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Co-infection of Middle Eastern respiratory syndrome coronavirus and pulmonary tuberculosis

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ARTICLE INFO

Article history:
Received 14 February 2020
Revised 25 June 2020
Accepted 19 August 2020
Available online 19 August 2020
Keywords:
Epidemic model
Middle eastern respiratory syndrome coronavirus (MERS-CoV)
Reproductive number
Stability analysis
Bifurcation
Sensitivity analysis
Numerical simulation

ABSTRACT

Co-infection of Middle Eastern respiratory syndrome, coronavirus and tuberculosis, TB has a complex clinical entities that has estimated worldwide; mostly, in the Middle East. Clinical studies have shown that the propagation of disease is faster in (MERS-CoV) and TB co-infection compared to those of mono-infection. Clinical reports have shown that treatment of tuberculosis (TB) increase the risk of (MERS-CoV) reactivation. In this article, we propose an epidemic model to represents the Middle East respiratory syndrome coronavirus and tuberculosis (TB) co-infection. To do this, we first find the basic reproductive number and analyze the stability of the model. The stability conditions are obtained in term of the basic reproductive number. We also study the bifurcation analysis of the model, using the central manifold theory. Sensitivity of the basic reproductive number is performed to understand the most sensitive parameters. Finally, we show the feasibility of the analytical work, by numerical simulation.

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1. Introduction

Commonly known by its abbreviation as TB, the disease tuberculosis is a contagious bacterial infection disease which can affect any area in the body. However, it most commonly affects the lungs. The obvious reason behind this is that the bacteria causing TB, mycobacterium tuberculosis, is transmitted through the air. Though the disease has been discovered much earlier, yet it remained incurable till the recent times resulting in havoc on large scale, wiping a one third of the world population [1,2].

A new coronavirus was identified in Saudi Arabia in 2012, known as Middle Eastern respiratory syndrome coronavirus (MERS-CoV) [3]. MERS-CoV is usually associated in the Middle East with an animal source. Besides human, MERS-CoV has been found in camels in several countries. Possibly, contact with camels causes infection in human. Human to human infection spreads through coughing. MERS-CoV has spread from ill people to others through close contact, such as taking care for or living with an infected person. Since April 2012 till date, there have been a total of 536 cases with 145 deaths, a case fatality rate of 27% with the majority being reported in the Middle East (Saudi Arabia, Jordan, and Qatar) [4,5]. The people who were affected with MERS-CoV developed severe acute respiratory illness along with the symptoms of fever, cough and shortness of breath.

Co-infection of MERS-CoV and tuberculosis, TB was first reported by Alfaraj et al. [6] in Saudi Arabia. They investigated two such cases in which MERS-CoV and pulmonary TB co existed. Case first was related to a child of 13 years who showed symptoms of fever, loss of weight, coughing and sweating during night for almost 2 months. Whereas, the second one was related to a female aging 30, who was coughing and had shortness of breath as well as weight loss of 2 kg during few weeks of the disease. The two patient had pulmonary tuberculosis TB and positive MERS-CoV. So the reported study suggest that a positive MERS-CoV attract the pulmonary tuberc ulosis, TB (Table 1, Fig. 1.

Mathematical modeling and analysis are used to understand and forecast the dynamics of infectious diseases, see for instance, [8–16]. Several researchers developed various mathematical models by taking into account different biological feasible parameters to further elaborate the co-infection of the diseases in the community [17–19]. Particularly, Akinyi et al., had formulated a mathematical model elaborating the consequences of wrong diagnosis and cure of pneumonia as malaria [20]. The result of the study suggests that the diagnosis of pneumonia and malaria can accurately be done if the basic reproductive number is less then unity. Another study has been proposed by David et al., to investigate the co-dynamics of HIV/AIDS and pneumonia [21]. Similarly, Tilahun et al. [22] investigated the co-dynamics of pneumonia and typhoid

https://doi.org/10.1016/j.chaos.2020.110205
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fever diseases with optimal control and cost-effective analysis. In addition to this, various authors studied the co-infection of different infectious diseases [23–26].

Moreover, a number of case studies have also perform to study the transmission and co-infection of MERS-CoV, Assiri et al. [4], Azhar et al. [5], Alfaraj et al. [6], Abdulhaq et al. [7]. In the reported study, the authors used some statistical tools and laboratory confirm investigation rather than the theory of dynamical system.

In 2017, a case study has been done to investigate the co-infection of MERS-CoV with other respiratory diseases [6], which suggest that a person infected with MERS-CoV have more chances to attract other respiratory diseases, especially, tuberculosis (TB) and pneumonia. However, to the best of our knowledge there is no study for the co-dynamics of MERS-CoV and tuberculosis, TB. Therefore, in the current study, we will formulate and analysis the co-infection model for MERS-CoV and TB to fill the gap.

