
\[
\frac{1}{\mu + \mu_D} \approx 46.5 \text{ years},
\]
and so
\[
\mu_D \approx 0.00519 \text{ year}^{-1}.
\]

To estimate the transmission rate of hepatitis D, the literature place \( R^D_0 \approx 1.01 \) when \( \nu = 0.00025 \text{ year}^{-1} \), with an \( R^D_0 \approx 1.09 \) under an average lifespan of 55.6 years \([34]\). When considering a lifespan of \( \frac{1}{\mu} = 56.5 \text{ years} \), and the birth rate \( b = 0.046 \text{ year}^{-1} \), we have that \( R^D_0 \approx 1.25 \) when \( \nu = 0.00025 \text{ year}^{-1} \). Given this estimate, and the parameter values from Table 1, it follows from (5) that
\[
\beta_D \approx 6.79 \text{ year}^{-1},
\]
and in the absence of vaccination that
\[
R^D_0 \approx 1.40.
\]
6.4.1 The proportion that develops active disease

To estimate the proportion of individuals that develop active disease we use current estimates that 90% of perinatal infections are active, 30% of childhood infections (6 years) are active, and 10% of other infections are active [26]. Thus, given that approximately 0.142% of individuals are classified as perinatal, 2.9% are classified as children under 6 years [17], it follows that

\[
\rho = 0.9(0.00142) + 0.29(0.028) + 0.1(0.96) \approx 0.10.
\]

6.5 Effective vaccination rate estimation

To estimate the effective vaccination rate of hepatitis B we make use of the HBV endemic and HDV free equilibrium, in addition to the HBV and HDV co-endemic equilibrium. Specifically, we solve to estimate the effective vaccination rate of hepatitis B

\[
V(S + V + A_B + C_B + R_B + [A_B A_D] + [C_B A_D] + [C_B C_D] + [C_B R_D])^{-1} = 0,
\]

where eqb represents either the HBV endemic and HDV free equilibrium, or the HBV and HDV co-endemic equilibrium, depending on scenario, and \( \theta \) is 10.72%, 22.23%, or 62.1%, depending on the high, intermediate, or low HBV endemicity, respectively.

References


