RT&A, No 4 (76)
Volume 18, December 2023

SURVIVAL ANALYSIS OF A MULTI-STATE SEMI-MARKOV MODEL ON INFECTIOUS DISEASE CONSIDERING VARIOUS LEVELS OF SEVERITY

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Abstract

The aim of the paper is to carry out survival analysis of a novel multi-state model on infectious disease considering various levels of severity using semi-Markov processes. Various levels of severity of the disease over time and transitions between these severity levels have been considered. Transition probabilities and expected waiting times are derived. Expressions for mean survival time, expected total time in home isolation, and expected total time in hospital are obtained. The analysis of the proposed model is carried out through numerical computation and plotting several graphs. Important conclusions are drawn. The modelling framework proposed here can be used to model any infectious disease irrespective of disease states. The study will be helpful in designing effective measures to control the infectious disease and selecting the appropriate intervention policies.

Keywords: Multi-state model, Markov property, Semi-Markov process, Transition probabilities

1. Introduction

Modelling infectious diseases has always been an area of interest for researchers in various fields for the sake of prevention and control of these diseases. According to World Health Organization 2019 report [17], infectious diseases are still in the top ten leading causes of death. In low income countries, six of the top ten causes of death are infectious diseases including neonatal conditions, lower respiratory infections, diarrhoeal diseases, malaria, tuberculosis, HIV/AIDS [17]. As per the above report, there was 50% drop in Disability Adjusted Life Years (DALYs) since 2000 due to infectious, maternal, perinatal and nutritional conditions.

Multi-state Markov models have been frequently used to study the progression of diseases such as cancer [7, 11, 15], HIV infection [4, 20], renal disease [9] and many more. For a Markov model, it is assumed that the holding time in a state is exponentially distributed. For many real-world situations, such as time to failure and time to discover a fault, the exponential distribution may be acceptable. In fact, the exponential distributions have memoryless property. In some cases,

the memoryless property could be seen as a problematic assumption. For example, patients who respond well to a treatment are likely to respond well to the treatment in the future, violating the Markov property [5]. To overcome this limitation, semi-Markov processes came into existence.

Semi-Markov processes are very important generalizations of Markov processes. While Markov processes assume that holding time in a state is exponentially distributed, semi-Markov processes relax the assumption allowing any arbitrary distributions for holding time in a state. Semi-Markov processes were defined by Levy [12] and Smith [14]. Since then, semi-Markov process concepts have been applied to solve various problems like electronics and missile related problems, to improve reliability of various systems, for cost-benefit analysis of a system, for economic decision making problem and so on. The field of biomedical science is not an exception to this, for example, see [1, 2, 6, 8, 10, 13, 16]. Weiss and Zelen [16] applied the theory of semi-Markov processes to the construction of a stochastic model for interpreting data obtained from clinical trials on patients with acute leukemia. Kao [10] derived results for computing the mean and variance of times in transient states and times to absorption in a transient semi-Markov process. Davidov [6] developed expressions for the steady-state probabilities for regenerative semi-Markov processes. Castelli et al. [2] performed cost-effective analysis to compare the follow-up strategies in colorectal cancer study. Goshu and Dessie [8] analysed hospital data obtained from a cohort of AIDS patients who have been under antiretroviral therapy follow-up and estimated the conditional probability of transitions between two states for a finite time period. Cao et al. [1] developed a semi-Markov model to analyse the long-term cost effectiveness of heart failure management programmes. Ramezankhani et al. [13] applied a multi-state semi-Markov model to estimate the number of years of life lost due to diabetes with and without cardiovascular disease.

However, the majority of the literature studies were focused on the disease's progressive stages and omitted the transitions back to normal state. We tried to bridge this gap through our article. There were some studies which included the transitions back to normal state however their main focus was to understand the threshold dynamics of the disease, for example, see [18], [19]. Further, since infectious diseases typically necessitate isolation, such as measles, cholera, diphtheria, infectious tuberculosis, plague, smallpox, yellow fever, and viral hemorrhagic fevers [3], home isolation is one of the possible states of our model. Moreover, through our model, we estimated the expected length of stay in home isolated state which has not been reported in previous studies. Besides, it is a well known fact that elderly patients, pregnant women and patients with co-morbidities are at risk of developing severe and critical illness and transition rates would be different in each category of severity illness. Thus, it becomes necessary to consider separate states for each category of severity. Keeping this in mind, we have considered the four states as mild disease state, moderate disease state, severe disease state and critical disease state. This brings another novelty to this model.

Keeping these in mind, a novel multi-state model for infectious disease based on the theory of semi-Markov processes is proposed. Various levels of severity of the disease over time have been considered. Thus, our model included every transition that a patient who is infected might experience. As in the model, the general scenario for an infectious disease have been considered, the model can be used to study and gain insights about any infectious disease. The paper is organized as follows. The newly developed multi-state semi-Markov model is described in Section 2. Transition probabilities and expected waiting times are derived and theoretical expressions regarding mean survival time, expected total time in home isolation and expected total time in hospital are obtained in Section 3. Numerical computations are performed in Section 4. Finally, conclusions are presented in Section 5.

2. Model Formulation

A semi-Markov model is proposed considering a person having an infectious disease showing the transition between various states. There are nine states in the model in which a healthy individual has the possibility to transit (see Figure 1). Infected persons can experience a range of clinical

manifestations, from no symptoms to critical illness. Infected persons can generally be divided into categories based on the severity of their illnesses: mild illness, moderate illness, severe illness, and critical illness. In light of this, we have taken into account the corresponding four states in increasing order of illness severity. Transitions from mild illness to moderate illness, moderate illness to severe illness, and so forth are permitted since a patient is at risk of developing severe and critical illness. Keeping this in mind, we have taken into consideration the deteriorating rates from mild illness to moderate illness, moderate illness to severe illness and so on. More details are described in the notations below.

Other assumptions made in the model are as under:
(i) All normal persons are exposed to the disease.
(ii) Testing of all infected persons is done.
(iii) Clinical testing is not perfect, i.e. there may be an error in testing.
(iv) Patient is home isolated if test results are false negative while patient is hospitalised if the test results are positive.
(v) All random variables are independent of each other.