In this paper, we study a susceptible infectious and recovered epidemic model of tuberculosis, TB and MERS-CoV that describe the co-infection of two infectious diseases spreading through a single population as motivated from the fact that a person who has MERS-CoV is having more chances to attract TB as compared to susceptible one. We review some of the literature associated with tuberculosis, TB and MERS-CoV, model and their theoretical impact. The host population consists of four epidemiological classes: susceptible to both diseases (TB, MERS CoV), infectious to TB and susceptible to MERS-CoV, infectious to MERS-CoV and susceptible to TB, infectious to both diseases and recovered from both the diseases. To find the transmission potential of diseases we develop a formula for the co-infection basic reproduction number by using next generation matrix method. We use Routh Hurwitz criteria for the local stability of the co-infection model. Our model revealed that the disease-free equilibrium of the co-infection model is locally asymptotically stable when the basic reproduction number is less than one, and therefore disease dies out after some period of time. While When the basic reproduction number is greater than one, epidemiology means that the disease will prevail and persist in the population. We also investigate the model for the global stability by using geometrical approaches. Sensitivity analysis was carried out on the model parameters in order to determine their impact on the disease dynamics. The backward bifurcation in a disease model has important qualitative implication; small change in certain parameters can produce large change in equilibrium behavior. We find backward bifurcation by using central manifold theory. Numerical simulation of the co-infection model was carried out and the results are displayed graphically and discussed.

The paper is organized as follows: In Section 2, we propose a mathematical model containing non linear system of ODE, and define all parameters used in the model. In Section 3, we find bounded ness and positivity of the solution. In Section 4, we find equilibria and the basic reproductive no. In Section 5, we analyze the local and global stability for both the equilibria. In Section 6, we study the possibility of bifurcation and sensitivity analysis. We
perform numerical simulation to verify the results in Section 7. In Section 8, we give conclusion and shed some light on possible future research direction.

2. Background and the model formulation

The model propose MERS-CoV causing to camel population C(t) and also human population. We divide the human population into five classes, susceptible individuals S(t), those individuals which are infected with TB are represented by I(t), while individuals that are infected with MERS are denoted by I_m(t). Individuals who are co-infected by TB and MERS-CoV are I_{m\tau}(t). TB and MERS-CoV co-infectious recovered is also examined and are denoted by R_{m\tau}(t). The total population is classified into six different compartment. Thus the proposed model takes the following form:

\[
\begin{align*}
\frac{dS(t)}{dt} &= \pi + \omega R_{m\tau}(t) - (\gamma_t + \gamma_m + \mu)S(t), \\
\frac{dI(t)}{dt} &= \gamma_t S(t) - (\gamma_m + k_1 + \mu)I(t), \\
\frac{dI_m(t)}{dt} &= \gamma_m S(t) - (\gamma_1 + k_2 + \mu)I_m(t), \\
\frac{dR_{m\tau}(t)}{dt} &= \sigma I_m(t) - \omega R_{m\tau}(t) - \mu R_{m\tau}(t), \\
\frac{dC(t)}{dt} &= P + \tau_1 I_m(t) + \tau_2 I_{m\tau}(t) - \mu C(t). \\
\end{align*}
\tag{1}
\]

with initial condition:

\[S(0) > 0, \quad I(0) > 0, \quad I_m(0) > 0, \quad R_{m\tau}(0) > 0, \quad C(0) > 0, \]

where \(\pi\) represents the birth rate or death rate of susceptible individuals. Individuals losing their transient defence from recovered sub-class and moving to susceptible class at a rate \(\omega\). The TB infected individuals can get treatment or die due to TB with a rate \(k_1\). Similarly MERS-CoV infected individuals either can get treatment or dies due to MERS-CoV with a rate \(k_2\). The subclass infected with both TB and MERS-CoV could take cure with a rate \(\sigma\) and avail immunity for short time, one or both the disease. Each individuals can receive tuberculosis TB with a force of infection: \(\gamma_t = \frac{I}{I + I_m}\) and MERS infection with a force of infection: \(\gamma_m = \frac{I_m}{I + I_m}\).\(u\) is the rate of excretion of MERS causing from camel population. The inherent death causing rate in subclasses of the human population is \(\mu\). The magnitude of co-infection sub-class is made more intensity from infected sub-class through catching TB disease with \(\gamma_1\) infections force as well as TB infected group through catching MERS fever with \(\gamma_m\) force of infection. The MERS causing camel population \((C)\) grows due to contact with camel or caring for an infected camel with a rate \(P\) and increase from the release of virus from the individuals who are infected and those who are co-infected individuals through a rate of \(\tau_1\) and \(\tau_2\). Death rate resulting due to MERS is \(\mu_c\). In order to prove mathematical and biological feasibility, we show the fundamental properties with the help of the following results.

