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Research Article

A Mathematical Study on Coronavirus Model with Two Infectious States

V.S.V. Naga Soundarya Lakshmi* and A. Sabarmathi

Department of Mathematics, Auxilium College, Vellore 632 006, Tamilnadu, India
***Corresponding author:** san9sak14@gmail.com

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Abstract. A SIR model is formulated for COVID-19 with initial and secondary states. Existence and uniqueness of solutions, stability of the model and basic reproduction number were derived. In this article, the vulnerability of COVID-19 in Tirupathur district, Tamilnadu, India is discussed to exhibit the flow of variables of the model using numerical simulations. Also, analysis of recovered is explored for Siddha and allopathy treatments.

Keywords. COVID-19; Stability; SIR model; Basic reproduction number; Siddha; Allopathy

Mathematics Subject Classification (2020). 34L99; 34L30

1. Introduction

Coronaviruses (CoVs) are a major group of viruses known to be responsible for wide spectrum of diseases in multiple species. The CoVs affecting human population are referred to as *Human Coronaviruses* (HCoVs), which leads to multiple respiratory diseases, such as common cold, pneumonia, bronchitis, severe acute respiratory syndrome, and *middle east respiratory syndrome* (MERS). CoVs are RNA viruses that require *RNA dependent RNA Polymerases* (RdRPs) for various steps in their life cycle. Action of RdRP is needed in several steps in the life cycle of CoVs and thus RdRPs constitute potential targets for drugs and other therapeutic interventions for the treatment of diseases caused by CoVs [1].

We are aware of COVID-19 which is an infectious disease caused by a newly discovered Coronavirus: 2019-nCoV (2019 novel coronavirus). Now Coronavirus is familiar among us which affected worldwide and gave a clear outlook of Pandemic diseases. It spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes. In December 2019, a pneumonia outbreak was reported in Wuhan, China. The first case in India was reported on 30th January 2020. India is currently has the largest number of confirmed cases in the world after the United states.

The first case in Tamilnadu was reported on 7 March 2020. Tamilnadu has the second highest number of confirmed cases in India after Maharastra but the case fatality rate in Tamilnadu is lowest in the country. Among all the 37 districts of Tamilnadu, Chennai being worst affected. In particular in Tirupathur district the first case was reported on 1 April 2020. The patients were treated in two ways Siddha and allopathy in Tirupathur district, Tamilnadu.

The Siddha system of medicine is practised in southern part of India especially in Tamilnadu which treats not only body but also mind and soul. The word 'Siddha' has its origin from the Tamil word 'Siddhi' which means 'an object to be attained'. Siddha traditional medicines are used till date in many parts of Tamilnadu.

Allopathy refers to modern medicine that is the board category of medical practice that is sometimes called Western medicine or English medicine. The term 'Allopathy' is drawn from Greek in which 'Allos' means 'different and 'Pathos' means 'Suffering'.

Many researchers were developed models for COVID-19. Dighe *et al*. [4] discussed the transmission of middle East respiratory system of coronavirus in dromedary camels by a mathematical model. Chen *et al*. [2] explored a Bats-Hosts-Reservoir-People transmission network model and calculated the basic reproduction number to assess the transmissibility of SARS-COV-2. Yang and Wang [12] described the transmission dynamics of COVID-19 in Wuhan, China by SEIRV model. Li *et al*. [7] established a SEIQDR model to prevent and control COVID-19. Ivorra *et al*. [5] developed a SEIHRD model for COVID-19 and studied the case in China. Zeb and Alzahrani [13] developed a mathematical model to present the dynamical behaviour of COVID-19 by incorporating isolation class. Khoshnaw *et al*. [6] developed a model for COVID-19 and showed the spread of Virus by Sensitivity analysis.

Also, recently researchers use the new SIR models. Specifically, Mbabazi *et al*. [9] has investigated the SVECI model with carrier and vaccination states for pneumonia. Zephaniah *et al*. [14] discussed the streptococcus pneumonia with saturated incidence force of infection by SVEIR model. Otoo *et al*. [11] studied a SVCIR model with sympotomatic and asymptomatic carrier state. Okhuese [10] has established a reinfection endemic model SEIRUS for Covid-19. In this paper, we collected the data from Tirupathur Collectorate and formulated the model of SIR with two infectious states, initial state I_1 and secondary state I_2 for COVID-19.

