



Research article

Parameter analysis of an extended immuno-epidemiological model using sensitivity and elasticity methods

Sarbaz H. A. Khoshnaw^{1,2,*}

¹ Department of Mathematics, College of Basic Education, University of Raparin, Ranya, Sulaimani, Iraq

² Department of Artificial Intelligence, Faculty of Applied Sciences, Tishk International University, Erbil, Iraq

* **Correspondence:** Email: sarbazmath@gmail.com; Tel: +9647503161780.

Abstract: Immuno-epidemiological modeling has been widely studied for understanding disease spread and supporting global control efforts. Mathematical and computational methods are important tools to study interactions between the immune system and infectious diseases. This work presented an extended immuno-epidemiological model that describes the dynamics of the model transmission rates. This study includes some key outputs. First, we calculated the basic reproduction number, R_0 , which is used to assess disease transmissibility, design control strategies, and evaluate intervention effectiveness. Second, the local sensitivity analysis was numerically evaluated using non-normalization, half normalization, and full normalization techniques between the model states and parameters; it provides an important step forward in identifying the model critical parameters in the spreading of disease. Another model output was calculating the elasticity index between R_0 and the model parameters to identify the most critical parameters. Interestingly, numerical results showed the impact of the virus transmission rate, virus clearance rate, killing rate of infected cells, interferon degradation rate, and antibody production rate and discussed some model compartments for different parameter values. The findings help the local and international efforts in suggesting control strategies, optimizing interventions, and guiding public health decisions.

Keywords: Immuno–epidemiological model; mathematical modeling; sensitivity analysis; basic reproduction number

1. Introduction

Recently, Immuno-epidemiological modeling plays a great role in understanding how a disease spreads within a population. It helps international efforts to control the spreading of diseases within

the community. This area mainly focuses on computational tools and mathematical approaches to study the combination of immune system response and infections. Therefore, mathematical models are essential approaches to show topological dynamics and numerical approximate solutions. In addition, sensitivity and elasticity analysis can be effectively utilized for such systems to identify the model critical parameters and suggest control strategies.

There are several studies that have been developed for understanding virus-host immune interactions with epidemiological transmissions. For example, sensitivity analysis was used on Rift Valley fever disease to measure the impact of changes in model parameters on the infection dynamics [1]. The idea of sensitivity and elasticity analyses have been widely applied to quantify the impact of model parameters on important epidemiological outcomes such as the basic reproduction number, peak infection, and epidemic duration [2, 3]. These studies focus on the spreading of HIV and COVID-19, and identifying the critical parameters affecting transmission dynamics, public health interventions, and control strategies. Recently, some models have been extended that include heterogeneous contact patterns and behavior-based vaccination decisions.

Previous work has suggested eigenvector-based sensitivity analysis of age-structured contact patterns and information-driven vaccination models. This is to increase the efficiency and applicability of models for future predictions [4, 5]. In addition, a bidirectionally linked immuno-epidemiological model was presented for cholera disease given in [6]. They studied multiple equilibria and bifurcations, and showed how the feedback between immunity and infection can widely affect disease outcomes. A group of researchers extended the susceptible-infected-recovered (SIR) immuno-epidemiological model [7], they calculate some analytical approximate solutions to estimate the total number of infected cases and show how immune response parameters impact epidemic trajectories. The suggested models can theoretically be used to predict the disease and suggest control strategies and healthcare prevention.

In addition, another study presented the idea of sensitivity analysis to a malaria transmission model that includes unaware infected individuals and relapse dynamics. They highlighted the most key parameters of spreading the disease and suggested effective interventions in controlling malaria [8]. Interestingly, nanotechnology and mathematical modeling have been applied in viral infections, where epidemiological models can control viral-host interactions at the nano-level and understand infection dynamics and control strategies [9]. Recently, a seasonal influenza model was suggested to show gradual waning immunity dynamics. Showing the model immunity decaying can be useful for predicting long-term immunity effects and determining vaccination programs [10].

Recently, a mathematical model was proposed to examine the dynamics of infectious diseases, showing that behavioral responses and sensitivity analysis offer important insights into disease transmission and effective intervention strategies [11]. Another work presented an epidemiological modeling framework that combines environmental and biological elements, demonstrating that mathematical analysis can be a successful determinant affecting disease transmission and management [12]. Furthermore, a nonlinear epidemiological model was introduced to show behavioral dynamics and demonstrated that personal decision-making notably influences disease spread, highlighting the necessity of integrating behavioral and mathematical assessments for public health strategies [13]. Finally, a mathematical model was presented in biosciences to analyze the dynamics of infectious diseases and showed that sensitivity analysis serves as a valuable method for identifying key parameters and evaluating the reliability of strategies for disease control [14].

Although several immuno-epidemiological models have been proposed to study viral infection dynamics and computational simulations, most of them focus on equilibrium analysis and analytical solutions, while there are a few studies that provide the importance of critical parameters, which combine sensitivity and elasticity analysis with the basic reproduction number to provide a comprehensive assessment of parameter influence.

This limitation makes it difficult to study the model dynamics in detail and identify the model critical parameters on the transmission rates. For biological and public health models, identifying the most critical transmissions and immune-response parameters is essential for improving disease control strategies. As it is clear that many model parameters are estimated from experimental or clinical studies and are subject to uncertainty, evaluating their impact on model predictions is an important step forward in model validation and discussions. It can be concluded that parameter analysis can provide valuable guidance for experimental design, improve model reliability, and help public health interventions for disease prevention.

In this work, some important questions are addressed and discussed in detail regarding identifying the most critical parameters for the suggested immuno-epidemiological model. First, what are the correlations between the basic reproduction number and the model transmission rates? Based on this, to show how the model parameters impact the infection transmissions, the elasticity indexes are suggested. Such indexes can clearly show the direct and indirect relations between the basic reproduction number and model parameters. Second, how can sensitivity analysis be addressed in order to highlight the most sensitive compartments to the model parameters?

