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Decoding the double trouble: A mathematical modelling of co-infection dynamics of SARS-CoV-2 and influenza-like illness

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A B S T R A C T

After the detection of coronavirus disease 2019 (Covid-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, Hubei Province, China in late December, the cases of Covid-19 have spiralled out around the globe. Due to the clinical similarity of Covid-19 with other flulike syndromes, patients are assayed for other pathogens of influenza like illness. There have been reported cases of co-infection amongst patients with Covid-19. Bacteria for example Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumonia, Legionella pneumophila etc and viruses such as influenza, coronavirus, rhinovirus/enterovirus, parainfluenza, metapneumovirus, influenza B virus etc are identified as co-pathogens.

In our current effort, we develop and analysed a compartmental based Ordinary Differential Equation (ODE) type mathematical model to understand the co-infection dynamics of Covid-19 and other influenza type illness. In this work we have incorporated the saturated treatment rate to take account of the impact of limited treatment resources to control the possible Covid-19 cases.

As results, we formulate the basic reproduction number of the model system. Finally, we have performed numerical simulations of the co-infection model to examine the solutions in different zones of parameter space.

1. Introduction

Coronavirus belongs to a group of enveloped virus with a single-stranded RNA and viral particles bear a resemblance to a crown from which the name originates. It belongs to the order of Nidovirales, family of Coronaviridae, and subfamily of Orthocoronavirinae (Carlos et al., 2020). It can infect the mammals, including humans, giving rise to mild infectious disorders, sporadically causing to severe outbreaks clusters, such as those brought about by the "Severe Acute Respiratory Syndrome" (SARS) virus in 2003 in mainland China (Gralinski and Menachery, 2020).

After the first reported case of new coronavirus disease outbreak in Wuhan, Hubei province, People’s Republic of China, the virus has progressively disseminated to different countries in the world (Lai et al., 2020). WHO declared it as a global pandemic on 11 March, 2020 (Cucinotta and Vanelli, 2020). This disease can spread from person-to-person through the breathing in of respiratory droplets from an infected person or having the direct contact with contaminated surfaces (Bai et al., 2020).

The ending season and the culminating severity of the current Covid-19 pandemic wave are still unknown and unsettled issue. Meanwhile, the influenza season has collided with the current pandemic that could pave the way for more challenges. This possesses a larger threat to public health domain. It is still uncertain how the seasonal influenza-like illness (ILI) will have an impact on the long-term effects on the course of Covid-19 pandemic. Both viruses share similarities in transmission characteristics and alike clinical symptoms. ILI and Covid-19 have been reported to cause respiratory infection. The interplay between ILI and Covid-19 have been a major concern (Konala et al., 2020). An emerging study from England has shown that fatality amongst the people infected with both ILI and Covid-19 are twice as that of someone infected with the new coronavirus only (Iacobucci, 2020). An investigation conducted by the Public Health England (PHE) has shown that people infected with the two viruses were having higher risk of severe illness during the period from January to April 2020. According to the same analysis, most cases of co-infection occurred in older people, and the mortality rate was high. Reports from the USA point out that co-infection between Covid-19 and other respiratory
pathogens are notably more common compared to the initial data what suggest such an interplay is rare found in China (Kim et al., 2020; Chen et al., 2020). The authors in Hazra et al. (2020) report the co-infections between Covid-19 and other respiratory pathogens at a large urban medical centre in Chicago, Illinois. A study (Burrel et al., 2021) reveals that 7% of SARS-CoV-2-positive patients share the burden of co-infection with other respiratory viruses. According to that study the detection of other respiratory viruses in patients during this pandemic assumes the Covid-19 co-infection. The authors in Alosaimi et al. (2021) note that high prevalence of influenza-Covid-19 co-infection in their study. In Singh et al. (2020), the authors describe the cases of influenza and Covid-19 co-infection. During the last winter and autumn, the co-circulation of influenza-Covid-19 has taken a toll on the health of the patients and taxing the intensive care capacity (Covin and Rutherford, 2020; Belongia and Osterholm, 2020). The authors in the study (Bai et al., 2021) mention that co-infection with influenza A virus enhances the infectivity of Covid-19. This is undoubtedly, a significant threat that co-infection of ILI and Covid-19 possess.