3. Boundedness and positivity

**Theorem 1.** The solution of the proposed model (1) is bounded.

**Proof.** Let \(N(t)\) denotes the number of total population, then \(N(t) = S(t) + I(t) + I_m(t) + R_{m\tau}(t)\). Differentiation \(N(t)\) with regards to time and putting the expression for \(\frac{dS}{dt}, \frac{dI}{dt}, \frac{dI_m}{dt}, \frac{dR_{m\tau}}{dt}, \frac{dC}{dt}\), we get

\[
\frac{dN(t)}{dt} = \pi - k_1(I + I_m + I_{m\tau}) - k_2(I + I_m + I_{m\tau}) - \mu N(t). \tag{2}
\]

If there is no death from MERS and TB then the above Eq. (2) become

\[
\frac{dN(t)}{dt} \leq \pi - \mu N(t). \tag{3}
\]

The solution of Eq. (3) and calculating it at some \(t \to \infty\), we get\(\Omega_2 = \left\{ (S(t), I(t), I_m(t), I_{m\tau}(t), R_{m\tau}(t)) | R_{m\tau}(t) \leq \frac{\pi}{\mu} \right\} \),

If there is no discharge of virus from camel then \(\frac{dC(t)}{dt} = P + \tau_1 I_m(t) + \tau_2 I_{m\tau}(t) - \mu_c C(t)\) becomes

\[
\frac{dC(t)}{dt} \leq P - \mu_c C(t). \tag{4}
\]

The solution of (4) yields

\[\Omega_2 = \left\{ (C(t) \in R_+, 0 < C(t) \leq \frac{P}{\mu_c} ) \right\} \]

\[\square\]

**Theorem 2.** If \(S_0 > 0, I_0 > 0, I_m > 0, I_{m\tau} > 0, R_{m\tau} > 0, C_0 > 0\) so all the solution \(S(t), I(t), I_m(t), I_{m\tau}(t), R_{m\tau}(t), C(t)\) are also positive.

**Proof.** Let us define \(t_1, t_2 = sup\{t > 0 : S(t) > 0, I(t) > 0, I_m(t) > 0, I_{m\tau}(t) > 0, R_{m\tau}(t) > 0, \text{ for all } t \in [0, t]\} \). Since \(S_0 > 0, I_0 > 0, I_m > 0, I_{m\tau} > 0, R_{m\tau} > 0, C_0 > 0\), thus \(t_1 > 0\) if \(t < \infty\) then necessarily \(S(t)\) is bounded. Applying alternation of constant formula, we get solution of Eq. (5),

\[S(t_1) = S(0) \exp{\int^t_0 (\gamma_1 + \gamma_m + \mu)ds} + \int^t_0 (\pi + \omega R_{m\tau}) \exp{(\gamma_1 + \gamma_m + \mu)}ds. \]

Furthermore, as the variables are positive in \([0, t_1]\), \(S(t_1) > 0\). Similarly \(I(t_1) > 0, I_m(t_1) > 0, I_{m\tau}(t_1) > 0, 0 < C(t_1) < C_0\), that is contradiction to our supposition. Thus \(t_1 = \infty\). Consequently, all the solutions are positive. \(\square\)

4. Equilibria and basic reproductive number

We discuss qualitative study of the model (1). For this we find equilibria of the model (1). There are two types of equilibria: one is the disease free equilibria and the other is endemic equilibria. The first one that is DFE of the suggested model (1) is representing by \(F_0\) and define for \(F_0 = (\text{"S}_0, 0, 0, 0, \text{C}_0)\), and

\[S_0 = \frac{\pi}{\mu}, \quad C_0 = \frac{P}{\mu_c}. \tag{6}\]

Basic reproductive number is defined as the threshold amount which analyze if an epidemic appear or the infection dies out. That is the predicted average number of recent infections produced by a single infection directly and indirectly, while being entered in a fully susceptible population. For the reproductive number, we use the method of Driessche and Watmough [27–29]. Suppose \(\chi = (k_1(t), k_m(t), k_{m\tau}(t))^T\), we have

\[
\frac{d\chi}{dt} = \mathbf{F} - \mathbf{V}. \tag{7}
\]
In Eq. (7), the matrices \( \tilde{F} \) and \( \tilde{V} \) contain the nonlinear and linear terms respectively which are expressed as

\[
\tilde{F} = \begin{pmatrix}
\frac{\gamma S - \gamma m h}{\gamma t_m} & 0 & 0 & 0 \\
0 & \frac{\nu}{\mu} & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix},
\]

\[
\tilde{V} = \begin{pmatrix}
(k_1 + \mu) h & (k_2 + \mu) h & (k_1 + k_2 + \sigma + \mu) h & (\tau_1 h + \tau_2 h - \mu_c) \\
0 & (k_2 + \mu) h & (k_1 + k_2 + \sigma + \mu) h & (\tau_2 h - \mu_c) \\
0 & 0 & (k_1 + k_2 + \sigma + \mu) h & (\tau_1 h - \mu_c) \\
0 & 0 & 0 & (\tau_1 h - \mu_c)
\end{pmatrix}.
\]