The following states are considered in the model:

S_0	Normal state
S_1	Asymptomatic state
S_2	Symptomatic state
S_3	Home isolated state
S_4	Mild disease state
S_5	Moderate disease state
S_6	Severe disease state
S_7	Critical disease state
S_8	Death state

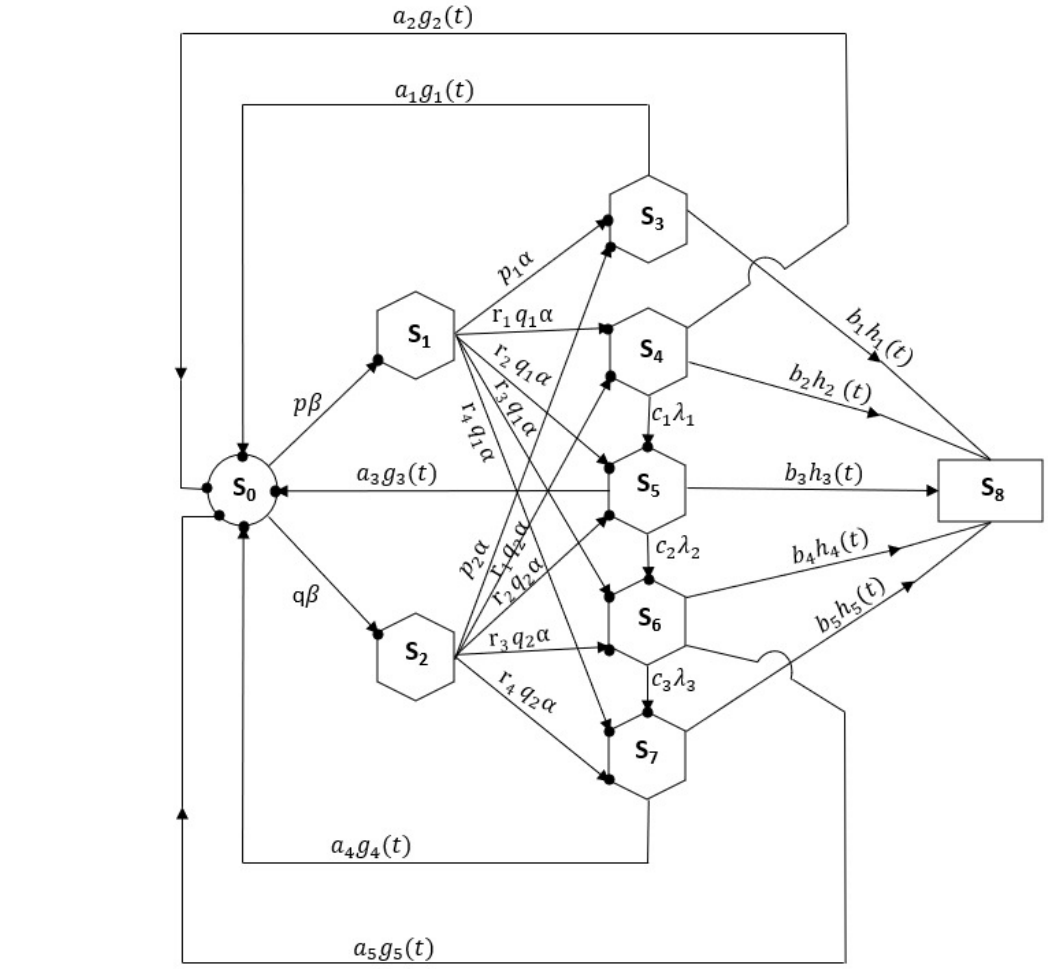
The following notation is used:

β	incidence rate
α	testing rate
$\lambda_1/\lambda_2/\lambda_3$	deteriorating rate from mild illness to moderate illness/moderate illness to severe illness/severe illness to critical illness
$g_1(t)/g_2(t)/g_3(t)/g_4(t)/g_5(t)$	probability density function of recovery time in home isolated state/mild disease state/moderate disease state/severe disease state/critical disease state
$G_1(t)/G_2(t)/G_3(t)/G_4(t)/G_5(t)$	cumulative distribution function of recovery time in home isolation/mild disease state/moderate disease state/severe disease state/critical disease state
$h_1(t)/h_2(t)/h_3(t)/h_4(t)/h_5(t)$	probability density function of time to death in home isolation/mild disease state/moderate disease state/severe disease state/critical disease state
$H_1(t)/H_2(t)/H_3(t)/H_4(t)/H_5(t)$	cumulative distribution function of time to death in home isolation/mild disease state/moderate disease state/severe disease state/critical disease state
$W_i(t)$	probability that the patient is in home isolation at instant t without passing through any other state

p/q	probability of an infected person to be asymptomatic/ symptomatic ($p+q=1$)
p_1/q_1	probability of an asymptomatically infected person to be tested false negative/positive ($p_1+q_1=1$)
p_2/q_2	probability of an symptomatically infected person to be tested false negative/positive ($p_2+q_2=1$)
$r_1/r_2/r_3/r_4$	probability that a patient is diagnosed with mild illness/ moderate illness/severe illness/critical illness ($r_1+r_2+r_3+r_4=1$)
a_2/b_2	probability that an home isolated person will recover/ move to death state ($a_1+b_1=1$)
$a_2/b_2/c_1$	probability that a person with mild illness will recover to normal state/move to death/deteriorate to moderate illness ($a_2+b_2+c_1=1$)
$a_3/b_3/c_2$	probability that a person with moderate illness will recover to normal state/move to death/deteriorate to severe illness($a_3+b_3+c_2=1$)
$a_4/b_4/c_3$	probability that a person with severe illness will recover to normal state/move to death/deteriorate to critical illness ($a_4+b_4+c_3=1$)
a_5/b_5	probability that a person with critical illness will recover to normal state/move to death state ($a_5+b_5=1$)

The following symbols/abbreviations are used:

SpO_2	Pulse oximetry
R.R.	Respiratory Rate
*	Laplace Transform symbol
**	Laplace Transform symbol
©	Laplace Convolution symbol
Ⓢ	Laplace-Stieltjes Convolution symbol



Normal State

Infected State

Death State

Figure 1: *State Transition Diagram. Possible states which an individual may occupy are depicted in the figure.*

