International Journal of Scientific & Engineering Research, Volume 5, Issue 11, November-2014
ISSN 2229-5518

Strategies for controling the spread of Hepatitis B virus in adult population

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Abstract

Hepatitis B virus (HBV) disease continues to spread among the adult population, though the disease is gradually driven towards eradication among infants and children due to vaccination. We present a deterministic model for controlling the spread of HBV among the adult population using adult catch-up vaccination and change in sexual habits as control measures. Using Senegal demographic data, we compute the disease prevalence for different combinations of levels of the two measures. We also compute the associated cost suggesting, under budget limitation, how to choose optimal intervention strategy.

Keywords: Catch-up vaccination, Hepatitis B virus infection, Disease prevalence, Intervention strategies, and Education/awareness program.

1 Introduction

Approximately two billion people worldwide have been infected sometimes during their life time by Hepatitis B virus (HBV) and about 350 million are currently living with HBV chronic infection, while an estimated 600,000 individuals die each year due to the disease [13, 14]. HBV is a blood-borne and sexually transmitted virus. When an individual is infected with HBV, the virus becomes present in his/her blood and others body fluids. Hence, the virus can be transmitted through sexual contact, the use of contaminated syringes and needles, or by the sharing of personal items such as razors or toothbrushes. The virus can also be passed from mother to child at birth.

Although transmission of hepatitis B virus (HBV) has been documented to occur between heterosexuals, homosexual men are generally recognized as the group at greatest risk of acquiring hepatitis B as a result of sexual activity [6, 18, 1]. The consequences of HBV infection can be severe, including the development of hepatic insufficiency, cirrhosis and hepatocellular carcinoma. Most acutely infected HBV individuals recover from the infection within six months, but nearly 10% become chronically infected. There is no effective treatment (cure) for chronic HBV but there is vaccination against HBV infection, which is 95% effective [13]. This vaccination is not only effective for healthy individuals, but it is also effective for those individuals who were infected with HBV within the preceding 2 weeks. Unfortunately, infected individuals do not present clinical symptoms for at least one month.

The spread of hepatitis B infection varies widely throughout the world. In some regions, over 10% of the population is positive for hepatitis B surface antigen (HBsAg), which indicates active infection. Countries are classified as having low endemic rates ($< 2\%$ of the population has the antibody to HBsAg), intermediate endemic rates (2-8% positive for HBsAg), or high endemic rates ($> 8\%$ positive for HBsAg). Hepatitis B is highly endemic in China, South East Asia, and Africa. Most people in high endemic regions become infected with HBV during childhood. In the high endemic region, where the prevalence is above 10% in the general population, the transmission occurs frequently by vertical transmission from mother to child at birth [21, 16]. In the Middle East and Indian subcontinent, the prevalence of individuals chronically infected by HBV in the general population are estimated to be 2-5%. Western Europe and North America are the low endemic region

with less than 1% of the population chronically infected, mostly as a result of horizontal transmission among young adults by sexual activity and contaminated needles for injecting drugs [19].

Recent studies show that behavior change can play significant role in the control of the spread of infectious diseases (e.g. HIV) [10, 8, 17, 4, 9]. Hence, understanding the effect of behavioral change on the spread of HBV can help identify effective control measures required to curtail the spread of the disease.

In this paper, we develop a mathematical model for the spread of HBV and use it to evaluate strategies that include both change in sexual habits and vaccination. We quantify the financial investments associated with such strategies and determine the benefits in reducing HBV prevalence resulting from the financial investments.

2 Model Formulation

Based on the characteristics of HBV transmission, we divide the sexually active population N into five distinct compartments:

- S: compartment of people susceptible to HBV infection
- E: compartment of people latently infected by HBV
- A: compartment of people acutely infected by HBV
- C: compartment of people chronically infected by HBV
- R: compartment of people who are immunized/vaccinated against HBV infection

