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Modeling Hepatitis B Virus Transmission Dynamics in a Heterosexual Population on Complex Graphs

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Abstract Hepatitis B is a global threat as approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV) and 350–400 million people are chronic HBV surface antigen (HBs Ag) carriers. The objective of this study is to simulate the dynamics of HBV transmission under two different partnership structures and different interventions and predict the prevalence of HBV virus. A graph was generated under two scenarios: first, the node-degrees obey the power law distribution and secondly, the node-degrees are each restricted to having one link (partner). In either case, it is assumed that the partnership durations follow Weibull distribution. The results show that behavioural change from multiple partnerships and effective condom usage are the best strategy for the control of HBV prevalence in a heterosexual population. Therefore, efforts should be directed at creating awareness on the importance of monogamy and use of condoms.

Keywords Modeling, monogamy, power law distribution, Weibull distribution

1. Introduction

Hepatitis means inflammation of the liver. Hepatitis B is a contagious liver disease that results from infection with the hepatitis B virus. When first infected, a person can develop an illness which can be mild, with few or no symptoms, or an illness that is serious, requiring hospitalization and sometimes leading to liver failure. Acute hepatitis B refers to the period when a person first becomes infected with the virus. This is the time a person is most likely to have symptoms. Some people develop antibodies (proteins found in the blood or body fluids that help fight infection) and these people recover, which leads to protection from future infection. Other people, especially infants and young children, do not recover. Instead, the infection remains and becomes a "chronic" or lifelong infection. Chronic hepatitis B refers to infection when the hepatitis B virus continues to be active in the person's body for more than 6 months. Over time, chronic infection damages the liver and causes scarring, liver failure, and sometimes liver cancer. While there is no cure for hepatitis B infection, treatment can slow the damage to the liver. Infected children have up to a 90% chance of developing chronic infection [1].

Hepatitis B is one of the world's most serious health problems. Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV) and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers [2-7].

HBV infection can be transmitted from mother to child (vertical), contact with an infected person (horizontal transmission), sexual contact (homosexual and heterosexual transmission) with infected partners, exposure to blood or other infected fluids and contact with HBV contaminated instruments [8-9].

HBV control measures include vaccination, education, screening of blood and blood products; and treatment [10]. However, hepatitis B viral mutants can emerge in patients as a result of selection pressure from either immune response or treatment options. The concern is that carriers with HBV mutants can still infect vaccinated individuals and mount resistance to antiviral drugs [11-12].

Epidemiological models help to capture infection or disease transmission mechanisms in a population in a mathematical frame-work to predict the behavior of the disease spread through the population. Mathematical models have become important tools in analyzing the spread and control of infectious diseases. Understanding the transmission characteristics of infectious diseases in communities, regions and countries across the world in model frame works can lead to better approaches to decreasing the transmission of these diseases [13].

Recently, mathematical models have been used to study the transmission dynamics of HBV in various communities, regions and countries across the world. Anderson and May [13] proposed a simple deterministic, compartmental mathematical model to investigate the effects of carriers on the transmission of HBV. Anderson and May [14] and Williams *et al* [15] presented models of sexual transmission of HBV, which include heterogeneous mixing with respect to age and sexual activity. Edmunds *et al* [16] explored the relation between the age at infection with HBV and the development of the carrier state. Medley *et al* [17] proposed a model to show that the prevalence of infection is largely determined by a feedback mechanism that relates the rate of transmission, average age at infection and age-related probability of developing carriage following infection. Thornley *et al* [18] applied the model of Medley *et al* [17] to predict chronic hepatitis B infection in New Zealand. The prevalence of HBV in developing countries is different from that in developed countries, since it appears that the rate of transmission in childhood is the major determinant of the level of HBV endemicity and little is known on the rates and patterns of sexual contact in developing countries [19]. Mclean and Blumberg [20] and Edmunds *et al* [21] studied models of HBV transmission in developing countries and Williams *et al* [15] described a model of HBV in UK. O'Leary *et al* [22] proposed a mathematical model to investigate the effect of Hepatitis B vaccine and anti-viral treatment among the Canadian Inuit population. An optimal control model of Hepatitis B transmission dynamics was proposed. Zou *et al* [23] proposed a mathematical model to investigate the transmission dynamics and prevalence of HBV in mainland China. Zou *et al* [24] used a mathematical model to study the sexual transmission dynamics of hepatitis B virus in China. Zhang et al [25] proposed a model to explore the transmission dynamics of hepatitis B virus in China.