The Jacobian matrix of \( \tilde{F} \) and \( \tilde{V} \) at disease free equilibrium \( F_0 \), is given by

\[
F = \begin{pmatrix}
\frac{\epsilon \pi}{\mu} & 0 & \frac{\epsilon \pi}{\mu} & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix},
\]

\[
V = \begin{pmatrix}
(k_1 + \mu) & 0 & 0 & 0 \\
0 & (k_2 + \mu) & 0 & 0 \\
0 & 0 & (k_1 + k_2 + \sigma + \mu) & 0 \\
0 & 0 & 0 & (k_2 + \mu)
\end{pmatrix}.
\]

\( R_0 \) is therefore the spectral radius of next generation matrix \( \tilde{R} = FV^{-1} \). Hence the basic reproduction number \( R_0 \) for our proposed model (1) becomes

\[
R_0 = R_{0m} + R_{om}.
\]  

(8)

where

\[
R_{0m} = \frac{\epsilon \pi}{\mu (k_1 + \mu)},
\]

\[
R_{om} = \frac{\pi \tau_1}{\mu \mu_c k_1 (k_2 + \mu)}.
\]

The endemic equilibrium point is represented by \( E_1 = (S^*, I^*, I_{m}^*, I_{m}^{0*}, R_{m}^*) \) and it occurs when the disease present in the population, where

\[
S^* = \frac{\pi (\omega + \mu) + \omega \phi I_{m}^{0*}(t)}{(\omega + \mu)(\gamma + \gamma m + \mu)},
\]

\[
I_{m}^* = \frac{\gamma m \pi (\omega + \mu) + \omega m \phi I_{m}^{0*}(t)}{(\omega + k_1 + \mu)(\gamma + \gamma m + \mu)},
\]

\[
I_{m}^{0*} = \frac{\gamma \pi (\omega + \mu) + \gamma m \phi I_{m}^{0*}(t)}{(\omega + k_1 + \mu)(\gamma + \gamma m + \mu)},
\]

\[
R_{m}^* = \frac{2 m \gamma m \gamma (\omega + \mu) + \gamma m I_{m}^{0*}(t)}{(\omega + \mu)(\gamma + \gamma m + \mu)},
\]

\( R_{m}^{0*} = \phi I_{m}^{0*}(t) \), \( \frac{\omega}{(\omega + \mu)} \).

5. Stability analysis

To show the local asymptotic stability of the proposed model (1) at disease free equilibrium \( F_0 \), we use the following result.

**Theorem 3.** If \( R_0 < 1 \), then the model (1) at disease free equilibrium point \( F_0 \) is locally asymptotically stable, and for \( R_0 > 1 \) it is unstable.

**Proof.** The Jacobian matrix of the model (1) at disease free equilibrium point \( F_0 \) is

\[
J_1 = \begin{pmatrix}
-\mu & -A_1 & 0 & -A_1 & \omega & -A_2 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -Q_3 & 0 & 0 \\
0 & 0 & 0 & 0 & \phi & -Q_4 \\
0 & 0 & \tau_1 & \tau_2 & 0 & -\mu_0
\end{pmatrix},
\]

(9)

where \( Q_1 = (k_3 + \mu + (1 - R_{0p})) \), \( A_1 = \frac{\epsilon \pi}{\mu} \), \( A_2 = \frac{\epsilon \pi}{\mu} \), \( Q_2 = (k_2 + \mu + (1 - R_{0c})) \), \( Q_3 = (k_1 + k_2 + \sigma + \mu) \), \( Q_4 = (\omega + \mu) \). By row operation reducing the matrix (9) to echelon form, so the resulting matrix is given by

\[
J_1 = \begin{pmatrix}
-\mu & -A_1 & 0 & 0 & \omega & -A_2 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \tau_1 & \tau_2 & 0 & -\mu_0
\end{pmatrix}.
\]

The above matrix shows that all the eigenvalues are negative if \( (R_{0p}, R_{0c}) < 1 \), so it ensures the local asymptotic stability of the disease free equilibrium. □

For the global stability, we have the following results.

**Theorem 4.** For \( R_0 < 1 \), the model (1) at disease free equilibrium \( F_0 \) is globally asymptotically stable, and unstable otherwise.

**Proof.** Let \( \kappa_1 = (S(t), R_{m}(t)) \) and \( \kappa_2 = (I(t), I_{m}(t), I_{m}(t)) \) represents the number of uninfected and infected person, \([30,31]\). Define \( F_0 = (k_0, 0) \), where

\[
k_0 = \left(\frac{\pi}{R_{0m}}\right).
\]

\[
G(\kappa_1, \kappa_2) = \left(\frac{\pi + \omega R_{m}(t)-(\gamma + \gamma m + \mu)S_0}{\phi I_{m}^{0*}(t) - \omega R_{m}(t) - \mu R_{m}(t)}\right).
\]

(10)

\[
H(\kappa_1, \kappa_2) = \left(\frac{\gamma S(t) - (\gamma m + k_1 + \mu)I(t)}{\gamma m(t) - (\gamma m + k_2 + \mu)I_{m}(t)}\right).
\]

