Available online: March 26, 2019

Commun. Fac. Sci. Univ. Ank. Ser. A1 Math. Stat.
Volume 68, Number 2, Pages 1586–1595 (2019)
DOI: 10.31801/cfsuasmas.544126
ISSN 1303–5991 E-ISSN 2618-6470
http://communications.science.ankara.edu.tr/index.php?series=A1

A MATHEMATICAL MODEL OF HEPATITIS B TRANSMISSION IN TURKEY

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Abstract. Hepatitis B infection is one of the serious viral infections that is treating the global health. Turkey has an intermediate endemicity for hepatitis B. In this study, a classical SIR model for hepatitis B virus (HBV) transmission is proposed and analyzed. Based on the available data of Republic of Turkey Ministry of Health, associated parameters are estimated and the fitted model is shown by appropriate simulations. The basic reproductive number is obtained by using the estimated parameters. Finally, we discuss the sensitivity of parameters and the effect of changes of parameters in the spread of disease.

1. Introduction

Hepatitis B virus (HBV) causes an infectious disease hepatitis B which results in human morbidity and mortality through the consequences of chronic infection [12]. WHO (World Health Organization) reported that approximately 257 million people were living with chronic HBV infection all over the world in 2015 [1]. The prevalence of HBV infection varies geographically and Turkey is one of the countries with intermediate endemicity for hepatitis B infection [6]. Most common transmission routes for HBV are prenatal transmission at birth, horizontal transmission to/between young children, sexual contact and injecting drug use. Additionally, contaminated blood or blood products and unsafe medical practices can cause the transmission of disease [12].

There are two main serologic markers (specific antigens and antibodies) to detect hepatitis B virus. The surface antigen HBsAg is found in the serum of infected individuals within 1 to 10 weeks after being infected by HBV. If this marker can be still detected after six months through serological tests, the HBV becomes chronic [4]. The surface antigen HBeAg is released into the blood just after the liver cells are infected which means the viral replication continues. The lack of antigens HBsAg

Received by the editors: May 29, 2018; Accepted: February 10, 2019.
2010 *Mathematics Subject Classification.* Primary 05C38, 15A15; Secondary 05A15, 15A18.
Key words and phrases. Mathematical modeling, SIR models, Hepatitis B.

and HBeAg and the existence of anti-HBs enable to classify a patient as recovered and immunized against the infection [19].

Turkey has a moderate prevalence of chronic hepatitis with approximately 4% of the population who are HBsAg-positive and seroepidemiological studies in Turkey show that the rates of HBsAg positivity is decreasing from south-east to west in all age groups [10]. Unfortunately, there is no routine HBsAg screening system for HBV infection in Turkey and the data on the epidemiology of HBV infections are mainly collected from blood donors [6]. In this study, we use the data collected from the reports of Republic of Turkey, Ministry of Health [11]. This data set did not consist of the exact numbers of HBsAg-positive individuals, that is why we consider the rough data obtained from the given bar diagram.

We propose a mathematical model for the spread of Hepatitis B in Turkey using the classical approach for epidemiological modeling that is known as SIR (Susceptible-Infectious-Recovered) model [18]. Many researchers have preferred to use this type of modeling approach to examine the transmission dynamics of HBV infections. Liang et al. review the studies on mathematical modelling of HBV transmission within the years $1994-2015$ [20]. Since the compartmental models are strictly associated with population characteristics, modeling strategies with local data play an important role for understanding the general HBV transmission mechanism [27, 26]. Suitable extensions, such as including the factors like age, sex and immigration and/or vaccination policy might help to improve the model and enable to get more realistic consequences. Nevertheless, as our study is the first mathematical model that aims to analyze and interpret the spread of HPV in Turkey, we do not discuss the additional components. The results of our research would be helpful to generate better mathematical models and give an idea of optimal preventing and controlling strategies for the spread of the disease.

2. The Mathematical Model

According to the modeling approach of Kermack and McKendrick we assume to have three different compartments: the susceptibles S are individuals who have the potential getting infected, the infectives I are individuals who are infected and able to transmit HBV and the compartment of recovered individuals R consists of people who are dead or have recovered and have gained permanent immunity. Thus we start to considering the traditional SIR model with demography:

$$\begin{aligned} \frac{dS}{dt} &= \alpha - \beta SI - \mu S, \\ \frac{dI}{dt} &= \beta SI - (\gamma + \mu)I, \\ \frac{dR}{dt} &= \gamma I - \mu R, \end{aligned} \tag{2.1}$$

with initial conditions $S(0) = S_0$, $I(0) = I_0 > 0$ and $R(0) = 0$.