To address these gaps, this study develops and analyzes the extended immuno-epidemiological model given in [15]. It includes the interactions among target cells, infected cells, free virus, interferon, B-cells, and antibodies. The extended model is analyzed for model equilibrium points and numerical simulations. In addition, local sensitivity analysis is calculated using non-normalized, half normalized, and fully normalized sensitivity coefficients, while elasticity analysis is employed to identify the most important critical parameters on the basic reproduction number. Interestingly, such methods can effectively show the most effective biological processes governing infection dynamics and provide insights that can help local and international efforts.

The organization of this paper is as follows. In Section 2, we suggest an extended model for an immuno-epidemiological model based on our assumptions and model transmissions. In Section 3, we calculate the basic reproduction number using the next generation matrix based on free disease equilibrium point E_0 . The elasticity indexes between model parameters and R_0 are presented in Section 4. Then, the model local sensitivities based on the estimated values and the initial model states discussed in Section 5. We present some numerical simulations for the model state dynamics in Section 6. Finally, some conclusions and suggestions are given in Section 7.

2. An immuno-epidemiological model

In this section, we modify an immuno-epidemiological model given in [15], which describes the interaction between the target cells, viruses, interferon (a group of signaling proteins), B-cells (B lymphocytes), and antibodies (immunoglobulins). The model includes six compartments: the total number of target cells, T , free virus, V , infected cells, I , interferon, A , B-cells, B , and antibodies, F .

The model also includes nineteen parameters that describe the rate of model transmissions. We

extended the previous model and we added the natural death of target cells, infected cells, virus, and B-cells, which denoted by d_1, d_2, d_3 , and d_4 , respectively. We have also changed the rate of virus transmissions to $\frac{\beta TV}{T+V}$, and used the logistic growth rate, $gT(1 - \frac{T}{C_T})$, for the production of target cells. All these changes are shown in Figure 1.

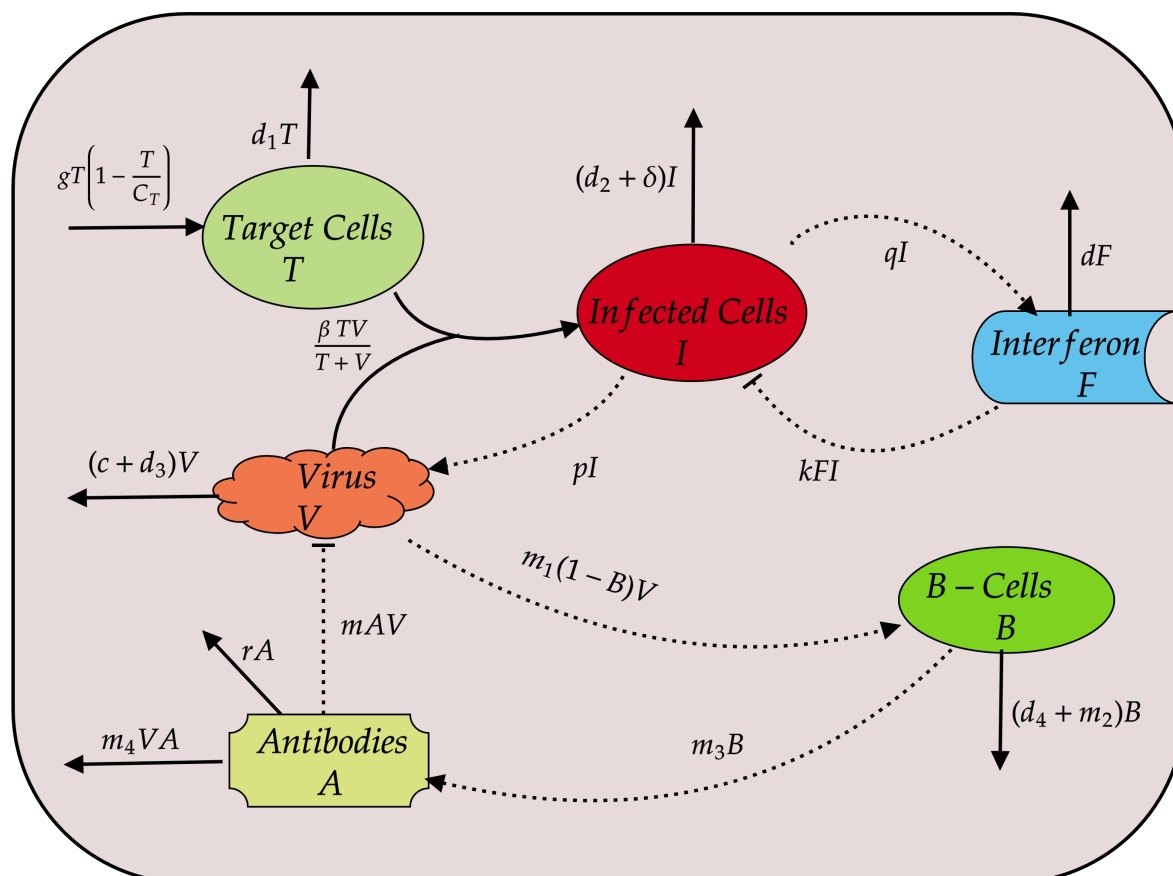


Figure 1. The model diagram for an immuno-epidemiological model.

According to the model constant rates given in Figure 1, target cells are produced with a logistic rate $gT(1 - \frac{T}{C_T})$, die with a natural death rate d_1T , and become infected by virus at a transmission rate $\frac{\beta TV}{T+V}$. The infected compartment increases at rate $\frac{\beta TV}{T+V}$, die by the virus at rate δI , and die with a natural death rate d_2I . The interferon can eliminate the infected cells by inducing programmed cell death (apoptosis) at a rate kFI .

In addition, the rate of interferon production depends on the constant rate qI and the degradation rate of the interferon is given by dF . Furthermore, free viruses are produced by infected cells at a rate pI , clearing virus at a rate cV , die with a natural death rate d_3V , and have a rate of virus loss per unit of antibodies mAV . B-cells can increase by $m_1(1 - B)V$, deactivate with rate m_2B , and die with a natural death rate d_4B . Finally, antibodies are produced from B-cells at a rate m_3B , degrade at a rate rA , and have a rate of antibody loss per virion m_4VA .

