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Data-driven models for the risk of infection and hospitalization during a pandemic: Case study on COVID-19 in Nepal

Khagendra Adhikari [a], Ramesh Gautam [b], Anjana Pokharel [c], Kedar Nath Uprety [d], Naveen K. Vaidya [e,f,g,*]

[a] Amrit Campus, Tribhuvan University, Kathmandu, Nepal
[b] Ratna Rajya Laxmi Campus, Tribhuvan University, Kathmandu, Nepal
[c] Padma Kanya Multiple Campus, Tribhuvan University, Kathmandu, Nepal
[d] Central Department of Mathematics, Tribhuvan University, Kathmandu, Nepal
[e] Department of Mathematics and Statistics, San Diego State University, San Diego, CA, USA
[f] Computational Science Research Center, San Diego State University, San Diego, CA, USA
[g] Viral Information Institute, San Diego State University, San Diego, CA, USA

ABSTRACT

The newly emerging pandemic disease often poses unexpected troubles and hazards to the global health system, particularly in low and middle-income countries like Nepal. In this study, we developed mathematical models to estimate the risk of infection and the risk of hospitalization during a pandemic which are critical for allocating resources and planning health policies. We used our models in Nepal's unique data set to explore national and provincial-level risks of infection and risk of hospitalization during the Delta and Omicron surges. Furthermore, we used our model to identify the effectiveness of non-pharmaceutical interventions (NPIs) to mitigate COVID-19 in various groups of people in Nepal. Our analysis shows no significant difference in reproduction numbers in provinces between the Delta and Omicron surge periods, but noticeable inter-provincial disparities in the risk of infection (for example, during Delta (Omicron) surges, the risk of infection of Bagmati province is: ~ 98.94 (89.62); Madhesh province: ~ 12.16 (5.1); Karnali province ~31.16 (3) per hundred thousands). Our estimates show a significantly low level of hospitalization risk during the Omicron surge compared to the Delta surge (hospitalization risk is: ~ 10% in Delta and ~ 2.5% in Omicron). We also found significant inter-provincial disparities in the hospitalization rate (for example, ~ 6% in Madhesh province and ~ 21% in Sudur Paschim) during the Delta surge. Moreover, our results show that closing only schools, colleges, and workplaces reduces the risk of infection by one-third, while a complete lockdown reduces the infections by two-thirds. Our study provides a framework for the computation of the risk of infection and the risk of hospitalization and offers helpful information for controlling the pandemic.

1. Introduction

The COVID-19 pandemic has expanded globally in multiple waves, resulting in considerable clinical expenses due to the emergence of new Corona Virus strains. Despite the global control efforts and the development of vaccines, the disease has triggered a catastrophic impact with more than 692.58 million cases and more than 6.90 million deaths as of 3 August 2023 (Worldometer, 2023). Notably, during the pandemic, a lack of knowledge about the risk of circulating new strains, which may be more contagious and capable of evading the immune response of previously infected or vaccinated individuals, may lead to unusually high cases (Islam et al., 2022). Due to the uncertainty and variability in disease severity across different strains, there are often insufficient resources and preparedness, resulting in overwhelmed hospitalizations and shortages of medical staff, equipment, and beds. Consequently, individuals may postpone seeking medical attention and neglect preventive measures, which can ultimately increase the risk of death, as witnessed in Nepal and India during the Delta variant outbreak (Adhikari et al., 2022; Malik, 2022). The uncertainty on the risk of infection and hospitalization may have a greater impact, especially on developing countries like Nepal, because of the resource limitations. Thus, estimating the real-time risk of infection and hospitalization is crucial for assessing disease transmission and managing medical resources to minimize the burden of pandemics.