Proper and appropriate nursing and treatment processes can significantly reduce the outcome of epidemics in society. In traditional epidemiological modelling assumption, the treatment rate is hypothesised to be constant or correspond to the number of infected people and the recovery rate reckons on the available medical resources such as test kits, ventilators, nursing facilities, efficiency of treatment etc. In the course of the ongoing pandemic, we have noticed how this pandemic has stretched the healthcare systems of different countries around the globe while registering high mortality (Cavallino et al., 2020; Armocida et al., 2020; Spivack, 1993; Gai and Tobe, 2020). In the classical epidemiological models, it is very common to use the treatment function as \( T(\frac{I}{\eta}) \), where \( \eta \) is positive but in the situation of sudden epidemic or pandemic when the infected population is very large then it is not always possible to provide such a type of treatment which is proportional to the infected number of individuals and \( I \) is the number of infected people. To circumvent the crux, the authors in Wang and Ruan (2004) have introduced a constant treatment rate of the form and demonstrated different bifurcations. But to sustain such a constant treatment rate might be plausible when there are a small number of infected individuals as the medical resources are limited (Griffin, 2019). Following this, the authors in Zhou and Fan (2012), Zhonghua and Yaohong (2010), Zhang and Liu (2008) have modified the treatment rate by taking account of Holling type II functional response as given below: \( T(\frac{I}{\eta}) = \frac{\eta}{1+\frac{I}{\gamma}} \), and have explored the model dynamics to understand the importance of limited medical resources and facilities in the dissemination of infectious diseases. It is important to note that this function is clearly an increasing function of \( I \) and is bounded above by the least upper bound \( \eta/\gamma \). This functional form of saturated treatment can provide a better rationale for different disease outbreaks such as SARS, Dengue etc (Zhou and Fan, 2012) in a new region because we know from our ongoing Covid-19 pandemic experience that in the beginning of an outbreak there is a lack of effective treatment due to either negligence or lack of knowledge about the disease. But afterwards the treatment is being increased with the gain of knowledge about the disease as well scaling up medical facilities (Barlow et al., 2021). Eventually, the treatment rate is outstretched to its maximum given the boundedness of medical resources of any country (Armocida et al., 2020). Here, \( \eta \) represents cure rate and \( \gamma \) denotes the extent of the effect of the infected individuals being delayed for treatment (Zhonghua and Yaohong, 2010).

Epidemiological models are quite beneficial to examine the co-infection dynamics and to estimate the treatment facilities. There are several studies concentrating on the coexistence of two infectious agents in the susceptible hosts (Blyuss and Krynychko, 2005; Mallela et al., 2016; Asaduzzaman et al., 2015; Tilahun, 2019). The authors in Arefin et al. (2020) have proposed a mean-filed based mathematical model that includes the simultaneous spreading of two strains of an ILI and the acceptance of vaccination which is based on evolutionary game theory in an infinite and well-mixed population. Recent studies compiled in Tanimoto (2021), have demonstrated how do the behavioural strategies can potentially minimise the individual risk as well as introduced the idea of universal dilemma strength. In Gao et al. (2016), the authors have proved a sufficient condition for coexistence of two infectious diseases. In the same vein, the authors in Tang et al. (2016) have proposed a new mathematical model Zika-dengue model while describing coupled dynamics of Zika-dengue. The authors in Merler et al. (2008) have asserted that pandemic outbreaks can possibly be controlled by co-infection with other acute respiratory infections that enhances the transmissibility of influenza virus. These suggest that co-infection can potentially change the course of current ongoing pandemic and induce multiple waves (Cacciapaglia et al., 2021; Fisayo and Tsukagoshi, 2021).

The basic reproduction number \( R_0 \) is a critical metric in epidemiology and it is used to determine whether a disease will persist in a population or not (Diekmann et al., 2010). Although it is a very useful threshold, it comes with some restrictions too. Many diseases are endemic to certain regions around the globe and henceforth, giving rise to the cases of co-infection in the communities. Therefore, it becomes necessary to study invasion reproductive numbers (IRNs) (Olawoyin and Kribs, 2019; Nuño et al., 2007; Britnee Crawford, 2009). It is defined as the number of secondary infections produced by an infected individual in a population where one or more other pathogens are endemic. This critical threshold has similar behaviour as of \( R_0 \), i.e. if the IRN of an infectious agent is larger than 1, then the pathogen can transmit in a population infected with other diseases.

Since the first pneumonic case of Covid-19, reported in Wuhan City, Hubei Province, China, the world is witnessing the ravaging impact of this global pandemic. It is acknowledged that Indian Government has implemented timely control measures to mitigate the spread of this pandemic. However, in the current situation, medical resources are in a critical need and especially for an ethnically diverse country like India. This has in fact left an influence in the pattern of Covid-19 dissemination. The interplay of Covid-19 and other ILI, is of utmost importance as the cases of co-infection induces a higher cases of mortality. From the perspective of public health control, it is significant to quantify and analyse the burden of co-infection on the medical resources and consequently help to curb the cases of Covid-19. To address this major issue, we have proposed a deterministic dynamic model featuring the co-infection in a saturated medical facility. The primary goal of this current endeavour is to investigate the impact of co-infection in the dynamics of Covid-19. Additionally, we derive the analytical expression of IRN to understand the influence of ILI on the potential spread of Covid-19. We also perform the sensitivity analysis to figure out the essential parameters while taking account of limited medical resources in the modelling framework.

