Research Article

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Standard routine techniques of modeling of tick-borne encephalitis

Abstract: Tick-borne encephalitis (TBE) is a flaviviral vector-borne disease, which is spread by a tick named *Ixodes persulcatus* in domestic animals as well as in humans. In this article, susceptible, exposed, infected, recovered model; with no immunity after getting recovered is taken. The only possible immunity is before getting the disease (in our model). The vaccination details are also discussed in the article. Hence, SEIS (susceptible, exposed, infected and again susceptible with zero removal from the specie compartment) is used to construct a mathematical model of TBE. TBE is acute inflammation of the brain parenchyma. After becoming viral in European states and some Asian countries, especially in China, this is an emerging viral disease in Pakistan. After constructing a model, formula for the basic reproduction number R_0-like threshold has been derived by using the next-generation matrix method. The formula for R_0-like threshold is used to evaluate whether the disease is going to be outbroken in the respective area from which the specific data are taken into consideration. The main motivation behind selection of this topic is to address the unawareness of this disease specifically in Pakistan and in its neighboring countries when there persists probability for the outbreak of this disease. Some equilibrium points and their local stability is also discussed. Numerical computations and graphs are also presented to validate the results.

Keywords: mathematical modeling, stability, vector-borne disease, encephalitis, basic reproduction number, immune

1 Introduction

Vector-borne disease is one of the most discussed viral diseases in the contemporary epoch. When vector such as mosquito, tick and bug bites a susceptible host, the infection paves the way for the severe disease. Tick-borne disease is the worst disease among vector-borne diseases. Recently, a mind-boggling disease tick-borne encephalitis (TBE) has been found as the widespread one in European states as well as in some Asian countries [38]. This is an emerging arboviral morbidity characterized by severe acute and chronic neurological infections in humans. The disease is caused by a flavivirus (TBE virus [TBEV]), which is transmitted mainly by *Ixodes persulcatus* ticks from a wild vertebrate host to humans, domestic animals or through consumption of unpasteurized milk products [5,7].

TBEV is endemic in central, northern and eastern Europe, Russia and the Far East, including Mongolia, the northern part of China and Japan from Asia [10]. Globally, the number of clinical cases of TBE is estimated to be amidst 10,000 and 12,000 a year and in Europe more than 3,000 human TBE cases are hospitalized each year [13].

Various parts of Europe, Central Asia and East Asia are the endemic countries of TBE. The people who travel, hike and do camping in forested areas are at high risk. Specifically, the span of March to November is crucial for the spread of this disease [22]. Outbreak of TBE in Germany by the pathogen

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Ixodes ricinus has been analyzed in a recent article [17]. This disease has gained momentum and attracted biologists as well as mathematicians.

The clinical symptoms of the infection are biphasic [8,10,33]. The incubation time is between 2 and 28 days, with an approximate average of 7 days. The first phase known as viremic phase lasts between 2 and 8 days, and symptoms of this phase are slight fever, flu, headache etc. The second phase is critical in which the virus spreads to the central nervous system and causes anorexia, fever, headache, vomiting, photophobia and often sensory changes such as visual disturbances, paresis, paralysis or even state of coma. Death might occur as soon as 1 week after the onset of clinical morbidity.

World Health Organization recommends immunization for all people living in the areas where the disease is common or supposed to be outbroke [11]. There are two types of immunity one can develop after vaccination [22]. Partial immunity refers to half or less than the required vaccination rate, and partially immune people live under the risk of getting TBE. Complete immunity refers to full immunity after getting the required vaccination rate [8,10,33]. However, the dose of vaccination is different in different countries. For instance, in Austria, the recommended basic vaccination schedule consists of two vaccinations ≈4 weeks apart followed by a third vaccination after 5–12 months and a fourth vaccination after >3 years. For persons <60 years of age, additional booster immunizations are recommended every 5 years; this interval is reduced to 3 years for persons >60 years of age [32].

The beauty of mathematics is well explored when it is applied on real life phenomena. It has been said that both Mathematics and Biology are opposite terms out-and-out with respect to their applications in real life. However, mathematical modeling on different contagious diseases has helped scientific research to get the solution more accurately and commendably, and for more details see refs. [3,4,14,15,24,40]. In the field of biosciences, mathematical modeling on different diseases got momentum in the twentieth century. Models on diseases such as Zika virus [23] and mathematical model on gonorrhea provide ample assimilation regarding disease as well as the way to control it [2,6,9,20,21,25,28–30,35].