Nepal, one of the least developed countries in the world, has been severely impacted by the COVID-19 pandemic (Adhikari et al., 2022; Ben, 2021; Bhandari and Hannah Peterse, 2021). Specifically, the second and third waves with the respective Delta and Omicron variants swept across the country from the beginning of April 2021, resulting in one million cases and 12,019 deaths (MoHP, 2022) until 1 December 2022. During the peak of the second wave of COVID-19 (end of May 2021), Nepal experienced a terrifying shortage of hospital beds, ICU beds, ventilators, and oxygen cylinders, which resulted in a loss of potentially preventable lives (Ben, 2021; Bhandari and Hannah Peterse,

* Corresponding author at: .
E-mail address: nvaidya@sdsu.edu (N.K. Vaidya).

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2021). The first case of Omicron in Nepal was detected on 6 December 2021 (Poudel, 2021). On 23 January 2022, the Omicron variant constituted 88% of the new cases (Poudel, 2022) and then quickly swept across the country but with significantly less severe cases than the Delta wave (Worldometer, 2023; MoHP, 2022).

The seven provinces of Nepal have various contact patterns of population because of the diverse geographical areas, distinct lifestyles, cultural practices, economic circumstances, and levels of urbanization in these areas (Pantha et al., 2021), which also pose challenges in testing and reporting COVID-19 cases. As a result, each of Nepal's seven provinces had specific vulnerabilities during Delta and Omicron surges. These distinctive features highlight the importance of context-specific distinct Nepalese data set with a multi-phasic trend of disease dynamics to perform an in-depth analysis of the risk of infection and hospitalization in the context of the geographic and demographic heterogeneity among the provinces of Nepal.

The effective reproduction number is widely used to assess the speed of an epidemic; if it is greater than one, the disease is rising (van den Driessche and Watmough, 2002). However, due to the differences in the size of the susceptible population, the number of infected individuals, and the population's contact pattern, two localities with the same effective reproduction number may be vulnerable in different magnitudes (different magnitudes of incidence) during the pandemic. In such situations, estimating the risk of infection and hospitalization is essential, which can better describe epidemic status and healthcare capabilities. Limited clinical case studies (Dorabawila et al., 2022; Berumen et al., 2020; Lehnig et al., 2021; Tang et al., 2020; Rajiv and Jeffrey, 2020; Xiang et al., 2022) and a handful of mathematical models (Bhatia and Klausner, 2020; Wan et al., 2020; Mizumoto and Chowell, 2020; Meehan et al., 2020) estimate the risk of infection and hospitalization. However, none of these studies have combined mathematical models with real-time incidence data, active hospitalization, and population contact patterns, constituting the essential factors associated with disease transmission and controls. Such data-driven mathematical models can accurately estimate and quantify the real-time risk of infection and hospitalization during the pandemic (Adhikari et al., 2022; Pantha et al., 2021; Nabi, 2020).

In this study, we developed data-driven models to estimate the real-time risk of infection and hospitalization. Then we implemented our models on the data of COVID-19 in Nepal to estimate the province-wise time-dependent reproduction numbers, the risk of disease, and the risk of hospitalization. Using our models, we compared the Delta and Omicron waves and their impacts on the province-level community and healthcare systems. Furthermore, we used our model to evaluate the effects of intervention policies on the risk of infections.

2. Methods

2.1. Data

The countrywide and province-wise data were obtained from various available sources, including the official websites of the Ministry of Health and Population Nepal (MoHP, 2022) and the Central Bureau of Statistics (Central Bureau of Statistics (CBS), 2022). We considered the data containing the daily new COVID-19 cases and the active hospitalization cases in seven provinces of Nepal from 1 April 2021 to 31 March 2022, covering both Delta and Omicron waves. Based on the information about the circulating viral strains, we assumed that the Delta surge occurred between 1 April and 30 December 2021 and that the Omicron surge occurred from 1 January to 31 March 2022.