According to the hypothesis of conservation of the population, we have $S(t) + I(t) + R(t) = N$, where N is the constant population size [13]. Here, parameter α and μ represent a constant birth rate and a constant death rate, respectively. Parameter β is defined as the transmission rate which represents how fast a susceptible individual becoming infected with HBV. Finally, parameter γ is the recovery rate which controls the rate at which recovered individuals become reinfected by the HBV. All of those parameters are assumed to be positive for being biologically sensible.

We reduce the model equation (2.1) since R is decoupled with the first two equations and obtainable from the equation $S(t) + I(t) + R(t) = N$. We seek the equilibria using the classical linearization techniques, $\frac{dS}{dt} = \frac{dI}{dt} = 0$ [13]. So we have

$$\begin{aligned} \alpha - \beta SI - \mu S &= 0, \\ \beta SI - (\gamma + \mu)I &= 0. \end{aligned} \tag{2.2}$$

The disease-free state corresponds to $I = 0$. The equilibrium for disease-free state $E_{df}(S^*, I^*) = (\frac{\alpha}{\mu}, 0)$ is obtained from equations (2.2). Similarly, taking $I \neq 0$ reads the endemic state for the model (2.1) and the equilibrium for endemic state is then $E_d(S^*, I^*) = (\frac{\gamma+\mu}{\beta}, \frac{\alpha}{\gamma+\mu} - \frac{\mu}{\beta})$. We evaluate the Jacobian matrix of the system (2.2)

$$J = \begin{bmatrix} -\beta I - \mu & -\beta S \\ \beta I & \beta S - (\gamma + \mu) \end{bmatrix}.$$

For the stability analysis we find the exact value of Jacobian matrix at the equilibria. Thus we have

$$J_{df} = \begin{bmatrix} -\mu & -\beta\frac{\alpha}{\mu} \\ 0 & \beta\frac{\alpha}{\mu} - (\gamma + \mu) \end{bmatrix}$$

at the disease-free state. The eigenvalues $\lambda_1 = -\mu$ and $\lambda_2 = \beta\frac{\alpha}{\mu} - (\gamma + \mu)$ are obtained from the characteristic equation given by $det\,(J_{df} - \lambda I) = 0$ where λ is the eigenvalues of J_{df}. The necessary and sufficient condition for the asymptotic stability of disease-free equilibria is that the real parts of all eigenvalues be negative [17]. Therefore, $\lambda_1 = -\mu < 0$ and the stability of the disease-free equilibrium depends on the parameters α, β, γ and μ. If $\lambda_2 = \beta\frac{\alpha}{\mu} - (\gamma + \mu) < 0$ then both eigenvalues become negative. Assuming that in the beginning of an epidemic, $S(0) = S_0 > 0$, $I(0) = I_0 > 0$ and $R(0) = 0$ are given, we define the basic reproduction rate $\mathfrak{R}_\circ = \frac{\beta}{\gamma+\mu}$ which determines the expected number of secondary cases generated from an infected individual. This is a threshold value for the behavior of the epidemic, i.e. epidemic spreads if $\mathfrak{R}_\circ > 1$ and dies out if $\mathfrak{R}_\circ < 1$ [13, 14].

The Jacobian matrix of the system (2.2) that we use for the calculation of eigenvalues of endemic equilibrium reads

$$J_d = \begin{bmatrix} -\dfrac{\alpha\beta}{\gamma+\mu} & -(\gamma+\mu) \\ -\mu + \dfrac{\alpha\beta}{\gamma+\mu} & 0 \end{bmatrix}.$$

Thus we obtain the characteristic equation $\lambda^2 + \dfrac{\alpha\beta}{\gamma+\mu}\lambda - \mu(\gamma+\mu) + \alpha\beta = 0$ in the quadratic form. The real part of the eigenvalues λ_1 and λ_2 are negative if and only if $\dfrac{\alpha\beta}{\gamma+\mu} > 0$ and $-\mu(\gamma+\mu) + \alpha\beta > 0$ according to the Routh-Hurwitz conditions for analyzing a two dimensional system [17]. More precisely, we rewrite

$$\begin{aligned} -\mu(\gamma+\mu) + \alpha\beta > 0 \quad &\Leftrightarrow \quad -\mu > -\frac{\alpha\beta}{\gamma+\mu} \\ &\Leftrightarrow \quad \frac{\mu}{\alpha} < \mathfrak{R}_\circ. \end{aligned}$$

This result satisfies that the endemic equilibrium is asymptotically stable if $\dfrac{\mu}{\alpha} < \mathfrak{R}_\circ$.