Mathematical models are of great importance in natural sciences, particularly in physics. Physical theories are almost invariably expressed using mathematical models. In the early twentieth century, William Hamer and Ronald Ross applied the law of mass action to explain epidemic behavior of diseases. Two aspects are involved in the initial formulation of the law of mass action: (1) the equilibrium aspect concerning the composition of a reaction mixture at equilibrium and (2) the kinetic aspect concerning the rate equations for elementary reactions. Hence, physics plays an elementary role to determine the epidemic behavior of infectious diseases such as chicken pox, measles and TBE.

In a previous study, a mathematical model on TBE was constructed [17]. Question arises if there was already a model constructed on the said disease, what was the need to construct another one or specifically what makes this model unique and different to the cited one? The answer lies in the fact that the kind of extension of susceptible, infected, recovered (SIR) used in both papers is different. The assumptions made to construct a model were different than the assumptions made by us, which is totally based on the facts taken from authentic platform such as World Health Organization. TBE along-with this new proposed model, we have given a try to derive formula for basic reproduction number or more specifically Ro-like threshold which explains the required threshold yielding to get disease outbroken in the area premises.

In Section 2, methodology is discussed, which is opted while modeling TBE. Next-generation method is used to find out the general formula for basic reproductive number. Transmission matrix and transition matrix are used to calculate the spectral radius, which further helps us in deriving the formula for basic reproductive number.

In Section 3, final results are described, which comprise the final formula for R_0-like threshold. This formula is amply capable to decide whether the disease will be outbroken in the regional premises or not on the basis of parameters collected from the area concerned. In Section 4, equilibrium points and their local stability are discussed. Numerical computations and graphical analysis are presented in Section 5. In Section 6, the concern and importance of this model are discussed. Some future perspectives are described in Section 7.

2 Description of the basic model of TBE

SIR model is commonly used for mathematical modeling of such type of problems [27]. This model is a modified and extended version of an SIR model in which there are two categories of the population, human population and tick population, where three compartments of human population and two of ticks persist. For the sake of simplicity, different parameters are used to represent different characterizations for human as well as tick population. The parameters are described as follows:

2.1 Compartments of human population:

(1) susceptible humans; S_h,
(2) exposed humans; E_h,
(3) infectious humans; I_h.

2.2 Compartments of tick population:

(1) susceptible ticks; S_t,
(2) infectious ticks; I_t.

Both the species are restricted to their own compartments and are strictly prohibited to move from one compartment to the compartment of other specie, which means that neither humans nor ticks would leave their respective specie compartment. It is pertinent to mention that immunity from the disease after the second phase of infection is not possible. If an individual has gone through the required dose of vaccination, then he is said to be attained complete immunity and is free from all sorts of the risk emerging from TBEV. However, a person who is partially immune and has not attained the required dose of vaccination is at risk and there are certain chances for him to get affected. There is a chance for an exposed person to recover and return to the susceptible compartment after recovery before becoming infectious. The susceptible human "S_h" becomes exposed when an infectious *Ixodes* tick "I_t" interacts with him and transfers the TBEV to him at the rate of "β_1." After this, susceptible human "S_h" becomes exposed "E_h" and moves to the exposed compartment. A person who has not been given proper treatment before the virus finds the cell where it would get multiplied becomes infectious "I_h" and moves to the infectious compartment at the rate of "α_h." On the other hand, if an exposed person gets timely treatment, he would be able to return to the susceptible compartment after getting recovered at the rate of "R_h." The infectious individuals after getting recovered will then return to the susceptible compartment but they would not get immunity. Some of the infectious ones can die of TBE at the rate of "e_h." However, at any stage natural death may occur at the rate of "d_h." (Here natural death means any kind of death other than death due to TBE.) *Ixodes* susceptible tick "S_t" gets infected when he bites an infectious human "I_h" at the rate of infection "β_2." At the rate of "α_t," tick moves to the infectious compartment and then dies out. The recovery of ticks is not possible albeit. The flow chart given in Figure 1 has been created to get the hang of our model, and arrows are used to show the interactions. Based on the
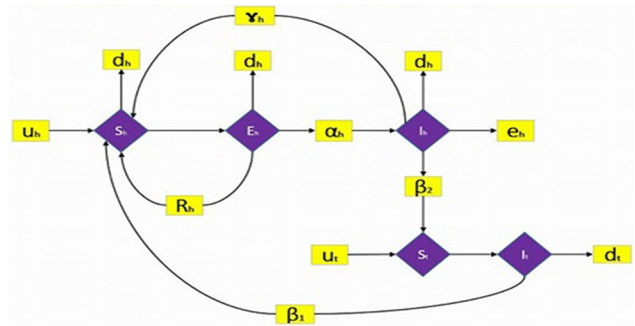