The infection process is defined by the Holling type-II infection function $\frac{\beta VT}{V + T}$, which has been widely used from earlier immuno-epidemiological models. It indicates the biological constraints of virus-cell interactions. In contrast to the traditional bilinear incidence βVT , the saturating formulation considers the limited number of susceptible target cells and receptor-binding sites, avoiding excessively high infection rates when viral load increases significantly. Biologically, every successful infection event involves one virus particle penetrating a susceptible target cell and starting intracellular replication. Consequently, the infection term manifests as a loss in the free-virus equation and as a gain in the infected-cell equation, maintaining the biological mass balance between virus adsorption and the generation of infected cells. This approach has been effectively used in earlier within-host immuno-epidemiological models and offers a more accurate depiction of viral infection dynamics

The dynamics of the immuno-epidemiological model are expressed by the following nonlinear system of differential equations:

$$\begin{aligned}
 \frac{dT}{dt} &= gT\left(1 - \frac{T}{C_T}\right) - \frac{\beta VT}{V + T} - d_1T, \\
 \frac{dI}{dt} &= \frac{\beta VT}{V + T} - kFI - (d_2 + \delta)I, \\
 \frac{dV}{dt} &= -\frac{\beta VT}{V + T} + pI - mAV - (c + d_3)V, \\
 \frac{dF}{dt} &= qI - dF, \\
 \frac{dB}{dt} &= m_1(1 - B)V - (d_4 + m_2)B, \\
 \frac{dA}{dt} &= m_3B - rA - m_4AV,
 \end{aligned} \tag{2.1}$$

with the initial model states $T(0) = T_0 > 0$, $V(0) = V_0 > 0$, $I(0) = I_0 \geq 0$, $F(0) = F_0 \geq 0$, $B(0) = B_0 \geq 0$, and $A(0) = A_0 \geq 0$.

The model compartments and transmission rates with their biological meaning and estimate values are given in Table 1, where B is a unitless number between 0 and 1. We define B as the normalized activated B-cells. Therefore, the term $1 - B$ from Figure 1 is mathematically and biologically consistent because B represents the fraction of activated B-cells, not the actual number of initial B-cells.

Table 1. The model initial states and parameters with their biological meaning and estimated values.

Symbols	Biological descriptions	Estimated values	Sources
$T(0)$	Initial target cells	4×10^8	[16, 17]
$I(0)$	Initial infected cells	10	[17, 18]
$V(0)$	Initial free virus	1×10^6	[18, 19]
$F(0)$	Initial interferon	1	[17, 20]
$B(0)$	Initial B-cells	10,000	[16]
$A(0)$	Initial antibodies	0.01	[16, 19]
g	Growth rate of healthy target cells	0.8	[15]
β	Rate of transmission from target cells to infected cells	2×10^{-5}	[15]
C_T	Carrying capacity (maximum capacity) of the target-cell population	7×10^7	[15]
d_1	Natural death of target cells	0.01	[21]
δ	Death rate of infected cells	3	[15]
d_2	Natural death rate of infected cells	0.01	[17, 18, 34]
p	Virus production rate	0.35	[15]
q	Interferon production rate	1×10^{-7}	[15]
k	Killing rate of infected cells per unit of interferon	3	[15]
d	Interferon degradation rate	2	[15]
c	Virus clearance rate	20	[15]
d_3	Natural death rate of virus	0.02	[18, 30, 34]
m_1	Rate of B-cell activation per virion	1×10^{-4}	[15]
m_2	Rate of B-cell deactivation	0.01	[15]
d_4	Natural death rate of B-cells	0.02	[31–33]
m_3	Antibody production rate from B-cells	12,000	[15]
m	Rate of viral loss per unit of antibodies	0.2	[15]
m_4	Rate of antibody loss per virion	0.04	[15]
r	Antibody degradation rate	0.2	[15]

3. Basic reproduction number

An important immuno-epidemiological quantity that can be used to measure transmission rates is the basic reproduction number, denoted by R_0 [22]. Accordingly, the next-generation matrix approach is used to calculate the basic reproduction number R_0 for the suggested model Eq. 2.1. This threshold has been calculated for such models that include both asymptomatic and symptomatic cells. To calculate this quantity mathematically, we consider a system of differential equations as follows:

$$\frac{dy_i}{dt} = f_i(y) \text{ for } i = 1, 2, \dots, k. \quad (3.1)$$

We assume that $y = (y_1, y_2, \dots, y_k)^T$ are model compartments, which can be divided into two classes: m infected compartments $(y_1, y_2, \dots, y_m)$ and n non-infected (healthy) compartments

$(y_{m+1}, y_{m+2}, \dots, y_k)$, where $k = m + n$.

Consider the new infection rate in the i^{th} compartment as $\mathcal{F}_i(y)$, and we assume

$$\mathcal{M}_i(y) = V_i^-(y) - V_i^+(y),$$

where $\mathcal{V}_i^+$ is the rate of transfer of individuals into the i^{th} compartment and $\mathcal{V}_i^-$ is the rate of transfer of individuals out of the i^{th} compartment, see Figure 2:

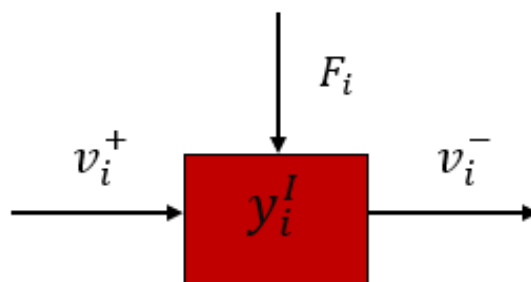


Figure 2. Entering and leaving fluxes for a given compartment y_i^I .