2. Model formulation and description

The host population is \( N \) and we divide the population into the following classes according to their health status: susceptible (\( S_H \)), infected with Covid-19 only (\( I_C \)), infected with ILI only (\( I_F \)), co-infected (infected with Covid-19 and ILI simultaneously) (\( R_{CF} \)), recovered from Covid-19 (\( R_C \)), recovered from ILI (\( R_F \)), and recovered from co-infection (\( R_{CF} \)). In our model \( s_H \) represents the constant recruitment rate, \( \mu_H \) is the natural death rate, \( \alpha \) and \( \beta \) denote the effective transmission probability rates with which susceptible individuals become infected with Covid-19 and ILI, respectively. We also take account of the transmission probabilities to be infected only with Covid-19, ILI or both diseases after having the contact with a co-infected individuals as: \( a(1−\beta), (1−a)\beta \) and \( a\beta \). We also include the disease induced death rates into our model. \( \delta_C, \delta_F \) and \( \delta_{CF} \) represent the death rates for the Covid-19, ILI and co-infected individuals, respectively. Natural recovery rates for the Covid-19, ILI and co-infected individuals are denoted as \( T_C, T_F \).
and \( \gamma_{CF} \). We further consider a saturated treatment function rate as 
\[
h(I_F) = \frac{a_I}{1 + \alpha I_F},
\]
where \( J = C, F \) and \( CF \) respectively. We have not taken account of reinfection and exposed state and henceforth it is of SIR type model. To construct the ODE based co-infection model, we have followed Blyuss and Kryuchko (2005), Gao et al. (2016). We present the schematic diagram of the model (1) in the Fig. 1.

The model equations are following:

\[
\begin{align*}
\frac{dS_H}{dt} &= \lambda_H - \mu_H S_H - \alpha(1 - \beta) + \beta(1 - a) + a \beta S_H I_C F \\
\frac{dI_C}{dt} &= a S_H I_C + a(1 - \beta) S_H I_C F - (\mu_H + \delta_C + \gamma_C) I_C \\
\frac{dR_C}{dt} &= \gamma_C I_C + h(I_C) - \mu_H R_C \\
\frac{dR_F}{dt} &= \gamma_F I_F + h(I_F) - \mu_H R_F.
\end{align*}
\]

In this paper, we further explore the SIR epidemic model with saturated treatment function as 
\[
h(I_F) = \frac{a_I}{1 + \alpha I_F}, \quad \text{where} \quad J = C, F \text{ and } CF \text{ respectively.}
\]

### 3. Qualitative analysis

#### 3.1. Infectious model with Covid-19 only

In this subsection, analytical findings are made taking into consideration SARS Covid-19 only. The model equations are following:

\[
\begin{align*}
\frac{dS_H}{dt} &= \lambda_H - \mu_H S_H - \alpha S_H I_C \\
\frac{dI_C}{dt} &= a S_H I_C - \mu_H I_C - \delta_C I_C - \gamma_C I_C - h(I_C) \\
\frac{dR_C}{dt} &= \gamma_C I_C + h(I_C) - \mu_H R_C,
\end{align*}
\]

#### 3.1.1. Invariant region

Total population is \( N_C = S_H + I_C + R_C \). Differentiating w.r.t time t and substituting the required expressions, we get:

\[
\frac{dN_C}{dt} \leq \lambda_H - \mu_H N_C.
\]

After solving Eq. (3) provides the invariant region as,

\[
\Psi = (S_H, I_C, R_C) \in \mathbb{R}^3 : 0 \leq N_C \leq \frac{\lambda_H}{\mu_H}
\]

Hence, the solution set is bounded in \( \Psi \).

### Table 1. Parameters used in the model (1).

| Parameter | Description | Value or range | References |
|-----------|-------------|----------------|------------|
| \( s_H \) | Recruitment rate. | Varies over states | Sardar et al. (2020) |
| \( \mu_H \) | Natural mortality rate | Varies over states | Sardar et al. (2020) |
| \( \gamma_C \) | Recovery rate of Covid-19 | Varies over states | Sardar et al. (2020) |
| \( \gamma_E \) | Average case fatality rate of Covid-19 | Varies over states | Sardar et al. (2020) |
| \( a \) | Covid-19 transmission probability | \([0.09, 0.89]\) | Mahajan et al. (2020) |
| \( \tau_F \) | Recovery rate of ILI | \([0.071, 0.099]\) | Blyuss et al. (2018) |
| \( \alpha \) | Average case fatality rate of ILI | \([0.01, 0.021]\) | Blyuss et al. (2018) |
| \( \beta \) | ILI transmission probability | \([0.01, 0.78]\) | Kharis and Amidii (2018) |
| \( \gamma_{CF} \) | Recovery rate of co-infection | Assumed | |
| \( \delta \) | Average case fatality rate of co-infection | \([0.0189, 0.0332]\) | Nadim and Chattopadhyay (2020) |
| \( \eta \) | Cure rate | \([0.2, 0.95]\) | Sezer et al. (2017) |
| \( \zeta \) | Extent of saturation | \([0.008, 0.25]\) | Sezer et al. (2017) |

### 3.1.2. Positivity of solution

Utilising the first equation of system (2) and after rewriting it as,

\[
\frac{dS_H}{dt} \geq S_H(-\mu_H - a I_C).
\]

On evaluating, it yields,

\[
S_H \geq S_H(0) \exp\left(-\frac{\mu_H + a I_C}{\mu_H} t\right).
\]

Similarly, the result follows for other equations proving the positivity of solutions.