Figure 1: Description of the basic model of TBE.

aforementioned assumptions we have the following systems of equations for human and tick compartments:

$$\frac{dS_h}{dt} = \mu_h N_h - \frac{\beta_1 S_h I_t}{N_h} - \nu S_h - d_h S_h + R_h E_h + \gamma_h I_h,$$
$$\frac{dE_h}{dt} = \frac{\beta_1 S_h I_t}{N_h} - R_h E_h - d_h E_h - \alpha_h E_h,$$
$$\frac{dI_h}{dt} = \alpha_h E_h - \gamma_h I_h - d_h I_h - e_h I_h, \tag{1}$$
$$\frac{dS_t}{dt} = \mu_t N_t - \frac{\beta_2 S_t I_h}{N_t} - d_t S_t,$$
$$\frac{dI_t}{dt} = \frac{\beta_2 S_t I_h}{N_t} - d_t I_t.$$

The system (1) of differential equations is named the TBE system of ordinary differential equations (ODEs), provided that total human population $N_h(t)$ and $N_t(t)$ satisfy the following condition:

$$S_h(t) + E_h(t) + I_h(t) = N_h(t) \text{ and } S_t(t) + I_t(t) = N_t(t),$$

where the parameters used in system of differential equations (1) and (5) are given in Table 1.

A threshold quantity which determines the possibility of a disease to occur or dies out is known as R_0-like threshold. R_0 is the number of secondary infections caused by a single infective introduced to a susceptible population [19]. In epidemiological models, if the value of $R_0 > 1$, then the disease will outbreak and the value of $R_0 < 1$ implies that disease will die out. The value of R_0-like threshold for different diseases is different. For instance, R_0 for HIV disease is 3 and R_0 for SARS is 5. Both the values were calculated by using the same method, otherwise we would not have been able to conclude that SARS is worse than HIV. From the docket of few important methods for calculating R_0-like threshold such as Anderson and May method, Jacobian method and next-generation matrix method, we have used the next-generation matrix method [12].

Table 1: Parameters

S_h	Susceptible humans
E_h	Exposed humans
I_h	Infectious human
S_t	Susceptible ticks
I_t	Infectious ticks
N_h	Total human population
N_t	Total tick population
μ_h	Human birth rate
β_1	Rate of human infection
β_2	Rate of tick infection
V	Human vaccination rate
d_h	Human natural death rate
e_h	Human infected death rate
R_h	Rate at which exposed humans get recovered and become susceptible again
γ_h	Rate at which human after getting recovered become susceptible again
α_h	Rate at which exposed humans become infectious
d_t	Ticks natural death rate

Next-generation matrix is a method involving transmission and transition matrices, and spectral radius of the negative product between transmission matrix and inverse of transition matrix gives the value of R_0. For further elaboration of transmission matrix and transition matrix see ref. [12].

3 Methodology and results

In this section, the reproductive number R_0 for TBEV is calculated. Next-generation matrix is the widely used method to find R_0-like threshold [41]. It precisely deals with the transmission and transition rates inside the infected subsystem. For the stability analysis of mathematical model of TBE, next-generation matrix is used. In the method, two kinds of matrices are used to calculate the value of R_0-like threshold. One is the transmission matrix and the other is the transition matrix. The transmission matrix, T, denotes the pathogen passing between all stages of the infection subsystem. It is calculated by taking Jacobian of all the transmission rates:

$$T = \begin{bmatrix} 0 & 0 & \beta_1 \\ 0 & 0 & 0 \\ 0 & \beta_2 & 0 \end{bmatrix}. \tag{2}$$

The transition matrix, Σ, denotes all other transitions to and from the infection subsystem. It is calculated by taking Jacobean of all the transition rates.