The contact rate, which depends upon the mobility of the population, plays a vital role in disease transmission. Since the population is a heterogeneous mixture of different age groups with different mobility and contact patterns, we utilized a previous study's age-specific contact rates for Nepal (Prem et al., 2017). Here, a contact is defined as either skin-to-skin contact, such as a kiss or handshake (a physical contact), or a two-way conversation with three or more words in the physical presence of another person but no skin-to-skin contact (a nonphysical contact) (Prem et al., 2017). Based on the previous studies (Prem et al., 2017; Mossong et al., 2008), we estimated an average of 19.31 contacts per person daily. The contact matrix, including population mixing patterns and distribution of contacts by age groups, is presented in Fig. 1. We calculated the group-wise contact rate using the weighted arithmetic mean of contact rates of different age groups. Details of the study design and data collection procedure of contact rate are provided in the previous study (Prem et al., 2017).

Table 1
Total population of Nepal and its provinces. The third column contains the populations used in our study.

Regions	Total population	Population for the study (0.9255 × Total population)
Nepal	29,136,808	26,966,116
Province 1	4,972,021	4,601,605
Madhesh province	6,126,288	5,669,880
Bagmati province	6,084,082	5,630,818
Gandaki province	2,479,745	2,295,004
Lumbini province	5,124,225	4,742,470
Karnali province	1,694,889	1,568,620
Sudur Paschim province	2,711,270	2,509,280

We took the total population of Nepal and its seven provinces from the recently published results of the population census of Nepal (2021) (Central Bureau of Statistics (CBS), 2022). Since about 7.45% of Nepalese are in foreign countries (Central Bureau of Statistics (CBS), 2022), we only took 92.55% of the total population for our study. The total population and population used in our study are given in Table 1. We assumed the infectious period of the Delta variant to be 10 days (Herrero, 2021) and that of the Omicron variant to be 7 days (Ontario Agency for Health Protection and Promotion (Public Health Ontario), 2021; Walensky, 2021).

2.2. Estimation of the effective reproduction number (R_t)

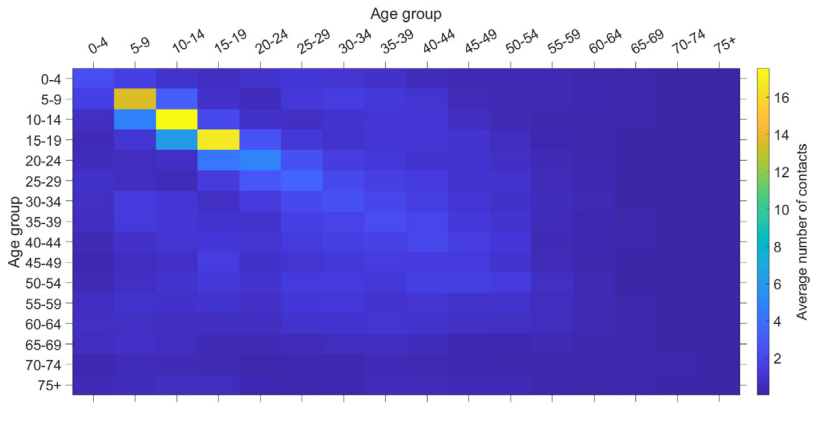
The effective reproduction number, R_t, is the real-time estimation of the reproduction number that represents the average number of secondary infections from an infected individual in his/her infectious period at time t (Thompson et al., 2019). Here, we used the Maximum Likelihood Method (MLM) described in the previous studies (Cori et al., 2013; Thompson et al., 2019) to estimate the effective reproduction number. We require two data sets to estimate R_t using MLM: the number of new cases (incidence of cases) over time and the generation time (time duration between the primary and secondary infection). The generation time is usually not observable but can be approximated with the serial interval (Kuk and Ma, 2005), which is defined as the time between the onset of symptoms of primary cases and that of secondary cases (Wallinga and Teunis, 2004). Many studies (Zhang et al., 2020; Talmoudi et al., 2020; Challen et al., 2020; Rai et al., 2021) have reported that the serial interval follows a Gamma distribution with certain means and standard deviations.

