Dynamical Transmission Model of MERS-CoV in Two Areas

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Abstract. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a disease first reported in Saudi Arabia in 2012 and it can be transmitted from human to human. This disease has spread to several other countries, most confirmed cases have displayed symptoms of severe acute respiratory illness and many of these patients have died. This research is aimed to construct a mathematical model for the transmission of MERS-CoV in two areas by separating the human population into two groups; susceptible and infectious groups. The dynamics of the disease is studied by a compartmental model involving ordinary differrential equations. The basic reproductive number of this disease is discussed to control the outbreak of this disease. Sensitivity analysis of this model is performed to determine the relative importance of the model parameters to the MERS-CoV transmission.

Keywords: MERS-CoV, transmission model, basic reproductive number, sensitivity analysis
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INTRODUCTION

In recent years, mathematical models are increasingly used by researchers to understand the transmission of infectious diseases (H. W. Hethcote, 2000). Many models for the spread of infectious diseases in populations have been analyzed mathematically and applied to specific diseases (Z. Ma and J. Li, 2009). Mathematical modelling plays a keyrole in policy making, including risk assessment and control programme evaluation in reducing morbidity and mortality (N. Chitnis, *et al.*, 2008).

Middle East respiratory syndrome coronavirus (MERS-CoV), previously known as novel coronavirus was first identified in humans in 2012. It can cause severe acute respiratory disease, particularly in people with underlying conditions. The MERS-CoV is a potential pandemic disease, cases of this disease has been reported in some countries. As of 11 September 2015, World Health Organization (WHO) global case count was 1,569 laboratory-confirmed cases of MERS-COV, including at least 554 deaths (case fatality rate 35.31%) since the first cases were reported in September 2012 (WHO, 2015). All cases have had a history of residence in or travel to the Middle East (>90% Saudi Arabia), or contact with travellers returning from these areas (L. M. Gardner and C. R. MacIntyre, 2014). Until now, there is no vaccine for this disease.

Mathematical modeling for disease transmission has been done by many different authors to understand the dynamical spread of disease in humans, for example in S. Syafruddin and M. S. M. Noorani (2011), B. Yong (2007), and Z. Feng, *et al*. (2000). Models for infectious disease are helpful for prevention and control of emerging infectious disease like MERS-CoV. Here a SISI (S for susceptible and I for infectious) epidemiological model for human to human in two areas describing MERS-CoV disease transmission is presented, as well as the associated basic reproductive number. Firstly, we formulate a SISI model to describe the transmission of MERS-CoV in two areas. Next, we evaluate the basic reproductive number using the next generation matrix method. Basic reproductive number is discussed in order to identify influential model parameters, so with controlling parameters in it, the outbreak of the disease can be eliminated. Finally, we analyze sensitivity of the model in order to determine the influence of the input parameters on the model outputs. Based on this analysis, we can find which parameters are most sensitive to the MERS-CoV transmission model.

MATHEMATICAL MODEL

The model describes the dynamic of MERS-CoV transmission. We divide the population (N) into two areas, namely area x and y. In each area, we have two sub-populations, according to their disease status; population who are susceptible to infection (S_x and S_y) and population who have the disease (I_x and I_y). Initially, there are susceptible and infectious humans in each area. Individuals are born into the susceptible class and individuals susceptible to infection. There is a natural death rate of human population from each compartment and its value is same in both areas of population. Someone who gets infected and then recovers will return to the susceptible class. The susceptible population in area x (S_x) is increased by recruitment of individuals a_1, susceptible individuals from area y leave to area x with rate α_2, and infected individuals in area x recover with rate d. This population is reduced through infection

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within area x with transmission rate β (moving to class I_x), susceptible individuals from area x leave to area y with rate α_1 (moving to class S_y), individuals from area y leave to area x and they infected with transmission rate $\omega\alpha_2$, and by natural death with rate b. The population of infectious individuals is increased by infection of susceptible within area x with transmission rate β, infected individuals from area y leave to area x with rate α_2, and individuals from area y leave to area x and they infected with transmission rate $\omega\alpha_2$. It is diminished by death due to disease with rate c, by recovery from the disease with rate d (moving to class S_x), and infected individuals from area x leave to area y with rate α_1 (moving to class I_y).