(11)

\[
d\kappa_1 = \kappa_1 - \kappa_1^1 \kappa_2^1 = \left(\frac{\pi - \mu S(t)}{\phi I_{m}^{0*}(t) - \omega R_{m}(t) - \mu R_{m}(t)}\right).
\]

From Eq. (11) as \( t \to \infty \), \( \kappa_1 \to \kappa_1^1 \). So \( \kappa_1 = \kappa_1^1 \) is globally asymptotically stable. To show the 2nd condition, i.e., \( H(\kappa_1, \kappa_2) = Bk_1 - \tilde{H}(\kappa_1, \kappa_2) \), we have

\[
Bk_1 - \tilde{H}(\kappa_1, \kappa_2) = \left(\frac{c_{11} \epsilon 0}{0 - c_{22} 0}{\left(\frac{I(t)}{I_{m}(t)} - \frac{I(t)}{I_{m}(t)}\right)}\right).
\]

(12)

where \( c_{11} = (\gamma m + k_1 + \mu), \ c_{22} = (k_2 + \mu), c_{32} = (1 - p) \gamma, c_{33} = (k_1 + k_2 + \sigma + \mu) \), so matrix \( B \) and \( \tilde{H}(\kappa_1, \kappa_2) \) are given by

\[
B = \left(\frac{c_{11} \epsilon 0}{0 - c_{22} 0}{\left(\frac{\sigma(t)}{0 - c_{33}}\right)}\right), \ \tilde{H}(\kappa_1, \kappa_2) = \left(\frac{\sigma(t)}{0 - c_{33}}\right).
\]

(13)

From Eq. (13), it is clear that the matrix \( B \) is M-matrix that is the off diagonal element are non-negative. But \( G(\kappa_1, \kappa_2) < 0 \). Thus condition 2, are not satisfied, and hence by Lemma1, the disease free equilibrium point \( F_0 \) may not be globally asymptotically stable. □

5.1. Impact of TB on MERS CoV

To described the impact of TB on MERS, we express \( R_{0m} \) in term of \( R_{0m} \)

\[
R_{0m} = \frac{\pi \tau_1}{\mu \mu_c k_1 (k_2 + \mu)}.
\]

\[
\mu = \frac{R_{0m} \mu_c k_1 (k_2 + \mu)}{\pi \tau_1}.
\]
The substitution of $\mu$ in $R_0$ leads to the following equation

$$R_0 = \frac{(\pi \mu) (R_0 \mu k (k_2 + \mu))}{(k_1 + \mu) \pi \tau_1}.$$  

To find out the impact of both disease on each other, we have

$$\frac{dR_0}{dR_0} = \frac{(\pi \mu) (\mu k (k_2 + \mu))}{(k_1 + \mu) \pi \tau_1} > 0.$$  

which shows that due to the increase in MERS cases, TB is also increases. Similarly, if the number of cases in TB increase, MERS cases also increases.

### 6. Bifurcation analysis

Here, we explore to study bifurcation analysis by applying the method introduced in [32]. Such theorem consists of two essential quantities the coefficient that is $a$ and $b$, of the usual form indicating the dynamics of the central manifold theory. The sign of the coefficient $a$ and $b$ determine the nature of bifurcation. Specially if $\alpha < 0$, $b > 0$, their is forward bifurcation; if $\alpha > 0$ and $b > 0$ the bifurcation is backward. By applying the above technique, we present the following result.

**Theorem 5.** In case $R_0 < 1$, $v_0 = \sigma \mu \mu \epsilon = (\epsilon^* \omega + \mu) > 0$. Then the system (1) undergoes the backward bifurcation at $R_0 = 1$. If $R_0 > 1$, then the system undergoes a forward bifurcation at $R_0 = 1$.

**Proof.** Firstly, the rate of transmission $\epsilon$ and $\tau_1$ are considered to be bifurcation parameters, so that $R_0 = 1$ and $R_0m = 1$ if and only if

$$\epsilon = \epsilon^* = \frac{\mu (k_1 + \mu)}{\pi}$$

and

$$\tau_1 = \frac{\mu \mu \epsilon k (k_2 + \mu)}{\pi}.$$  

Now we will make the following change of variables:

$$S = w_1, \quad l_1 = w_2, \quad l_2 = w_3, \quad l_3 = w_4, \quad R_0 = w_5, \quad C = w_6.$$  

Using the vector notation $\psi = (w_1, w_2, w_3, w_4, w_5, w_6)^T$. The TB and MERS model can be written in the form $\frac{d\psi}{dt} = \mathbf{G}(\psi)$ with $\mathbf{G} = (g_1, g_2, g_3, g_4, g_5, g_6)^T$ as shown below

$$\begin{align*}
\frac{dw_1}{dt} &= \pi + \omega \left(\psi_1 + \gamma_1 + \mu \psi_1\right), \\
\frac{dw_2}{dt} &= \gamma_1 \psi_1 - \psi_1 (\gamma_1 + \mu \psi_1), \\
\frac{dw_3}{dt} &= \gamma_3 \psi_1 - \psi_1 (\gamma_3 + \mu \psi_1), \\
\frac{dw_4}{dt} &= \gamma_3 \psi_2 - (k_1 + k_2 + \mu \psi_1), \\
\frac{dw_5}{dt} &= \phi \omega \psi - \omega \psi_5 - \mu \psi_6, \\
\frac{dw_6}{dt} &= P + \tau_1 \psi_3 + \tau_2 \psi_4 - \mu \psi_5. 
\end{align*}$$