2. Formulation of model

Figure 1 shows the transition of Coronavirus SIR model with two infectious states.

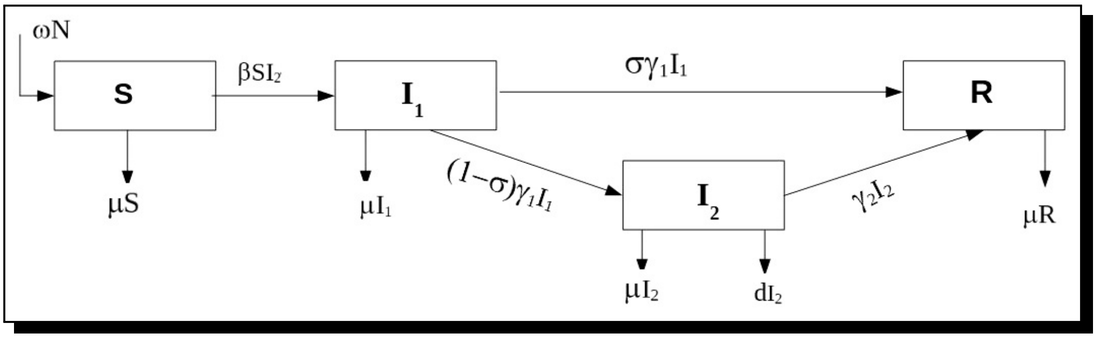


Figure 1. COVID-19 SIR model with two infectious state

The above transition of Coronavirus is represented by the following system of four ODEs

$$\left.\begin{aligned}
\frac{dS}{dt} &= \omega N(t) - \mu S(t) - \beta S(t) I_2(t) \\
\frac{dI_1}{dt} &= \beta S(t) I_2(t) - \sigma\gamma_1 I_1(t) - (1-\sigma)\gamma_1 I_1(t) - \mu I_1(t) \\
\frac{dI_2}{dt} &= (1-\sigma)\gamma_1 I_1(t) - \gamma_2 I_2(t) - \mu I_2(t) - d I_2(t) \\
\frac{dR}{dt} &= \sigma\gamma_1 I_1(t) + \gamma_2 I_2(t) - \mu R(t).
\end{aligned}\right\} \tag{2.1}$$

With the initial conditions as $S(t), I_1(t), I_2(t), R(t) \geq 0$. Also, $\sigma, \beta, \gamma_1, \gamma_2, \mu, \omega, d > 0$.
Where $S(t)$, $I_1(t)$, $I_2(t)$, $R(t)$ are the Susceptible, Initial infectious state, Secondary infectious state and Recovery state, respectively, and ω — Average birth rate, μ — Average death rate, β — Transition infectious rate, σ — Fraction who is not suffer with severe COVID-19, γ_1, γ_2 — Recovery rate from initial infection and secondary infection, d — disease induced death rate, N — Total Population.

We assume the following:

(1) I_1 has no risk of death.

(2) $\gamma_1 > \gamma_2$, the recovery rate of I_1 is greater than the recovery rate of I_2.

3. Existence and Uniqueness of Solution

To prove the existence and uniqueness of the solution of the system (2.1) we use the following theorem and lemma.

Theorem 3.1 (Existence and Uniqueness Theorem). *Let* $\frac{dy}{dx} = f(x,y)$, $y(x_0) = y_0$ *and* $f(x,y)$ *be continuous on a domain* $\{D = (x,y)/x_0 - a < x < x_0 + a; y_0 - b < y < y_0 + b\}$ *with the Lipschitz condition* $\|f(x,y_1) - f(x,y_2)\| \leq K\|y_1 - y_2\|$ *where* K *is a positive integer, then there exist bounded solution in* D. *Further more, if* $f(x,y)$ *is Lipschitz continuous with respect to* y *on a rectangle* $R = \{(x,y)/x_0 - c < x < x_0 + c; y_0 - b < y < y_0 + b; c < a\}$ *then there is a unique solution* $y(t)$ *in* R [8].