$$\Sigma = \begin{bmatrix} -(R_h + d_h + \alpha_h) & 0 & 0 \\ \alpha_h & -(\gamma_h + d_h + e_h) & 0 \\ 0 & 0 & -d_t \end{bmatrix},$$

where $-T\Sigma^{-1}$ is given by the following matrix:

$$-T\Sigma^{-1} = \begin{bmatrix} 0 & 0 & \dfrac{\beta_1}{d_t} \\ 0 & 0 & 0 \\ \dfrac{\beta_2 \alpha_h}{(R_h + d_h + \alpha_h)(\gamma_h + d_h + e_h)} & \dfrac{\beta_2}{(\gamma_h + d_h + e_h)} & 0 \end{bmatrix}.$$

R_0 is the spectral radius of $-T\Sigma^{-1}$ (matrices derived above). Hence, we get the following:

$$R_0 = \rho(-T\Sigma^{-1}) = \sqrt{\dfrac{\beta_1}{d_t}\left(\dfrac{\beta_2 \alpha_h}{(R_h + d_h + \alpha_h)(\gamma_h + d_h + e_h)}\right)}.$$

The formula computed in the equation is the required formula to calculate the basic reproductive value of TBEV. From the derived formula of R_0, it can be seen that:

(1) R_0^2 is directly proportional to $\beta_1 \beta_2$, which shows that with the increase in the rate of transmission between humans and ticks the value of R_0 increased with squared escalation.

(2) R_0^2 is inversely proportional to the product of two factors $(R_h + d_h + \alpha_h)$ and $(\gamma_h + d_h + e_h)$ which is of exposed population and of infected population, respectively, reflecting the fact that exposed are becoming either susceptible or infective and infective are becoming either susceptible or going to die. So, there is de-escalation of population in both compartments, i.e., exposed and infective. The higher the speed of population jumping into other compartment, the lower the value of R_0^2.

(3) R_0^2 is inversely proportional to the death rate of tick, which shows that the increase in death rate of ticks will result in decrease in R_0^2.

(4) Due to the unavailability of precise data of the disease, the accurate value of R_0^2 could not be calculated; one of the major reasons is that the disease is so rare and data are not provided in the literature so far.

4 Equilibrium points and their local stability

To discuss the equilibrium points of the mathematical models, first we do some modifications of system (1) by

considering the assumption of fractions as: $x_1 = \frac{S_h}{N_h}$, $x_2 = \frac{I_h}{N_h}$, $x_3 = \frac{E_h}{N_h}$, $x_4 = \frac{I_t}{N_t}$, $x_5 = \frac{S_h}{N_t}$, which further simplify system (1) as:

$$\left.\begin{aligned}
\frac{dx_1}{dt} &= \mu_h - x_1(\alpha x_4 + \nu + d_h) + R_h x_3 + x_2 I_h, \\
\frac{dx_2}{dt} &= \alpha x_1 x_4 - (R_h + d_h + \alpha_h)x_3, \\
\frac{dx_3}{dt} &= \alpha h_3 - (r_h + d_h - e_h)x_x, \\
\frac{dx_4}{dt} &= \alpha x_5 - d_t x_4, \\
\frac{dx_5}{dt} &= \mu_t - (\alpha + d_t)x_6.
\end{aligned}\right\} \qquad (3)$$

For the ease of handling calculations, the following notation is assumed for the modified system (3): $\mu_h = \alpha_1$, $\nu = \alpha_2$, $d_h = \alpha_3$, $R_h = \alpha_4$, $I_h = \alpha_5$, $\alpha_h = \alpha_6$, $r_h = \alpha_7$, $e_h = \alpha_8$, $\alpha = \alpha_9$, $d_t = \alpha_{10}$, $\mu_t = \alpha_{11}$, $h_t = \alpha_{12}$ and the following system is obtained:

$$\left.\begin{aligned}
\frac{dx_1}{dt} &= \alpha_1 - x_1(\alpha x_4 + \alpha_2 + \alpha_3) + \alpha_4 x_3 + x_2 \alpha_5, \\
\frac{dx_2}{dt} &= \alpha x_1 x_4 - (\alpha_4 + \alpha_3 + \alpha_6)x_3, \\
\frac{dx_3}{dt} &= \alpha \alpha_{12} - (\alpha_7 + \alpha_3 - \alpha_8)x_2, \\
\frac{dx_4}{dt} &= \alpha_9 x_5 - \alpha_{10} x_4, \\
\frac{dx_5}{dt} &= \alpha_{11} - (\alpha_9 + \alpha_{10})x_5.
\end{aligned}\right\} \qquad (4)$$

The biologically meaningful equilibria are disease-free equilibrium (DFE) and endemic equilibrium, depending on S_h, I_h, E_h and S_t and I_t. To find DFE, all time derivatives of x_1, x_2, x_3, x_4 and x_5 are set equal to zero, whose biological meaning is "without infection;" then, we obtain:

$$E_0 = (1, 0, 0, 0, 0, 0).$$

The Jacobian technique at DFE is used for system (4). By adopting this technique, the local stability of DFE is found.