The Jacobian matrix of model (1) at disease free equilibrium point $R_0$ is

$$J_1 = \begin{bmatrix}
-\mu & -A_1 & 0 & -A_1 & \omega & -A_2 \\
0 & -Q_1 & 0 & A_1 & 0 & 0 \\
0 & 0 & -Q_2 & 0 & 0 & A_2 \\
0 & 0 & 0 & -Q_3 & 0 & 0 \\
0 & 0 & 0 & \phi & -Q_4 & 0 \\
0 & 0 & \tau_1 & \tau_2 & 0 & -\mu \mu_\epsilon \end{bmatrix},$$

where $Q_1 = (k_1 + \mu), A_1 = \frac{\sigma \mu \epsilon}{\mu}, Q_2 = (k_2 + \mu + (1 - R_0 \mu)), Q_3 = (k_1 + k_2 + \sigma + (1 - \mu) \mu_\epsilon), Q_4 = (\omega + \mu)$. First we calculate the right eigenvector $J(E_1)$, which are denoted as

$$H = [h_1, h_2, h_3, h_4, h_5, h_6]^T.$$  

The above matrix can be written in the following form

$$-\mu h_1 - A_1 h_2 - A_1 h_4 + \omega h_5 - A_2 h_6 = 0, \quad -Q_1 h_2 + A_1 h_4 = 0,$$

$$-Q_2 h_3 + A_2 h_6 = 0, \quad -Q_3 h_4 + \phi h_4 - Q_4 h_5 = 0,$$

$$\tau_1 h_3 + \tau_2 h_4 - \mu \mu_\epsilon h_6 = 0.$$  

where $h_1 = \frac{\mu}{\mu_\epsilon} (A_2 h_5), \quad h_2 = h_5 = h_4 = 0, \quad h_3 = \frac{1}{\mu_\epsilon} Q_3 A_2 h_6 > 0, \quad h_6 = \frac{1}{\mu_\epsilon} Q_3 h_3.$

Now, we calculate the left eigen vectors of $J_1$ given by $C = (c_1, c_2, c_3, c_4, c_5, c_6)^T$. Thus

$$\begin{bmatrix}
-\mu & 0 & 0 & 0 & 0 & -2 \\
A_1 & -Q_1 & 0 & 0 & 0 & 0 \\
0 & -Q_2 & 0 & -\tau_1 & 0 & 0 \\
0 & 0 & -Q_3 & \phi & -\tau_2 & 0 \\
0 & 0 & 0 & -Q_4 & 0 & 0 \\
0 & 0 & -\mu_\epsilon & \tau_1 & \tau_2 & 0 
\end{bmatrix} \begin{bmatrix}
c_1 \\
c_2 \\
c_3 \\
c_4 \\
c_5 \\
c_6 
\end{bmatrix} = 0.$$  

which gives

$$-\mu c_1 = 0, \quad -A_1 c_1 - Q_1 c_2 = 0, \quad -Q_2 c_3 + \tau_1 c_5 = 0,$$

$$A_1 c_1 + A_2 c_2 - Q_3 c_4 + \phi c_5 + \tau_2 c_6 = 0, \quad \omega c_1 - c_4 c_5 = 0, \quad -A_2 c_1 + A_2 c_2 - \mu_\epsilon c_5 = 0.$$  

Solving Eq. (18) gives, $c_1 = c_2 = c_5 = 0, \quad c_3 = \frac{1}{\mu_\epsilon} Q_3 A_2 c_4, \quad c_6 = \frac{1}{\mu_\epsilon} (A_2 c_4).$ Hence the coefficients $a$ and $b$ are defined by

$$a = \sum_{i,j,k=1}^{n} c_i h_i h_j \frac{\partial^2 f_k}{\partial X_i \partial X_j}, \quad \psi_0, \quad 0, \quad 0, \quad 0, \quad C_0)$$

$$b = \sum_{i,j,k=1}^{n} c_i h_i h_j \frac{\partial^2 f_k}{\partial X_i \partial h_k}, \quad \psi_0, \quad 0, \quad 0, \quad 0, \quad C_0).$$

Substituting the values, which becomes

$$a = \frac{3c_4 h_3 \tau_1 \rho \omega k \tau_1 \psi_0}{\mu \mu_\epsilon A_1}, \quad b = \frac{\sigma \omega \omega^2 h_3}{\mu \mu_\epsilon Q_3}.$$  

where $\psi_0$ is defined in theorem (5). Thus, the system (1) show forward or backward bifurcation on $R_0 = 1$ depending on the sign of $\psi_0$.  

