Supplementary Materials

Insight into Delta Variant Dominated Second Wave of COVID-19 in Nepal

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1. Transmission dynamics model

To develop a transmission dynamics model based on the $SEIR$ framework, the total population is divided into high- and low-risk regions. The high-risk region consists of 22 districts, which have an open border with India and/or have highly populous cities, such as Kathmandu, Kaski, Chitawan, and Surkhet. The remaining districts belong to the low-risk region. The map of Nepal showing the high and low risk region is shown in the figure 1.

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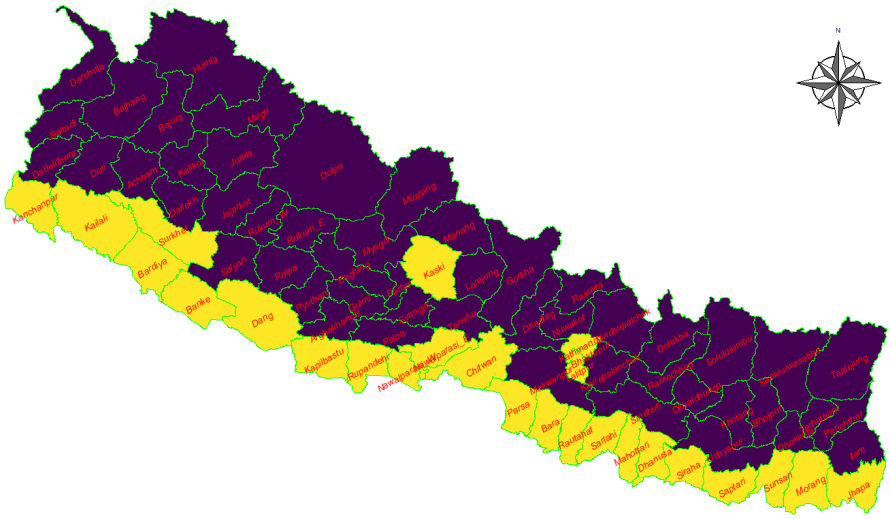

Figure 1: **A map of Nepal**. To create the map, the data (shapefile format) was obtained from the official webpage (`http://dos.gov.np`) of the government of Nepal (Accessed on April 23, 2021). The map was then created using cartography package in R. The yellow region constitute the districts of high risk region and that of deep blue is low risk region.

The population of each region is divided into sixteen distinct compartments: S_H, S_L (susceptible), E_H, E_L (exposed), I_{RH}, I_{RL} (recorded infectious), I_{RH}, I_{NL} (non-recorded infectious), M_H, M_L (Medical care), I_{cH}, I_{cL} (ICU), V_H, V_L (Ventilator) and R_H, R_L (recovered), where the suffixes H and L are used to indicate the high- and low-risk regions, respectively. Λ_H and Λ_L represent the birth rate in the high and the low-risk regions, respectively.

The immigrants from abroad enter only the high-risk region at the rate of $\lambda(t)$. Among the immigrants $\lambda(t)$, a portion ϕ is tested by the antigen, and the rest $(1-\phi)$ entered to the community without the antigen test. The portion ρ of the immigrants with a positive test result entered the recorded infected class (I_{RH}) of the high-risk region and the remaining immigrants (negative test result) entered the susceptible class. The immigrants without antigen test entered to the susceptible and non-recorded infectious (I_{NH}) with the same portion as that of tested immigrants. Since the low-risk region does not have a border

with India, there is no recruitment from immigration in low-risk regions.

$\gamma(t)$ represents the mobility rate between two regions with corresponding classes (susceptible, exposed, non-recorded infectious, and recovered). The transmission rate from recorded infected individuals of both regions, non-recorded infectious individuals in the high-risk region, and non-recorded infectious individuals in low-risk region are denoted by β_1, $\beta_2(t)$, and $\beta_3(t)$, respectively. The exposed individuals become infectious at the rate of δ, among which a portion θ are recorded and the remaining $(1-\theta)$ remain non-recorded in both regions.