Lemma 3.2. *If* $f(x,y)$ *has continuous partial derivative* $\frac{\partial f_i}{\partial y_j}$ *on a bounded closed domain* R, *is a set of real numbers. Then it satisfies a Lipschitz condition in* R [8].

Proof. To prove the main theorem, from (2.1) we consider the following:

$$f_1 = \omega N(t) - \mu S(t) - \beta S(t)I_2(t), \tag{3.1}$$

$$f_2 = \beta S(t)I_2(t) - \sigma\gamma_1 I_1(t) - (1-\sigma)\gamma_1 I_1(t) - \mu I_1(t), \tag{3.2}$$

$$f_3 = (1-\sigma)\gamma_1 I_1(t) - \gamma_2 I_2(t) - \mu I_2(t) - dI_2(t), \tag{3.3}$$

$$f_4 = \sigma\gamma_1 I_1(t) + \gamma_2 I_2(t) - \mu R(t). \tag{3.4}$$

Now, we show that the partial derivatives $\frac{\partial f_i}{\partial y_j}$, $i,j = 1,2,3,4,5$ are bounded and continuous. We derive the following partial derivatives for the model equations (3.1)-(3.4).

From (3.1), we have $\frac{\partial f_1}{\partial S}, \frac{\partial f_1}{\partial I_1}, \frac{\partial f_1}{\partial I_2}, \frac{\partial f_1}{\partial R} < \infty$.

From (3.2), we have $\frac{\partial f_2}{\partial S}, \frac{\partial f_2}{\partial I_1}, \frac{\partial f_2}{\partial I_2}, \frac{\partial f_2}{\partial R} < \infty$.

From (3.3), we have $\frac{\partial f_3}{\partial S}, \frac{\partial f_3}{\partial I_1}, \frac{\partial f_3}{\partial I_2}, \frac{\partial f_3}{\partial R} < \infty$.

From (3.4), we have $\frac{\partial f_4}{\partial S}, \frac{\partial f_4}{\partial I_1}, \frac{\partial f_4}{\partial I_2}, \frac{\partial f_4}{\partial R} < \infty$.

It is clear that the above partial derivatives are continuous and bounded.

Hence, there exist a unique solution of (2.1) in the region D which completes the proof. □

4. Equilibrium Analysis

Now, let $s(t) = \frac{S(t)}{N}$, $i_1(t) = \frac{I_1(t)}{N}$, $i_2(t) = \frac{I_2(t)}{N}$, $r(t) = \frac{R(t)}{N}$ and $r(t) = 1 - s(t) - i_1(t) - i_2(t)$.
Therefore, (2.1) is reduced to the following equations:

$$\frac{ds}{dt} = \omega - \mu s - \beta s i_2, \tag{4.1}$$

$$\frac{di_1}{dt} = \beta s i_2 - (\gamma_1 + \mu)i_1, \tag{4.2}$$

$$\frac{di_2}{dt} = (1-\sigma)\gamma_1 i_1 - (\gamma_2 + \mu + d)i_2. \tag{4.3}$$

The steady states are $G_0(0,0,0), G_1(\bar{s}, \bar{i}_1, 0), G_2(s^*, i_1^*, i_2^*)$.

Case 1: Trivial steady state $G_0(0,0,0)$ exists always.

Case 2: For $G_1(\bar{s}, \bar{i}_1 k, 0)$ (i.e. Absence of secondary infection).
Let $\bar{s}$, $\bar{i}_1$ be the positive solutions of $\frac{ds}{dt} = 0$, $\frac{di_1}{dt} = 0$.
From (4.1) and (4.2), $G_1(\bar{s}, \bar{i}_1, 0) = G_1\left(\frac{\omega}{\mu}, 0, 0\right)$, which is the disease free equilibrium.