When a person is infected with HBV, he/she does not show clinical symptom for a period of approximately 3 months (i.e. the latent infection stage). During this period the disease either clears or it progresses to the acute stage. At the acute stage, the disease can still be cleared, otherwise, it proceeds to the chronic stage. People at the latent stage are asymptomatic while people at the acute stage are sometimes symptomatic (including yellowing of the skin and eyes (jaundice), dark urine, extreme fatigue, nausea, vomiting and abdominal pain). Surprisingly enough, people with chronic HBV do not show any symptom although they can infect susceptible people and they are also at high risk of developing chronic liver disease, including cirrhosis (scarring of the liver), liver failure, and liver cancer. An important difference between the latent stage and the acute stage is that people in the latent stage cannot infect susceptibles while people in the acute stage are infectious. People in the compartment R are those who either contracted the disease and had it cleared or those who have been vaccinated against HBV.
We assume that the death rate is the same in all compartments except the compartment of people chronically infected by HBV whose mortality rate is significantly higher.

The HBV compartmental model is shown schematically in Figure 1:

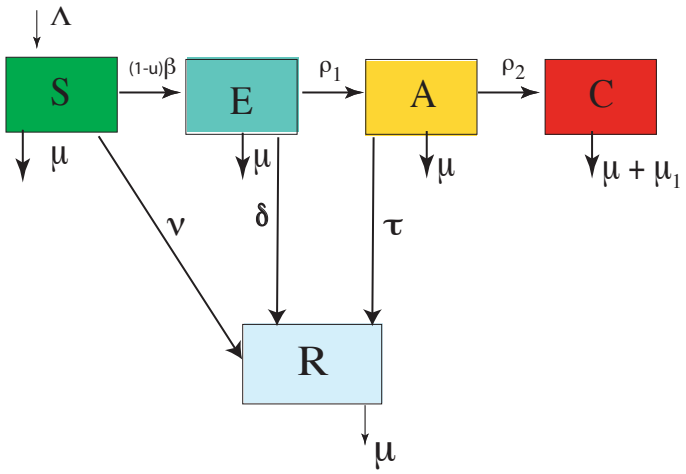

Figure 1: Schematic diagram for HBV transmission with vaccination ν and sexual behavioral change u as control measures.

The following system of differential equations describes the rates of change between the five compartments of Figure 1:

$$\begin{cases} \frac{dS}{dt} = \Lambda - \frac{(1-u)\beta S}{N}(A+C) - \nu S - \mu S \\ \frac{dE}{dt} = \frac{(1-u)\beta S}{N}(A+C) - \delta E - \rho_1 E - \mu E \\ \frac{dA}{dt} = \rho_1 E - \rho_2 A - \tau A - \mu A \\ \frac{dC}{dt} = \rho_2 A - \mu_1 C \\ \frac{dR}{dt} = \nu S + \delta E + \tau A - \mu R \end{cases} \quad (1)$$

where $N = S + E + A + C + R$.

The parameters interpretation is given in Table 1.

Parameter	interpretation
Λ	inflow of susceptibles
μ	natural death rate in the population
β	transmission rate
τ	acute HBV recovery rate from A to R
δ	latent HBV recovery rate from E to R
ρ_1	progression rate from E to A
ρ_2	progression rate from A to C
ν	effective vaccination rate for S
μ_1	HBV disease-induced death rate
u	control of sexual behavioral change

Table 1: Parameter interpretation

3 Initial conditions and model parameter estimates.

To simulate the model, we use data from Senegal, a country with high endemic HBV. However, the model can be applied to other countries with similar HBV situation. The HBV prevalence in Senegal is $> 8\%$ and there is no prevention program towards controlling HBV transmission among the sexually active population. Moreover, the vaccination of the children against HBV only started less than a decade ago, thus, currently leaving a large portion of the adult population without HBV immunity.