Public health policy on the design of various HBV control programs has benefitted a lot from the recommendations of the previous mathematical modelers and much success has been recorded. However, available data in various regions on the prevalence of HBV infection show a slow pace of control [26]. Much still needs to be done until HBV infection is eradicated from the global community.

The model by Zou *et al* [25] forms the motivation for this study. In their work, a mathematical model was proposed to study the sexual transmission dynamics and prevalence of HBV infection in mainland China. While they used ordinary differential equations, use is being made of graphs here.

However, these aforementioned classical epidemiological models ignore the importance of the complex patterns and structures of social interactions on the spread of diseases. So, most of the earlier epidemiological models trivialize the social aspects of disease transmission. However, since the middle of the twentieth century, sociologists, mathematicians have been studying social networks and have come up with a large literature spanning many different aspects of social networks from empirical, conceptual and methodological points of view [27].

The plan of this work is as follows. Section 2 is devoted to graphs and modeling. Section 3 is devoted to model description. Simulation experiments are performed in section 4. Results are presented and discussed in sections 5 and 6 respectively. Finally conclusion is passed in section 7.

2. Graphs and Modeling

Graphs used in the literature can be classified on the properties of interest. From the dynamism point of view, graphs or networks can be classified as static or dynamic depending on whether their structures change with time. From the field of application perspective, we have social networks, information networks, technological networks, epidemic networks, to mention a few. Each of these types of networks can be narrowed to specific networks. Graph classifications based on degree distribution exist. For instance, scale-free graphs, Poisson graphs. Graphs such as unipartite, bipartite or multipartite are based on the node types. For a general knowledge of graphs and their theory, refer to [28-38]

Real world network are large, and in most cases it is virtually impossible to describe them in detail or to give an accurate model for how they came to be. To circumvent this problem, random graphs have been considered as network models. The field of random graphs was established in late 1950s and early 1960s. For detail, see Hofstad [28].

In this article, our interest is in social networks and how they affect the epidemiology of diseases, especially, sexually transmitted infections. A social network is a social structure made up of individuals (or organizations) called nodes which are connected by some specific types of interdependency, such as friendship, enmity, common interest, financial exchange, dislike, sexual relationship or relationship of beliefs, knowledge or prestige. For detail of social network analysis, refer to Wasserman and Faust [39]. A sexual contact network is a set of individuals who are connected by sexual relationships (partnerships).

2.1. Graph Models for Sexually Transmitted Infection

We make a scanty review of graph models of interest, from where we pick our research question. For a review of graph or network-based models, refer to Quax [40] and Tolentino [41]. Bai *et al* [42] propose a network spreading model for HIV, wherein each individual is represented by a node of the transmission network and the edges are the connections between individuals along which infection may spread. The sexual activity of each individual, measured by its degree, is not homogeneous but obeys power law distribution. Sloot *et al* [43] did stochastic simulation of HIV population through complex networks. The node-degrees obey power law distribution while the time evolution of the network is determined by a Markov process. Kretzchmar *et al* [44] did modeling prevention strategies for gonorrhea and chlamydia using stochastic network simulations. Their simulation model is discrete time Markov model describing pair formation and separation and disease transmission as stochastic processes. Morris and Kretzchmar [45] used stochastic simulations to investigate the effect of concurrent partnerships on transmission dynamics in networks. Quax [40] did modeling and simulation of propagation of infectious diseases in a homosexual population. The author constructed Kronecker graphs, with the node degrees obeying the power law distribution. In most of these studies, it is found out that, in time steps, either an edge is formed or dissolved between nodes with equal probability or that a new random graph is regenerated at every time step. In practice, all the nodes have varying partnership durations. While some partnerships are stable relationships with long durations, others are casual relationships with short term durations. The assumption of equal probability for the dissolution of every relationship or equal probability for relationship formation may not be realistic. Althaus and Roellin [46] argue that sexual partnership durations are best described by a Weibull distribution, indicating increased robustness with ongoing duration. So, our graph model is based on the argument that the node-degrees may obey the power law or any other distribution and the partnership durations obey Weibull distribution.