Many scientist have preferred to use the mathematical modeling approach that represents the transmission of infectious diseases we mentioned above. This fundamental model is not only appropriate for hepatitis B transmission [24, 25, 5, 27] but also suitable for many different infectious diseases, e.g. measles, smallpox, influenza etc. In that sense, this model and its analyses can be found in several studies on epidemiological models [23, 22, 21]. However, we provide a novel approach for estimating the process of hepatitis B spread in Turkey via a well known SIR model. The transmission of hepatitis B in Turkey is mostly studied from a medical and statistical point of view [8, 9, 10, 11]. At the end we suggest to discuss the transmission process of HBV in Turkey via a mathematical model.

3. An application of the model to the data of Hepatitis B in Turkey

3.1. **Data analysis and model assumptions.** We test the fundamental SIR model explained above with the data collected by [11]. They published the collected data set with bar diagrams and did not emphasis the exact numerical values of data. Therefore, we use the plotted diagram explaining the age distribution among the reported cases of acute hepatitis B in Turkey between the years 2005-2011 as a rough data set in our work. See the figure 1 that is generated according to the diagram given in [11].

As we are not interested in the spatial age structure in our basic model, we evaluate the total number of infected individuals in each year between 2005-2011 and apply the cubic spline method via using the command 'interp1' by `Matlab R2018a` to interpolate the given data for a slight look to the continuous curve. (See figure 2). Though this interpolation we plot a continuous curve instead of the

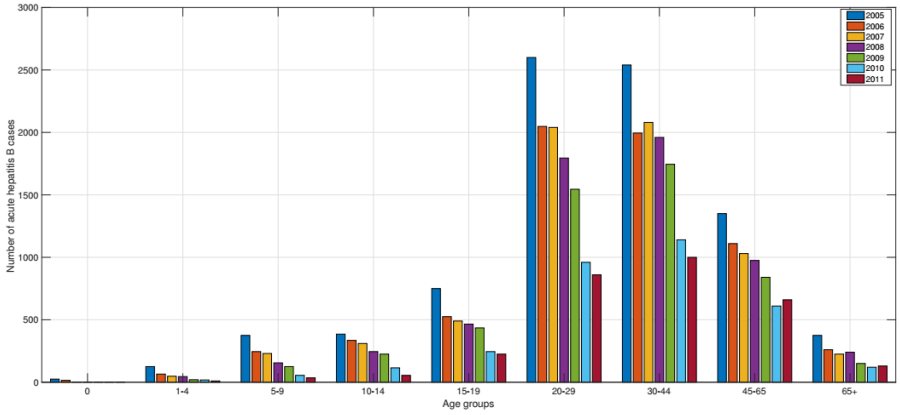

FIGURE 1. The age distribution among the reported cases of acute hepatitis B in Turkey (generated from the data published by [11]).

discrete data set so that we visualize the possible behavior of the HBV infection. Certainly, this interpolation does not dependent on the suggested model. Since we

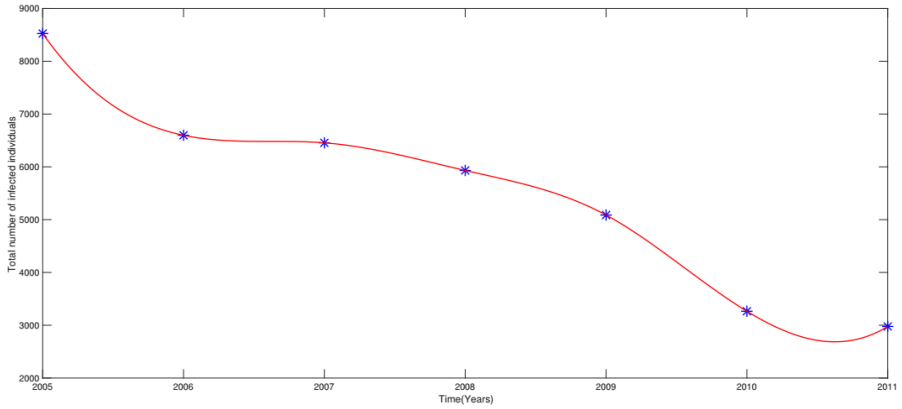

FIGURE 2. The total number of infected individuals among the reported cases of acute hepatitis B in Turkey and an interpolation of the associated data (generated from the data published by [11])
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have a data set of acute HBV cases in Turkey for 7 years, we take in the account the demographic processes for this period of time. However we consider a closed population, where we choose the parameters α and μ equal. Here is important to underline that the parameters α and μ remain independent of the disease. Turkish