Among the recorded infectious, a portion ω of infected entered the medical care class, and the remaining $(1-\omega)$ enter the class without medical care in both regions. From the medical care class, the severe patients enter an extreme medical care class at the rate ν, among whom a portion ψ require the ventilators and the remaining $(1-\psi)$ portion are admitted to ICU. The rate of recovery from the recorded class without medical care and non-recorded infectious class is denoted by η and those from medical care, ICU, and ventilator are denoted by $\alpha_m,\ \alpha_c,$ and α_v, respectively. The natural death rate is denoted by μ and the disease-induced death rate for recorded and non-recorded infectious are k and k', respectively. The disease-induced death rate for medical, ICU, and ventilator are $k_1,\ k_2$, and k_3, respectively. The schematic diagram of the model is shown in Figure 2.

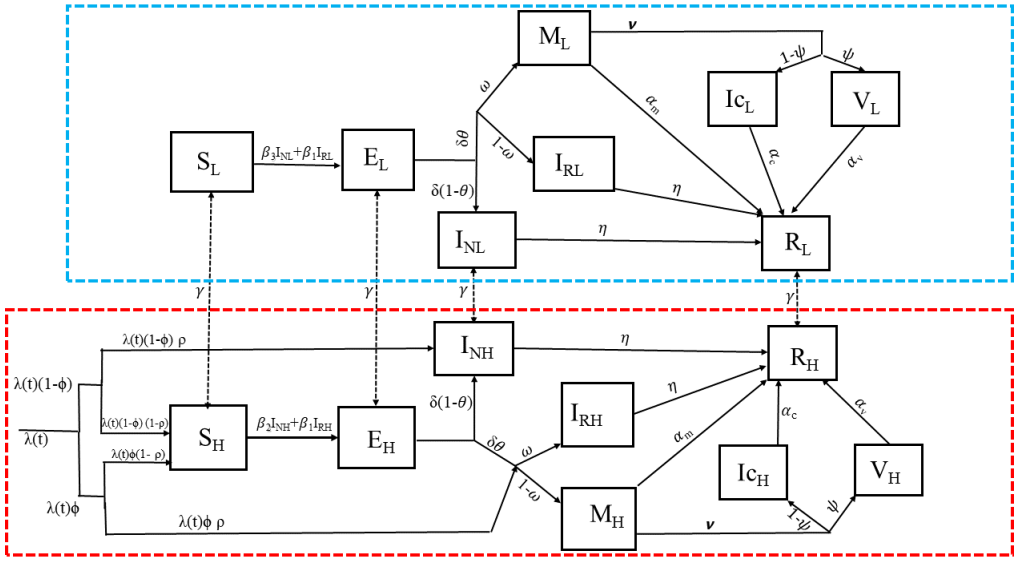

Figure 2: **The compartmental diagram of the model**. The compartments within the red box and the blue box belong to the high- and the low-risk regions, respectively. The arrow represents the transfer from one compartment to another. For clarity, the natural and disease-induced death rates are not shown in the diagram.

The dynamical system consisting of ODEs of the model is as follows:

$$\frac{dS_H}{dt} = \Lambda_H + \gamma S_L - \frac{(\beta_2 I_{\mathrm{NH}} + \beta_1 I_{\mathrm{RH}})\, S_H}{N_H} - (\gamma + \mu) S_H + \lambda(1-\rho)(1-\phi) + \lambda(1-\rho)\phi \tag{1}$$

$$\frac{dS_L}{dt} = \Lambda_L + \gamma S_H - \frac{(\beta_3 I_{NL} + \beta_1 I_{\mathrm{RL}})\, S_L}{N_L} - (\gamma + \mu) S_L \tag{2}$$

$$\frac{dE_H}{dt} = \frac{(\beta_2 I_{\mathrm{NH}} + \beta_1 I_{\mathrm{RH}})\, S_H}{N_H} + \gamma E_L - (\gamma + \delta + \mu) E_H \tag{3}$$

$$\frac{dE_L}{dt} = \frac{(\beta_3 I_{NL} + \beta_1 I_{RL})\, S_L}{N_L} + \gamma E_H - (\gamma + \delta + \mu) E_L \tag{4}$$

$$\frac{dI_{NH}}{dt} = \delta(1-\theta) E_H + \gamma I_{NL} - (\eta + k' + \mu) I_{NH} + \lambda\rho(1-\phi) - \gamma I_{NH} \tag{5}$$