In addition, the infected compartments are denoted by $y^I \in R^m$ and the non-infected compartments are defined by $y^N \in R^n$. Therefore, the model differential Eq. 3.1 takes the following form:

$$\begin{aligned} \frac{dy_i^I}{dt} &= \mathcal{F}_i(y^I, y^N) - \mathcal{M}_i(y^I, y^N), \quad i = 1, 2, \dots, m, \\ \frac{dy_j^N}{dt} &= \mathcal{G}_j(y^I, y^N), \quad j = 1, 2, \dots, n. \end{aligned} \quad (3.2)$$

Finally, we can define the matrices $\mathcal{H}$ and $\mathcal{W}$ with components as follows:

$$\begin{aligned} \mathcal{H} &= \left[\frac{\partial \mathcal{F}_i}{\partial y_j^I} (E_0) \right], \\ \mathcal{W} &= \left[\frac{\partial \mathcal{M}_i}{\partial y_j^I} (E_0) \right], \end{aligned} \quad (3.3)$$

where the matrix $\mathcal{W}$ is non-singular and the matrix $\mathcal{H}$ is non-negative, and E_0 is the free equilibrium point of Eq. 3.1. Thus, the basic reproduction number R_0 can be calculated from the spectral radius, or dominant eigenvalue, of the next generation matrix $\mathcal{H}\mathcal{W}^{-1}$. This quantity is defined by the following expression:

$$R_0 = \rho(\mathcal{H}\mathcal{W}^{-1}),$$

where ρ represents the spectral radius. Readers can find more details about the basic reproduction number and the idea of the next generation method in references [23–25].

The free disease equilibrium (FDE) point for Eq. 2.1 is given below:

$$E_0 = \left(C_T \left(1 - \frac{d_1}{g} \right), 0, 0, 0, 0, 0 \right).$$

The basic reproduction number (R_0) for E_0 is calculated as follows:

$$\text{Let } y^I = \begin{bmatrix} I \\ V \end{bmatrix}, \quad y^N = \begin{bmatrix} T \\ F \\ B \\ A \end{bmatrix},$$

$$\text{and } \frac{d}{dt} \begin{bmatrix} I \\ V \end{bmatrix} = \begin{bmatrix} \frac{\beta VT}{V+T} \\ 0 \end{bmatrix} - \begin{bmatrix} kFI + (d_2 + \delta)I \\ \frac{\beta VT}{V+T} - pI + mAV + (c + d_3)V \end{bmatrix}.$$

$$\text{Then, } \mathcal{F}(T, I, V, F, B, A) = \begin{bmatrix} \frac{\beta VT}{V+T} \\ 0 \end{bmatrix} \text{ and}$$

$$\mathcal{M}(T, I, V, F, B, A) = \begin{bmatrix} kFI + (d_2 + \delta)I \\ \frac{\beta VT}{V+T} - pI + mAV + (c + d_3)V \end{bmatrix}.$$

At infection-free equilibrium E_0 , and using Eq. 3.3, we have

$$\mathcal{H} = \left(\frac{\partial \mathcal{F}}{\partial (I, V)} \right) \Big|_{(E_0)} = \begin{bmatrix} 0 & \beta \\ 0 & 0 \end{bmatrix},$$

$$\mathcal{W} = \left(\frac{\partial \mathcal{M}}{\partial (I, V)} \right) \Big|_{(E_0)} = \begin{bmatrix} d_2 + \delta & 0 \\ -p & \beta + d_3 + c \end{bmatrix}, \text{ and}$$

$$\mathcal{W}^{-1} = \frac{1}{(d_2 + \delta)(\beta + d_3 + c)} \begin{bmatrix} \beta + d_3 + c & 0 \\ p & d_2 + \delta \end{bmatrix}.$$

Therefore, the next generation matrix is given as below:

$$HW^{-1} = \frac{1}{(d_2 + \delta)(\beta + d_3 + c)} \begin{bmatrix} p\beta & \beta(d_2 + \delta) \\ 0 & 0 \end{bmatrix}.$$

Thus, HW^{-1} has two eigenvalues: $\lambda_1 = 0$, and $\lambda_2 = \frac{p\beta}{(d_2 + \delta)(\beta + d_3 + c)}$. The basic reproduction number is given by the spectral radius of HW^{-1} , which takes the following form:

$$R_0 = \frac{p\beta}{(d_2 + \delta)(\beta + d_3 + c)}. \quad (3.4)$$

4. Elasticity of R_0

In this section, we explain the correlations between the model parameters and the basic reproduction number, R_0 . This method is called elasticity. It indicates which parameters have a significant impact on R_0 . Accordingly, we consider an immuno-epidemiological model with q parameters (ω_j) for $j = 1, 2, \dots, q$. We define an elasticity index between the model parameters ω_j and basic reproduction number R_0 . This is known as the normalized sensitivity index. It measures the relative change of R_0 with regard to ω_j , represented by $\mathcal{E}_{\omega_j}^{R_0}$. Then, the elasticity index is given by

$$\mathcal{E}_{\omega_j}^{R_0} = \frac{\partial R_0}{\partial \omega_j} \times \frac{\omega_j}{R_0}. \quad (4.1)$$

In addition, this quantity shows the proportional importance of the model transmission rates. The sign of this index shows whether R_0 grows (positive sign) or decreases (negative sign) with the parameter. As a result, the elasticity index for each parameter of Eq. 2.1 is as follows:

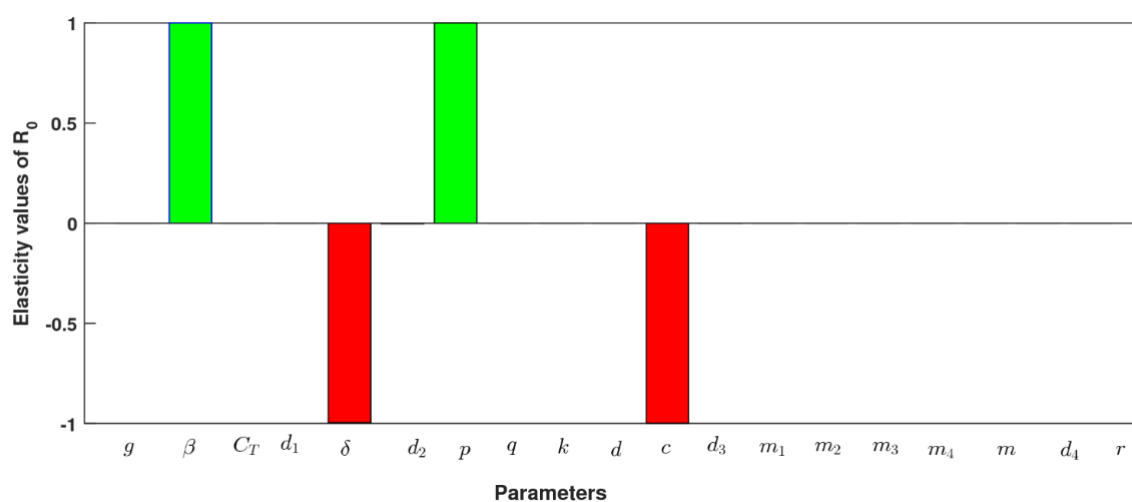
$$\mathcal{E}_p^{R_0} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0} = 1, \quad \mathcal{E}_\beta^{R_0} = \frac{\partial R_0}{\partial \beta} \times \frac{\beta}{R_0} = \frac{d_3 + c}{\beta + d_3 + c}, \quad \mathcal{E}_{d_2}^{R_0} = \frac{\partial R_0}{\partial d_2} \times \frac{d_2}{R_0} = \frac{-d_2}{d_2 + \delta},$$