Assuming that the secondary cases at time t generated by the cases infected at time s ($s = 1, 2, \dots, t$) follow the Poisson distribution with mean $R_t\psi_t = R_t \sum_{s=1}^{t} I_{t-s} w_s$, where $\psi_t = \sum_{s=1}^{t} I_{t-s} w_s$ and w_s is a Gamma distribution of serial interval describing the infectiousness at time s after infection, the likelihood function of secondary cases is

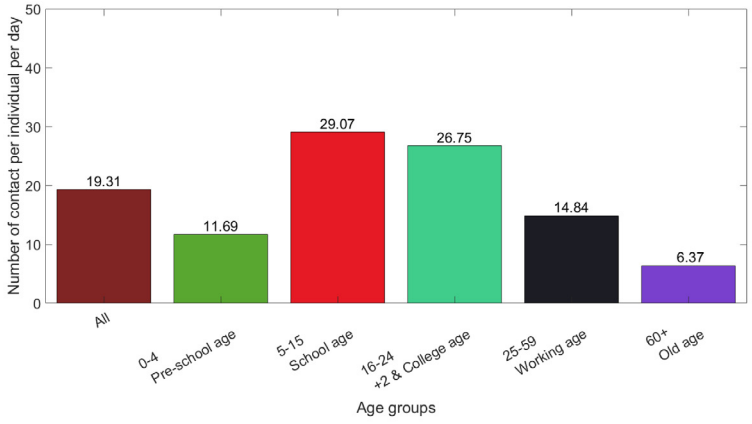
$$L(R_t) = \frac{(R_t\psi_t)^{I_t}\, e^{-R_t\psi_t}}{I_t!}.$$

We assumed that the reproduction rate R_t remains constant over the small time period $[t-\tau,\ t]$ and is denoted as $R_{t,\tau}$. The likelihood of the secondary cases over the time period $[t-\tau,\ t]$ with given previous incidences $I_0, I_1, \dots, I_{t-\tau-1}$ is

$$L(R_{t,\tau}) = \prod_{s=t-\tau}^{t} \frac{(R_{s,\tau}\psi_{s,\tau})^{I_s}\, e^{-R_{s,\tau}\psi_{s,\tau}}}{I_s!}. \quad (1)$$



(a)



(b)

Fig. 1. (a) Age-specific contact matrix for Nepal (Prem et al., 2017). The two axes that start at the top left of the matrix represent the age groups that make up the population. (b) The average number of contacts per individual per day of different age groups in Nepal. The age groups are split into the following categories: preschool, school, 10+2 and college, working, and old age.

Using a Bayesian framework with a Gamma distributed prior with parameters (a, b), the posterior joint distribution of $R_{t,\tau}$ is given by a Gamma distribution with the parameters

$$\left(a + \sum_{s=l-\tau}^{t} I_s, \quad \frac{1}{\frac{1}{b} + \sum_{s=l-\tau}^{t} \psi_s} \right).$$

For our base-case computations, we used the serial interval with the Gamma distribution with a mean of 4.7 days and a standard deviation of 2.9 days for the Delta variant (Musa et al., 2020), and a mean of 3.5 days and standard deviation of 2.4 days for the Omicron variant (Backer et al., 2022). For the computation of reproduction numbers, we used the 'EpiEstim' package of R-software (R 4.2.1) (Cori et al., 2013; Thompson et al., 2019).

2.3. Estimation of risk of infection

We assumed that C_t represents the instantaneous contacts of an individual at time t and C is the average (expected) number of daily contacts. We assumed the contact (C_t) follows a Poisson distribution with mean C, i.e., $C_t \sim \text{Pois}(C)$. We further assumed that N is the total population, which we assumed to be constant during the short period of a single surge, and I_t and I_t^A are the number of new infections and active infections at time t, respectively. Taking ζ as the average infectious period (in days), $I_t^A = \sum_{s=t-\zeta}^{t} I_s$. Thus, the average contacts of an individual with the infectious people at time t is $C_t I_t^A / N$.