$$\frac{dI_{NL}}{dt} = \delta(1-\theta) E_L + \gamma I_{NH} - (\eta + k' + \mu) I_{NL} - \gamma I_{NL} \tag{6}$$

$$\frac{dI_{RH}}{dt} = \delta\theta(1-\omega) E_H + \lambda\rho\phi(1-\omega) - (\eta + k + \mu) I_{\mathrm{RH}} \tag{7}$$

$$\frac{dI_{RL}}{dt} = \delta\theta(1-\omega) E_L - (\eta + k + \mu) I_{RL} \tag{8}$$

$$\frac{dM_H}{dt} = \delta\theta E_H \omega + \lambda\rho\omega\phi - (k_1 + \mu + \alpha_m + \nu)\, M_H \tag{9}$$

$$\frac{dM_L}{dt} = \delta\theta\omega E_L - (\alpha_m + k_1 + \mu + \nu)\, M_L \tag{10}$$

$$\frac{dI_{cH}}{dt} = \nu(1-\psi) M_H - (\alpha_c + k_2 + \mu)\, I_{cH} \tag{11}$$

$$\frac{dI_{cL}}{dt} = \nu(1-\psi) M_L - (\alpha_c + k_2 + \mu)\, I_{cL} \tag{12}$$

$$\frac{dV_H}{dt} = \nu\psi M_H - (\alpha_c + k_2 + \mu)\, V_H \tag{13}$$

$$\frac{dV_L}{dt} = \nu\psi M_L - (\alpha_c + k_2 + \mu)\, V_L \tag{14}$$

$$\frac{dR_H}{dt} = \alpha_c I_{cH} + \alpha_m M_H + \eta(I_{RH} + I_{NH}) + \alpha_v V_H + \gamma R_L - (\mu + \gamma) R_H \tag{15}$$

$$\frac{dR_L}{dt} = \alpha_c I_{cL} + \gamma R_H + \alpha_m M_L + \eta(I_{NL} + I_{RL}) + \alpha_v V_L - (\gamma + \mu) R_L. \tag{16}$$

Here, $N_H = S_H + E_H + I_{RH} + I_{NH} + M_H + I_{cH} + V_H + R_H$ and $N_L = S_L + E_L + I_{RL} + I_{NL} + M_L + I_{cL} + V_L + R_L$.

2. Modeling vaccination program

We extended our model to incorporate the vaccination program by further dividing each compartment into vaccinated and non-vaccinated compartments

except the recorded infectious compartments and medical compartments. For our study period, we assumed that there is no loss of immunity of vaccinated and recovered people. In the vaccinated compartments, there is a reduced infection rates and a reduced rates of hospitalization and medical care. The schematic compartmental diagram of the model with vaccination program is shown in Figure 3.