### 6.1. Sensitivity analysis

In this section we present analysis of sensitivity of a few parameters used in the proposed model. This will help us to know the parameters that have a significant effect on reproductive number. In order to do this, we apply the technic given in [33,34]. Sensitivity index of basic reproductive number $R_0$, is given by

$$\Delta R_0^h = \frac{\partial R_0}{\partial R_0} \frac{R_0}{R_0},$$

where $h$ is parameter. Since $R_0 = \max[R_0, R_0m]$, we separately, present the sensitivity analysis of $R_0$ and $R_0m$ as:
Both, $\Delta R_0$ and $\Delta R_1$, allow us to understand the change in the reproduction number with respect to the change in a parameter. Using these indices, we find the parameters that highly affect the reproduction number. It is clear from the sensitivity indices that there is a direct relation between $R_0$ and the set of parameters $S_1 = [\epsilon, \mu]$, while inverse relation with the set of parameters $S_2 = [k_1, k_2, \mu_c]$. This shows that increase in the value of parameters $S_1$ significantly increases the value of the threshold quantity, while increase in the value of parameters $S_2$ decreases the value of the threshold quantity (Table 2).

### Table 2
Sensitivity indices of different parameters.

| Parameter | Parameter definition | Sensitivity indices |
|-----------|----------------------|--------------------|
| $R_0$     | $R_0$ of TB          |                    |
| $\pi$     | Birth rate           | 1                  |
| $\epsilon$| Infectious rate of TB| 1                  |
| $\mu$     | Natural causing death rate | -1.3220 |
| $k_1$     | Death rate due to TB  | -0.95380           |
| $k_{1m}$  | Basic reproduction number of MERS only |                 |
| $k_2$     | Death rate due to MERS | -0.67796 |
| $\mu_c$   | Death rate of camel population | -0.9999 |
| $\tau_1$  | Discharge of virus from Camel | 1 |

#### 7. Numerical simulation

In this section, we solved the proposed deterministic co-infection model by using Runge-Kutta method of order 4th, see for detail [35]. To further understand the dynamical behavior of the proposed model, we used numerical simulation to verify our analytical findings. In order to do this, we assumed some value of parameters, and some are taken from published data given in Table 3, to simulate the co-infection model. The choice of numerical values of the parameter are taken in such a way that would be more
biologically feasible. We also assume the time interval is 100 months with initial population for susceptible $S(t)$, infected with TB $I_t(t)$, infected with MERS-CoV $I_{m}(t)$, co-infected with TB and MERS-CoV $I_{tm}(t)$, recovered with TB and MERS $R_{tm}(t)$ and camel population $C(t)$. The application of Runge-Kutta method of order 4th on the proposed model leads to the following system:

\[
\begin{align*}
\frac{S^{i+1} - S^i}{I} &= \pi - \omega R^i - (\gamma_1 + \gamma_m + \mu)S^{i+1}, \\
\frac{I_t^{i+1} - I_t^i}{I} &= \gamma_1 S^{i+1} - (\gamma_m + k_1 + \mu)I_t^{i+1}, \\
\frac{I_{m}^{i+1} - I_{m}^i}{I} &= \gamma_m S^{i+1} - (\gamma_m + k_2 + \mu)I_{m}^{i+1}, \\
\frac{I_{tm}^{i+1} - I_{tm}^i}{I} &= \gamma_1 I_{m}^{i+1} + \gamma_1 I_{tm}^{i+1} - (k_1 + k_2 + \sigma + \mu)I_{tm}^{i+1}, \\
\frac{R_{tm}^{i+1} - R_{tm}^i}{I} &= \sigma I_{tm}^{i+1} - \omega R_{tm}^{i+1} - \mu R_{tm}^{i+1}, \\
\frac{C^{i+1} - C^i}{I} &= P + \tau_1 I_{tm}^{i+1} + \tau_2 I_{tm}^{i+1} - \mu_c C^{i+1}.
\end{align*}
\]

Table 3

| Notation | Value | Source | Parameter | Value | Source |
|----------|-------|--------|-----------|-------|--------|
| $\phi$   | 0.09  | estimated | $\mu$     | 0.022 | estimated |
| $\omega$ | 0.026 | estimated | $k_1$      | 0.0002 | [5]     |
| $k_2$    | 0.05  | estimated | $\sigma$   | 0.065 | [36]   |
| $\mu_c$  | 0.023 | estimated | $\tau_1$   | 0.04  | [37]   |
| $\gamma_1$ | 0.004 | estimated | $P$        | 0.014 | estimated |
| $\epsilon$ | 0.01  | estimated | $\omega$   | 0.008 | estimated |

Fig. 3. The variation of different parameters and its effect on the basic reproductive number.

7.1. Algorithm

Step 1: $S(0)=0, I_t(0) = 0, I_{m}(0) = 0, I_{tm}(0) = 0, R_{tm}(0)=0, C(0) = 0$.