3. Analysis

Let $q_{ij}(t)/Q_{ij}(t)$ represents probability density function/cumulative distribution function of first passage time from state S_i to state S_j without visiting any other state in $(0,t]$. Thus, the time dependent transition probabilities are given by

$$\begin{array}{lll}
q_{01}(t) = p\beta e^{-\beta t} & q_{02}(t) = q\beta e^{-\beta t} & q_{13}(t) = p_1\alpha e^{-\alpha t} \\
q_{14}(t) = r_1q_1\alpha e^{-\alpha t} & q_{15}(t) = r_2q_1\alpha e^{-\alpha t} & q_{16}(t) = r_3q_1\alpha e^{-\alpha t} \\
q_{17}(t) = r_4q_1\alpha e^{-\alpha t} & q_{23}(t) = p_2\alpha e^{-\alpha t} & q_{24}(t) = r_1q_2\alpha e^{-\alpha t} \\
q_{25}(t) = r_2q_2\alpha e^{-\alpha t} & q_{26}(t) = r_3q_2\alpha e^{-\alpha t} & q_{27}(t) = r_4q_2\alpha e^{-\alpha t} \\
q_{30}(t) = a_1g_1(t) & q_{38}(t) = b_1h_1(t) & q_{40}(t) = a_2g_2(t) \\
q_{45}(t) = c_1\lambda_1 e^{-\lambda_1 t} & q_{48}(t) = b_2h_2(t) & q_{50}(t) = a_3g_3(t) \\
q_{56}(t) = c_2\lambda_2 e^{-\lambda_2 t} & q_{58}(t) = b_3h_3(t) & q_{60}(t) = a_4g_4(t) \\
q_{67}(t) = c_3\lambda_3 e^{-\lambda_3 t} & q_{68}(t) = b_4h_4(t) & q_{70}(t) = a_5g_5(t) \\
q_{78}(t) = b_5h_5(t) & &
\end{array}$$

The steady state transition probabilities, $p_{ij} = \lim\limits_{t\to\infty} \int_0^t q_{ij}(t)\,dt$ are obtained as

$$\begin{array}{lllll}
p_{01} = p & p_{02} = q & p_{13} = p_1 & p_{14} = r_1q_1 & p_{15} = r_2q_1 \\
p_{16} = r_3q_1 & p_{17} = r_4q_1 & p_{23} = p_2 & p_{24} = r_1q_2 & p_{25} = r_2q_2 \\
p_{26} = r_3q_2 & p_{27} = r_4q_2 & p_{30} = a_1 & p_{38} = b_1 & p_{40} = a_2 \\
p_{45} = c_1 & p_{48} = b_2 & p_{50} = a_3 & p_{56} = c_2 & p_{58} = b_3 \\
p_{60} = a_4 & p_{67} = c_3 & p_{68} = b_4 & p_{70} = a_5 & p_{78} = b_5
\end{array}$$

Let T_i denote the waiting time in state S_i then the expected waiting time in state S_i is given by $\mu_i = \int_0^\infty P(T_i > t)\,dt$. Thus, the expected waiting times are obtained as

$$\begin{array}{ll}
\mu_0 = \dfrac{1}{\beta} & \mu_1 = \dfrac{1}{\alpha} \\
\mu_2 = \dfrac{1}{\alpha} & \mu_3 = -a_1g_1^{*'}(0) - b_1h_1^{*'}(0) \\
\mu_4 = \dfrac{c_1}{\lambda_1} - a_2g_2^{*'}(0) - b_2h_2^{*'}(0) & \mu_5 = \dfrac{c_2}{\lambda_2} - a_3g_3^{*'}(0) - b_3h_3^{*'}(0) \\
\mu_6 = \dfrac{c_3}{\lambda_3} - a_4g_4^{*'}(0) - b_4h_4^{*'}(0) & \mu_7 = -a_5g_5^{*'}(0) - b_5h_5^{*'}(0)
\end{array}$$

The expected waiting time in state S_i given that the next state visited is S_j, is defined as $m_{ij} = \int_0^\infty tq_{ij}(t)\,dt = -q_{ij}^{*'}(0)$. Thus, the following relations are satisfied:

$$\begin{array}{l}
m_{01} + m_{02} = \mu_0 \\
m_{13} + m_{14} + m_{15} + m_{16} + m_{17} = \mu_1 \\
m_{23} + m_{24} + m_{25} + m_{26} + m_{27} = \mu_2 \\
m_{30} + m_{38} = \mu_3 \\
m_{40} + m_{45} + m_{48} = \mu_4 \\
m_{50} + m_{56} + m_{58} = \mu_5 \\
m_{60} + m_{67} + m_{68} = \mu_6 \\
m_{70} + m_{78} = \mu_7
\end{array}$$

Theorem 1. If T_0 is the mean survival time for the patient starting in state S_0 then

$$T_0 = \frac{N}{D},$$

where

$$N = \mu_0 + p_{01}\mu_1 + p_{02}\mu_2 + p_{01}p_{13}\mu_3 + p_{01}p_{14}\mu_4 + p_{01}p_{15}\mu_5 + p_{01}p_{16}\mu_6 + p_{01}p_{17}\mu_7 + p_{02}p_{23}\mu_3 + p_{02}p_{24}\mu_4 + p_{02}p_{25}\mu_5 + p_{02}p_{26}\mu_6 + p_{02}p_{27}\mu_7 + p_{01}p_{14}p_{45}\mu_5 + p_{01}p_{15}p_{56}\mu_6 + p_{01}p_{16}p_{67}\mu_7 + p_{02}p_{24}p_{45}\mu_5 + p_{02}p_{25}p_{56}\mu_6 + p_{02}p_{26}p_{67}\mu_7 + p_{01}p_{14}p_{45}p_{56}\mu_6 + p_{02}p_{24}p_{45}p_{56}\mu_6 + p_{01}p_{15}p_{56}p_{67}\mu_7 + p_{02}p_{25}p_{56}p_{67}\mu_7 + p_{01}p_{14}p_{45}p_{56}p_{67}\mu_7 + p_{02}p_{24}p_{45}p_{56}p_{67}\mu_7$$

and

$$D = 1 - p_{01}p_{13}p_{30} - p_{01}p_{14}p_{40} - p_{01}p_{15}p_{50} - p_{01}p_{16}p_{60} - p_{01}p_{17}p_{70} - p_{02}p_{23}p_{30} - p_{02}p_{24}p_{40} - p_{02}p_{25}p_{50} - p_{02}p_{26}p_{60} - p_{02}p_{27}p_{70} - p_{01}p_{14}p_{45}p_{50} - p_{01}p_{15}p_{56}p_{60} - p_{01}p_{16}p_{67}p_{70} - p_{02}p_{24}p_{45}p_{50} - p_{02}p_{25}p_{56}p_{60} - p_{02}p_{26}p_{67}p_{70} - p_{01}p_{14}p_{45}p_{56}p_{60} - p_{01}p_{15}p_{56}p_{67}p_{70} - p_{02}p_{24}p_{45}p_{56}p_{60} - p_{02}p_{25}p_{56}p_{67}p_{70} - p_{01}p_{14}p_{45}p_{56}p_{67}p_{70} - p_{02}p_{24}p_{45}p_{56}p_{67}p_{70}.$$

Proof. Let $\phi_i(t)$ denote the cumulative distribution function of passage time from state S_i to the absorbing state.