### 3.1.3. Disease free equilibrium (DFE) and basic reproduction number \( R_{0C} \)

On substituting \( I_C = 0 \), system (2) possesses the disease free equilibrium point \( (\frac{dS_H}{dt}, 0, 0) \). Thereby, \( R_C \) is evaluated using the next generation matrix method approach as,

\[
R_C = \frac{a \lambda_H}{\mu_H (\mu_H + \delta_C + \gamma_C + \eta)}.
\]

### 3.1.4. Local stability of DFE

**Theorem 1.** The DFE of system (2) is locally asymptotically stable if \( R_{0C} < 1 \) and unstable if \( R_{0C} > 1 \).

**Proof.** The variational matrix governing the system at DFE is;

\[
J_C = \begin{bmatrix}
-\mu_H & -a \lambda_H & 0 \\
0 & -\mu_H - \mu_H - \delta_C - \gamma_C - \eta & 0 \\
0 & \gamma_C + \eta & -\mu_H
\end{bmatrix}.
\]

The eigenvalues are given by \( \lambda_1 = -\mu_H, \lambda_2 = -\mu_H \) with \( \lambda_3 = \frac{a \lambda_H}{\mu_H} - \mu_H - \delta_C - \gamma_C - \eta = R_{0C} - 1 \) having real negative part if and only if \( R_{0C} < 1 \) which proves the theorem.
3.1.5. Global stability of DFE

**Theorem 2.** The DFE of system (2) is globally asymptotically stable if $R_0 < 1$.

**Proof.** Define Lyapunov function as;

$$L = a \cdot I_C,$$

$$\frac{dL}{dt} = a \cdot s_H \cdot y_C - a \cdot (\mu_H + \delta_C + \gamma_C + h(I_C))$$

$$\Rightarrow \frac{dL}{dt} = (a \cdot s_H) / (\mu_H + \delta_C + \gamma_C + h(I_C)).$$

$$\frac{dL}{dt} < 0$$ if $R_0 < 1$.

Hence, the result follows.

3.1.6. Endemic equilibrium analysis

The endemic equilibrium is $E^*_f = (S^*_f, I^*_C, R^*_C)$ where, $S^*_f = \frac{\lambda_H}{\mu_H + a \cdot \sigma_C}$, $R^*_C = \frac{S^*_f}{1 + \frac{\lambda_H}{\mu_H + a \cdot \sigma_C}}$ and $I^*_C$ is a positive root of the quadratic equation,

$$I^*_C = b_1 I^*_C + b_2 = 0,$$

where $b_1 = \mu_H \cdot a + a + \frac{a \cdot s_H \cdot \gamma_C}{\mu_H + a \cdot \sigma_C}$ and $b_2 = (1 - R_0) \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C} \left( \frac{\lambda_H}{\mu_H + a \cdot \sigma_C} + \gamma_C \right)^2.$

**Theorem 3.** The endemic equilibrium is globally stable in region $\phi$ if,

$$I. \mu_H (\mu_H + \delta_C + \gamma_C - \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C}) > a \cdot s_H \cdot \gamma_C,$$

$$II. \mu_H (\mu_H + \delta_C + \gamma_C - \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C}) > \frac{\gamma_C}{\delta_C} \left( \frac{\lambda_H}{\mu_H + a \cdot \sigma_C} + \gamma_C \right)^2.$$

**Proof.** Define $V = \frac{1}{2} (S_H - S^*_f)^2 + \frac{1}{2} (I_C - I^*_C)^2 + \frac{1}{2} (R - R^*_C)^2$. Differentiating with respect to time $t$, we get,

$$\frac{dV}{dt} = (S_H - S^*_f) \frac{dS_H}{dt} + (I_C - I^*_C) \frac{dI_C}{dt} + (R - R^*_C) \frac{dR_C}{dt}. $$

On substituting the required expressions and simplifying, we get,

$$\frac{dV}{dt} = (S_H - S^*_f)^2 \left[ \mu_H - \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C} \right] (I_C - I^*_C)^2 \left[ \mu_H - \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C} \right] (R_C - R^*_C)^2 \left[ \mu_H - \frac{a \cdot s_H}{\mu_H + a \cdot \sigma_C} \right].$$

Thus, $\frac{dV}{dt}$ is negative definite in the region $\phi$ subject to the fulfillment of conditions I and II.

4. Co-infection model system

In this section we find the basic reproduction number, $R_0$ of the entire model system as defined in (1) after following the Next Generation Matrix (NGM) method as described in Diekmann et al. (2010). $R_0$ characterises the average number of new reported cases of an infection caused by one infected individual, in a completely susceptible population. Entries relate to the numbers of newly infected individuals in the various categories in consecutive generations.