We now assume P_t to be the probability that a single contact with infectious people leads to successful infection and S_t to be the number of susceptible individuals at time t. Then the number of new infections at time t is $C_t \frac{I_t^A}{N} P_t S_t$. Also, since the effective reproduction number is R_t, the number of new infections generated by a single infectious individual at time t is R_t/ζ. On average, the total new cases generated by all infectious people I_t^A at time t is $R_t I_t^A/\zeta$. Thus we have

$$C_t \frac{I_t^A}{N} P_t S_t = R_t I_t^A/\zeta$$
$$\implies P_t = R_t N/(\zeta C_t S_t),$$

which gives the probability of infection at a single contact with an infectious person. Then, $(1 - P_t)$ represents the probability that a single contact with infectious people does not result in a successful infection. There are $C_t I_t^A/N$ contacts of an individual with infectious people at time t. Then, the probability that non of these contacts with infectious people results in a successful infection is $(1 - P_t)^{C_t I_t^A/N}$. Thus, the probability of infections (i.e., the risk of infection at time t) is

$$1 - (1 - P_t)^{C_t I_t^A/N}.$$

The computations of the risk of infection were carried out in MATLAB 2021a (The MathWorks, Inc.).

2.4. Estimation of risk of hospitalization

We considered time-to-hospitalization a random variable because it is randomly influenced by various factors, such as the severity of illness,

access to healthcare, demographic factors, the geographic variation that are subject to variation and uncertainty. These factors can differ both across individuals and geographic regions, resulting in heterogeneity in the distribution of time-to-hospitalization. We assume g_h to be the probability distribution of the time-to-hospitalization after becoming infected at time h and $\mathcal{H}_t$ to be the risk of hospitalization at time t of an infection. Therefore, the number of new hospitalized cases at time t is $\mathcal{H}_t \sum_{h=1}^{t} I_{t-h} g_h = \mathcal{H}_t \lambda_t$, where $\lambda_t = \sum_{h=1}^{t} I_{t-h} g_h$. Denoting ν as the average duration of the stay at the hospital, the number of active hospitalized cases at time t is

$$\sum_{j=t-\nu+1}^{t} \mathcal{H}_j \lambda_j.$$

We assumed that the active hospitalization cases follow the Poisson process. Then the likelihood of active hospitalized cases H_t with given hospitalization rate $\mathcal{H}_t$, incidences $I_0, I_1, I_2, \ldots, I_t$, and distribution g_h is:

$$P(H_t | I_0, I_1, I_2, \ldots, I_t, g_h, \mathcal{H}_t) = \frac{\left(\sum_{j=t-\nu+1}^{t} \mathcal{H}_j \lambda_j\right)^{H_t} e^{-\sum_{j=t-\nu+1}^{t} \mathcal{H}_j \lambda_j}}{H_t!}.$$

Using a Bayesian framework with a Gamma distributed prior with parameters (θ, ϕ) for $\mathcal{H}_t$, i.e., $\mathcal{H}_t \sim \text{Gamma}(\theta, \phi)$, the posterior joint distribution of $\mathcal{H}_t$ is

$$\begin{aligned} & P(\mathcal{H}_t | I_0, I_1, I_2, \ldots, I_t, H_t, g_h) \\ \propto\ & P(H_t | I_0, I_1, I_2, \ldots, I_t, g_h, \mathcal{H}_t)\ P(\mathcal{H}_t) \\ =\ & \frac{\left(\sum_{j=t-\nu+1}^{t} \mathcal{H}_j \lambda_j\right)^{H_t} e^{-\sum_{j=t-\nu+1}^{t} \mathcal{H}_j \lambda_j}}{H_t!} \cdot \frac{\mathcal{H}^{\theta-1} e^{-\frac{\mathcal{H}}{\phi}}}{\Gamma(\theta)\phi^{\theta}}. \end{aligned}$$