Meanwhile, the susceptible population in area y (S_y) is increased by recruitment of individuals a_2, susceptible individuals from area x leave to area y with rate α_1, and infected individuals in area y recover with rate d. This population is reduced through infection within area y with transmission rate β (moving to class I_y), susceptible individuals from area y leave to area x with rate α_2 (moving to class S_x), individuals from area x leave to area y and they infected with transmission rate $\omega\alpha_1$, and by natural death with rate b. The population of infectious individuals is increased by infection of susceptible within area y with transmission rate β, infected individuals from area x leave to area y with rate α_1, and individuals from area x leave to area y and they infected with transmission rate $\omega\alpha_1$. It is diminished by death due to disease with rate c, by recovery from the disease with rate d (moving to class S_y), and infected individuals from area y leave to area x with rate α_2 (moving to class I_x).

The detailed transition between these four compartments is depicted in Fig. 1.

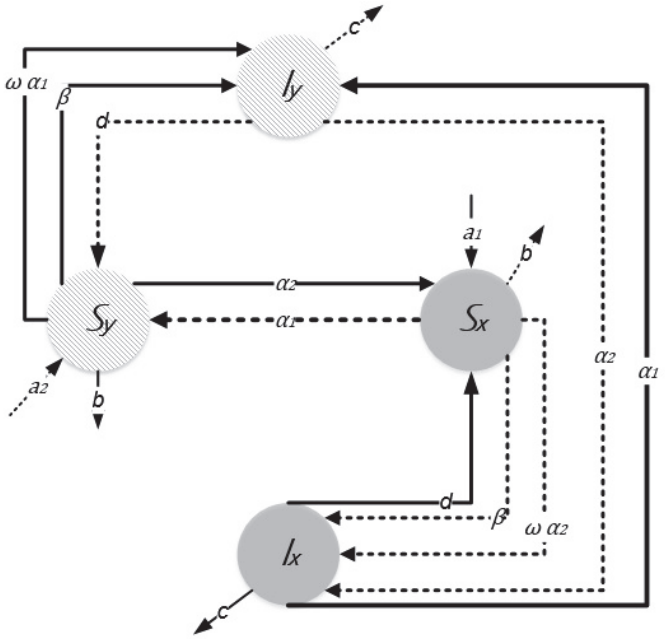

FIGURE 1. A transmission diagram of the SISI MERS-CoV model in two areas

With the assumptions given and the illustrations in Fig. 1, we obtain the following four-dimensional system of nonlinear differential equation for the MERS-CoV transmission:

$$\left.\begin{aligned}
\frac{dI_x(t)}{dt} &= \frac{\beta\, S_x I_x}{S_x+I_x} - (c+d+\alpha_1)\, I_x + \alpha_2\, I_y + \frac{\omega\,\alpha_2\, S_y\, I_y}{S_y+I_y} \\
\frac{dI_y(t)}{dt} &= \frac{\beta\, S_y I_y}{S_y+I_y} - (c+d+\alpha_2)\, I_y + \alpha_1\, I_x + \frac{\omega\,\alpha_1 S_x\, I_x}{S_x+I_x} \\
\frac{dS_x(t)}{dt} &= a_1 - \frac{\beta\, S_x I_x}{S_x+I_x} - (b+\alpha_1)\, S_x + \alpha_2\, S_y + d\, I_x - \frac{\omega\,\alpha_2\, S_y\, I_y}{S_y+I_y} \\
\frac{dS_y(t)}{dt} &= a_2 - \frac{\beta\, S_y I_y}{S_y+I_y} - (b+\alpha_2)\, S_y + \alpha_1\, S_x + d\, I_y - \frac{\omega\,\alpha_1 S_x\, I_x}{S_x+I_x}
\end{aligned}\right\} \quad (1)$$