$$\mathcal{E}_\delta^{R_0} = \frac{\partial R_0}{\partial \delta} \times \frac{\delta}{R_0} = \frac{-\delta}{d_2 + \delta}, \quad \mathcal{E}_{d_3}^{R_0} = \frac{\partial R_0}{\partial d_3} \times \frac{d_3}{R_0} = \frac{-d_3}{\beta + d_3 + c}, \quad \mathcal{E}_c^{R_0} = \frac{\partial R_0}{\partial c} \times \frac{c}{R_0} = \frac{-c}{\beta + d_3 + c},$$

and the elasticity indexes for the other model parameters are zero. We can compute the elasticity indexes based on the model parameter values given in Table 2:

Table 2. Elasticity values of R_0 regarding the model parameters.

Parameters	$\mathcal{E}_{\omega_j}^{R_0}$
g	0
β	0.9999
C_T	0
d_1	0
δ	-0.9966
d_2	-0.0033
p	1
q	0
k	0
d	0
c	-0.9990
d_3	-0.0009
m_1	0
m_2	0
m_3	0
m_4	0
m	0
d_4	0
r	0

**Figure 3.** Elasticity values of R_0 regarding the model parameters.

The elasticity indexes given in Table 2 are calculated using MATLAB codes for the initial states and suggested parameter values. Results are graphically shown in Figure 3. There are different signs for the indexes including positive signs such as with β and p or negative signs such as with d_2 , d_3 , δ , and c . The other parameter indexes are zero, see Figure 3. For instance, positive values suggest that increasing

these parameters leads to a rise in R_0 , causing the virus to spread more rapidly. On the other hand, a negative value suggests that an increase in these parameters could lead to a lower basic reproduction number and less impact on the spreading virus. Finally, there are strong positive correlations between R_0 and parameters β and p , suggesting that R_0 is highly sensitive to the rate of transmission from the target cells to the infected cells and on the virus production rate. On the other hand, there is a strong negative relation between R_0 and the death rate of infected cells, δ , and virus clearance rate, c .

5. Sensitivity analysis

Recently, the idea of sensitivity analysis has been used as an important technique for infectious disease models. Based on this method, the most sensitive parameters and variables can be easily determined. There are two common types of sensitivity: called local and global sensitivity [26]. In this study, we consider an infectious disease model with q parameters (ω_j) for $j = 1, 2, \dots, q$ and k compartments (y_i) for $i = 1, 2, \dots, k$. The model differential equation is given below:

$$\frac{dy_i}{dt} = f_i(y, \omega), \quad (5.1)$$

where $y \in \mathbb{R}^k$ and $\omega \in \mathbb{R}^q$. Mathematically, there are three techniques to calculate the local sensitivity: non-normalization, half normalization, and full normalization. In addition, we introduce a sensitivity coefficient quantity for each y_i with respect to each parameter ω_j , defined by $S_{\omega_j}^{y_i}$. The first approach is called the non-normalization sensitivity, given as:

$$S_{\omega_j}^{y_i} = \frac{\partial y_i}{\partial \omega_j}. \quad (5.2)$$

The second one is called the half normalization sensitivity, given as:

$$S_{\omega_j}^{y_i} = \left(\frac{1}{y_i} \right) \left(\frac{\partial y_i}{\partial \omega_j} \right). \quad (5.3)$$

The last one is called the full normalization sensitivity, given as:

$$S_{\omega_j}^{y_i} = \left(\frac{\omega_j}{y_i} \right) \left(\frac{\partial y_i}{\partial \omega_j} \right). \quad (5.4)$$

The suggested sensitivity approaches can be applied to show how input parameters affect output variables. In addition, important techniques of mode analysis in the field of systems biology can be found in [23, 26–28]. These techniques can also be used for delay differential equations. This shows that sensitivity analysis can effectively identify the most critical parameters and time delays, providing valuable insights into parameter estimation, model validation, and the control of complex biological and engineering systems [29]. As it is clear that determining the model critical parameters based on the sensitivity analysis is the main aim in this study, we apply the suggested methods on the model differential equations given in Eq. 2.1. All sensitivity analysis results here were performed using the SimBiology Toolbox in MATLAB. The model was simulated over the time interval $t = [0, 10]$ days and the numerical solver used in this simulations is *ode15s*, which is appropriate for stiff systems of

ordinary differential equations. Model sensitivities were evaluated throughout the simulation interval using the estimated parameter values given in Table 1. Local sensitivities were computed by solving the forward sensitivity equations simultaneously with the state equations. Three sensitivity measures were used: full normalizations, half normalizations, and non-normalizations, see Figures 4–6. In addition, we used SimBiology’s forward sensitivity equations, where there is no perturbation size. All local sensitivities were computed by solving the sensitivity equations directly rather than by parameter perturbation. Moreover, three-dimensional sensitivity plots are given in this manuscript using the SimBiology Toolbox because they simultaneously show the sensitivities of all model state variables with respect to all model parameters in a single figure. Interestingly, the results assist us in understanding the model better and allow us to identify which model parameters are crucial.