The individual in state S_0 at $t = 0$ can reach the absorbing state at time t in two possible ways:
(i) The individual transited from state S_0 to state S_1 in time τ ($\tau < t$) and reached the absorbing state in $t - \tau$ time.
(ii) The individual transited from state S_0 to state S_2 in time τ ($\tau < t$) and reached the absorbing state in $t - \tau$ time.

Thus, we obtain
$\phi_0(t) = Q_{01}(t)\textcircled{S}\phi_1(t) + Q_{02}(t)\textcircled{S}\phi_2(t)$

Similarly, the following equations are obtained:
$\phi_1(t) = Q_{13}(t)\textcircled{S}\phi_3(t) + Q_{14}(t)\textcircled{S}\phi_4(t) + Q_{15}(t)\textcircled{S}\phi_5(t) + Q_{16}(t)\textcircled{S}\phi_6(t) + Q_{17}(t)\textcircled{S}\phi_7(t)$
$\phi_2(t) = Q_{23}(t)\textcircled{S}\phi_3(t) + Q_{24}(t)\textcircled{S}\phi_4(t) + Q_{25}(t)\textcircled{S}\phi_5(t) + Q_{26}(t)\textcircled{S}\phi_6(t) + Q_{27}(t)\textcircled{S}\phi_7(t)$
$\phi_3(t) = Q_{30}(t)\textcircled{S}\phi_0(t) + Q_{38}(t)$
$\phi_4(t) = Q_{40}(t)\textcircled{S}\phi_0(t) + Q_{45}(t)\textcircled{S}\phi_5(t) + Q_{48}(t)$
$\phi_5(t) = Q_{50}(t)\textcircled{S}\phi_0(t) + Q_{56}(t)\textcircled{S}\phi_6(t) + Q_{58}(t)$
$\phi_6(t) = Q_{60}(t)\textcircled{S}\phi_0(t) + Q_{67}(t)\textcircled{S}\phi_7(t) + Q_{68}(t)$
$\phi_7(t) = Q_{70}(t)\textcircled{S}\phi_0(t) + Q_{78}(t)$

Taking Laplace-Stieltjes transform of the above system of equations, rearranging the terms and solving the above system of equations for $\phi_0^{**}(s)$, we obtain

$$\phi_0^{**}(s) = \frac{N_1(s)}{D_1(s)}$$

where

$$N_1(s) = \begin{vmatrix} 0 & -Q_{01}^{**}(s) & -Q_{02}^{**}(s) & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & -Q_{13}^{**}(s) & -Q_{14}^{**}(s) & -Q_{15}^{**}(s) & -Q_{16}^{**}(s) & -Q_{17}^{**}(s) \\ 0 & 0 & 1 & -Q_{23}^{**}(s) & -Q_{24}^{**}(s) & -Q_{25}^{**}(s) & -Q_{26}^{**}(s) & -Q_{27}^{**}(s) \\ Q_{38}^{**}(s) & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ Q_{48}^{**}(s) & 0 & 0 & 0 & 1 & -Q_{45}^{**}(s) & 0 & 0 \\ Q_{58}^{**}(s) & 0 & 0 & 0 & 0 & 1 & -Q_{56}^{**}(s) & 0 \\ Q_{68}^{**}(s) & 0 & 0 & 0 & 0 & 0 & 1 & -Q_{67}^{**}(s) \\ Q_{78}^{**}(s) & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

and

$$D_1(s) = \begin{vmatrix} 1 & -Q_{01}^{**}(s) & -Q_{02}^{**}(s) & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & -Q_{13}^{**}(s) & -Q_{14}^{**}(s) & -Q_{15}^{**}(s) & -Q_{16}^{**}(s) & -Q_{17}^{**}(s) \\ 0 & 0 & 1 & -Q_{23}^{**}(s) & -Q_{24}^{**}(s) & -Q_{25}^{**}(s) & -Q_{26}^{**}(s) & -Q_{27}^{**}(s) \\ -Q_{30}^{**}(s) & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ -Q_{40}^{**}(s) & 0 & 0 & 0 & 1 & -Q_{45}^{**}(s) & 0 & 0 \\ -Q_{50}^{**}(s) & 0 & 0 & 0 & 0 & 1 & -Q_{56}^{**}(s) & 0 \\ -Q_{60}^{**}(s) & 0 & 0 & 0 & 0 & 0 & 1 & -Q_{67}^{**}(s) \\ -Q_{70}^{**}(s) & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{vmatrix}$$

Solving the above determinants, we get

$$\begin{aligned} N_1(s) = {} & Q_{01}^{**}(s)Q_{13}^{**}(s)Q_{38}^{**}(s) + Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{48}^{**}(s) + Q_{02}^{**}(s)Q_{23}^{**}(s)Q_{38}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{48}^{**}(s) + Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{58}^{**}(s) + Q_{01}^{**}(s)Q_{16}^{**}(s)Q_{68}^{**}(s) \\ & + Q_{01}^{**}(s)Q_{17}^{**}(s)Q_{78}^{**}(s) + Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{58}^{**}(s) + Q_{02}^{**}(s)Q_{26}^{**}(s)Q_{68}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{27}^{**}(s)Q_{78}^{**}(s) + Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{58}^{**}(s) \\ & + Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{56}^{**}(s)Q_{68}^{**}(s) + Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{58}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{56}^{**}(s)Q_{68}^{**}(s) + Q_{01}^{**}(s)Q_{16}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{26}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) + Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{68}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{68}^{**}(s) + Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) \\ & + Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) \\ & + Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{78}^{**}(s) \end{aligned}$$

$$\begin{aligned} D_1(s) = {} & 1 - Q_{01}^{**}(s)Q_{13}^{**}(s)Q_{30}^{**}(s) - Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{40}^{**}(s) - Q_{02}^{**}(s)Q_{23}^{**}(s)Q_{30}^{**}(s) \\ & - Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{50}^{**}(s) - Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{40}^{**}(s) - Q_{01}^{**}(s)Q_{16}^{**}(s)Q_{60}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{50}^{**}(s) - Q_{01}^{**}(s)Q_{17}^{**}(s)Q_{70}^{**}(s) - Q_{02}^{**}(s)Q_{26}^{**}(s)Q_{60}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{27}^{**}(s)Q_{70}^{**}(s) - Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{50}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{50}^{**}(s) - Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{56}^{**}(s)Q_{60}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{56}^{**}(s)Q_{60}^{**}(s) - Q_{01}^{**}(s)Q_{16}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{26}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) - Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{60}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{60}^{**}(s) - Q_{01}^{**}(s)Q_{15}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{25}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) \\ & - Q_{01}^{**}(s)Q_{14}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) \\ & - Q_{02}^{**}(s)Q_{24}^{**}(s)Q_{45}^{**}(s)Q_{56}^{**}(s)Q_{67}^{**}(s)Q_{70}^{**}(s) \end{aligned}$$