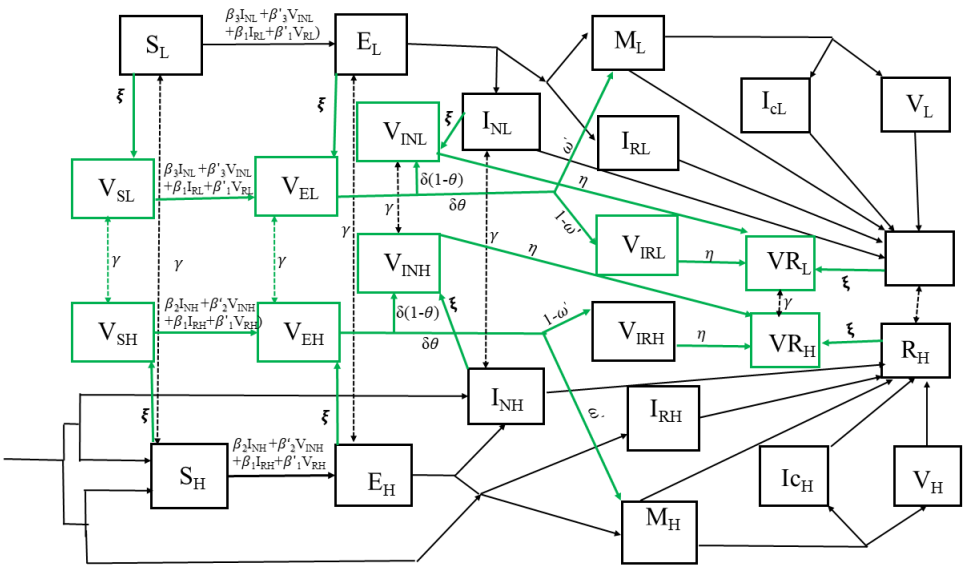

Figure 3: **The compartmental diagram of the model with vaccination**. The green boxes represent the vaccinated compartments. All other rates of transfer between compartments are the same as in Figure 2 except transmission rates and hospitalization rates ($\beta_i', i = 1, 2, 3$, and ω').

3. Computation of reproduction number

3.1. Next generation method

3.1.1. Reproduction number of the whole country

First we calculate the diseases free equilibrium point. At the disease free equilibrium point the portion of positive antigen test is zero, i.e $\rho = 0$, and we use the pre-pandamic condition $\lambda = \lambda(0)$ and $E_H = E_L = I_{RH} = I_{RL} = I_{NH} =$

$I_{NL} = M_H = M_L = I_{cH} = I_{cL} = V_H = V_L = 0$. We get the following disease free equilibrium point: $E^* = (S_H^*, S_L^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$, where

$$S_H^* = \frac{\lambda(0)(\gamma+\mu) + (\gamma+\mu)\Lambda_H + \gamma\Lambda_L}{\mu(2\gamma+\mu)},\ S_L^* = \frac{\gamma\lambda(0) + \gamma\Lambda_H + (\gamma+\mu)\Lambda_L}{\mu(2\gamma+\mu)}.$$

We now divide the compartments into two groups: infected $\vec{x} = (x_i, i = 1, 2, ..., 12) = (E_H, E_L,$
$I_{RH}, I_{RL}, I_{NH}, I_{NL}, M_H, M_L, I_{cH}, I_{cL}, V_H, V_L)$ and non-infected $\vec{y} = (y_j, j = 1, 2, 3, 4) = (S_H, S_L, R_H, R_L)$. Then the system (1-16) can be written as:

$$x_i' = f_i(\vec{x}, \vec{y}) \text{ and } y_j' = g_j(\vec{x}, \vec{y}) \text{ for } i = 1, 2, ..., 12, j = 1, 2, 3, 4.$$

The right hand side of the system of infected compartments can be written as: $f_i(\vec{x}, \vec{y}) = F_i(\vec{x}, \vec{y}) - V_i(\vec{x}, \vec{y})$, where $F_i(\vec{x}, \vec{y})$ contains the terms representing the new infections in compartment i and $V_i(\vec{x}, \vec{y})$ contains the terms containing the difference between the transfer of individuals out of and into the compartment i. Then we construct the following two matrices using $F = \left(\frac{\partial F_i}{\partial x_i}\right)$ and $V = \left(\frac{\partial V_i}{\partial x_i}\right)$ at the diseases free equilibrium (DFE) point as follows:

$$F = \begin{pmatrix} A_{6\times6} & 0_{6\times6} \\ 0_{6\times6} & 0_{6\times6} \end{pmatrix},\ V = \begin{pmatrix} B_{8\times6} & 0_{6\times6} \\ 0_{4\times6} & C_{6\times6} \end{pmatrix},$$

where

$$A = \begin{pmatrix} 0 & 0 & \frac{\beta_1 S_H^*}{N_L^*} & 0 & \frac{\beta_H S_H^*}{N_H^*} & 0 \\ 0 & 0 & 0 & \frac{\beta_1 S_L^*}{N_L} & 0 & \frac{\beta_L S_L^*}{N_L^*} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$B = \begin{pmatrix} \gamma+\delta+\mu & -\gamma & 0 & 0 & 0 & 0 \\ -\gamma & \gamma+\delta+\mu & 0 & 0 & 0 & 0 \\ -\delta\theta(1-\omega) & 0 & k+\eta+\mu & 0 & 0 & 0 \\ 0 & -\delta\theta(1-\omega) & 0 & k+\eta+\mu & 0 & 0 \\ -\delta(1-\theta) & 0 & 0 & 0 & \gamma+\eta+\mu+k' & -\gamma \\ 0 & -\delta(1-\theta) & 0 & 0 & -\gamma & \gamma+\eta+\mu+k' \\ -\delta\theta\omega & 0 & 0 & 0 & 0 & 0 \\ 0 & -\delta\theta\omega & 0 & 0 & 0 & 0 \end{pmatrix},$$