To apply the NGM approach, we notice that the variables associated with Covid-19, ILL and co-infected stages are $(I_C, I_F, I_{CF})$ and $S_H$ as the susceptible compartments. Denoting $Y_I = (I_C, I_F, I_{CF})$ and $Y_H = S_H$, we can rewrite the associated system as the difference between the new-infection terms (inflow) and outflow terms then we have,

$$\frac{dy_I}{dt} = F_{CF}(Y_S, Y_I) - V_{CF}(Y_S, Y_I)$$

$$F_{CF} = \begin{bmatrix} a \cdot s_H \cdot y_C + (a \cdot (1 - \beta) \cdot s_H \cdot I_C) - (\beta I_F + I_{CF}) I_C \\ \beta \cdot s_H \cdot y_C + (\beta \cdot (1 - a) \cdot s_H \cdot I_C) - (a \cdot I_C + I_{CF}) I_F \\ a \cdot s_H \cdot I_F + (a \cdot I_F + a \cdot I_{CF}) I_C + (a \cdot I_C + a \cdot I_{CF}) I_F \\ \mu_H I_C + \delta_C I_C + \gamma_C I_C + h(I_C) \\ \mu_F I_F + \delta_F I_F + \gamma_F I_F + h(I_F) \\ \mu_{CF} I_{CF} + \delta_{CF} I_{CF} + \gamma_{CF} I_{CF} + h(I_{CF}) \end{bmatrix}$$

$$V_{CF} = \begin{bmatrix} a \cdot s_H \cdot y_C + (a \cdot (1 - \beta) \cdot s_H \cdot I_C) - (\beta I_F + I_{CF}) I_C \\ \beta \cdot s_H \cdot y_C + (\beta \cdot (1 - a) \cdot s_H \cdot I_C) - (a \cdot I_C + I_{CF}) I_F \\ a \cdot s_H \cdot I_F + (a \cdot I_F + a \cdot I_{CF}) I_C + (a \cdot I_C + a \cdot I_{CF}) I_F \\ \mu_H I_C + \delta_C I_C + \gamma_C I_C + h(I_C) \\ \mu_F I_F + \delta_F I_F + \gamma_F I_F + h(I_F) \\ \mu_{CF} I_{CF} + \delta_{CF} I_{CF} + \gamma_{CF} I_{CF} + h(I_{CF}) \end{bmatrix}.$$

So, after computing the Jacobians of $F_{CF}$ and $V_{CF}$ at the disease free equilibrium (DFE) point, i.e. $F_{CF}$ and $V_{CF}$ respectively, we have the NGM $F_{CF} V_{CF}^{-1}$. The matrices for $F_{CF}$ and $V_{CF}$ are described in Box I.

According to van den Driessche and Watmough (2002), the basic reproduction number $R_0$ is defined as the spectral radius of NGM at DFE. So,

$$R_0 = \max \{ R_{0f}, R_{0j}, R_{0cf} \},$$

where $R_{0f}, R_{0j}$ and $R_{0cf}$ are defined to be the basic reproduction numbers associated with Covid-19 only, Influenza like illness (ILI) and co-infected with Covid-19 and ILI. The expressions for $R_{0j}$ and $R_{0cf}$ are derived as:

$$R_{0j} = \frac{\beta \lambda_H}{\mu_H (\mu_H + \delta_F + \gamma_F + \eta)} \quad \text{and} \quad R_{0cf} = \frac{a \cdot \beta \cdot \lambda_H}{\mu_H (\mu_H + \delta_{CF} + \gamma_{CF} + \eta)}.$$
The disease free equilibrium point given by
\[ \text{DFE and if} R > 1, \text{then ILI can invade the DFE.} \]

We analyse what happens when Covid-19 invades the model (1) is already infected with a single pathogen and in our case, 1 + \( R \) is the invasion reproduction number associated with Covid-19 and ILI respectively. Hence, the main result follows from Castillo-Chavez et al. (2002) which was stated below.

**Theorem 4.** The disease free equilibrium point given by (5), the terms represent the basic reproduction numbers corresponding to infection with Covid-19 and ILI with \( R > 0 \), then Covid-19 can invade the DFE and if \( R > 1 \), then ILI can invade the DFE. In general, if \( R > 1 \), then either Covid-19 or ILI or Co-infection can invade the model system (1).

An invasion reproduction number \( R_{inv} \), can determine if the model system (1) is already infected with a single pathogen and in our case, it is ILI. We analyse what happens when Covid-19 invades the model system at the ILI equilibrium i.e. when \( R > 1 \).

The epidemiological metric \( R_{inv} \) can be interpreted as the average number of new infected states that are being produced after an introduction of an average of one Covid-19 infected agent into the population infected with ILI.