Case 3: For $G_2(s^*, i_1^*, i_2^*)$ (i.e. Endemic Equilibrium)
Let s^*, i_1^*, i_2^* be the positive solutions of $\frac{ds}{dt} = 0$, $\frac{di_1}{dt} = 0$, $\frac{di_2}{dt} = 0$. From (4.1),

$$\begin{aligned}
&\omega - \mu s^* - \beta s^* i_2^* = 0 \\
\Longrightarrow\quad & -(\mu + \beta i_2^*)s^* = -\omega \\
\Longrightarrow\quad & \beta i_2^* + \mu = \frac{\omega}{s^*}
\end{aligned}$$

$$\implies \quad i_2^* = \frac{-\mu}{\beta} + \frac{\omega}{\beta s^*} \tag{4.4}$$

From (4.2),

$$\beta s^* i_2^* - (\gamma_1 + \mu) i_1^* = 0$$

$$\implies \quad \beta s^* i_2^* = (\gamma_1 + \mu) i_1^*$$

$$\implies \quad s^* = \frac{(\gamma_1 + \mu) i_1^*}{\beta i_2^*} \tag{4.5}$$

From (4.3),

$$(1-\sigma)\gamma_1 i_1^* - (\gamma_2 + \mu + d) i_2^* = 0$$

$$\implies \quad (1-\sigma)\gamma_1 i_1^* = (\gamma_2 + \mu + d) i_2^*$$

$$\implies \quad \frac{i_1^*}{i_2^*} = \frac{\gamma_2 + \mu + d}{(1-\sigma)\gamma_1} \tag{4.6}$$

Using (4.6) in (4.5),

$$s^* = \frac{(\gamma_1 + \mu)(\gamma_2 + \mu + d)}{\beta(1-\sigma)\gamma_1}.$$

Using s^* in (4.4),

$$i_2^* = \frac{-\mu}{\beta} + \frac{\omega(1-\sigma)\gamma_1}{(\gamma_1 + \mu)(\gamma_2 + \mu + d)}.$$

Using i_2^* in (4.6),

$$i_1^* \frac{-\mu(\gamma_2 + \mu + d)}{(1-\sigma)\gamma_1} + \frac{\omega}{(\gamma_1 + \mu)}.$$

Hence, the endemic equilibrium is

$$(s^*, i_1^*, i_2^*) = \left(\frac{(\gamma_1 + \mu)(\gamma_2 + \mu + d)}{\beta(1-\sigma)\gamma_1}, \left(\frac{\omega}{\gamma_1 + \mu} - \frac{\mu(\gamma_2 + \mu + d)}{(1-\sigma)\gamma_1} \right), \left(\frac{\omega(1-\sigma)\gamma_1}{(\gamma_1 + \mu)(\gamma_2 + \mu + d)} - \frac{\mu}{\beta} \right) \right).$$

5. Stability Analysis

To find the local stability of (4.1)-(4.3). By the Routh-Hurwitz criteria, the system is locally stable for $S^3 + a_2 S^2 + a_1 S + a_0 = 0$ if and only if $a_2 > 0$, $a_0 > 0$, $a_2 a_1 > 0$.

The Jacobian matrix for the system (4.1)-(4.3) is

$$\begin{pmatrix} -\beta i_2 - \mu & 0 & -\beta s \\ \beta i_2 & -(\mu + \gamma_1) & \beta s \\ 0 & (1-\sigma)\gamma_1 & -(\gamma_2 + \mu + d) \end{pmatrix}. \tag{5.1}$$

At the interior equilibrium (5.1) becomes

$$\begin{pmatrix} \frac{-\omega}{s} & 0 & -\beta s \\ \beta i_2 & \frac{-\beta s i_2}{i_1} & \beta s \\ 0 & (1-\sigma)\gamma_1 & \frac{-(1-\sigma)\gamma_1 i_1}{i_2} \end{pmatrix}. \tag{5.2}$$