Mean survival time for the patient starting in state S_0 is given by

$$T_0 = lim_{s\to 0}\frac{1-\phi_0^{**}(s)}{s}$$

Using the above value of $\phi_0^{**}(s)$, we obtain

$$T_0 = \frac{N}{D},$$

where

$$\begin{aligned}N &= \mu_0 + p_{01}\mu_1 + p_{02}\mu_2 + p_{01}p_{13}\mu_3 + p_{01}p_{14}\mu_4 + p_{01}p_{15}\mu_5 + p_{01}p_{16}\mu_6 + p_{01}p_{17}\mu_7 \\ &+ p_{02}p_{23}\mu_3 + p_{02}p_{24}\mu_4 + p_{02}p_{25}\mu_5 + p_{02}p_{26}\mu_6 + p_{02}p_{27}\mu_7 + p_{01}p_{14}p_{45}\mu_5 \\ &+ p_{01}p_{15}p_{56}\mu_6 + p_{01}p_{16}p_{67}\mu_7 + p_{02}p_{24}p_{45}\mu_5 + p_{02}p_{25}p_{56}\mu_6 + p_{02}p_{26}p_{67}\mu_7 \\ &+ p_{01}p_{14}p_{45}p_{56}\mu_6 + p_{02}p_{24}p_{45}p_{56}\mu_6 + p_{01}p_{15}p_{56}p_{67}\mu_7 + p_{02}p_{25}p_{56}p_{67}\mu_7 \\ &+ p_{01}p_{14}p_{45}p_{56}p_{67}\mu_7 + p_{02}p_{24}p_{45}p_{56}p_{67}\mu_7\end{aligned}$$

and

$$\begin{aligned}D &= 1 - p_{01}p_{13}p_{30} - p_{01}p_{14}p_{40} - p_{01}p_{15}p_{50} - p_{01}p_{16}p_{60} - p_{01}p_{17}p_{70} - p_{02}p_{23}p_{30} \\ &- p_{02}p_{24}p_{40} - p_{02}p_{25}p_{50} - p_{02}p_{26}p_{60} - p_{02}p_{27}p_{70} - p_{01}p_{14}p_{45}p_{50} - p_{01}p_{15}p_{56}p_{60} \\ &- p_{01}p_{16}p_{67}p_{70} - p_{02}p_{24}p_{45}p_{50} - p_{02}p_{25}p_{56}p_{60} - p_{02}p_{26}p_{67}p_{70} - p_{01}p_{14}p_{45}p_{56}p_{60} \\ &- p_{01}p_{15}p_{56}p_{67}p_{70} - p_{02}p_{24}p_{45}p_{56}p_{60} - p_{02}p_{25}p_{56}p_{67}p_{70} - p_{01}p_{14}p_{45}p_{56}p_{67}p_{70} \\ &- p_{02}p_{24}p_{45}p_{56}p_{67}p_{70}.\end{aligned}$$

■

Theorem 2. Expected total time in home isolation for the patient starting in state S_0 is given by

$$\frac{\mu_3(p_{01}p_{13} + p_{02}p_{23})}{D},$$

where D has been already specified in Theorem 1.

Proof. Let $\psi_i(t)$ denote the probability that the patient is in home isolation at instant t, given that the patient entered state S_i at $t = 0$. Proceeding on similar lines shown in Theorem 1, we obtained the following recursive relations:

$\psi_0(t) = q_{01}(t)\copyright\psi_1(t) + q_{02}(t)\copyright\psi_2(t)$
$\psi_1(t) = q_{13}(t)\copyright\psi_3(t) + q_{14}(t)\copyright\psi_4(t) + q_{15}(t)\copyright\psi_5(t) + q_{16}(t)\copyright\psi_6(t) + q_{17}(t)\copyright\psi_7(t)$
$\psi_2(t) = q_{23}(t)\copyright\psi_3(t) + q_{24}(t)\copyright\psi_4(t) + q_{25}(t)\copyright\psi_5(t) + q_{26}(t)\copyright\psi_6(t) + q_{27}(t)\copyright\psi_7(t)$
$\psi_3(t) = W_3(t) + q_{30}(t)\copyright\psi_0(t)$
$\psi_4(t) = q_{40}(t)\copyright\psi_0(t) + q_{45}(t)\copyright\psi_5(t)$
$\psi_5(t) = q_{50}(t)\copyright\psi_0(t) + q_{56}(t)\copyright\psi_6(t)$
$\psi_6(t) = q_{60}(t)\copyright\psi_0(t) + q_{67}(t)\copyright\psi_7(t)$
$\psi_7(t) = q_{70}(t)\copyright\psi_0(t)$
where
$W_3(t) = 1 - a_1G_1(t) - b_1H_1(t)$

Taking Laplace transform of the above system of equations and solving for $\psi_0^*(s)$, we obtain

$$\psi_0^*(s) = \frac{N_2(s)}{D_1(s)},$$

where
$N_2(s) = W_3^*(s)(q_{01}^*(s)q_{13}^*(s) + q_{02}^*(s)q_{23}^*(s))$
and $D_1(s)$ has been already specified in Theorem 1.

Expected total time in home isolation for the patient starting in state S_0 is given by

$$\begin{aligned}\int_0^\infty \psi_0(t)\,dt &= lim_{s\to 0}\ \psi_0^*(s) \\ &= \frac{\mu_3(p_{01}p_{13} + p_{02}p_{23})}{D},\end{aligned}$$

where D has been already specified in Theorem 1. ■

Theorem 3. Expected total time in hospital for the patient starting in state S_0 is given by

$$\frac{1}{D}(p_{01}p_{14}\mu_4 + p_{01}p_{15}\mu_5 + p_{01}p_{16}\mu_6 + p_{01}p_{17}\mu_7 + p_{02}p_{24}\mu_4 + p_{02}p_{25}\mu_5 + p_{02}p_{26}\mu_6 + p_{02}p_{27}\mu_7 + p_{01}p_{14}p_{45}\mu_5 + p_{01}p_{15}p_{56}\mu_6 + p_{01}p_{16}p_{67}\mu_7 + p_{02}p_{24}p_{45}\mu_5 + p_{02}p_{25}p_{56}\mu_6 + p_{02}p_{26}p_{67}\mu_7 + p_{01}p_{14}p_{45}p_{56}\mu_6 + p_{02}p_{24}p_{45}p_{56}\mu_6 + p_{01}p_{15}p_{56}p_{67}\mu_7 + p_{02}p_{25}p_{56}p_{67}\mu_7 + p_{01}p_{14}p_{45}p_{56}p_{67}\mu_7 + p_{02}p_{24}p_{45}p_{56}p_{67}\mu_7),$$

where D has been already specified in Theorem 1.