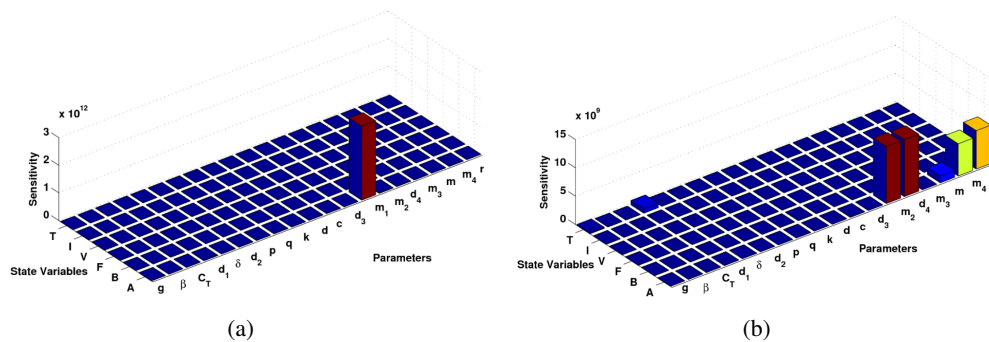


Figure 4. Local sensitivity analysis with the non-normalization method of all variables in computational simulations using MATLAB with respect to (a) all parameters and (b) all parameters except μ_1 .

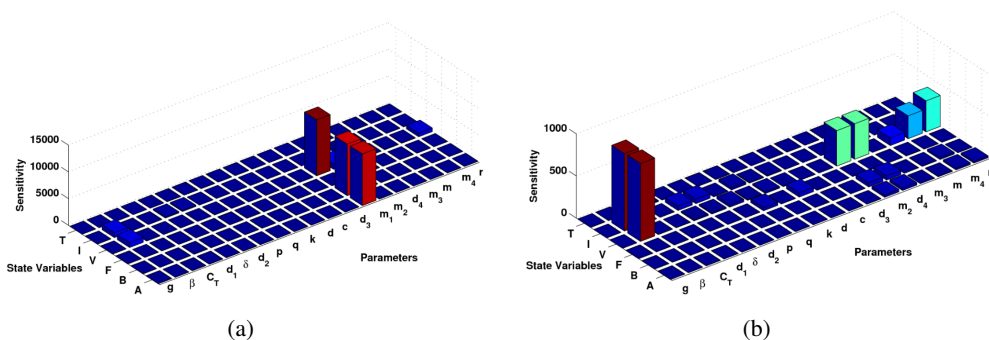


Figure 5. Local sensitivity analysis with the half normalization method of all variables in computational simulations using MATLAB with respect to (a) all parameters and (b) all parameters except μ_1 .

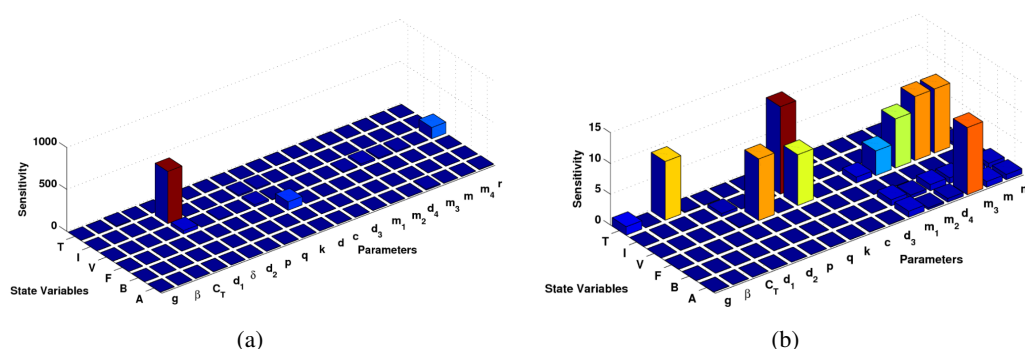


Figure 6. Local sensitivity analysis with the full normalization method of all variables in computational simulations using MATLAB with respect to (a) all parameters and (b) all parameters except μ_1 .

The simulated results given in Figures 4–6 show that some model compartments are sensitive with respect to the critical model parameters. This shows how input model parameters affect the output states based on the suggested techniques of local sensitivity. For instance, using the non-normalization technique of sensitivity analysis, antibodies A are more sensitive to m_1 (rate of B-cell activation per virion) compared to the other relevant parameters; see Figure 4(a). In addition, there are also some sensitivities between antibodies and m_2, d_4, m, m_4 , and r ; see Figure 4(b). In Figure 5, variable V (free virus), B-cells, and antibodies are very sensitive to the model parameter m_1 , and the model states I and V are more sensitive to β compared to other parameters. Furthermore, Figure 6(a) shows that variable I (infected cells) is very sensitive to parameter δ . Interestingly, based on the results given by the full normalization technique in Figure 6(b), we can identify different levels of sensitivity between model compartments and model parameters.

6. Numerical results and discussion

Computational simulations give an important step forward in analyzing the model state dynamics and identifying the model critical parameters in the spreading of virus. The model parameter values used in this study are listed in Table 1. Since the transmission parameters represent rates or probabilities, their values belong in the interval $[0, 1]$. To show the impact of these parameters on the model dynamics, we selected several alternative values within this biologically feasible range and calculated additional numerical simulations. Actually, we used a different time interval to show that the solutions approach their steady-state values (level off). Thus, the simulation intervals were chosen to clearly illustrate the complete dynamical behavior of the model rather than using a single fixed time horizon for all figures.

Therefore, the numerical results were calculated based on the initial states and selected model parameters using the System Biology Toolbox (SBedit) for MATLAB; see Figures 7 and 8. Accordingly, there are different model dynamics for initial population model states and estimated parameters. For example, Figure 7 shows the impact of the transmission rate, β , virus clearance rate, c , and killing rate of infected cells, k , on infected cells over time. It is clear that if the value of β is increased from 0.02 to 0.06, then the number of infected cells will dramatically increase, see Figure

7(a). On the other hand, there will be less infected cells over time when the values of c and k become bigger and bigger; see Figures 7(b) and (c). In addition, Figures 8(a)-(c) show the impact of the virus clearance rate, c , on free virus dynamics, interferon degradation rate, d , on interferon dynamics, and antibody production rate, m_3 , on antibody dynamics for different parameter values, respectively. It can be concluded that an increase in the virus clearance rate (c) and interferon degradation rate (d) will decrease the number of free virus and interferons over time, while a higher antibody production rate (m_3) leads to more antibodies.