Statistical Institute (TUIK) reported that the population growth rate of Turkey is about 1.24% in 2016-2017 and then natural death rate 0.53% in 2016 [2]. Thus we determine first $\alpha = \mu = 1.24$ and than $\alpha = \mu = 0.53$. Since we are working in a relative wide rage, our assumption is not correct but reasonable. We also ignore the immigration and migration factors with this assumption. Additionally, we use the proportion of infected individuals to the total number of population in Turkey at the given year in our simulations. TUIK reported that the number of population in Turkey is: 67.743.052 in 2005, 68.626.337 in 2006, 69.496.513 in 2007, 70.363.511 in 2008, 71.241.080 in 2009, 72.1375.46 in 20010 and 73.0586.38 in 2011. So, we suppose to have the total number of population $N = 1$ and we are mainly interested in the proportion of infected individuals to the total population.

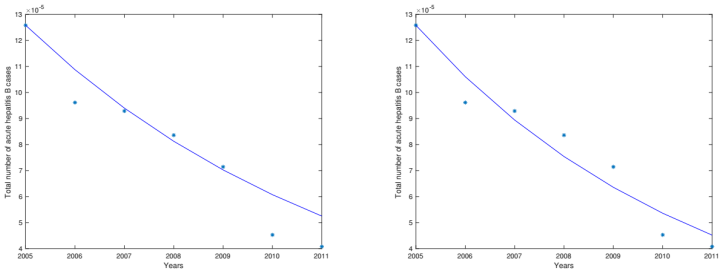
Hepatitis B has a complex transmission mechanism with two main different phases: acute and chronic carrier hepatitis. If the immune system is not able to clear the virus from body completely, the acute phase converts in to the chronic phase [28]. We define 'recovery' as leaving from the acute infectious phase in our model because we only have a data set of individuals of acute HBV. Since the recovery rate of a disease is determined from epidemiological data through evaluating the average infectious period, it does not have a big difference among different countries. Liang at al. [20] has compiled a set of parameters used in epidemiological models for HBV and most of the researchers have fixed the parameter $\gamma = 0.025$ per year as we do in this work.

We finally focus on the transmission rate β which directly effect the basic reproduction rate $\mathfrak{R}_\circ = \frac{\beta}{\gamma+\mu}$ for the HBV in Turkey. In this step, we seek the 'best' parameter set of the suggested SIR model 2.1 via using the method of Least Squares(MLS) [15]. Although we have chosen one of the simplest approaches of the SIR model, it still cannot be solved analytically. We solve the system of differential equations numerically using the `Matlab` function 'ode45'. The function needs a set of initial values for parameters and a time course for the solution. The MLS finds a solution by minimizing the sum of the squares of the errors. The method results better only if the observed data points are close to the model. We set a function defining the sum of the squares of errors

$$S = \Big(y_i - f(x_i, \theta) \Big)^2$$

where y_i is the points of the data set and $f(x_i, \theta)$ is the model function with the vector of unknown parameters θ. We consider the vector of unknown parameters $\theta = \{\alpha, \mu, N, \beta, \gamma\}$ where all of the parameters of the model need always be positive, thereby the biologically meaning does not vanish. Once evaluating the function for MLS we estimate the parameter set that minimizes the objective function. In that purpose, we use the `Matlab` function 'fminsearch' which implements the Nelder-Mead direct search simplex algorithm [29]. This process gives out the estimated transmission rate $\beta = 1.0943$ and estimated basic reproduction $\mathfrak{R}_\circ = 0.8651$ for the choose of $\alpha = \mu = 1.24$ and the estimated transmission rate $\beta = 0.3942$ and

estimated basic reproduction $\mathfrak{R}_o = 0.6972$ for the choose of $\alpha = \mu = 0.53$. The model simulation curve for the acute HBV cases and the model representations with the parameter set $\theta = \{\alpha, \mu, N, \beta, \gamma\} = \{1.24, 1.24, 1, 1.0943, 0.025\}$ and with the $\theta = \{\alpha, \mu, N, \beta, \gamma\} = \{0.53, 0.53, 1, 0.3942, 0.025\}$ are given in figure 3.