7. **Numerical simulation**

7.1. Data fitting

We implement our model fitting for an epidemic period starting from when the Indian government formally announced the index cases of Covid-19 for the different states. We follow the authors in Oksuzhae and Omane (2020) while performing the model fitting and the data has been downloaded from Anon (2020). Collected data contains the days under the lockdown period too and hence the impact of lockdown on the disease dynamics shall inherently capture the transmission rates in the different states of India. Using the available cumulative number of reported data, we actively seek to estimate the unknown model parameters and fit the infection trajectories of different states of India. Estimated parameters pertaining to the Covid-19 model are shall use the forms expressed as in \( E_0^\mathcal{U} \). We use the NGM approach to derive an invasion metric \( R_{inv} \) associated with Covid-19 and ILI and thereafter we compute \( R_{inv} \). After following the notation in (4), we have the equation in Box III.
\[
\frac{dY_{\text{Inv}}}{dt} = F_{\text{Inv}}(Y_S, Y^*_I) - V_{\text{Inv}}(Y_S, Y^*_I) \tag{7}
\]

\[
F_{\text{Inv}} = \begin{bmatrix}
S_H a - I_p \beta & 0 & -S_H a (\beta - 1) \\
-I_p a & S_H \beta & -I_p a - S_H \beta (a - 1) \\
I_p (a + \beta) & 0 & I_p a + S_H a \beta
\end{bmatrix}
\]

\[
V_{\text{Inv}} = \begin{bmatrix}
\delta_c + \eta + \gamma_c + \mu_H & 0 & 0 & \frac{\eta}{I_p^{z+1}} & 0 \\
0 & \delta_F + \gamma_F + \mu_H + \frac{\eta}{I_p^{z+1}} & 0 & 0 & \delta_c + \eta + \gamma_c + \mu_H
\end{bmatrix}
\]

\[
NGM_{\text{Inv}} = \begin{bmatrix}
\frac{I_p a - S_H a}{\delta_c + \eta + \gamma_c + \mu_H} & \frac{S_H \beta (I_p^{z+1})^2}{\delta_c + \eta + \gamma_c + \mu_H + I_p^{z+1} \mu_H + I_p^{z+1} \mu_H} \\
\frac{I_p a}{\delta_c + \eta + \gamma_c + \mu_H} & \frac{S_H \beta (I_p^{z+1})^2}{\delta_c + \eta + \gamma_c + \mu_H + I_p^{z+1} \mu_H + I_p^{z+1} \mu_H}
\end{bmatrix}
\]

**Box III.**

![Graphs showing the comparison between the reported Covid-19 cases in various states and the simulation of $I_c(t)$ from the model described in (2).](image)

Fig. 2. The comparison between the reported Covid-19 cases in Gujarat, Maharashtra, Rajasthan, Uttar Pradesh, West Bengal, Delhi, Madhya Pradesh, Telengana, Haryana and the simulation of $I_c(t)$ from the model described in (2).

found to be heterogenous in the magnitude and potentially it shows the different infection paths. One thing is important to note that as at the time when the first Covid-19 case was declared in India, it would be extremely difficult to determine the exact number of individuals who...
were already infected. Hence, it might be an aspect that reflects through the heterogeneous distribution of the estimated parameters.

Fig. 2 shows that our model (2) is able to predict the temporal course of daily reported cases of Covid-19 at the national scale where the green dots are the reported cases and the red curves are fitting curves. It is readily observable from the fitted model that the growth is of exponential type and the influence of lockdown is clearly noticeable.

7.2. Real time $R_0$ estimation

Precise assessment of the parameters that identify infectious transmission is crucial to optimise the different containment strategies. An epidemiological metric termed as the time-dependent reproduction $R_t$ has acquired much needed appreciation due to the fact that it can estimate the expected number of secondary cases caused by each infected people in a temporal way (Nishiura and Chowell, 2009). The magnitude of $R_t$ can provide us the information about the extremity of Covid-19 over different time points.

To derive the relationship between the daily Covid-19 incidence data and $R_t$, we have employed the EpidEstim package (Cori et al., 2021). We can observe from the Fig. 3 that the value of $R_t$ ranges between 4.5 to 0.5. It is also noticeable that the temporal changes in the spread of Covid-19 in India, is highly heterogenous. India declared 24th of March, 2020, a nationwide lockdown for 21 days and its influence can be visible in the Fig. 3 as the value of $R_t$ decreases. The magnitude of $R_t$ differed across all the Indian states. Average $R_t$ is found to be 1.98.
with (95% CI 1.93 − 2.06) for the entirety of India during that period of interval and in the lockdown phase it is 2.77 (95% CI 2.65 − 2.92). We have observed the geographic differences in the magnitude of $R_t$ across India. For example, $R_t$ is observed to be greater than 2.5 for Maharashtra, Delhi, Telengana, whereas it is noticed to be lesser than 2.5 for UP, West Bengal, Rajasthan. $R_t$ is found to be greater than 1 for most of the states during that period.