3. Model Description

In this paper we consider a population that is divided into two types, namely, adult males and females, where each individual is in one of the states: susceptible, acute infection state, carrier state and carriers in state of treatment. Initially susceptible individuals can become infected after contact with infected individuals. We adopt the recipe by Jaquet and Pechal [47] and represent each of the infected states by some arbitrary number L of states I_n $(n = 1,\dots,L)$, each corresponding to one "stage" of the disease. Each of these stages is characterized by a real parameter $\alpha_n$which we call infectiousness and which determines the probability that an individual in that stage infects another susceptible individual.

3.1. Modeling of sexual contact networks

We construct a network model as a dynamical bipartite graph, where a population is compartmentalized into female and female susceptible subpopulations, wherein each individual is represented by a node and the edges are the links between the individuals. First, we use the power-law distribution to generate degree sequences for the subpopulations and the graph constructed using the mechanism of configuration model. The power law distribution can be mathematically represented by

$p(k) = k^{-\gamma},\ k \leq k_{max}$ where k is the number of sexual partners *per year* and γ is a parameter of the distribution. Small γ denotes more limited sexual contact behaviour and corresponds to a smaller value of $k$max indicating the promiscuity and vice versa. Latora *et al* [48] reports that the sexual contact network in Burkina Faso is a scale-free network. They estimated the exponent γ in the distribution for the numbers of partners for the male population to be 2.9(0.1). The survey in Sweden has shown that the values of the exponent γ in the distributions of the numbers of female and male populations were 3.1(0.2) and 2.6(0.3) respectively. For a review of sexual contact network models and other standard epidemiological models, refer to Liljeros *et al* [27].

Secondly, we generate a degree sequence where every node has one link (partner) and generate the bipartite graph by the same mechanism of configuration model

3.2. Modeling the spread of HBV on Graphs

The emphasis is on HBV heterosexual contact network, wherein compartments of males and females are each subdivided into four states: susceptible, acute infection state, carrier state and carriers in state of treatment. We adopt the recipe by Bai *et al* [42] with modification to reflect the realism of HBV transmission dynamics. As in their article, our model is implemented by computer simulation with a time step equal to one year. The simulation processes are in the sequel:

(1) We set the number of susceptible individuals and select a number of infected nodes randomly.

(2) At each time step for each susceptible node i, denote m_1, m_2 *and* m_3 for the numbers of its neighbouring infected nodes in the acute state, in the carrier state, and in the carrier state receiving treatment respectively. If the node i is a male, then the probability that i will become infected in the next time step is
$p_1 = 1 - (1 - \beta_{1f})^{m_1}(1 - \beta_{2f})^{m_2}(1 - \beta_{3f})^{m_3}$
β is the transmission probability per sexual partner. Similarly, for each susceptible female node i
$p_2 = 1 - (1 - \beta_{1m})^{m_1}(1 - \beta_{2m})^{m_2}(1 - \beta_{3m})^{m_3}$

(3) At each time step, each infected node may die with probability ε_1 (for the infected in the acute phase), ε_2 (for the infected in the carrier state) and ε_3 (for the infected carrier on treatment). We set ε_1=0.0165, $\varepsilon_2 = 0.025$ and $\varepsilon_3 = 0.02$.

(4) At each time step, each susceptible node die with probability ε_4 . We set $\varepsilon_4 = 0.015$ (which corresponds to a life expectancy of about 65 years.

(5) At each time step, the dead nodes are replaced each with probability ξ ($\xi = 0.019$). This choice is made based on the assumption of constant population, with ξ equal to the average of $\varepsilon_i, i = 1, .., 4$.

(6) At each time step, infected nodes in the acute phase proceed to the carrier state with probability $\lambda_1 = 1$. we assume that 60% of infected nodes in the carrier state are diagnosed and proceed for treatment with probability $\lambda_2 = 0.45$.

(7) At each time step, each sexual partnership is dissolved based on the probability distribution of partnership durations. To be specific, we use Weibull distribution. Also, all the nodes that have lost partnerships randomly re-connect to other disconnected nodes. This is common among casual partners like prostitutes and promiscuous men.

4. Simulation

We perform the following simulation experiments. In all the experiments, it is assumed that the partnership durations follow the Weibull distribution. We fix the initial population size at 3000 with the number of males equal to the number of females and also the female and male degree sequences come from the same distribution. We consider endemic and epidemic situation. In epidemic situation, we assume the population is wholly susceptible, except two infected individuals that randomly invade the population. In the endemic situation, we assume that about 10% of the population is infected. In the first experiment, we consider a situation where there is no usage of condoms and only two individuals are randomly infected initially, with the degree sequence following the power law distribution. The result is displayed in Figure 1. Secondly, we consider a situation where 80% of the population imbibes the use of condoms and only two individuals are randomly infected initially, with the degree sequence following the power law distribution. The result is shown in Figure 2.