Initial conditions

The initial year for our simulations is 2005. The adult population (Age 15 years and above) in Senegal was approximately 5.8 million [5]. According to Vray et al [20], the prevalence of HBs antigen (HBsAg shows active hepatitis B infection) carriage during the year 2005 was about 15-20% in the general population; we take the mean, 17.5%, to be the prevalence of people infected by HBV in the adult population. Hence, the total number of individuals acutely and chronically infected with HBV was 1.02 million. Acute infection lasts approximatively 1/2 year and 90% of infected individuals clear the virus within 6 months [13]. We assume that chronically infected individuals live

approximately 20 years after infection which is about 40 times the time it takes acute HBV infection to progress to the chronic stage. Since only 10% of the infected individuals proceed to the chronic case, the number of chronically infected individuals is about 4 times that of the number of acutely infected individuals. Hence, $A(0) = 0.204$ million and $C(0) = 0.816$ million. We assume that the number of individuals in the latent stage is approximately same as that in the acute stage (i.e. $E(0) = A(0) = 0.204$).
In 2005 approximately 3% recovered from the disease and became immune. Since the total population in Senegal was significantly smaller during the 25 years preceding 2005, we take the number of recovered individuals in 2005 to be 35%, that is $R(0) = 2.03$ million. Also, we take $S(0) = 2.55$ so that the total population sum up to 5.8 .

Parameter	Units	Value	Reference
Λ	million / year	0.225	[2] and Estimate
μ	1/year	0.025	[5]
β	1/year	0.95	[15] and Estimate
ρ_1	1/year	2.0433	[13] and Estimate
ρ_2	1/year	2.4079	[13] and Estimate
μ_1	1/year	0.0693	[13] and Estimate
τ	1/year	0.7133	[13] and Estimate
δ	1/year	3.6652	Estimate
ν	1/year	$0 \leq \nu \leq 1$	variable
u	1/year	$0 \leq u \leq 1$	variable

Table 2: Parameter values, using data from Senegal.

Natural death rate (μ)**:** The life expectancy in Senegal in 2005 for individuals who are not chronically HBV infected was 55 years [5]. Hence, their natural death rate μ satisfies $\dot{N} = -\mu N$ and $N(\frac{55}{2}) = \frac{1}{2}N(0)$. Thus, $\mu = \frac{ln2}{27.5} = 0.025$.

Disease induced death rate (μ_1)**:** According to the World Health Organization [13], at least $15 - 25\%$ of the adults who develop chronic HBV die as a result of the disease rather than by natural death. We assume that chronic HBV infection occur at an average age of 25 years. Given that chronically infected individuals live for about 20 years as earlier stated, we

have

$$\frac{1}{2}C(0) = C(10) = C(0)e^{-10\mu_1}.$$

This implies that $\mu_1 = \frac{ln2}{10} = 0.0693$.

Constant recruitment rate (Λ)**:** In a steady state, if the population were all healthy, $\frac{\Lambda}{\mu}$ would be equal to the total adult population $N(t)$. If we assume that the total adult population will eventually become healthy and stabilize at 9 million, we get $\Lambda = N \times \mu = 0.225$ million per year.

Removal rates $(\delta,\ \tau)$**:** Using information from [13], 90% of healthy adults infected with HBV will recover and completely clear the virus within six months. We assume that 60% of those who recovered are at the latent stage of the infection while the remaining 30% have progressed to the acute stage of the infection before recovery. Then, we have

$$E(\frac{1}{4}) = 0.4E(0) \quad where\ E(t) = E(0)e^{-\delta t}.$$

Hence, $\delta = 4ln(\frac{10}{4}) = 3.6652$.
Similarly, 30% of the acutely infected individuals recover after about 6 months. So,

$$A(\frac{1}{2}) = 0.7A(0) = A(0)e^{-\frac{1}{2}\tau}.$$

Therefore, $\tau = 2ln(\frac{10}{7}) = 0.7133$

Progression rates (ρ_1, ρ_2)**:** As a result of the recovery of some acute infected individuals, we only have 40% infected individuals left who can progress to the chronic stage. So, we estimate $\rho_1 = 4ln(\frac{10}{6}) = 2.0433$. In the same way, we have only 70% in the acute stage who can progress to the chronic stage. So, we estimate $\rho_2 = 2ln(\frac{10}{3}) = 2.4079$.

Rate of infection (β)**:** A study in 1993 shows 14.0% prevalence among pregnant Senegalese [15]; we assume that this also is the prevalence of HBV infected people in the sexually active population. To estimate the parameter (β), we use Berkeley Madonna software to fit our model to these two prevalences (14% initial prevalence for the year 1993 and 17.5 % prevalence for the year 2005). Taking $\nu = 0$ and $u = 0$ (no vaccination and no education policy), we get $\beta = 0.95$.