7.3. Impact of transmission parameters

In this section we explore the influence of the transmission parameters ($\alpha$ and $\beta$) on the populations infected with Covid-19, ILI and co-infection cases ($I_C$, $I_F$ and $I_{CF}$) respectively. Here, we vary the values of $\alpha$ and $\beta$ and observe the influence on the prevalence on the population.

For the demonstration purpose, we have chosen the initial conditions to be $S(0) = 995$, $I_C(0) = 5$, $I_F(0) = 2$, $I_{CF}(0) = 3$, $R_C(0) = 0$, $R_F(0) = 0$ and $R_{CF}(0) = 0$. Parameter values are from the Table: (Number). Infection profiles of the model’s state variables are depicted in the Fig. 4 and Fig. 5 wherein it is visible the influence of transmission parameters ($\alpha$ and $\beta$) on the prevalence of Covid-19, ILI and co-infection. With the increase in the transmission rates, the sharp surge in infected population is noticeable and similarly with the lower magnitude of transmission rates, reduction in the infected population can give us the assurance of the measurements that are taken account to reduce the spread of Covid-19. It is interesting to the note that the dynamics of the model is not symmetric (see Fig. 4 and Fig. 5) to the changes performed in two different transmission parameters in spite of being symmetric in the model formulations. Fig. 5 shows us that higher transmissibility of Covid-19, can create a sudden upsurge of cases of Covid-19 and co-infected people. The interplay between the transmissibility of Covid-19 and ILI are very interesting to notice and it is being reflected in the dynamics of co-infected population. Even the low level of transmissibility of Covid-19, can be a hindrance for the eradication of co-infected cases whereas the influence of transmissibility of ILI is not equally important. Therefore, it is of utmost importance to curb the value of $\alpha$ to protect the vulnerable population.

7.4. Impact of cure rate

In order to further analyse the model (1), we have chosen to observe the influence of cure rate on compartments that include Covid-19, ILI and co-infected population.

Dynamical behaviour of these compartments is interesting to note in the constant changes of $\eta$. From the Fig. 6, it is noticeable the changes in the cure rate can bring the cases of Covid-19, ILI down and consequently the cases of co-infection can also be brought down accordingly. Finally, as conceived, we can notice that with the increase in medical facilities like test kits, ventilators, nursing facilities, efficiency of treatment etc, the infected population ($I_C$, $I_F$, $I_{CF}$) get recovered and a substantial reduction happens in the infected population. This observation can lead us to conclude that the better cure rate should be considered as an effective tool to reduce the infection amongst the susceptible population.

7.5. Time series

Investigations in the time series can allow us to get further inside in the consequences of the cases when the values of $R_0$ is greater than one or less than one. The situation when $R_0 < 1$, the disease-free equilibrium point is the only attractor for the system whereas when $R_0 > 1$, then the endemic equilibrium point. Fig. 8 depicts the first case and the Fig. 7 depicts the latter. In this scenario, cases of Covid-19 can be reduced classically by simply increasing the value of $\eta$.

Additionally, in Fig. 9, we have shown the prevalence of the infected population with Covid-19, ILI and co-infection under two different situations.

It is clear from the Fig. 9 that if the value of $R_0$ is greater than 1 then the prevalence of Covid-19, ILI and co-infected people are non-zero and the burden of people infected with Covid-19 and co-infected is higher.
Fig. 6. The prevalence of Covid-19, ILI and co-infected population.

Fig. 7. The prevalence of Covid-19, ILI and co-infected population.

Fig. 8. The prevalence of Covid-19, ILI and co-infected population.

Fig. 9. The prevalence of Covid-19, ILI and co-infected population.
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In our effort we focus primarily on global sensitivity analysis (GSA) which investigates the response of model output variables to the model parameters variation.

We have used Sobol’ method as we would like to gather the information about the response of \( R_0 \), to a certain parameter while all interactions are taken into the account. Given the higher value of transmissibility of Covid-19 (Petersen et al., 2020), we choose to investigate all interactions are taken into the account. Given the higher value of \( R_0 \), it is interesting to investigate the obstructive effects of co-infection in a completely susceptible human population where ILI already exists. The mathematical expression of co-infection in a completely susceptible human population where ILI already exists. The mathematical expression of \( R_0 \) can be attributed to the implementation of public health measures including social distancing, restrictions in mobility, contact tracing etc and a possible improvement in medical care facilities. Similar trend of reduction of \( R_0 \) in India has been observed just like in China or in USA (Yuan et al., 2020; Singh et al., 2021). Earlier studies (Senapati et al., 2021; Shih et al., 2021; Achaiah et al., 2020) have addressed a varied magnitude of \( R_0 \) from 1.03 to 4.18. These studies have utilised different data sources and the methods to find \( R_0 \). The time intervals considered in these studies are also different from our endeavour. So, these estimates cannot be compared readily.