and

$$C = \begin{pmatrix} p & 0 & 0 & 0 & 0 & 0 \\ 0 & p & 0 & 0 & 0 & 0 \\ -\nu(1-\psi) & 0 & q & 0 & 0 & 0 \\ 0 & -\nu(1-\psi) & 0 & q & 0 & 0 \\ -\nu\psi & 0 & 0 & 0 & r & 0 \\ 0 & -\nu\psi & 0 & 0 & 0 & r \end{pmatrix}.$$

Here $p = k_1 + \mu + \alpha_m$, $\quad q = \alpha_c + k_2 + \mu$, and $r = k_3 + \mu + \alpha_v$.

The largest eigenvalue of the matrix FV^{-1} gives the basic reproduction number as follows:

$$R_0 = \frac{1}{2}\left(D + \sqrt{D^2 - 4E}\right), \tag{17}$$

where

$$D = \frac{\beta_1 T_1 S_H^* N_L^* + \beta_1 T_1 S_L^* N_H^* + \beta_2 T_3 S_H^* N_L^* + \beta_3 T_3 S_L^* N_H^*}{N_H^* N_L^*},$$

$$E = \frac{S_H^* S_L^* \left(\beta_1^2 T_1^2 - \beta_1^2 T_2^2 + (\beta_2+\beta_3)\,\beta_1 T_1 T_3 - (\beta_2+\beta_3)\,\beta_1 T_2 T_4 + \beta_2\beta_3\left(T_3^2 - T_4^2\right)\right)}{N_H^* N_L^*},$$

$$T_1 = \frac{\delta\theta(1-\omega)(\gamma+\delta+\mu)}{(\delta+\mu)(2\gamma+\delta+\mu)(\eta+k+\mu)}, \qquad T_2 = \frac{\gamma\delta\theta(1-\omega)}{(\delta+\mu)(2\gamma+\delta+\mu)(\eta+k+\mu)},$$

$$T_3 = \frac{\gamma\delta(1-\theta)\,(2\gamma+\delta+\eta+k'+2\mu)}{(\delta+\mu)N_L(2\gamma+\delta+\mu)\,(\eta+k'+\mu)\,(2\gamma+\eta+k'+\mu)},$$

$$\text{and} \quad T_4 = \frac{\delta(1-\theta)\left(\delta\eta+\delta\mu+\eta\mu+\gamma\,(2\gamma+\delta+\eta+k'+2\mu)+\delta k'+\mu k'+\mu^2\right)}{(\delta+\mu)(2\gamma+\delta+\mu)\,(\eta+k'+\mu)\,(2\gamma+\eta+k'+\mu)}.$$

At the Diseases Free Eqilibrium (DFE) point, $S_H^* = N_H^*$, and $S_L^* = N_L^*$, then the basic reproduction number is obtained as:

$$R_0 = \frac{1}{2}\left(2\beta_1 T_1 + \beta_2 T_3 + \beta_3 T_3 + \sqrt{4\beta_2\beta_3 T_4^2 + 4\beta_1\beta_3 T_2 T_4 + 4\beta_1^2 T_2^2 + (\beta_2 - \beta_3)^2 T_3^2 + 4\beta_1\beta_2 T_2 T_3}\right). \tag{18}$$

The corresponding effective reproduction number is obtained by making the respective state variables of 17 as function of t.