(A) Least Squares fitting of the data on SIR model with the estimation of unknown parameter β for $\theta = \{\alpha, \mu, N, \beta, \gamma\} = \{1.24, 1.24, 1, 1.0943, 0.025\}$.

(B) Least Squares fitting of the data on SIR model with the estimation unknown parameter β for $\theta = \{\alpha, \mu, N, \beta, \gamma\} = \{0.53, 0.53, 1, 0.3942, 0.025\}$

FIGURE 3. Least Squares Fitting for SIR Model

The model simulations show that HBV is disappearing in Turkey, because of the condition $\mathfrak{R}_o < 1$. The variation of the parameter $\alpha = \mu$ between the values 0.53 and 1.24 cause different values of transmission rate $\beta = 0.3942$ and $\beta = 1.0943$, respectively. In both cases the system approaches to unstable endemic equilibrium. So, the endemic situation is not possible and we expect to achieve the disease-free equilibrium. As a first modeling approach estimating the transmission rate is an important step but actually the model simulation does not perfectly fit the real data, especially in years 2006, 2010 and 2011. In reality, the transmission rate β depends on many factors like age, sexual behavior, vaccination policy of the country, the need of blood or blood products in a specific disease etc. [12]. Further, we assumed to have the birth rate and the natural death rate constant instead of time and/or age dependent parameters. Nevertheless, we found a suitable parameter to the SIR model which is biologically feasible and satisfies the stability conditions given in section 2.

We now discuss the stability of the model for a different set of parameters at disease-free state and at the endemic state for analyzing the sensitivity. Table1 shows the classification of the disease-free equilibrium. The disease free equilibrium is stable if the basic reproductive number $\mathfrak{R}_o$ remains less than 1 whereas the disease free equilibrium is unstable if $\mathfrak{R}_o$ is greater than 1.

TABLE 1. Stability for disease-free state

$\alpha = \mu$	γ	β	λ_1	λ_2	$\mathfrak{R}_\circ$	Stability
0.53	0.025	0.3942	-0.5300	-0.1608	0.7102	Stable sink
1.24	0.025	1.0943	-1.2400	-0.1707	0.8651	Stable sink
0.3692	0.025	0.3942	-0.3692	0	1	Neutrally stable
0.1	0.025	0.3942	-0.1	0.2692	3.1536	Unstable saddle
0.3	0.025	0.3942	-0.3	0.0692	1.2129	Unstable saddle

Table 2 shows the classification of the endemic equilibrium. Here, the endemic equilibrium is stable if the basic reproductive number $\mathfrak{R}_\circ$ is greater than 1, and unstable if $\mathfrak{R}_\circ$ is less than 1.

TABLE 2. Stability for endemic state

$\alpha = \mu$	γ	β	λ_1	λ_2	$\mathfrak{R}_\circ$	Stability
0.53	0.025	0.3942	0.1689	-0.5358	0.6972	Unstable saddle
1.24	0.025	1.0943	0.1703	-1.2430	0.8651	Unstable saddle
0.3692	0.025	0.3942	-0.3692	0	1	Neutrally stable
0.1	0.025	0.3942	-0.1576 + 0.04535i	-0.1576 -0.04535i	3.1536	Stable spiral sink
0.3	0.025	0.3942	-0.0708	-0.2930	1.2129	Stable spiral sink

4. Conclusion

In this manuscript, we used a well known mathematical model for describing the transmission dynamics of hepatitis B in Turkey. We only take into account the acute phase of the disease. We evaluated the equilibria in the disease-free and endemic states and discussed stability of the equilibria for the disease. We estimated the transmission rate β and the basic reproductive number $\mathfrak{R}_\circ$ of the HBV according to the real data. The numerical simulations and sensitivity analysis of the parameters show the future prediction of the behavior of HBV in Turkey. According to this work, HPV in Turkey tends to be stable in disease-free state. The real data set also displays that the seroprevalence of the disease is decreasing between 2005-2011. As we found out that changes in demographic parameters can turn off a disease free state to an epidemic state. It means that we better concentrate on the factors which influence the demography in Turkey. Additionally, this approach may lead to analyses the transmission dynamics of HBV in Turkey with age structure, with the acute and chronic phases of the disease, with time dependent parameters, with vaccination process etc., since the basic reproduction rate strictly dependent on the transmission rate.

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