Theorem 4.1. *The infection-free equilibrium of system* (4) *is asymptotically stable (local asymptotically stable [LAS]) if R_O is less than one and is unstable on the other hand.*

Proof 4.1. To find the LAS of infection-free equilibrium, the Jacobian matrix of system (4) at the infection-free equilibrium is as follows: □

$$J = \begin{bmatrix} -\alpha_2\alpha_3 & \alpha_5 & \alpha_4 & -\alpha & 0 \\ 0 & 0 & -\alpha_3 - \alpha_4 - \alpha_6 & a & 0 \\ 0 & -\alpha_7 - \alpha_3 + \alpha_8 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\alpha_{10} & \alpha_9 \\ 0 & 0 & 0 & 0 & -\alpha_9 - \alpha_{10} \end{bmatrix}.$$

The characteristic equation implies that the first eigenvalue $\lambda = -(\mu_h + \nu)$ is negative. To further evaluate, the submatrix of matrix J is taken as:

$$J_1 = \begin{bmatrix} 0 & \beta_1 & \beta_2 & 0 \\ \beta_3 & 0 & 0 & 0 \\ 0 & 0 & \beta_4 & \beta_5 \\ 0 & 0 & 0 & \beta_6 \end{bmatrix},$$

where $\beta_1 = -\alpha_3 - \alpha_4 - \alpha_6$, $\beta_2 = \alpha$, $\beta_3 = -\alpha_7 - \alpha_3 + \alpha_8$, $\beta_4 = \alpha_{10}$, $\beta_5 = \alpha_9$ and $\beta_6 = -\alpha_9 - \alpha_{10}$. Characteristic equation corresponding to J_1 is as follows: $\lambda^4 + 3(\beta_4 + \beta_6)\lambda^3 + (3\beta_1\beta_3 + \beta_4\beta_6)\lambda^2 + (\beta_1\beta_3\beta_4 + \beta_3\beta_1\beta_6)\lambda + 3\beta_1\beta_3\beta_4\beta_6 = 0$.

For the sake of ease, equation (5) can be rewritten as:

$$\lambda^4 + 3a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \qquad (5)$$

where

$$\begin{aligned}
a_1 &= 3(\beta_4 + \beta_6), \\
a_2 &= (3\beta_1\beta_3 + \beta_4\beta_6), \\
a_3 &= (\beta_1\beta_3\beta_4 + \beta_3\beta_1\beta_6), \\
a_4 &= 3\beta_1\beta_3\beta_4\beta_6.
\end{aligned}$$

To prove the local asymptotic stability through the Routh–Hurwitz criterion [34,36], we prove that all coefficients in equation (5) are positive and $a_1a_2a_3 > a_4$ are greater than zero for $R_0 < 1$. It is quite clear that $a_i's$ are positive; hence, the first condition is fulfilled. For the second condition that $a_1a_2a_3 > a_4$ are greater than zero for $R_0 < 1$, of the Routh–Hurwitz criterion, we proceed as follows:

$$\begin{aligned}
a_1a_2a_3 &:= (3(r_h + d_h + u_h))(-r_h + d_h + v_h)(a_h + 2d_h)^2 \\
&\quad \times (a_h d_h + 4d_h^2 + 3d_h u_h + 3d_h v_h \\
&\quad - 3r_h^2 - 3r_h u_h + 3r_h v_h + 3u_h v_h), \\
a_4 &:= d_h(r_h + d_h + u_h)(-r_h + d_h + v_h)(a_h + d_h).
\end{aligned}$$

It is effortless to prove the second condition. Hence, both the conditions are fulfilled for R_0 less than one and the infection-free equilibrium point is LAS. Hence, it proves the theorem.