In the third experiment, we consider an endemic situation where 80% of the population adopts the use of condoms and only 285 individuals are infected initially, with the degree sequence following the power law distribution. The result is shown in Figure 3. In the fourth experiment we consider a situation where there is no use of condoms and only 2 individuals are randomly infected initially, with the degree sequence being monogamous. The result is shown in Figure 4. In the fifth episode, we consider a situation where there is 80% usage of condoms and only two individuals are randomly infected initially, with the relationships being monogamous. The result is displayed in Figure 5. In the sixth experiment, we consider a situation where 80% of the population adopts usage of condoms and only 300 individuals are randomly infected initially, with the relationships being monogamous. The result is displayed in Figure 6.

5. Results

The results of the simulation experiments are shown in the sequel.

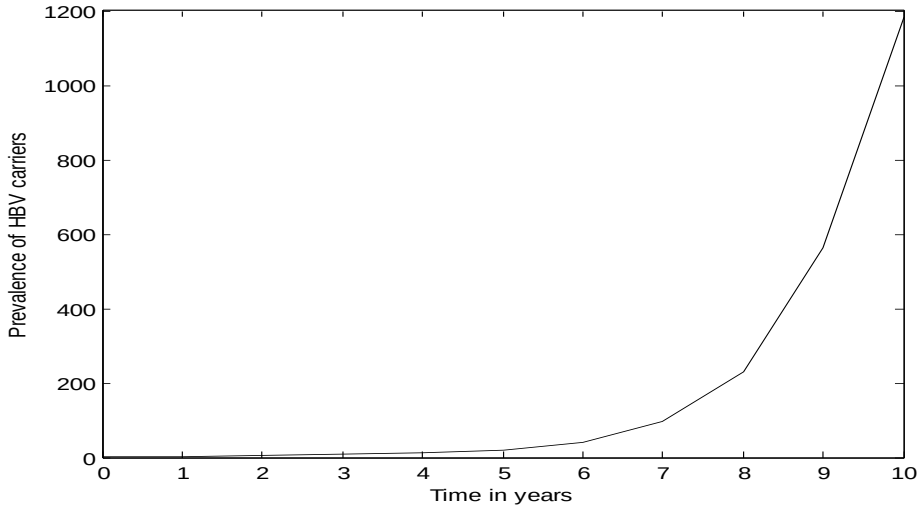

Figure 1: Prevalence of HBV infection under power-law and Weibull distribution without condom use; S=3000, I=2

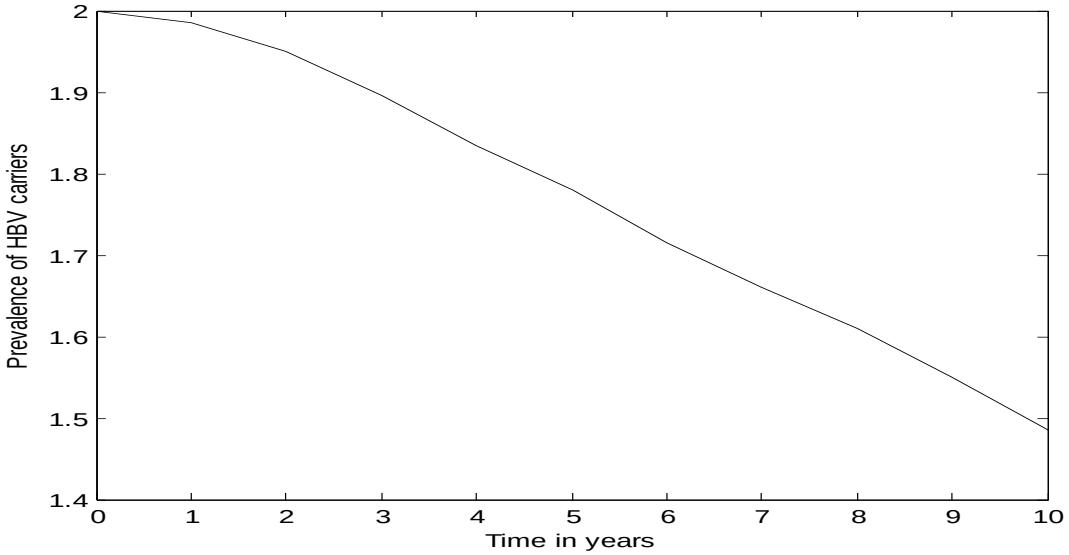

Figure 2: Prevalence of HBV infection under power-law and Weibull distribution with 80% condom use; S=3000,I=2