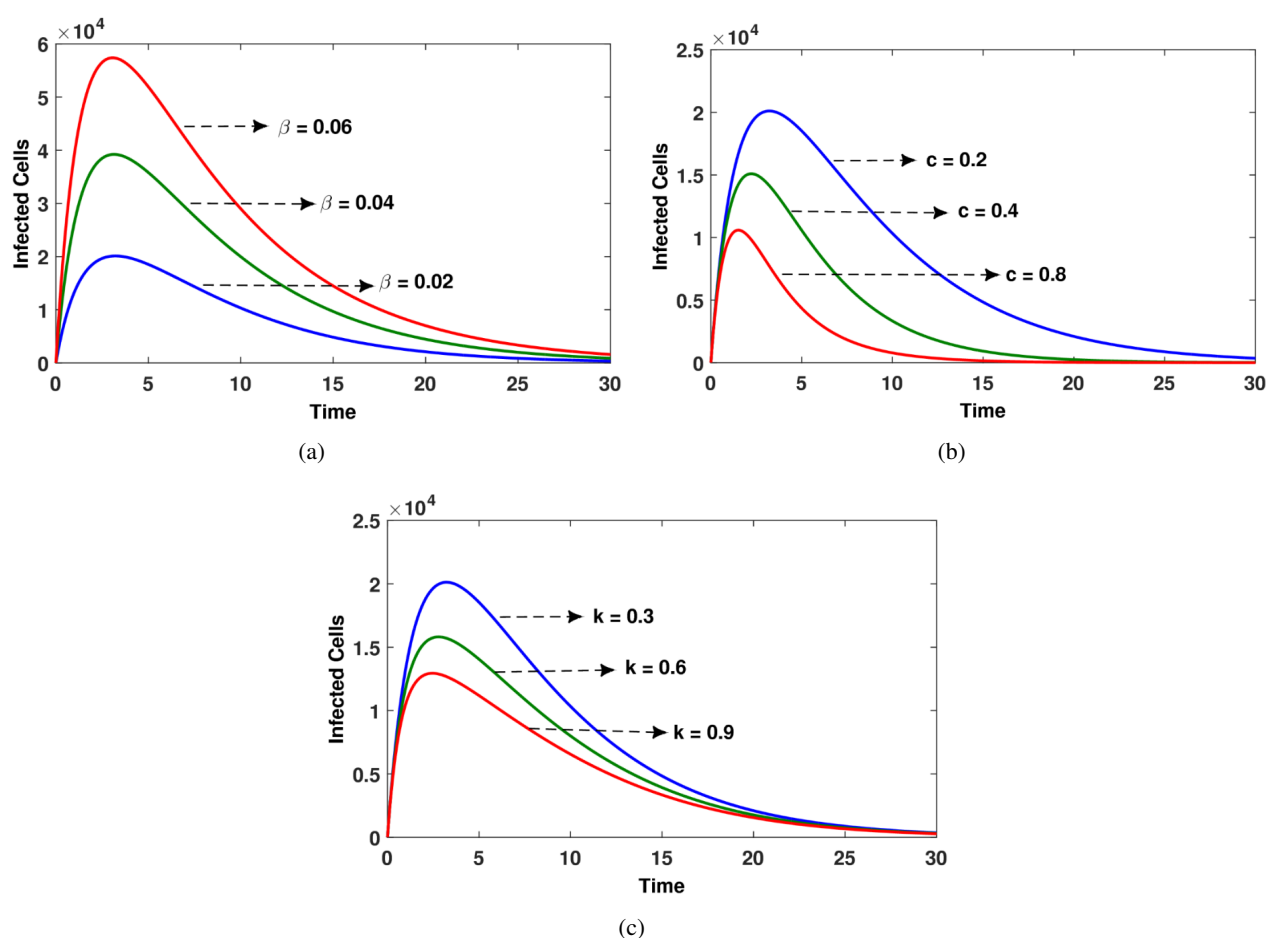


Figure 7. The effect of the transmission rate, β , virus clearance rate, c , and killing rate of infected cells, k , on infected cells.