The characteristic equation of (5.2) is given by

$$\begin{vmatrix} \frac{-\omega}{s}-\lambda & 0 & -\beta s \\ \beta i_2 & \frac{-\beta s i_2}{i_1}-\lambda & \beta s \\ 0 & (1-\sigma)\gamma_1 & \frac{-(1-\sigma)\gamma_1 i_1}{i_2}-\lambda \end{vmatrix} = 0 \tag{5.3}$$

$$\implies \quad \lambda^3 + \left(\frac{(1-\sigma)\gamma_1 i_1}{i_2} + \frac{\beta s i_2}{i_1} + \frac{\omega}{s}\right)\lambda^2 + \left(\frac{\omega(1-\sigma)\gamma_1 i_1}{s i_2} + \frac{\omega\beta i_2}{i_1}\right)\lambda + \beta^2 s i_2 (1-\sigma)\gamma_1 = 0. \tag{5.4}$$

Comparing (5.4) with

$$\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$$

where $a_0 = \beta^2 s i_2(1-\sigma)\gamma_1$; $a_1 = \frac{\omega(1-\sigma)\gamma_1 i_1}{s i_2} + \frac{\omega\beta i_2}{i_1}$; $a_2 = \frac{(1-\sigma)\gamma_1 i_1}{i_2} + \frac{\beta s i_2}{i_1} + \frac{\omega}{s}$; $a_0 > 0$; $a_2 > 0$; $a_2 a_1 > 0$ as ω, μ, σ, β, s, i_1, i_2, γ_1, γ_2 are positive.

Hence the system (4.1)-(4.3) is locally stable.

To find the global stability at (s^*, i_1^*, i_2^*), we construct the following Lyapunov function.

$$V(s,i_1,i_2) = \left[(s-s^*) - s^* \ln\frac{s}{s^*}\right] + l_1\left[(i_1-i_1^*) - i_1^*\ln\frac{i_1}{i_1^*}\right] + l_2\left[(i_2-i_2^*) - i_2^*\ln\frac{i_2}{i_2^*}\right]. \tag{5.5}$$

Differentiate (5.5) with respect to t,

$$\frac{dV}{dt} = \left(\frac{s-s^*}{s}\right)\frac{ds}{dt} + l_1\left(\frac{i_1-i_1^*}{i_1}\right)\frac{di_1}{dt} + l_2\left(\frac{i_2-i_2^*}{i_2}\right)\frac{di_2}{dt}.$$

Using the model equations (4.1)-(4.3),

$$\begin{aligned}\frac{dV}{dt} &= \left(\frac{s-s^*}{s}\right)[\omega-\mu s-\beta s i_2] + l_1\left(\frac{i_1-i_1^*}{i_1}\right)[\beta s i_2 - (\gamma_1+\mu)i_1] \\ &\quad + l_2\left(\frac{i_2-i_2^*}{i_2}\right)[(1-\sigma)\gamma_1 i_1 - (\gamma_2+\mu+d)i_2] \\ &= (s-s^*)\left[\frac{\omega}{s} - (\mu+\beta i_2)\right] + l_1(i_1-i_1^*)\left[\frac{\beta s i_2}{i_1} - (\gamma_1+\mu)\right] \\ &\quad + l_2(i_2-i_2^*)\left[\frac{(1-\sigma)\gamma_1 i_1}{i_2} - (\gamma_2+\mu+d)\right].\end{aligned}$$

At (s^*, i_1^*, i_2^*), we have

$$\begin{aligned}\frac{dV}{dt} &= (s-s^*)\left[\frac{\omega}{s} - \frac{\omega}{s^*}\right] + l_1(i_1-i_1^*)\left[\frac{\beta s i_2}{i_1} - \frac{\beta s^* i_2^*}{i_1^*}\right] + l_2(i_2-i_2^*)\left[\frac{(1-\sigma)\gamma_1 i_1}{i_2} - \frac{(1-\sigma)\gamma_1 i_1^*}{i_2^*}\right] \\ &= (s-s^*)\left[\omega\left(\frac{1}{s}-\frac{1}{s^*}\right)\right] + l_1(i_1-i_1^*)\left[\beta\left(\frac{s i_2}{i_1} - \frac{s^* i_2^*}{i_1^*}\right)\right] + l_2(i_2-i_2^*)\left[(1-\sigma)\gamma_1\left(\frac{i_1}{i_2} - \frac{i_1^*}{i_2^*}\right)\right] \\ &= (s-s^*)\omega\left(\frac{s^*-s}{ss^*}\right) + l_1\beta(i_1-i_1^*)\left(\frac{s i_2 i_1^* - s^* i_2^* i_1}{i_1 i_1^*}\right) + l_2(1-\sigma)\gamma_1(i_2-i_2^*)\left(\frac{i_1 i_2^* - i_2 i_1^*}{i_2 i_2^*}\right) \\ &= -\frac{\omega}{ss^*}(s-s^*)^2 + l_1\frac{\beta(i_1-i_1^*)}{i_1 i_1^*}(s i_2 i_1^* - s^* i_2^* i_1) + l_2\frac{(1-\sigma)\gamma_1(i_2-i_2^*)}{i_2 i_2^*}(i_1 i_2^* - i_2 i_1^*).\end{aligned}$$