4 Cost effectiveness of vaccination and education against HBV

4.1 Estimating cost of HBV adult vaccination

A dose of adult HBV vaccination costs \$0.42 [12]. For effective vaccination, an adult is usually given three doses of the vaccine at three different times, at total cost \$1.26. We added the overhead cost (vaccine storage, transportation, personnel, etc) to make the cost of \$3 per adult vaccination. Hence, the cost of vaccinating the susceptibles S is $c_1 = \$3 \times \nu \times S$ per year. Therefore, the estimated total cost of the vaccination program over a 10 year period $C_1 = (3 \times \nu) \times (S(0) + S(1) + \cdots + S(8) + S(9))$ million US dollars.

4.2 Estimation of cost prevention

The prevalence of HBV is defined by the quotient:

$$\pi = \frac{A + C}{S + E + A + C + R}$$

Observation from Ibadan, Nigeria, shows that there was a reduction in HBV prevalence among the sexually active population from 16.15% in 2001 to 11.28% in 2006 due to education and awareness [7]. We assume that with a similar intervention program in Senegal, the HBV prevalence would be reduced in the same proportion. We used Berkeley Madonna to evaluate the value of u which reduces the prevalence from 16.15% to 11.28% after six years without vaccination (for adults) and we get $u^* = 0.53$.

In order to determine the cost of the education and awareness program in Senegal corresponding to $u^* = 0.53$, we propose a strategy comprising radio and television HBV prevention advertisement, community based education and awareness campaign, and STI's diagnosis and testing program.

It is important to emphasize that it is difficult to estimate the annual cost of implementing education and awareness program because the costs associated with some of the programs change overtime and may also depend on the country of interest. Here, we only give rough cost estimates for the programs recurrent expenses with the assumption that most of the capital expenses (buildings, Infrastructures, etc) would have already been incurred.

Radio and Television program
We used the information that a minute of radio and television advertisements costs \$383 and \$2, 566 respectively [11]. Assuming that each of the advertisements runs once every other day all through the year and half of the advertisements are run by government owned stations at no cost, we calculate the annual cost of the radio advertisements as $0.5 \times 383 \times \frac{1}{2}(365) = \$34,949$ and the annual cost of the TV advertisements as $0.5 \times 2,566 \times \frac{1}{2}(365) = \$234,148$.

Community based education
We used a cost of \$3.0 per individual reached given in [11] as the estimated cost for HBV education and awareness program at the community level. With a target of 0.1 million people to be covered per year, the program will cost $\$3 \times 0.1 = \$0.3$ million.

Diagnosis and Testing of STIs
The cost of diagnosis and treatment of sexually transmitted infections (STI's) is estimated at \$12.66 per person [3]. We assume that 0.1 million people will be diagnosed and treated for STI's annually, costing $0.1 \times 12.66 = \$1.266$ million per year.

Adding the above costs, we find that the total cost of the intensive education and awareness program corresponding to $u^* = 0.53$ is approximately \$1.8 million. We assume that this cost is linear with respect to u, thus for any other u, we take the cost to be $c_2 = \frac{1.8}{u^*} \times u$ or $c_2 = 3.4 \times u$ million of U.S dollars per year. If this cost is relatively fixed over the the period of 10 years, then we estimate the cost of the education and awareness program over the 10 years period $C_2 = 34 \times u$ million US dollars.

4.3 Cost and impact of the policy prevention

In Table 3, we have computed the prevalence π of HBV in the sexually active population after 10 years, for various strategies (ν, u). We also computed the associated cost C_1 of vaccination intervention ν; the cost C_2 of education and awareness campaign for 10 years. This table may be helpful in choosing strategies for allocating a total budget C for vaccination (C_1) and for education and awareness (C_2) ($C = C_1 + C_2$).