Step 2: for $i = 1, 2 \ldots n - 1$.

\[
\begin{align*}
S^{i+1} &= \frac{S^i}{1 + I(\gamma_1 + \gamma_m + \mu)} + \frac{\ln - \ln R^i}{1 + I(\gamma_1 + \gamma_m + \mu)}, \\
I_t^{i+1} &= \frac{I_t^i}{1 + I(\gamma_1 + k_1 + \mu)} + \frac{I_t(\gamma_1 + \gamma_m + \mu)}{1 + I(\gamma_1 + \gamma_m + \mu)}, \\
I_{m}^{i+1} &= \frac{I_{m}^i}{1 + I(\gamma_m + k_2 + \mu)} + \frac{I_m(\gamma_1 + \gamma_2 + \mu)}{1 + I(\gamma_1 + \gamma_2 + \mu)}, \\
I_{tm}^{i+1} &= \frac{I_{tm}^i}{1 + I(\gamma_1 + k_2 + \mu)} + \frac{I_{tm}(\gamma_1 + \gamma_2 + \mu)}{1 + I(\gamma_1 + \gamma_2 + \mu)}, \\
R_{tm}^{i+1} &= \frac{R_{tm}^i}{1 + I(\omega + \mu)} + \frac{I_{tm}(\omega + \mu)}{1 + I(\omega + \mu)}, \\
C^{i+1} &= \frac{C^i}{1 + I_{tm}(\omega + \mu)} + \frac{I_{tm}(\omega + \mu)}{1 + I_{tm}(\omega + \mu)}.
\end{align*}
\]

Step 3: for $i = 1, 2, 3, \ldots, n - 1$, write $S^*(t_i) = S^*, I_t^*(t_i) = I_t^*, I_{m}^*(t_i) = I_{m}^*, R_{tm}^*(t_i) = R^*, C^*(t_i) = C^*$.

Once we execute the above algorithm with the help of Matlab software, we generate the graphs presented in Figs. 4 and 5, which represent the dynamics of susceptible (S(t)); infected with TB (I_t); infected with MERS-CoV (I_{m}(t)); co-infectious with TB and MERS-CoV (I_{tm}(t)); recovered with TB and MERS-CoV (R_{tm}(t)); and camel population (C(t)). Clearly, the solution trajectories of the compartmental population reaches to its equilibrium position, which ensure the
Fig. 4. The plots demonstrate the time dynamics of different compartmental population (susceptible, TB infected, MERS infected and Co-infected).

Fig. 5. The plots demonstrate the time dynamics of different compartmental population (recovered and camel population).

stability of the proposed model. Moreover, the biological interpretation of these results states that if the value of basic reproductive number is less than one, then the susceptible population decreases, while then become stable and shows that there will be always stable susceptible population, see Fig. 4a. The dynamics of $k(t)$, $m(t)$, $l_m(t)$ and $R_m(t)$ reveals that the number of these populations will be decreases and reaches to zero as shown in Figs. 4a–5a, while the dynamics of camel population describes that the camel population decreases up to 60 days while then reaches to its equilibrium position, which ensure that there will be always camel population as shown in Fig. 5. Which ensure the stability of the proposed model. One of the important factor is to find the relative
impact of the basic reproductive number to epidemic parameters as shown in Figs. 4 and 5.

8. Conclusion

In this paper, we developed a mathematical model to represent the Middle East respiratory syndrome and tuberculosis (TB) co-infection. We studied different mathematical analysis including positivity, boundedness and biological feasibility of the proposed model to investigate the well posedness of the model. The important quantity i.e., the basic reproductive ratio ($R_0$) is the key to the transmission dynamics, by which major epidemic may be prevented and prospects for the eradication of an infection. We find the basic reproductive number by using next generation matrix method and analyze the stability of equilibria. The condition of stability are obtained in term of the basic reproductive number. For local stability we used linearization and Routh-Harwitz criteria, while for the global stability we used geometrical approach. We also study the bifurcation analysis of the model using the central manifold theory. Sensitivity of the basic reproductive number is performed to understand the most sensitive parameters. On the basis of stability analysis. Finally all the theoretical results are supported with the help simulations and for easy understanding for general readers.

Our analytical results show that the susceptible $S(t)$, infected with $TB_{I_1}(t)$, infected with $MERS-CoV_{I_1}(t)$, co-infected with $TB$ and $MERS-CoV_{I_2}(t)$ and recovered with $TB$ and $MERS-CoV$ converge to equilibrium point. Which ensure the stability of the proposed model.

We also give clinical justification of patient having positive $MERS-CoV$ and pulmonary tuberculosis TB. In future, we are planning to develop an optimal mechanism on the basis of local dynamics and sensitivity analysis. This control strategy will help that how to eradicate the infection from the community. Work on such issue is in progress and will be reported soon in the form of a new article.

Declaration of Competing Interest

None.

CRedit authorship contribution statement

Bibi Fatima: Conceptualization, Data curation, Writing - original draft. Gul Zaman: Conceptualization, Data curation, Writing - original draft.

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