Proof. Let $\chi_i(t)$ denote the probability that the patient is in hospital at instant t, given that the patient entered state S_i at $t = 0$. Proceeding on similar lines shown in Theorem 1, we obtained the following recursive relations.

$\chi_0(t) = q_{01}(t)\copyright\chi_1(t) + q_{02}(t)\copyright\chi_2(t)$
$\chi_1(t) = q_{13}(t)\copyright\chi_3(t) + q_{14}(t)\copyright\chi_4(t) + q_{15}(t)\copyright\chi_5(t) + q_{16}(t)\copyright\chi_6(t) + q_{17}(t)\copyright\chi_7(t)$
$\chi_2(t) = q_{23}(t)\copyright\chi_3(t) + q_{24}(t)\copyright\chi_4(t) + q_{25}(t)\copyright\chi_5(t) + q_{26}(t)\copyright\chi_6(t) + q_{27}(t)\copyright\chi_7(t)$
$\chi_3(t) = q_{30}(t)\copyright\chi_0(t)$
$\chi_4(t) = W_4(t) + q_{40}(t)\copyright\chi_0(t) + q_{45}(t)\copyright\chi_5(t)$
$\chi_5(t) = W_5(t) + q_{50}(t)\copyright\chi_0(t) + q_{56}(t)\copyright\chi_6(t)$
$\chi_6(t) = W_6(t) + q_{60}(t)\copyright\chi_0(t) + q_{67}(t)\copyright\chi_7(t)$
$\chi_7(t) = W_7(t) + q_{70}(t)\copyright\chi_0(t)$
where
$W_4(t) = 1 - a_2G_2(t) - c_1(1 - e^{-\lambda_1 t}) - b_2H_2(t)$
$W_5(t) = 1 - a_3G_3(t) - c_2(1 - e^{-\lambda_2 t}) - b_3H_3(t)$
$W_6(t) = 1 - a_4G_4(t) - c_3(1 - e^{-\lambda_3 t}) - b_4H_4(t)$
$W_7(t) = 1 - a_5G_5(t) - b_5H_5(t)$

Taking Laplace transform of the above system of equations and solving for $\chi_0^*(s)$, we obtain

$$\chi_0^*(s) = \frac{N_3(s)}{D_1(s)},$$

where

$$\begin{aligned} N_3(s) = {} & W_4^*(s)(q_{01}^*(s)q_{14}^*(s) + q_{02}^*(s)q_{24}^*(s)) + W_5^*(s)(q_{01}^*(s)q_{15}^*(s) + q_{02}^*(s)q_{25}^*(s) \\ & + q_{01}^*(s)q_{14}^*(s)q_{45}^*(s) + q_{02}^*(s)q_{24}^*(s)q_{45}^*(s)) + W_6^*(s)(q_{01}^*(s)q_{16}^*(s) + q_{02}^*(s)q_{26}^*(s) \\ & + q_{01}^*(s)q_{15}^*(s)q_{56}^*(s) + q_{02}^*(s)q_{25}^*(s)q_{56}^*(s) + q_{01}^*(s)q_{14}^*(s)q_{45}^*(s)q_{56}^*(s) \\ & + q_{02}^*(s)q_{24}^*(s)q_{45}^*(s)q_{56}^*(s)) + W_7^*(s)(q_{01}^*(s)q_{17}^*(s) + q_{02}^*(s)q_{27}^*(s) \\ & + q_{01}^*(s)q_{16}^*(s)q_{67}^*(s) + q_{02}^*(s)q_{26}^*(s)q_{67}^*(s) + q_{01}^*(s)q_{15}^*(s)q_{56}^*(s)q_{67}^*(s) \\ & + q_{02}^*(s)q_{25}^*(s)q_{56}^*(s)q_{67}^*(s) + q_{01}^*(s)q_{14}^*(s)q_{45}^*(s)q_{56}^*(s)q_{67}^*(s) \\ & + q_{02}^*(s)q_{24}^*(s)q_{45}^*(s)q_{56}^*(s)q_{67}^*(s)) \end{aligned}$$

and $D_1(s)$ has been already specified in Theorem 1.

Expected total time in hospital for the patient starting in state S_0 is given by

$$\begin{aligned} \int_0^\infty \chi_0(t)\,dt &= lim_{s\to 0}\chi_0^*(s) \\ &= lim_{s\to 0}\frac{N_3(s)}{D_1(s)} \end{aligned}$$

Using the above value of $N_3(s)$ and simplifying we get the required result. ■

4. Numerical Computations

Numerical computations for the mean survival time, expected total time in home isolation, and expected total time in hospital have been performed. For illustrating our model results, the waiting time distributions are assumed as exponentials, as follows: $g_i(t) \sim exp(\gamma_i)$ and $h_i(t) \sim exp(\delta_i)$ where i=1,2,...,5.

The severity levels of the disease are defined as under.

mild illness	$SpO_2 \geq 94\%$ on room air and no shortness of breath
moderate illness	$90\% \leq SpO_2 < 94\%$ on room air or 24 <R.R.$\leq$ 30 breaths per minute
severe illness	$SpO_2 < 90\%$ on room air or R.R.>30 breaths per minute
critical illness	Respiratory failure or septic shock or multiple organ dysfunction or requires life sustaining treatment

In addition, the following values for parameters are assumed:
β=0.031/day, α=0.5/day, γ_1=0.074/day, γ_2=0.071/day, γ_3=0.055/day, γ_4=0.034/day, γ_5=0.023/day, λ_1=0.12/day, λ_2=0.15/day, λ_3=0.20/day, δ_1=0.0011/day, δ_2=0.0012/day, δ_3=0.0015/day, δ_4=0.0018/day, δ_5=0.0020/day, p=0.7, q=0.3, p_1=0.74, q_1=0.26, p_2=0.18, q_2=0.82, r_1=0.83, r_2=0.07, r_3=0.06, r_4=0.04, a_1=0.98, b_1=0.02, a_2=0.85, b_2=0.05, c_1=0.10, a_3=0.75, b_3=0.08, c_2=0.17, a_4=0.65, b_4=0.15, c_3=0.20, a_5=0.1, b_5=0.9.