Since the stay in hospital is shorter than the surge period, we assumed that $\mathcal{H}_t$ is constant for the time period $t-\nu$ to t. Then we obtained

$$\begin{aligned} & P(\mathcal{H}_t | I_0, I_1, I_2, \ldots, I_{t-\nu}, H_t, g_h) \\ \propto\ & \frac{\mathcal{H}_t^{H_t} \left(\sum_{j=t-\nu+1}^{t} \lambda_j\right)^{H_t} e^{-\mathcal{H}_t \sum_{j=t-\nu+1}^{t} \lambda_j}}{H_t!} \frac{\mathcal{H}_t^{\theta-1} e^{-\frac{\mathcal{H}_t}{\phi}}}{\Gamma(\theta)\phi^{\theta}} \\ \propto\ & \left(\mathcal{H}_t^{H_t+\theta-1} e^{-\mathcal{H}_t \left(\sum_{j=t-\nu+1}^{t} \lambda_j + 1/\phi\right)}\right) \frac{\left(\sum_{j=t-\nu+1}^{t} \lambda_j\right)^{H_t}}{H_t!}. \end{aligned}$$

Note that we used the Gamma distributed prior conjugate to the Poisson likelihood. From the expression above, the posterior distribution of $\mathcal{H}_t$, given the new cases and active hospitalized cases, conditional on the post-infection hospitalization timing distribution g_h, is a Gamma distribution with parameters

$$\left(\theta + H_t,\ \frac{1}{\frac{1}{\phi} + \sum_{j=t-\nu+1}^{t} \lambda_j}\right).$$

We obtained a sample of a certain size (m) drawn from this posterior distribution of $\mathcal{H}_t$ given new cases and active hospitalized data from which the posterior mean and 95% Credible Interval (CrI) of $\mathcal{H}_t$ were computed. Since the exact time of infection is not observable and people only admit to the hospital if they feel some complications, the time between the infection and hospitalization cannot be precisely measured. For our simulation, we considered a gamma-distributed duration between infection and hospital admission, with a mean of 3 days and a standard deviation of 2 days.

The computations of the risk of hospitalization were carried out in MATLAB 2021a (The MathWorks, Inc.).

2.5. Impact of non-pharmaceutical interventions (NPIs)

To model different levels of control interventions, we applied corresponding percentage reductions in average contact rates, e.g., a 70% control intervention would result in a 70% reduction in contact rates. As the Nepal Government implemented a significant level of lockdown during the Delta wave, we considered the 70% control intervention as the base case. During the Omicron wave, only primary and secondary schools were closed for a short period (from 11 January to 29 January 2022) (Kathmandu Post, 2022), which we did not expect to have a significant impact, so we assumed a 0% control intervention for the Omicron wave.

In our modeling, the overall impact of NPIs was represented by the reduction of contact rate, which we considered to be 0%, 40%, and 70% for simulations with different levels of control interventions. For the impact of NPIs in age groups (schools, colleges, and working), we reduced the contact rate of the respective age group by 70% while keeping the contact rates of other groups unchanged and calculated the corresponding average contact rates. With these assumptions and based on the previous study (Prem et al., 2017), we estimated the contact rates of 13.79 for the closure of schools and colleges, 14.65 for the closure of working places, and 5.79 for the lockdown.

3. Results

3.1. Reproduction number

As menionted earlier, the reproduction number indicates the trend of disease spread throughout the population (Dharmaratne et al., 2020). Specifically, if it is more than 1, the disease spread has an increasing trend, and if it is less than 1, the spread has a decreasing trend (van den Driessche and Watmough, 2002).