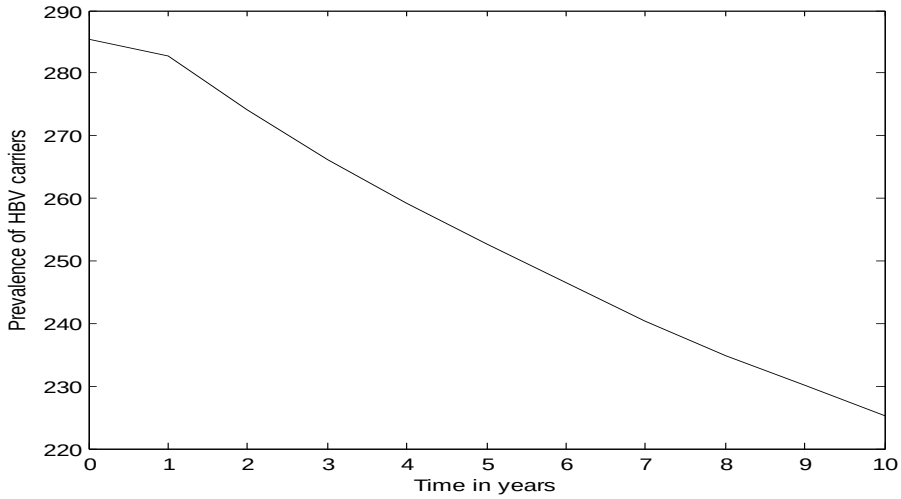

Figure 3: Prevalence of HBV infection under power-law and Weibull distribution with 80% condom use; S=3000, I=285

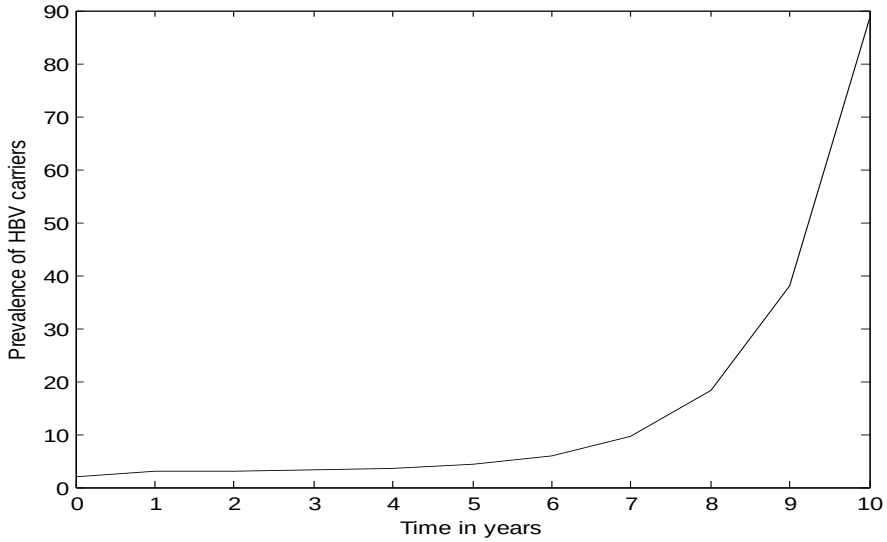

Figure 4: Prevalence of HBV infection under monogamy and Weibull distribution without condom use; S=3000, I=2