For the above values of parameters, we obtained mean survival time, expected total time in home isolation and expected total time in hospital and analysed how these parameters vary corresponding to perturbations in transmission rates, deteriorating rates, and death rates. The results obtained are depicted below. Figure 2-6 forecasts how variations in the transmission rate and death rates will affect the mean survival time. Figure 7 illustrates how the expected total time in home isolation changes as the recovery rate and death rate vary. Figure 8-11 predicts how perturbations in the recovery rates and deteriorating rates will affect the expected total time in hospital.

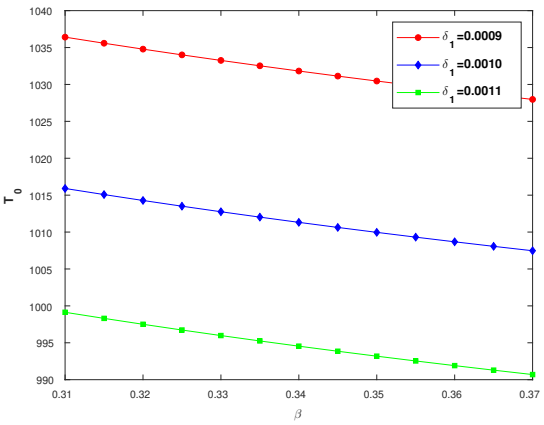


Figure 2: *A plot of T_0 with varied β and δ_1. The behaviour of the mean survival time (T_0) with respect to the transmission rate (β) for different values of death rate (δ_1) is demonstrated. From the figure, it can be seen that the mean survival time (T_0) decreases as the transmission rate (β) increases and gives lower values for higher values of death rate (δ_1).*

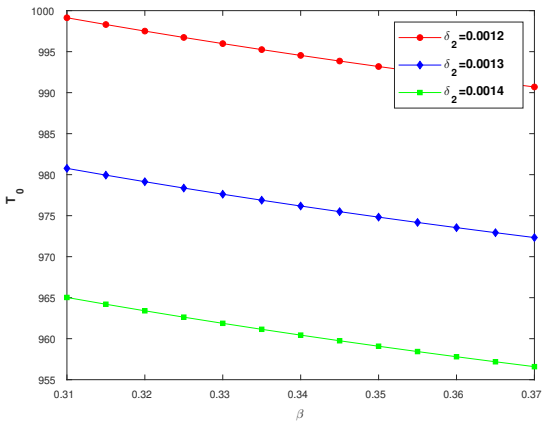


Figure 3: *A plot of T_0 with varied β and δ_2. The behaviour of the mean survival time (T_0) with respect to the transmission rate (β) for different values of death rate (δ_2) is demonstrated. From the figure, it can be seen that the mean survival time (T_0) decreases as the transmission rate (β) increases and gives lower values for higher values of death rate (δ_2).*

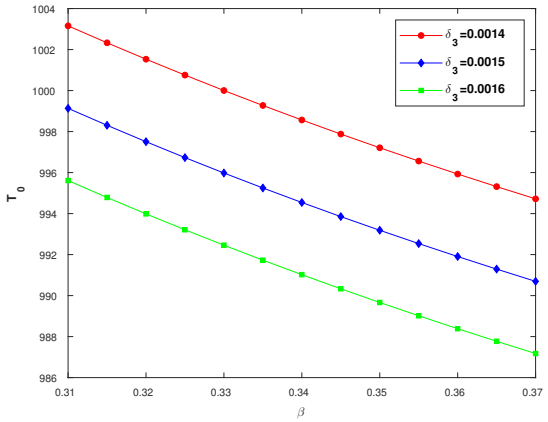


Figure 4: *A plot of T_0 with varied β and δ_3. The behaviour of the mean survival time (T_0) with respect to the transmission rate (β) for different values of death rate (δ_3) is demonstrated. From the figure, it can be seen that the mean survival time (T_0) decreases as the transmission rate (β) increases and gives lower values for higher values of death rate (δ_3).*

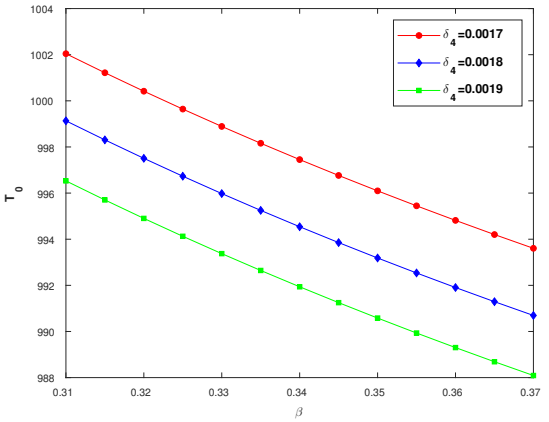


Figure 5: *A plot of T_0 with varied β and δ_4. The behaviour of the mean survival time (T_0) with respect to the transmission rate (β) for different values of death rate (δ_4) is demonstrated. From the figure, it can be seen that the mean survival time (T_0) decreases as the transmission rate (β) increases and gives lower values for higher values of death rate (δ_4).*

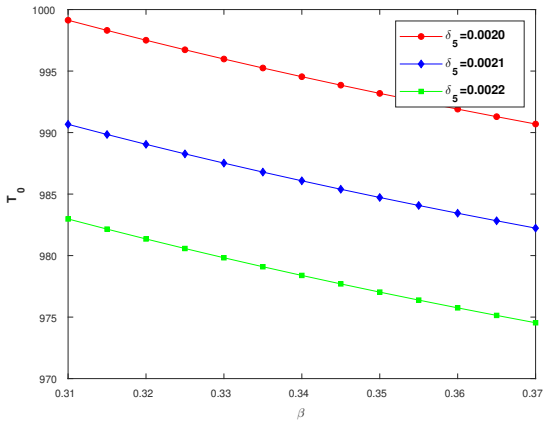


Figure 6: *A plot of T_0 with varied β and δ_5. The behaviour of the mean survival time (T_0) with respect to the transmission rate (β) for different values of death rate (δ_5) is demonstrated. From the figure, it can be seen that the mean survival time (T_0) decreases as the transmission rate (β) increases and gives lower values for higher values of death rate (δ_5).*