Choosing $l_1 = \frac{1}{\beta}$, $l_2 = \frac{1}{(1-\sigma)\gamma_1}$

$$\frac{dV}{dt} = -\frac{\omega}{ss^*}(s-s^*)^2 + \frac{(i_1-i_1^*)}{i_1 i_1^*}(s i_2 i_1^* - s^* i_2^* i_1) + \frac{(i_2-i_2^*)}{i_2 i_2^*}(i_1 i_2^* - i_2 i_1^*)$$

$$= -\frac{\omega}{ss^*}(s-s^*)^2 + \frac{1}{i_1 i_1^*}[s i_1 i_1^* i_2 - (i_1^*)^2 s i_2 - i_1^2 s^* i_2^* + i_1 i_1^* s^* i_2^*]$$
$$+ \frac{1}{i_2 i_2^*}[i_1 i_2 i_2^* - i_2^2 i_1^* - i_1 (i_2^*)^2 + i_2 i_1^* i_2^*]$$
$$= -\frac{\omega}{ss^*}(s-s^*)^2 + \left[s i_2 - \frac{i_1^*}{i_1} s i_2 - \frac{i_1}{i_1^*} s^* i_2^* + s^* i_2^*\right] + \left[i_1 - \frac{i_1^* i_2}{i_2^*} - \frac{i_1 i_2^*}{i_2} + i_1^*\right]$$
$$= -\frac{\omega}{ss^*}(s-s^*)^2 + \left[(s i_2 + s^* i_2^*) - \left(\frac{i_1^*}{i_1} s i_2 + \frac{i_1}{i_1^*} s^* i_2^*\right)\right] + \left[(i_1 + i_1^*) - \left(\frac{i_1^* i_2}{i_2^*} + \frac{i_1 i_2^*}{i_2}\right)\right].$$

Therefore, $\frac{dV}{dt} < 0$, as all the terms in R.H.S. are negative.
From, Lyapunov theorem the system (4.1)-(4.3) is globally asymptotically stable.

6. Basic Reproduction Number

We know that the largest eigen value of next generation matrix FV^{-1} is the basic reproduction number [3].
From (4.1)-(4.3) we have,

$$F = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & \beta s i_2 \\ 0 & 0 & 0 \end{bmatrix}, \; V = \begin{bmatrix} -\mu & 0 & -\beta s \\ 0 & -(\mu+\gamma_1) & 0 \\ 0 & (1-\sigma)\gamma_1 & -(\gamma_2+\mu+d) \end{bmatrix}, \; FV^{-1} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \frac{\beta s i_2 (1-\sigma)\gamma_1}{(\mu+\gamma_1)(\gamma_2+\mu+d)} & \frac{\beta s i_2}{(\gamma_2+\mu+d)} \\ 0 & 0 & 0 \end{bmatrix}.$$

Therefore, we have

$$R_0 = \frac{\beta(1-\sigma)\gamma_1}{(\mu+\gamma_1)(\gamma_2+\mu+d)}. \qquad (6.1)$$

7. Numerical Analysis

The natural birth rate of Tirupathur district in 2012 is 15.4 $\implies \omega = 0.0422$, and the natural death rate of Tirupathur district in 2012 is 7.94 $\implies \mu = 0.0218$.