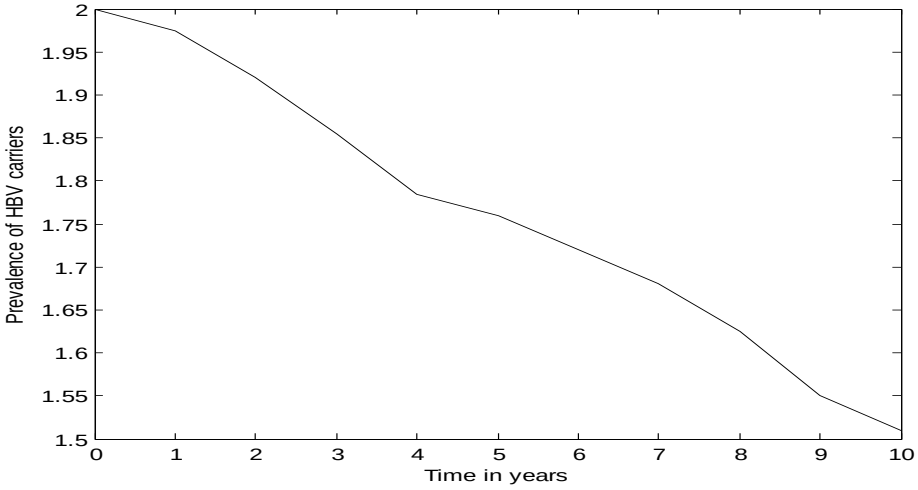

Figure 5: Prevalence of HBV infection under monogamy and Weibull distribution with 80% condom use; S=3000, I=2

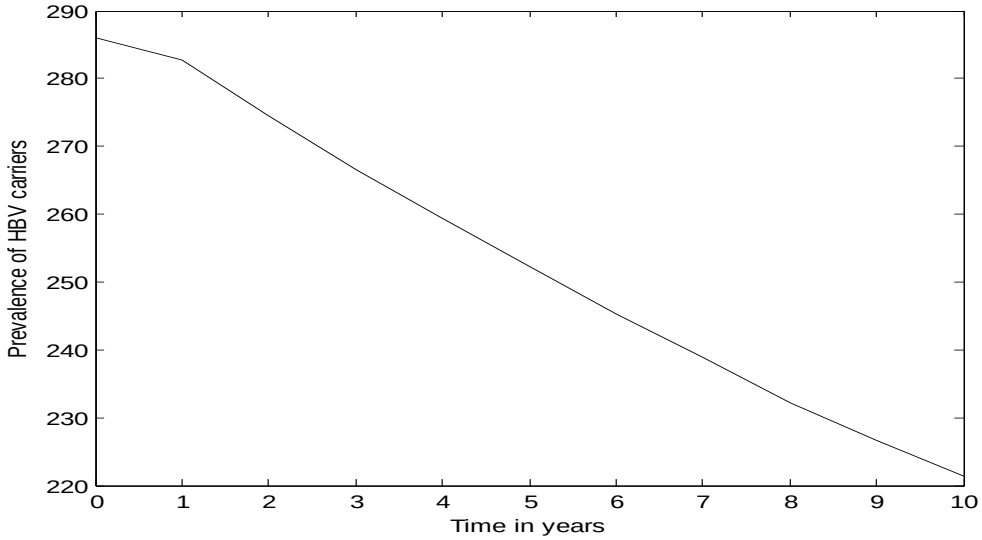

Figure 6: Prevalence of HBV infection under monogamy and Weibull distribution wit condom use; S=3000, I=285

6. Discussion

In this article, we have developed a graph-based model and investigated the transmission dynamics of HBV under different scenarios on it. The main results are shown in Figures 1 through 6. The result in Figure 1 shows that two index cases that randomly invade a population can cause an astronomical increase in the spread of HBV under power law distribution of the degree sequence in long term. The result in Figure 2 shows that, with 80% condom usage, two index cases that randomly invade a population cannot precipitate an epidemic. Figure 3 shows that, in an endemic situation with 285 initially infected, the degree distribution being power law and 80% condom usage applies, control is exercised on the spread of HBV. The result in Figure 4 shows that, under monogamy and no usage of condoms, in a population that is randomly invaded by two infected individuals, the prevalence of HBV increases slowly. Figure 5 shows that, under monogamy and 80% usage of condoms, in a population that is randomly invaded by two infected individuals, there is a possibility of eliminating HBV spread. Figure 6 shows that in a population where HBV is endemic, behavioral change from multiple partnerships to monogamy and effective condom usage can eliminate the prevalence.

7. Conclusion

In this article, we have developed and investigated the transmission dynamics of HBV on a complex graph. The partnership structures under power-law distribution of the degree sequence; and under monogamy were used. We assumed that the partnership durations obey the Weibull distribution. The results emphasize the importance of monogamy and condom usage. We therefore, recommend that to ensure speedy recovery from HBV burden as in HIV and other sexually transmitted infections, the members of highly endemic population are urged to desist from multiple partnership; and should apply condoms during intercourse.

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