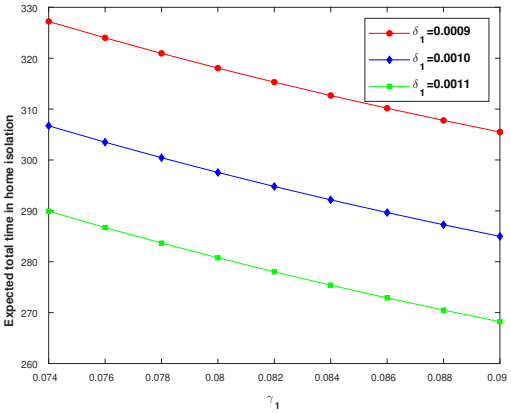


Figure 7: *A plot of expected total time in home isolation with varied γ_1 and δ_1. The behaviour of the expected total time in home isolation with respect to the recovery rate (γ_1) for different values of death rate (δ_1) is demonstrated. From the figure, it can be seen that the expected total time in home isolation decreases as the recovery rate (γ_1) increases and gives lower values for higher values of death rate (δ_1).*

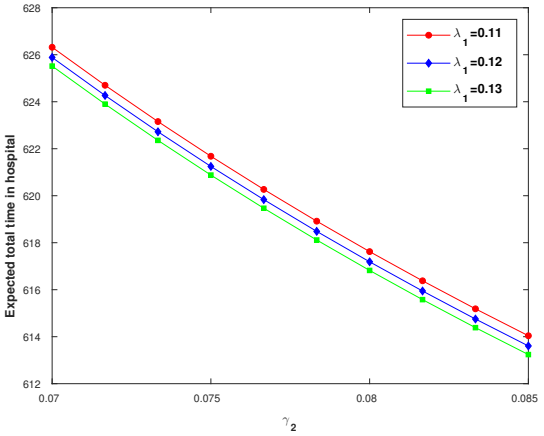


Figure 8: *A plot of expected total time in hospital with varied γ_2 and λ_1. The behaviour of the expected total time in hospital with respect to the recovery rate (γ_2) for different values of deteriorating rate (λ_1) is demonstrated. From the figure, it can be seen that the expected total time in hospital decreases as the recovery rate (γ_2) increases and gives lower values for higher values of deteriorating rate (λ_1).*

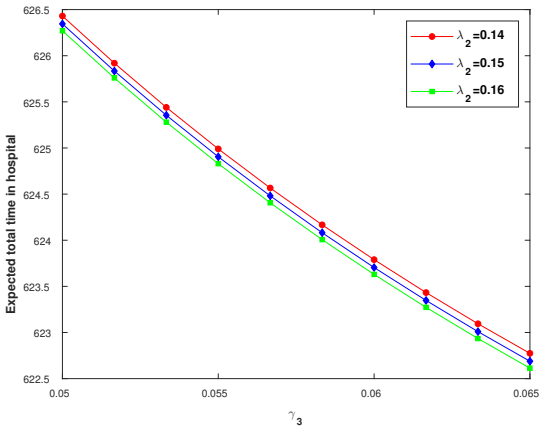


Figure 9: *A plot of expected total time in hospital with varied γ_3 and λ_2. The behaviour of the expected total time in hospital with respect to the recovery rate (γ_3) for different values of deteriorating rate (λ_2) is demonstrated. From the figure, it can be seen that the expected total time in hospital decreases as the recovery rate (γ_3) increases and gives lower values for higher values of deteriorating rate (λ_2).*

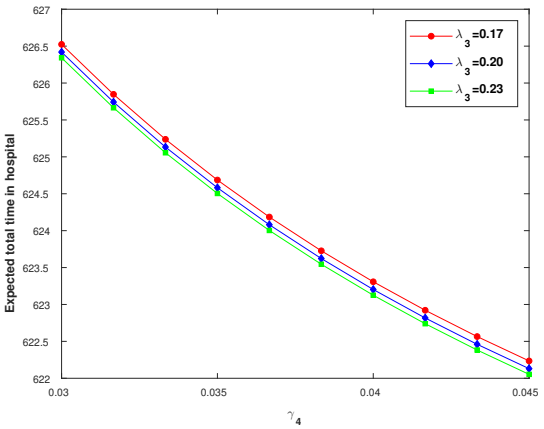


Figure 10: *A plot of expected total time in hospital with varied γ_4 and λ_3. The behaviour of the expected total time in hospital with respect to the recovery rate (γ_4) for different values of deteriorating rate (λ_3) is demonstrated. From the figure, it can be seen that the expected total time in hospital decreases as the recovery rate (γ_4) increases and gives lower values for higher values of deteriorating rate (λ_3).*

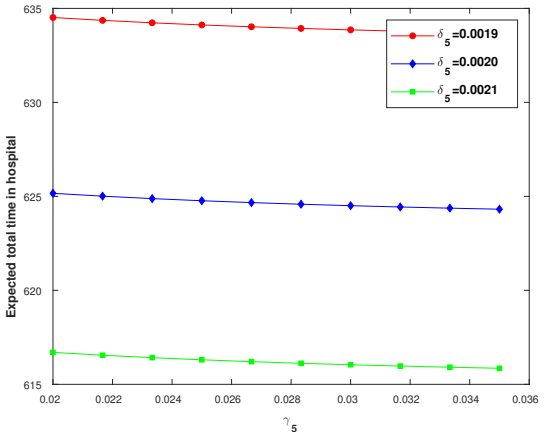


Figure 11: *A plot of expected total time in hospital with varied γ_5 and δ_5. The behaviour of the expected total time in hospital with respect to the recovery rate (γ_5) for different values of death rate (δ_5) is demonstrated. From the figure, it can be seen that the expected total time in hospital decreases as the recovery rate (γ_5) increases and gives lower values for higher values of death rate (δ_5).*

5. Conclusion

Designing prevention strategies and infection control policies can be benefitted using mathematical models of infectious diseases. On the basis of the idea of semi-Markov process, a new framework for modelling infectious diseases have been presented. The analysis of the model aids in examining the effects of various parameters on various system measures. According to the analysis presented,

it is concluded that the mean survival time declines as the disease's transmission rate rises and has lower values for greater values of death rate. The expected total time in home isolation reduces with rising recovery rates and has lower values for higher death rates. The expected total time in hospital decreases as the recovery rate increases and gives lower values for higher values of deteriorating rate. Through this article, the use and significance of semi-Markov models in understanding infectious diseases trends is demonstrated. This study may be helpful in selecting the optimal intervention tactics and creating effective infection control measures.

Declaration of Competing Interest

None.

Acknowledgement

The author Sujata Sukhija delightedly acknowledges Human Resource Development Group of Council of Scientific & Industrial Research (CSIR), India, for providing fellowship through file number 09/382(0258)/2020-EMR-I.

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