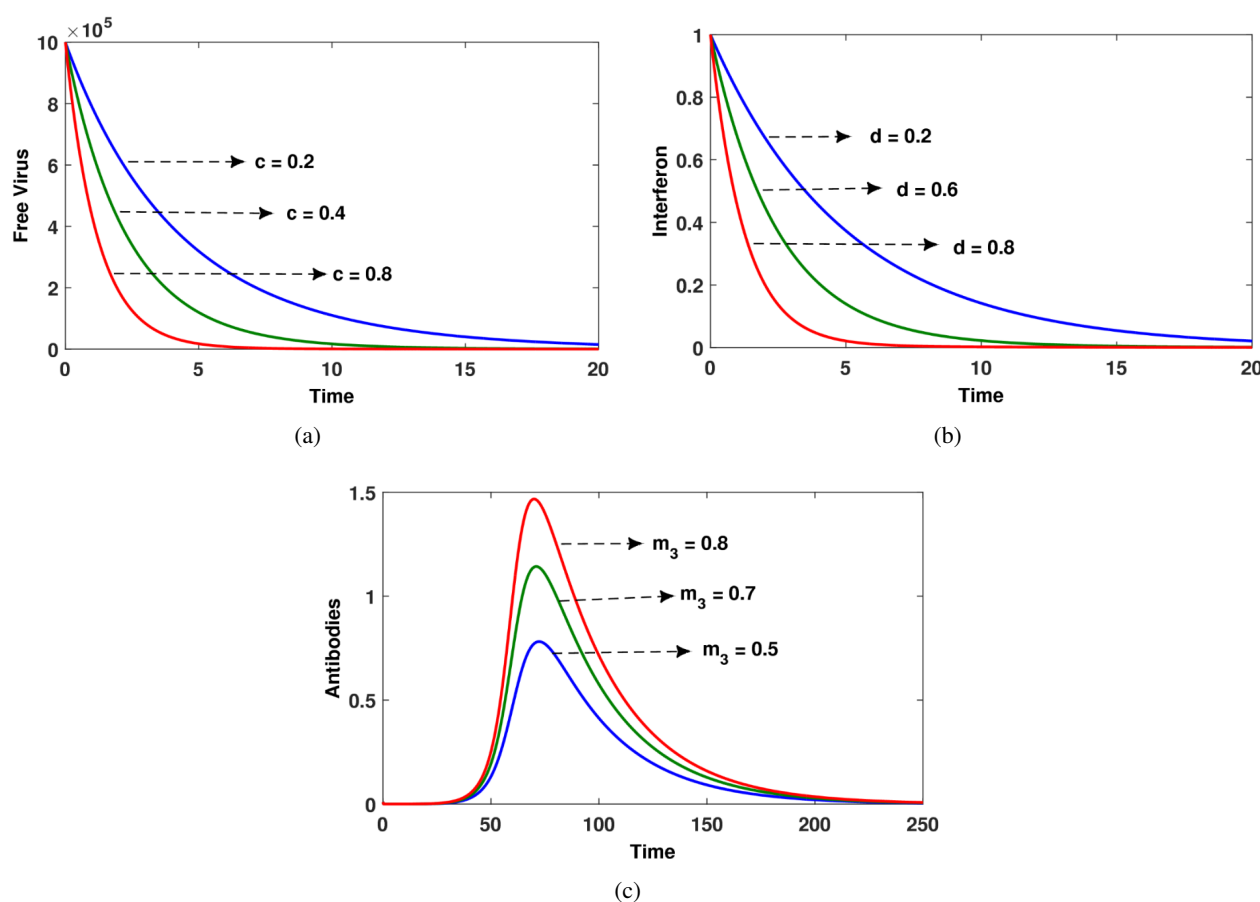


Figure 8. The effect of the virus clearance rate, c , on free virus, interferon degradation rate, d , on interferon, and antibody production rate, m_3 , on antibodies.

This study indicates that only a group of model parameters can effectively influence the infection dynamics. The proposed methods of model analysis, elasticity, and local sensitivity analysis show that the transmission rate β , virus clearance rate c , infected-cell death rate δ , and virus production rate p are the key parameters of greatest importance. These complementary approaches offer a thorough insight into the processes of the expanded disease transmission model. From a biological standpoint, understanding the transmission rates is anticipated since the virus transmissions can be directly controlled, resulting in a reduction of infected cells. This involves the infection of target cells by free virus.

These results can also be compared with earlier mathematical models concerning immuno-epidemiological systems. Similar results have been noted for models of influenza, HIV, and COVID-19. A key aspect of this study is the concurrent application of non-normalized, half normalized, and fully normalized local sensitivity analyses. The proposed techniques offer various insights and additional viewpoints for recognizing key parameters and enhancing the dependability of the sensitivity evaluation. Furthermore, the critical model parameters offer valuable approaches for intervention strategies from public health viewpoints. While the extended model provides significant insights into immuno-epidemiological dynamics, various limitations must be addressed. For instance,

the model has not been validated with clinical or experimental datasets, and it can also be examined for global sensitivity analysis.

7. Conclusions

The extended mathematical model here provides a great step forward in understanding the immuno-epidemiological model more effectively. The modified model used in this work may help local and international efforts to suggest more control strategies. Interestingly, the results provide more details regarding the critical parameters on the model compartments. The suggested techniques of local sensitivity, elasticity, and basic reproduction number were discussed and applied to the developed model based on the initial states and parameters.

In this study, we added and discussed additional biological processes, including logistic target-cell growth and the natural death rates of target cells, infected cells, viruses, and B-cells. In addition, Holling type-II infection function response was also added instead of the classical bilinear function. The extended model provides a more realistic biological system for describing virus-host interactions and immune responses. The basic reproduction number, R_0 , was derived using the next-generation matrix approach, and the local stability analysis used the fact that the disease-free equilibrium is locally asymptotically stable when $R_0 < 1$ and asymptotically unstable when $R_0 > 1$.

The elasticity analysis identified the most critical model parameters including the virus transmission rate β , virus production rate p , virus clearance rate c , infected-cell death rate δ , and virus natural death rate d_3 . For example, the transmission rate β shows the strongest positive impact on R_0 . It shows that reducing virus transmission is one of the most effective strategies for controlling disease spread. On the other hand, increasing virus clearance and virus death rates can directly reduce disease transmission. These findings provide quantitative evidence for prioritizing intervention strategies that limit viral transmission and enhance viral clearance.

The local sensitivity analysis further complemented the elasticity results by identifying how model parameters affect each state variable. The analyses demonstrated that infected cells are highly sensitive to the transmission rate β and infected-cell death rate δ , while antibodies are particularly sensitive to the B-cell activation rate m_1 and related immune parameters. Moreover, numerical simulations confirmed that increasing the virus transmission rate substantially increases the infected-cell population, whereas increasing the virus clearance rate c and infected-cell killing rate k effectively reduce the transmission rates. Similarly, a higher antibody production rate m_3 enhances antibody levels, highlighting its importance in strengthening the immune response.

Interestingly, the combination of stability analysis, elasticity analysis, sensitivity analysis, and numerical simulations provides a comprehensive understanding of the immuno-epidemiological dynamics. The results show that controlling virus transmission, enhancing virus clearance, promoting infected-cell elimination, and strengthening antibody production are the most effective mechanisms for reducing disease transmission. These findings may help local and international efforts of public health intervention strategies. Future work will focus on validating the model using clinical or experimental datasets and extending the framework to include optimal control strategies and parameter estimation for specific respiratory viral infections.

Finally, although the proposed model has not been validated against clinical or experimental data, this remains an important direction for future research. Model validation using influenza or other

respiratory virus datasets will be undertaken to evaluate its predictive accuracy and biological applicability.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The author declares no conflicts of interest in this paper.

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