In Fig. 2 (left column), we present our estimates of the effective reproduction number in Nepal and its provinces from 21 April to 31 December 2021 (the Delta wave). The reproduction number was higher than the threshold value one at the beginning of April 2021. Except for Gandaki province, the reproduction number in Nepal and all of its provinces exceeded two and peaked in the middle of April 2021 (Nepal: 2.20, 95% CrI [2.166, 2.23], Province 1: 2.18, 95% CrI [2.04, 2.32], Madhesh: 2.61, 95% CrI [2.12, 3.14], Bagmati: 2.28, 95% CrI [2.23, 2.33], Gandaki: 1.84, 95% CrI [1.79, 1.89], Lumbini: 2.29, 95% CrI [2.28, 2.30], Karnali: 2.44, 95% CrI [1.68, 3.32], and Sudur Paschim: 2.63, 95% CrI [2.38, 2.89]). These early R_t values indicate that at the beginning of the Delta wave, the infections were rapidly spreading across the country in a short period of time. The reproduction rate in Nepal and its provinces began to fall below the threshold value one after the middle of May 2021 (Nepal: May 17; Province 1, Bagmati, and Gandaki: May 16; Madhesh: May 25; Lumbini: May 14; Karnali: May 24; Sudur Paschim: May 14 2021). Madhesh, Karnali, and Sudur Paschim provinces, where fewer cases were reported, showed greater fluctuations in the temporal pattern of the effective reproduction number.

The first incidence of Omicron in Nepal was detected on 6 December 2021 (Poudel, 2021). After the first week of January 2022, cases surged and spread rapidly. On January 23 2022, 80% of new cases were Omicron (Poudel, 2022). So, we estimate the effective reproduction number from 1 January to 31 April 2022 to characterize the period of the Omicron surge (Fig. 2, right column). The reproduction number in Nepal and all provinces were at the threshold level ($R_t = 1$) in December 2021 during the Delta wave (Fig. 2, left column). After that, it rose quickly, peaking around the middle of January (Nepal: 2.17,