The variable domain of the model is

$$\Omega = \{(I_x, I_y, S_x, S_y) \in \mathbb{R}^4 : I_x, I_y, S_x, S_y \geq 0\}$$

and all parameters used in the model; $a_1, a_2, b, c, d, \beta, \alpha_1, \alpha_2$, and ω are positive. It can be verified that Ω is a positively invariant set with respect to model.

TABLE 1. Parameters used in Fig. 1 and their description

Description	Parameter
Number of newly recruited to the susceptible $\boldsymbol{x}$ population	a_1
Number of newly recruited to the susceptible $\boldsymbol{y}$ population	a_2
Natural death rate for susceptible individuals	b
MERS-CoV death rate of human population	c
Recovery rate from MERS-CoV	d
Transmission rate within an area	β
Movement rate of human population from area $\boldsymbol{x}$ leave to area $\boldsymbol{y}$	α_1
Movement rate of human population from area $\boldsymbol{y}$ leave to area $\boldsymbol{x}$	α_2
Transmission rate in different area	ω

The model (1) has two equilibrium points which are given by $E_0 = (I_x^*, I_y^*, S_x^*, S_y^*) = \left(0,0,\frac{a_1\alpha_2+a_2\alpha_2+a_1b}{b\,(\alpha_1+\alpha_2+b)}, \frac{a_1\alpha_1+a_2\alpha_1+a_2b}{b\,(\alpha_1+\alpha_2+b)}\right)$ and $E_1 = (I_x^{**}, I_y^{**}, S_x^{**}, S_y^{**})$. Equilibrium point E_0 represents the situation where only S_x^* and S_y^* exist and it is called disease free equilibrium (DFE) point whereas equilibrium point E_1 depicts the situation where all population exist and it is called endemic equilibrium (EE) point.

BASIC REPRODUCTIVE NUMBER

Basic reproductive number is an important threshold in mathematical epidemiology. This threshold conditions determine whether an infectious disease will spread in a susceptible population when the disease is introduced into the population (O. Diekmann and J. A. P. Heesterbeek, 2000). The threshold is calculated by using the spectral radius of a next generation (infection) matrix of a model (P. van den Driessche and J. Watmough, 2002). It is given mathematically as

$$R_0 = \rho(FV^{-1})$$

where ρ is defined as the spectral radius of the next generation matrix FV^{-1}, F is the rate of appearance of new infections in compartment i, and V is the transfer of individuals out of compartment i by all other means.

Given the DFE E_0. Basic reproductive number R_0 is calculated as the largest eigenvalue (spectral radius) of the matrix of partial derivatives (Z. Ma and J. Li, 2009):

$$F = \left[\frac{\partial \mathcal{F}_i(E_0)}{\partial x_j}\right] = \begin{bmatrix} \beta & \omega\alpha_2 \\ \omega\alpha_1 & \beta \end{bmatrix}$$

and

$$V = \left[\frac{\partial \mathcal{V}_i(E_0)}{\partial x_j}\right] = \begin{bmatrix} c+d+\alpha_1 & -\alpha_2 \\ -\alpha_1 & c+d+\alpha_2 \end{bmatrix}$$