ν	u	π	C_1	C_2	C
0.0	0.0	0.1831	0.0	0.0	0.0
0.0	0.2	0.1704	0.0	6.79	6.79
0.0	0.4	0.1536	0.0	13.58	13.58
0.0	0.6	0.1326	0.0	20.38	20.38
0.0	0.8	0.1085	0.0	27.17	27.17
0.2	0.0	0.1365	6.94	0.0	6.94
0.2	0.2	0.1278	7.46	6.79	14.25
0.2	0.4	0.1181	8.03	13.58	21.61
0.2	0.6	0.1173	8.65	20.38	29.03
0.2	0.8	0.0956	9.31	27.17	36.48
0.4	0.0	0.1182	10.32	0.0	10.32
0.4	0.2	0.1120	10.81	6.79	17.61
0.4	0.4	0.1054	11.34	13.58	24.93
0.4	0.6	0.0984	11.90	20.38	32.28
0.4	0.8	0.0910	12.49	27.17	39.66
0.6	0.0	0.1090	12.52	0.0	12.52
0.6	0.2	0.1043	12.93	6.79	19.72
0.6	0.4	0.0993	13.36	13.58	26.94
0.6	0.6	0.0942	13.81	20.38	34.19
0.6	0.8	0.0889	14.28	27.17	41.45
0.8	0.0	0.1036	14.24	0.0	14.24
0.8	0.2	0.0998	14.58	6.79	21.37
0.8	0.4	0.0958	14.93	13.58	28.52
0.8	0.6	0.0918	15.30	20.38	35.68
0.8	0.8	0.0877	15.68	27.17	42.85

Table 3: Values of π, C_1 (cost of ν), C_2 (cost of u), and the total cost $C = C_1 + C_2$ associated with different choices of ν and u. Note that the costs are in million US dollars

From Table 3, we see a trend which suggests that with the same total budget allocation C, it is more beneficial to use a larger fraction on catch-up vaccination than on education and awareness.

(i) Indeed, comparing $(\nu, u) = (0.2, 0.4)$ with $(\nu, u) = (0.8, 0.2)$, we see that with approximately the same budget of \$21.4 million we can reduce the prevalence to 0.0998 with $(0.8, 0.2)$ instead of 0.1181 with $(0.2, 0.4)$.

(ii) $(\nu, u) = (0.8, 0.6)$ yields prevalence of 0.0918 whereas $(\nu, u) = (0.2, 0.8)$ with larger budget yields a higher prevalence of 0.0956.

(iii) $(\nu, u) = (0.6, 0.4)$ yields prevalence 0.0993 whereas $(\nu, u) = (0.0, 0.8)$ with larger budget yields higher prevalence of 0.1085.

(iv) $(\nu, u) = (0.8, 0.0)$ yields prevalence of 0.1036 whereas $(\nu, u) = (0.2, 0.2)$ with slightly larger budget yields prevalence of 0.1278

5 Concluding Remarks

In this paper, we presented a mathematical model for a combined strategy of adult catch-up vaccination and change in sexual habits through education and awareness for controlling HBV spread among the adult population. The model was applied to Senegal, a country with high HBV prevalence. We also estimated the cost of implementing the proposed measures. Our model can be used to estimate the costs involved in reducing the prevalence of HBV through intervention by catch-up vaccination (expressed by a parameter ν) and by education and awareness program (expressed by a parameter u). We have illustrated our model by computing the prevalence of HBV after 10 years, using the same combination strategy (ν, u) for the entire period.

As Table 3 shows, with no intervention , the prevalence of HBV in Senegal, presently at 0.175 (17.5%) will climb up to 0.1831, whereas with total investment of about $40 million (over 10 years), it will decrease to 0.877. For intermediate investment, e.g. $21.61 million, the prevalence will decrease to 0.118.

Table 3 also shows a trend in the investment C_1 (for ν) and C_2 (for u): The prevalence after 10 years will be appreciably smaller if we invest more in ν and less in u, given a total budget $C(= C_1 + C_2)$. However, our estimate of the cost of education and awareness program is quite rough, it is borrowed from programs in other countries and for HIV. As more HBV epidemiological data become available, the estimate of the relative cost of C_1 and C_2 could become more precise and then the model will accordingly be revised to offer more precise predictions.

Acknowledgment
This work is supported by the National Science Foundation upon Agreement No. 0112050 and NSF African Biomathematics initiative Grant Award 6RT00014792.

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