Remark 4.1. To get the deeper insight about the local asymptotically stability (LAS), the remaining eigen values of Jacobean matrix "J" can be calculated from characteristic equation of Jacobean matrix "J_1" and is given as under:

$$
\lambda_1 = -\frac{a_1}{4} - \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
- \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
- \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}} \tag{6}
$$
$$
- \frac{(-a_1^3 + 4a_1 a_2 - 8a_3)}{\dfrac{4\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$

$$
\lambda_2 = -\frac{a_1}{4} - \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
+ \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{2} - \frac{4a_2}{3} - 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}
$$
$$
- \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}} \tag{7}
$$
$$
- \frac{(-a_1^3 + 4a_1 a_2 - 8a_3)}{\dfrac{4\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^2 + (A_2)^2})^{1/3}}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}.
$$

$$
\lambda_3 = -\frac{a_1}{4} + \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}} + \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}
$$
$$
- \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{2} - \frac{4a_2}{3} - 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}} - \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}} \tag{8}
$$
$$
+ \frac{(-a_1^3 + 4a_1 a_2 - 8a_3)}{\dfrac{4\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}} + \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}.
$$

$$
\lambda_4 = -\frac{a_1}{4} + \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}
$$
$$
+ \frac{\frac{1}{2}\sqrt{\frac{a_1^2}{2} - \frac{4a_2}{3} - 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}
$$
$$
- \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}} \tag{9}
$$
$$
+ \frac{(-a_1^3 + 4a_1 a_2 - 8a_3)}{\dfrac{4\sqrt{\frac{a_1^2}{4} - \frac{2a_2}{3} + 2^{1/3}A_1}}{3(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}}}
$$
$$
+ \frac{1}{(3 \times 2^{1/3})(A_2 + \sqrt{-4A_1^3 + (A_2)^2})^{1/3}},
$$

where $A_1 = (a_2^2 - 3a_1 a_3 + 12a_4)$ and $A_2 = 2a_2^3 - 9a_1 a_2 a_3 + 27a_3^2 + 27a_1^2 a_4 - 72a_2 a_4$.

By determining the sign of λ, λ_1, λ_2, λ_3 and λ_4 conclusion about stability can be made. If all eigenvalues are negative or purely imaginary or real part of complex eigenvalues are negative, then the system is asymptotically stable otherwise unstable for all possibilities of sign of eigenvalues.

5 Numerical computation and graphical analysis

To get the deeper insight of the role of R_0-like threshold, we solved the coupled system of ODEs given by (1). Runge-Kutta (RK) method of order 4 with initial conditions for the tick compartment is as follows:

$$
S_t(0) = 1,00,000; \quad I_t(0) = 0
$$

and initial conditions for the human compartment are as follows:

$$S_h(0) = 7,600; \quad E_h(0) = 0; \quad I_h(0) = 0$$
$$S_h(0) = 0; \quad E_h(0) = 7,600; \quad I_h(0) = 0$$
$$S_h(0) = 0; \quad E_h(0) = 0; \quad I_h(0) = 7,600.$$

The approximated data collected from Austria's 26 years TBE vaccination program are used [31]. RK method of order 4 is implemented for numerical solution of the coupled system of ODEs in MATLAB environment. MATLAB 2016 with double precision floating point operations is used to carry out all computations. TBE is solved. In order to avoid any error encountering, the values of the parameters are approximated and are not exact as given in the program. In order to keep the content precise and lucid, a population of anonymous state suffering from TBE has been taken into consideration. Figure 2 shows that the susceptibility to disease in humans decreases with time. Figure 2 shows that it is highest at initial time. But as the time passes by the human would leave the compartment either becoming exposed or immune.

Figure 3 represents the human population of the infected, and as per the aforementioned assumptions prior modeling, initially infected humans are zero but as the infection travels from exposed to infected, population of infected goes on increasing.

Figure 4 shows that the exposed humans are the same as the infected but the difference between both is that in the exposed compartment the growth of population is a bit faster than that of infected, where the growth of population would be steady.