where

$$\mathcal{F}_i(x) = \begin{bmatrix} \frac{\beta S_x I_x}{S_x+I_x} + \frac{\omega\alpha_2 S_y I_y}{S_y+I_y} \\ \frac{\beta S_y I_y}{S_y+I_y} + \frac{\omega\alpha_1 S_x I_x}{S_x+I_x} \\ d\,I_x \\ d\,I_y \end{bmatrix}, \qquad \mathcal{V}_i(x) = \begin{bmatrix} (c+d+\alpha_1)I_x - \alpha_2 I_y \\ (c+d+\alpha_2)I_y - \alpha_1 I_x \\ -a_1 + \frac{\beta S_x I_x}{S_x+I_x} + bS_x + \alpha_1 S_x - \alpha_2 S_y + \frac{\omega\alpha_2 S_y I_y}{S_y+I_y} \\ -a_2 + \frac{\beta S_y I_y}{S_y+I_y} + bS_y + \alpha_2 S_y - \alpha_1 S_x + \frac{\omega\alpha_1 S_x I_x}{S_x+I_x} \end{bmatrix}$$

Therefore, the next generation matrix is given as follows

$$FV^{-1} = \begin{bmatrix} \frac{\alpha_2(\alpha_1\omega+\beta)+\beta(c+d)}{(c+d)(c+d+\alpha_1+\alpha_2)} & \frac{\alpha_2(\beta+\omega(c+d+\alpha_1))}{(c+d)(c+d+\alpha_1+\alpha_2)} \\ \frac{\alpha_1(\beta+\omega(c+d+\alpha_2))}{(c+d)(c+d+\alpha_1+\alpha_2)} & \frac{\alpha_1(\alpha_2\omega+\beta)+\beta(c+d)}{(c+d)(c+d+\alpha_1+\alpha_2)} \end{bmatrix}$$

The spectral radius of the next generation matrix is

$$R_0 = \frac{\beta(\alpha_1+\alpha_2+2c+2d)+2\alpha_1\alpha_2\omega+\sqrt{\rho}}{2(\alpha_2+\alpha_1)(c+d)+(c+d)^2} \tag{2}$$

with

$$\rho = \beta^2(\alpha_1+\alpha_2)^2 + 4\alpha_1\alpha_2\omega\left((c+d+\alpha_2)(c+d+\alpha_1)\omega + 2\beta\left(\frac{1}{2}\alpha_1+\frac{1}{2}\alpha_2+c+d\right)\right)$$

As shown in (2), the basic reproductive number of system (1) depends on parameters $\beta, \alpha_1, \alpha_2, c, d$, and ω. Equilibrium point E_0 will be locally asymptotic stable iff $R_0 < 1$. It is easily verified that all eigenvalues are negative at this point. Meanwhile, equilibrium point E_1 exist iff $R_0 > 1$.

In this paper, we use parameter values $a_1 = 4{,}326, a_2 = 13{,}461, b = 0.01, c = 0.05, d = 0.1, \beta = 0.1$, and $\omega = 0.08$. As described in Fig. 2 and Fig. 3, the bigger the movement rate of human population (α_1 and α_2), the larger the rate of R_0.

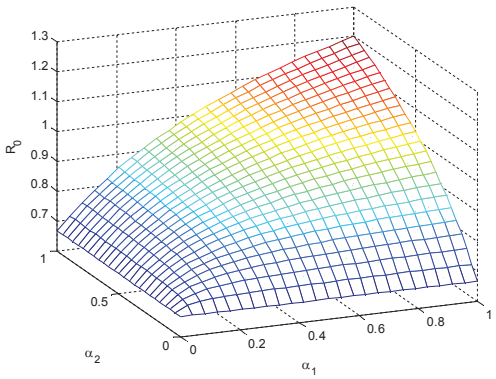

FIGURE 2. Plot of R_0 for variation α_1 and α_2

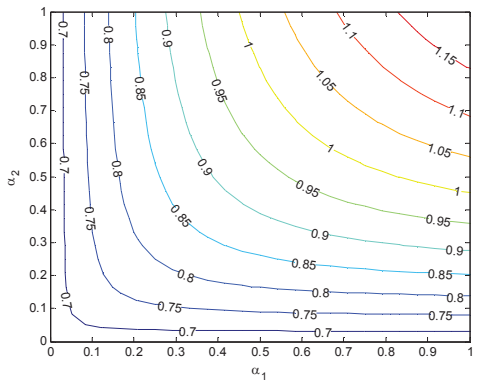

FIGURE 3. Level set of α_1 and α_2 with respect to R_0

In the next section, the sensitivity indices of R_0 related to the parameters in the model are calculated. Sensitivity indices allow us to measure the relative change in a variable when a parameter changes.