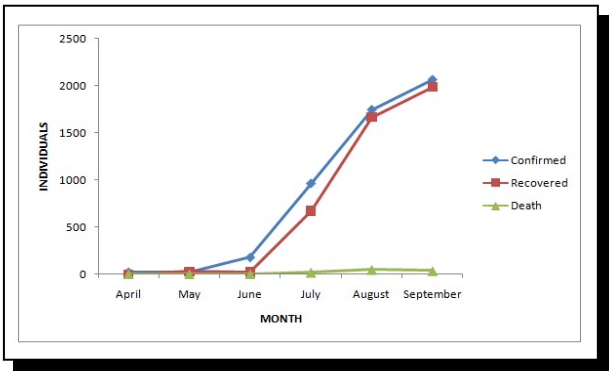


Figure 2. Transmission of Coronavirus in Tirupathur district

The death rate for allopathy treatment in Tirupathur district is $d = 0.0189$ and the death rate for Siddha treatment in Tirupathur district is $d = 0$. Let us assume $\beta = 0.5$, $\gamma_1 = 0.07$, $\gamma_2 = 0.05$ and the no risk factor $\sigma = 0.6$.

The reproduction number from (6.1) is given by

$$R_0 = \frac{\beta(1-\sigma)\gamma_1}{(\mu+\gamma_1)(\gamma_2+\mu+d)} = 1.681.$$

Figure 2 represents the transmission of Confirmed cases, Recovered cases and Death cases of Coronavirus in Tirupathur district as on 30.09.2020.

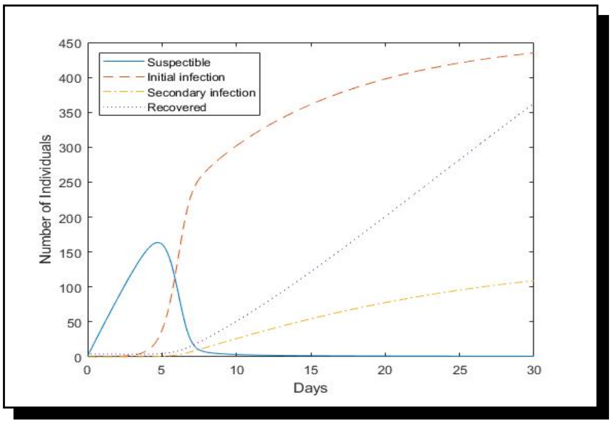
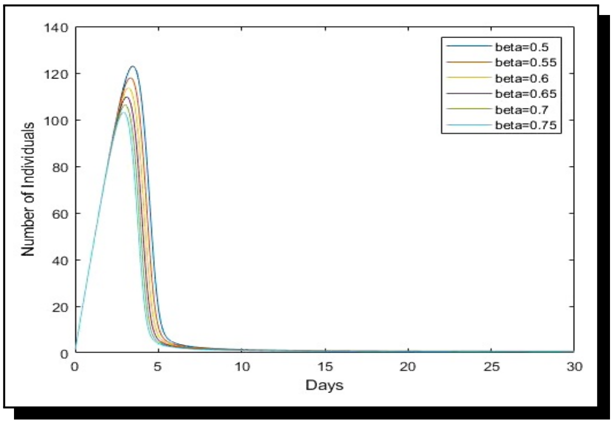


Figure 3. Flow of Variables with respect to Time

Figure 3 shows the flow of Susceptible, Initial infection, Secondary infection and Recovery for the model.



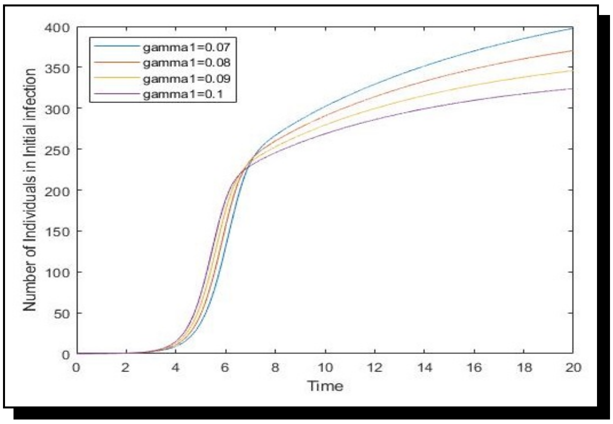


Figure 4. Susceptible class for different values of β **Figure 5.** Initial infection for different values of γ_1