3.1.2. Reproduction number of the high-risk region

Similar to the section 3.1.1, we construct the following two matrices for high risk region at DFE point as follows:

$$F_H = \begin{pmatrix} 0 & \frac{\beta_1 S_H^*}{N_H^*} & \frac{\beta_2 S_H^*}{N_H^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V_H = \begin{pmatrix} \gamma+\delta+\mu & 0 & 0 & 0 & 0 & 0 \\ -\delta\theta(1-\omega) & k+\eta+\mu & 0 & 0 & 0 & 0 \\ -\delta(1-\theta) & 0 & k'+\gamma+\eta+\mu & 0 & 0 & 0 \\ -\delta\theta\omega & 0 & 0 & \mu+\nu+k_1+\alpha_m & 0 & 0 \\ 0 & 0 & 0 & -\nu(1-\psi) & \mu+k_2+\alpha_c & 0 \\ 0 & 0 & 0 & -\nu\psi & 0 & \mu+k_3+\alpha_v \end{pmatrix}.$$

The dominated Eigenvalue of $F_H V_H^{-1}$ gives the basic reproduction number of the high-risk region as follows.

$$R_{H0} = \frac{S_H^*\delta\left(\beta_2(1-\theta)(\eta+k+\mu) + \theta\beta_1(1-\omega)(\gamma+\eta+k'+\mu)\right)}{N_H^*(\gamma+\delta+\mu)(\eta+k+\mu)(\gamma+\eta+k'+\mu)}. \tag{19}$$

. Using $N_H^* = S_H^*$ for DFE point, we obtain

$$R_{H0} = \frac{\delta\left(\beta_2(1-\theta)(\eta+k+\mu) + \theta\beta_1(1-\omega)(\gamma+\eta+k'+\mu)\right)}{(\gamma+\delta+\mu)(\eta+k+\mu)(\gamma+\eta+k'+\mu)}. \tag{20}$$

The corresponding effective reproduction number is obtained by making the respective state variables of 19 as function of t.

3.1.3. Reproduction number of the low-risk region

Similar to the section 3.1.1, we construct the following two matrices for low risk region at DFE point as follows:

$$F_L = \begin{pmatrix} 0 & \frac{\beta_1 S_L^*}{N_L^*} & \frac{\beta_3 S_L^*}{N_L^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V_L = \begin{pmatrix} \gamma+\delta+\mu & 0 & 0 & 0 & 0 & 0 \\ -\delta\theta(1-\omega) & k+\eta+\mu & 0 & 0 & 0 & 0 \\ -\delta(1-\theta) & 0 & k'+\gamma+\eta+\mu & 0 & 0 & 0 \\ -\delta\theta\omega & 0 & 0 & \mu+\nu+k_1+\alpha_m & 0 & 0 \\ 0 & 0 & 0 & -\nu(1-\psi) & \mu+k_2+\alpha_c & 0 \\ 0 & 0 & 0 & -\nu\psi & 0 & \mu+k_3+\alpha_v \end{pmatrix}.$$

The dominated eigenvalue of $F_H V_H^{-1}$ gives the basic reproduction number as follows.

$$R_{L0} = \frac{S_L^* \delta \left(\beta_1 \theta(1-\omega)(\gamma+\eta+k'+\mu) + \beta_3(1-\theta)(\eta+k+\mu)\right)}{N_L^*(\gamma+\delta+\mu)(\eta+k+\mu)(\gamma+\eta+k'+\mu)}. \tag{21}$$

Using $N_L^* = S_L^*$ for DFE point, we obtain

$$R_{L0} = \frac{\delta \left(\beta_1 \theta(1-\omega)(\gamma+\eta+k'+\mu) + \beta_3(1-\theta)(\eta+k+\mu)\right)}{(\gamma+\delta+\mu)(\eta+k+\mu)(\gamma+\eta+k'+\mu)}. \tag{22}$$

The corresponding effective reproduction number is obtained by making the respective state variables of 22 as function of t.

3.1.4. Maximum likelihood method on data

There are number of methods to estimate the basic reproduction number from the disease incidence data. Among them, the method proposed by White and Pagano [5, 6] known as the maximum likelihood method (MLM), is widely used in many studies.

We also calculate the effective Reproduction number (R_t) from the daily incidence data as a marker for the decrease or surge in infections from the real-time data. Time-varying R_t can be calculated using the time series of the infections and generation time distribution [3]. We use the approach developed by Thompson et al [2] for the estimation of effective reproduction numbers using the EpiEstem package of the R program. We take the mean serial interval as 4.7 days days, with an SD of 2.9 days days based on the previous study [4].