SENSITIVITY ANALYSIS

Since learning about the influence of the parameters on the behavior of the model is of much interest, it is critical to carry out a sensitivity analysis. The main goal of this section is to perform sensitivity analysis of MERS-CoV transmission model to the parameters describing it, i.e. to determine the amount that the entire model changes when each parameter is altered. Sensitivity analysis is often used to study how the variation in the output of a model can be apportioned, qualitatively or quantitavely, to different sources of variation, and of how the given model depends on the information fed into it (A. Saltelli, *et al*., 2000). Sensitivity analysis allows us to assess the impact that changes in a certain parameter will have on the model and it can help someone to determine which parameters are the key drivers of a model's results.

The sensitivity index of the basic reproductive number with respect to the parameter p is given as follows

$$SI_{R_0} = \frac{\frac{\partial R_0}{R_0}}{\frac{\partial p}{p}} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0}$$

Here we give two cases for sensitivity indices of R_0; $R_0 < 1$ and $R_0 > 1$. As shown in Table 2, parameter β gives the biggest positive effect on the change of R_0 than other parameters.

TABLE 2. Sensitivity indices of R_0

Parameter	$SI_{R_0<1}(\alpha_1 = 0.6, \alpha_2 = 0.2)$	$SI_{R_0>1}(\alpha_1 = 0.8, \alpha_2 = 0.6)$
c	−0.3326598246	−0.3332527390
d	−0.6653196494	−0.6665054780
β	+0.8030733632	+0.6454323343
α_1	+0.0520516272	+0.1536403789
α_2	+0.1428544841	+0.2006855042
ω	+0.1969266369	+0.3545676659

In Fig. 4, we show effects on the number of infected humans through parameters variation for condition $R_0 < 1$.