Figure 4 represents that as β increases the susceptible individuals decreases. From Figure 5, it is clear that the individuals in the initial infection decreases whenever γ_1 increases. Figure 6 shows that as γ_2 increases, the individuals in the secondary infection decreases. Figure 7 represents that the recovery rate decreases as σ decreases. Figure 8 gives a clear image of recovered by Siddha and allopathy treatments carried out in Tirupathur district where the Siddha leads a bit than the allopathy treatment.

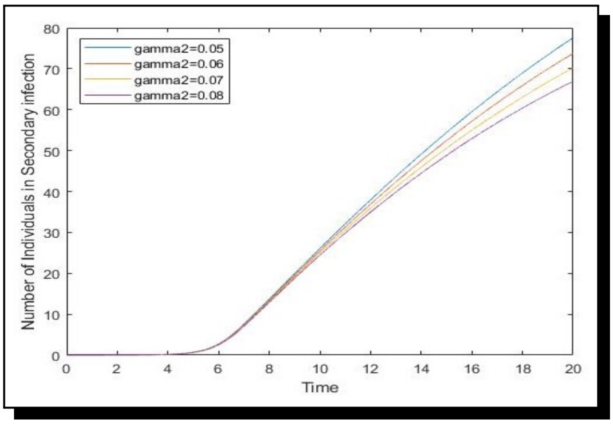


Figure 6. Secondary infection for values of γ_2

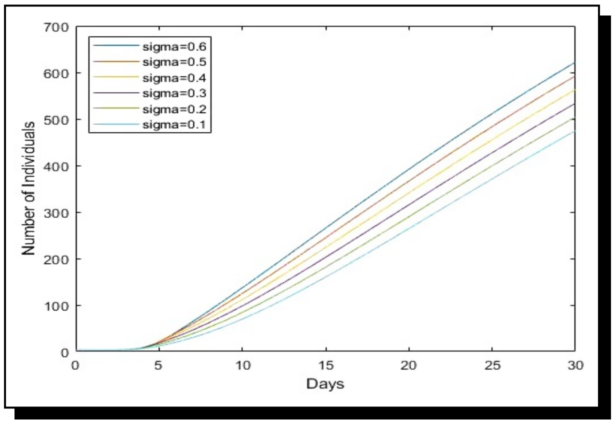


Figure 7. Recovered class for different values of σ

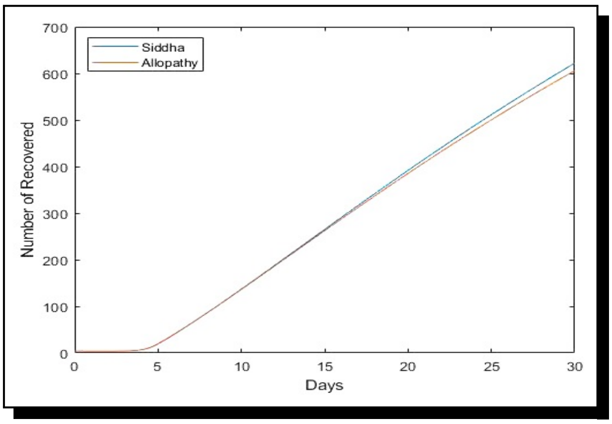


Figure 8. Recovery class of Siddha vs Allopathy

8. Conclusion

A SIR model with two infectious states initial and secondary is formulated. The Existence and Uniqueness of solution for the system is verified. The local and global stability of the model for the system is analysed. The reproduction number of the model is given by 1.681. The transition of Coronavirus in Tirupattur district and the flow of variables as Susceptible, Initial infection, Secondary infection and Recovered for different values of the parameter is given by numerical analysis. By comparing the treatments, it is clear that recovery by Siddha is lead to allopathy.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All the authors contributed significantly in writing this article. The authors read and approved the final manuscript.

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