3.2. Parameter estimation and model fitting to data

3.2.1. Data fitting

The model is fitted to the multiple data sets, containing the daily new cases of the whole country, the high-risk and low-risk regions, and patients in medical care, ICU, and ventilators. From our model, the recorded new infections in Nepal, the high-risk region, and the low-risk region, the number of patients in medical care, ICU and ventilator at time t can be computed using the following respective equations:

$$L_r(t) = \delta\theta E_H + \lambda(t)\phi\rho + \delta\theta E_L, \tag{23}$$

$$L_{rh}(t) = \delta\theta E_H + \lambda(t)\phi\rho, \tag{24}$$

$$L_{rl}(t) = \delta\theta E_L, \tag{25}$$

$$L_m(t) = \delta\omega\theta(E_H+E_L)+\lambda(t)\phi\rho\omega-\alpha_m(M_H+M_L)-k_1(M_H+M_L)-\nu(M_H+M_L), \tag{26}$$

$$L_c(t) = \nu(1-\psi)(M_H+M_L) - (k_2+\alpha_c)(M_H+M_L), \tag{27}$$

$$L_v(t) = \nu\psi(M_H+M_L) - (k_3+\alpha_v)(V_H+V_L). \tag{28}$$

We solve the system of differential equations numerically using a fourth-order Runge-Kutta method. We use the solutions to obtain the best-fit parameters via a nonlinear least-squares regression method that minimizes the following sum of the squared residuals:

$$J = \sum_{i=1}^{n} \big[\big(L_r(t_i) - \bar{L_r}(t_i)\big)^2 + \big(L_{rh}(t_i) - \bar{L_{rh}}(t_i)\big)^2 + \big(L_{rl}(t_i) - \bar{L_{rl}}(t_i)\big)^2 + \big(L_m(t_i) - \bar{L_m}(t_i)\big)^2 + \big(L_c(t_i) - \bar{L_c}(t_i)\big)^2 + \big(L_v(t_i) - \bar{L_v}(t_i)\big)^2 \big].$$

Here, $\beta_1, \beta_H, \beta_L, \theta, r_H, r_L, \gamma_1, \gamma_2, \omega, \nu, \psi, \alpha_m, \alpha_c, \alpha_v, \nu, k, k', k_1, k_2$, and k_3 are parameters to be estimated. $L_r(t_k), L_{rh}(t_i), L_{rl}(t_i), L_m(t_i), L_c(t_i), L_v(t_i)$ are model values and $\bar{L_r}(t_i), \bar{L_{rh}}(t_i), \bar{L_{rl}}(t_i), \bar{L_m}(t_i), \bar{L_c}(t_i), \bar{L_v}(t_i)$ are those given in the available data of the respective classes. n represents the total number of data points used for the model fitting.

In our study, all computations were carried out in MATLAB 2020a (The MathWorks, Inc.).

3.2.2. Initial values of the state variables

Description	State variables	Base Value	Reference
Susceptible population in high risk region	$S_H(0)$	12,818,000	Calculated
Susceptible population in low risk region	$S_L(0)$	6,479,000	Calculated
Exposed population in high risk region	$E_H(0)$	100	Assumed
Exposed population in low risk region	$E_L(0)$	80	Assumed
Recorded infectious population in high risk region	$I_{RH}(0)$	200	Assumed
Recorded infectious population in low risk region	$I_{RL}(0)$	100	Assumed
Non-Recorded infectious population in high risk region	$I_{NH}(0)$	1000	Assumed
Non-Recorded infectious population in low risk region	$I_{NL}(0)$	800	Assumed
Patients in medical care in high risk region	$M_H(0)$	0	Assumed
Patients in medical care in low risk region	$M_L(0)$	0	Assumed
Patients in medical care in high risk region	$I_{cH}(0)$	0	Assumed
Patients in medical care in low risk region	$M_{cL}(0)$	0	Assumed
Patients in medical care in high risk region	$V_H(0)$	0	Assumed
Patients in medical care in low risk region	$V_L(0)$	0	Assumed
Recovered population in high risk region	$R_H(0)$	460,8000	Calculated
Recovered population in low risk region	$R_L(0)$	256,8000	Calculated

References

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