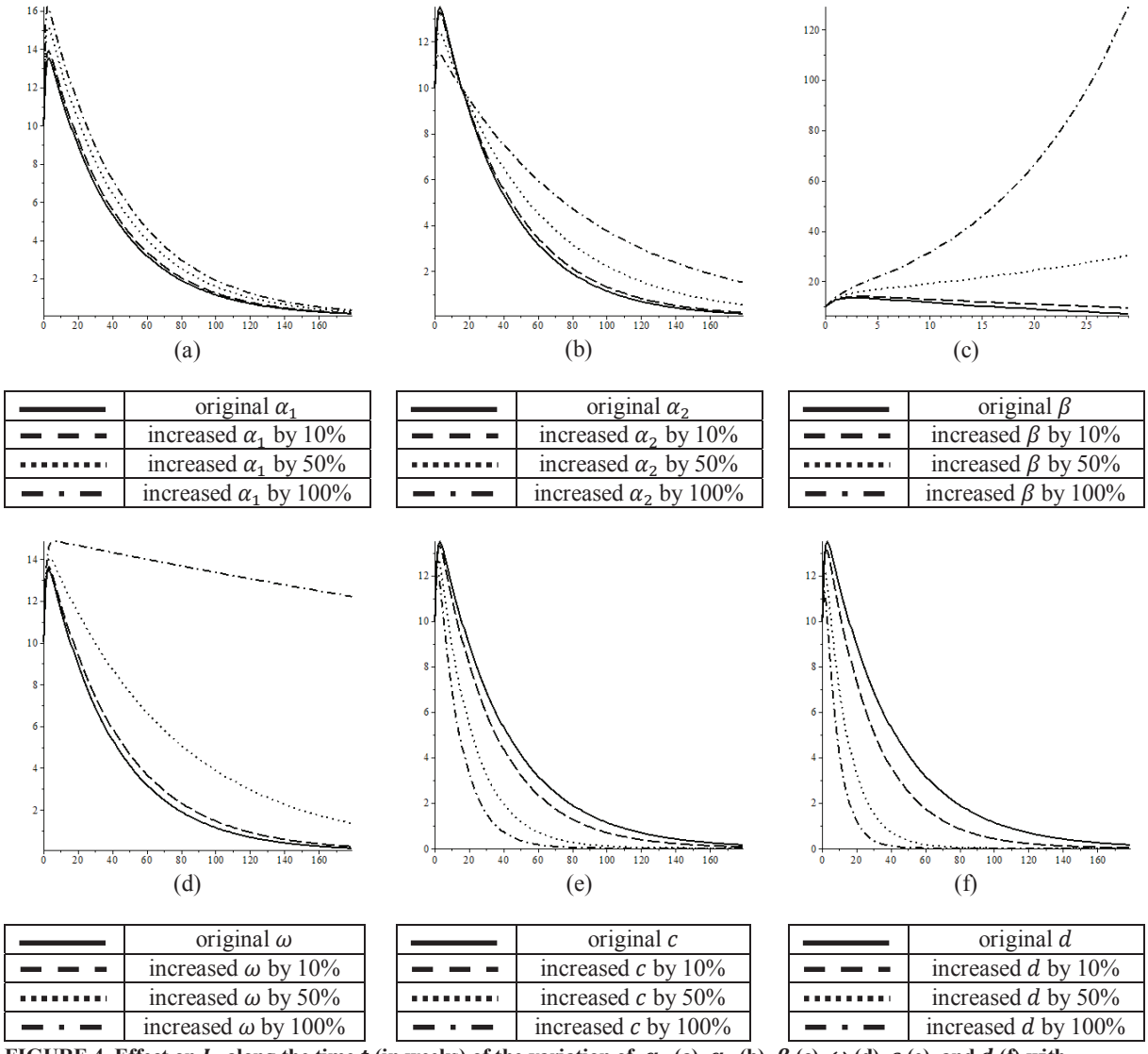

FIGURE 4. Effect on I_y along the time t (in weeks) of the variation of α_1 (a), α_2 (b), β (c), ω (d), c (e), and d (f) with $\alpha_1 = 0.6, \alpha_2 = 0.2$ ($R_0 < 1$)

In Fig. 5, we show effects on the number of infected humans through parameters variation for condition $R_0 > 1$.