One of the highlights of our work is the mathematical formulation of invasion reproduction number (Allen et al., 2019), which can mirror the situation whether Covid-19 can invade a susceptible population where another disease is already persistent (Iacobucci, 2020; Kim et al., 2020; Chen et al., 2020; Burrel et al., 2021; Hazra et al., 2020), with the aim to investigate the dynamics of co-infection. We would like to include that interplay between Covid-19 and ILI has a beneficial impact on the transmission of co-infection in a completely susceptible human population where ILI already exists. The mathematical expression of \( R_{inv} \) is similar to that of derived in Allen et al. (2019).

It is to be noted that the model considered in this work is a rudimentary mathematical model through which we have focussed to understand the main dynamics of the spread of Covid-19 and ILI in a limited medical facility setting. Nevertheless, pathogens or the strains of diseases interacting and infecting the hosts may not only promote each other but can also compete or try to be independent. Therefore, it is interesting to investigate the obstructive effects of co-infection on the Covid-19 transmission after including the evolutionary nature of this virus (May and Nowak, 1995; Lawton, 2020). Furthermore, other factors such as seasonality, spatial heterogeneity will be equally important to address.

7.6. Sensitivity analysis

Using sensitivity analysis, we can recognise which parameters are important providing the heterogeneity in the outcome of the basic reproduction number (\( R_0 \)). In our effort we investigate the global sensitivity analysis (GSA) which investigates the response of model output variables to the model parameters variation.

We have used Sobol’ method as we would like to gather the information about the response of \( R_0 \) to a certain parameter while all interactions are taken into the account. Given the higher value of transmissibility of Covid-19 (Petersen et al., 2020), we choose to investigate all interactions are taken into the account. Given the higher value of \( R_0 \), it is interesting to investigate the obstructive effects of co-infection in a completely susceptible human population where ILI already exists. The mathematical expression of co-infection in a completely susceptible human population where ILI already exists. The mathematical expression of \( R_0 \) can be attributed to the implementation of public health measures including social distancing, restrictions in mobility, contact tracing etc and a possible improvement in medical care facilities. Similar trend of reduction of \( R_0 \) in India has been observed just like in China or in USA (Yuan et al., 2020; Singh et al., 2021). Earlier studies (Senapati et al., 2021; Shih et al., 2021; Achaiah et al., 2020) have addressed a varied magnitude of \( R_0 \) from 1.03 to 4.18. These studies have utilised different data sources and the methods to find \( R_0 \). The time intervals considered in these studies are also different from our endeavour. So, these estimates cannot be compared readily.

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compared to the people infected with ILI only and the same holds true when we let the value of \( R_0 \) is to be less than 1.

8. Discussion and conclusion

Our work has revealed the co-infection dynamics of Covid-19 and ILI in the presence of non-linear treatment function in different states of India. After using our mathematical model with the available data at the initial phase of Covid-19 spread in India, we are able to fit the trajectories of the paths of Covid-19 infection over India and its exponential nature. By applying numerical simulations, we endeavour to understand the effect of saturated treatment in the course of co-infection. After finding the analytical expression of IRN, our current effort build on to the analytical tools which can be employed to understand the multiple-pathogens dynamical system.

We have carried out the sensitivity analysis of \( R_0 \) of the co-infected system with respect to the model parameters. The outcome identifies three key parameters: the transmission rate of Covid-19: \( a \), cure rate: \( \eta \) and the recruitment rate: \( \lambda_H \). It is to be noted that particularly for the SI index, it indicates each input’s individual contribution to variance. We use a more sophisticated visualisation to incorporate the second-order interactions between inputs estimated from the S2 values. In this case \( \eta \) has strong interactions with \( a \) and \( \lambda_H \) and then followed by the interaction between \( a \) and \( \lambda_H \). Here, the size of the ST and SI circles correlate with the normalised variable importances. Fig. 10 delivers a few important messages that shall be the matter of concern in the context of limited medical resources. Based on Sobol’ sensitivity index, Si, where \( i = 1, 2 \) three parameters are found to be primary contributors to the variance of transmissibility of Covid-19. It gives the information about the contributions of \( \eta, a, \lambda_H \) to the variance of basic reproduction number and the total effect index, ST includes both individual contributions and the interaction effects in consideration. It is evident that the influence of the effective transmission rate of Covid-19 and the treatment facility are very important to lower the value of \( R_0 \) along with reducing the number of susceptible. Higher number of susceptible will take toll on the medical resources and henceforth, lack of treatment facility can facilitate higher transmission of Covid-19.

Fig. 10. Sobol’ indices.

(a) Sobol’ indices

(b) Second-order interactions
Our modelling foundation is not only tailored to carry out the co-transmission of Covid-19 and ILI, but can be employed to general epidemiological co-transmitting diseases in a limited medical resources. Predicting the spread of epidemics and developing an early forewarning system for the limited yet demanding healthcare and volume have been put at the foreground of epidemiological modelling. It can be achieved through working and planning in a close collaboration with the theoreticians and local authorities. As a consequence, it shall bring a unique opportunity to inculcate novel ideas to demanding healthcare options and planning.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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