It is evident from Figures 2–5 that the solution to the coupled system of ODEs exists and is inline with numerical results obtained. Clearly, the susceptibility decreases as the infection increases to maximum. Likewise, the exposed ones are those who lie between susceptible and infected humans. The increase and
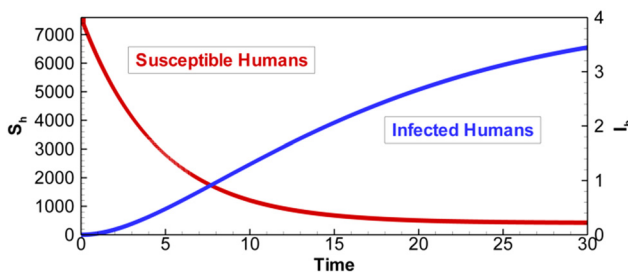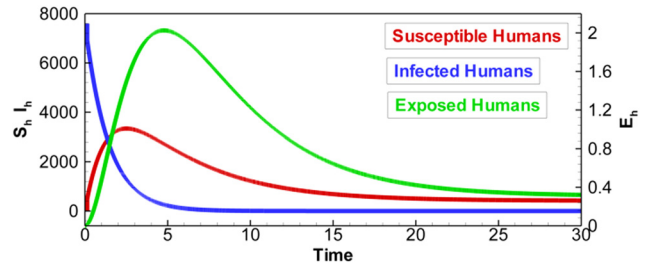
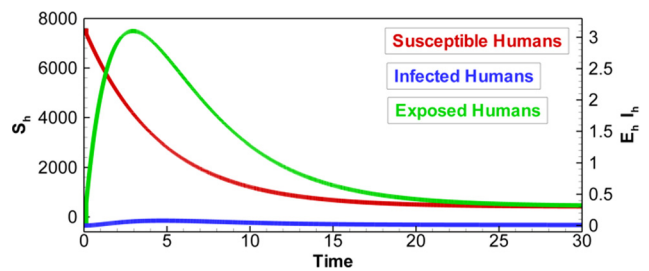**Figure 3:** Graph of susceptible & infected vs exposed human.

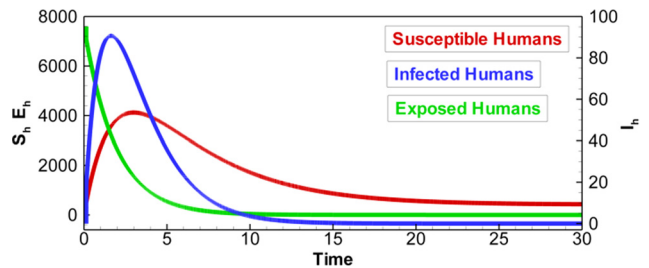**Figure 4:** Graph of infected & exposed vs susceptible human.

Figure 5: Graph of susceptible & exposed vs infected human.

decrease are witnessed from the graphs that our model confirms the growth and decay of population in different compartments.

Figure 2: Graph of susceptible vs infected human.

6 Discussion

Pakistan is an agrarian state and history of few decades bears witness to the fact that Pakistan has been suffering from vector-borne disease more than other viral diseases since the twentieth century [1,37]. Mosquitoes have been the primary vectors serving for devastating vector-borne diseases such as dengue, malaria and Japanese encephalitis. TBE has been a very rare disease in Pakistan

premises [39]. However, TBEV can follow the pattern of Crimean–Congo hemorrhage fever (CCHF) spread in Pakistan. The outbreak of this disease occurred due to a couple of reasons given as follows:

1. Unavailability of developed health-care system and insufficient equipment in the institutes to control CCHF [16].
2. Unawareness of the spread of this disease among general public because of the vastness of agricultural sector of Pakistan.
3. The migration of numerous refugees from endemic areas to Pakistan.

This disease started spreading in Pakistan via an infected domestic animal which later started affecting humans and *vice versa*.

Likewise, Pakistan is under the risk of TBE, which is already very common in its neighborhood countries i.e. China, Russia, Kazakhstan etc. and in European countries. Pakistan is not an isolated state, it is a trading partner of China and many other European countries. The import of animals such as pets, sheep and camels is very common in Pakistan. Risks are high to a considerable extent. Even unpasteurized milk can pave the way for this virus between an infected sheep and susceptible human and *Ixodes* ticks [18]. Some other factors such as climate change, global warming, increasing interdependence and urbanization can also become the reason for the outbreak of this disease. Pakistan has been found in the docket of top ten countries vulnerable to climate change [26], which is really dangerous and point of concern for Pakistan.

7 Future perspective

The future perspective of this work resides as follows:

1. After finding the precise data one can be able to predict accurately whether the disease is going to be endemic in the area premises or not.
2. More work on vector-borne disease and mathematical modeling will be promoted. Biological mathematical modeling will be promoted and enhanced.
3. Before getting extremely endemic, disease will be controlled.

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