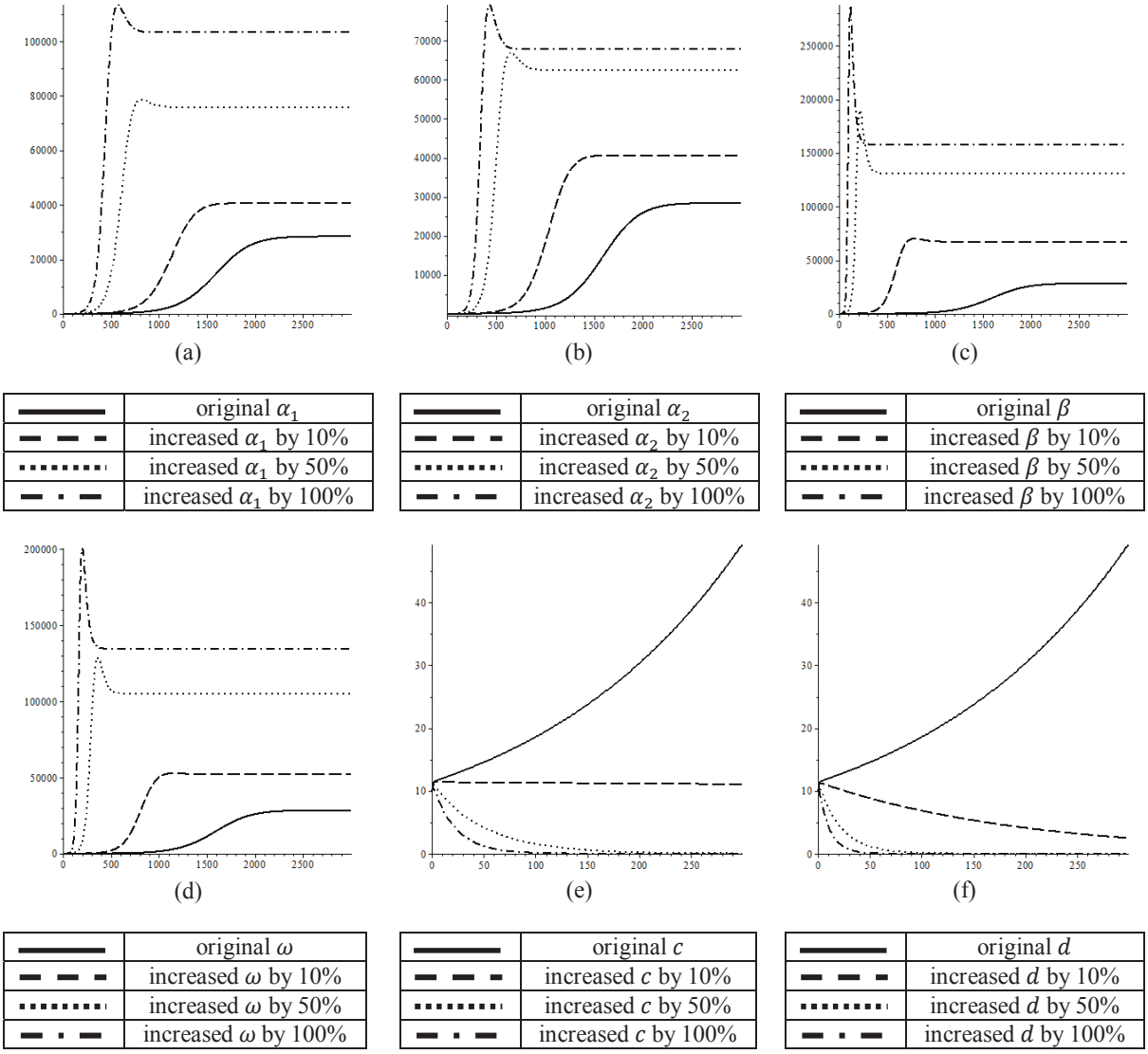

FIGURE 5. Effect on I_y along the time t (in weeks) of the variation of α_1 (a), α_2 (b), β (c), ω (d), c (e), and d (f) with $\alpha_1 = 0.8, \alpha_2 = 0.6$ ($R_0 > 1$)

In both figures (Fig. 4 and Fig. 5), it can be seen that parameters c and d have a negative sign in the sensitivity indices of R_0, while parameters $\beta, \alpha_1, \alpha_2$, and ω have a positive sign in the sensitivity indices of R_0.

CONCLUSION

This paper discusses about dynamical transmission model of MERS-CoV in two areas. The model has two equilibrium points, disease free equilibrium point E_0 and endemic equilibrium point E_1. The disease dies out if the basic reproductive number is less than unity and the disease is established in the population if the basic reproductive number is greater than unity. It can be seen from basic reproductive number that MERS-CoV transmission model in two areas depends on parameters $\beta, \alpha_1, \alpha_2, c, d$, and ω. From the sensitivity indices, the number of infected humans can be reduced by increasing c and d and/or decreasing $\beta, \alpha_1, \alpha_2$, and ω. We can see that β is the most positive sensitive parameter in the model. With controlling this parameter continuously, the number of infected humans can be decreased significantly.

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