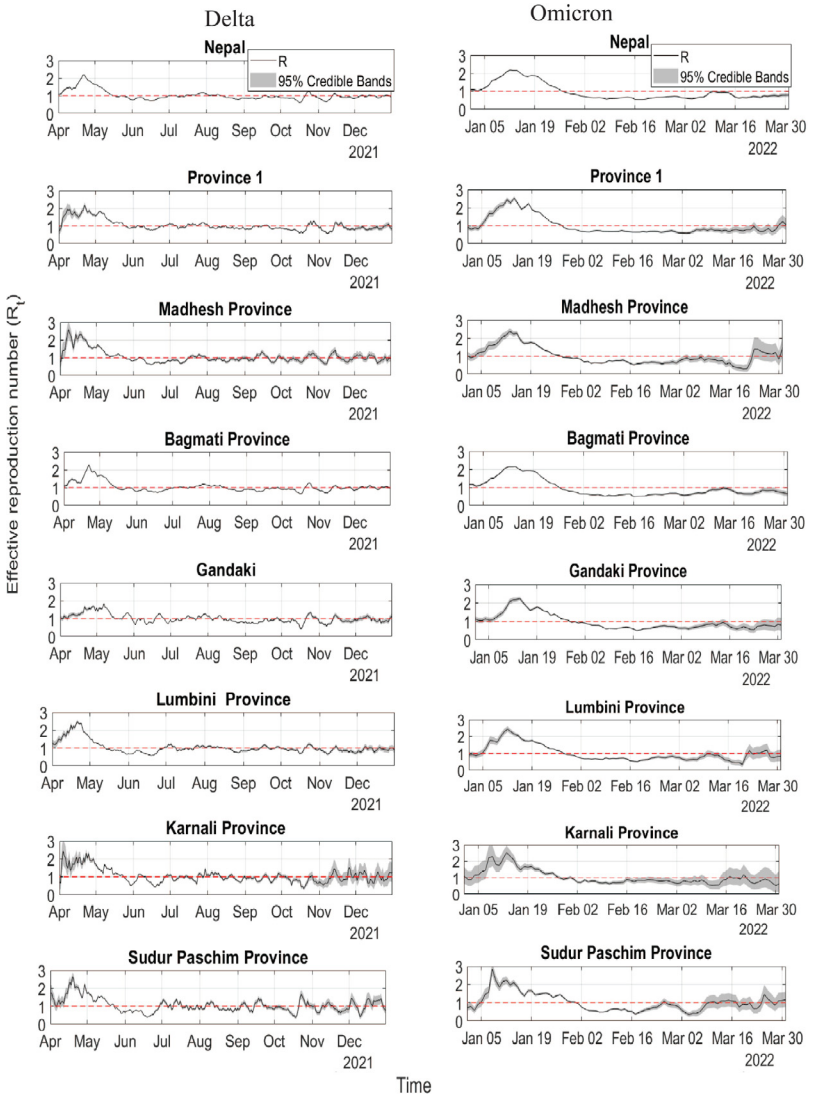


Fig. 2. The time-dependent effective reproduction number of COVID-19 in Nepal and its seven provinces during the Delta (Left column) and Omicron (Right column) waves. The gray-shaded region is the 95% credible interval for R_t. The horizontal red dashed line indicates the threshold value $R_t = 1$. The left column is the effective reproduction number during the Delta wave, and the right column is for the Omicron wave.

95% CrI [2.14, 2.21]; Province 1: 2.26, 95% CrI [2.15, 2.38]; Madhesh: 2.38, 95% CrI [2.21, 2.56]; Bagmati: 2.16, 95% CrI [2.13, 2.19]; Gandaki: 2.24, 95% CrI [2.130, 2.34]; Lumbini: 2.43, 95% CrI [2.27, 2.60]; Karnali: 2.52, 95% CrI [2.12, 2.96]; and Sudur Paschim: 2.85, 95% CrI [2.47, 3.25]), before rapidly dropping below the threshold value of one from the last week of January 2022 for the rest of the year. We observed that the reproduction number remained greater than one for about a month (1st to last week of January 2022) during the Omicron surge. In certain provinces (Madhesh, Lumbini, Karnali, and Sudur Paschim), we noticed a wider range of credible intervals for the estimated R_t at the end of April 2022. This increased variability may be due to the fact that there were fewer reported new cases, with more fluctuations. The results shown in Fig. 2 reveal that the reproduction numbers related to the Omicron and Delta variants are not considerably different even though quite different COVID-19 cases were reported in Nepal and all its provinces.

3.2. Risk of infection

The timely estimation of the risk of infection is essential to track the dynamics of the diseases and valuable to determine the need for amplification or the relaxation of public health control measures. We used our model to compare the risk of infection of COVID-19 during Delta and Omicron surges in Nepal and its provinces. The estimated maximum risk of infection of Delta surge in Nepal and its provinces is shown in Table 2. The temporal pattern of the risk of infection during the Delta and Omicron surges is shown in Fig. 3.

The risk of infection during the Delta wave increased sharply from mid-April 2021 and peaked in the second week of May 2021 in Nepal (Fig. 3, left column). The Bagmati province, which contains Nepal's most densely populated capital city, had the peak risk for infection two weeks sooner than the other provinces (first week of May 2021). Our estimates showed that Bagmati province was the highest risk zone (98.94, 95% CrI [32.99, 181.31] per hundred thousand), while Madhesh province remained the lowest risk zone (12.16, 95% CrI [4.05, 22.29] per hundred thousand) (Table 2). Interestingly, despite being the most densely populated province (600 people/km^2) (Central Bureau of Statistics (CBS), 2022) and having a larger R_t value, the Madhesh province had a lower risk of infection compared to other regions.

We also estimated the risk of COVID-19 infection during the Omicron wave (1 January to 31 March 2022). The temporal pattern of the risk of infection during the Omicron surge is shown in Fig. 3 (right column), and the estimated risk is shown in Table 2. Starting from a minimal risk at the beginning of January 2022, the risk of infection

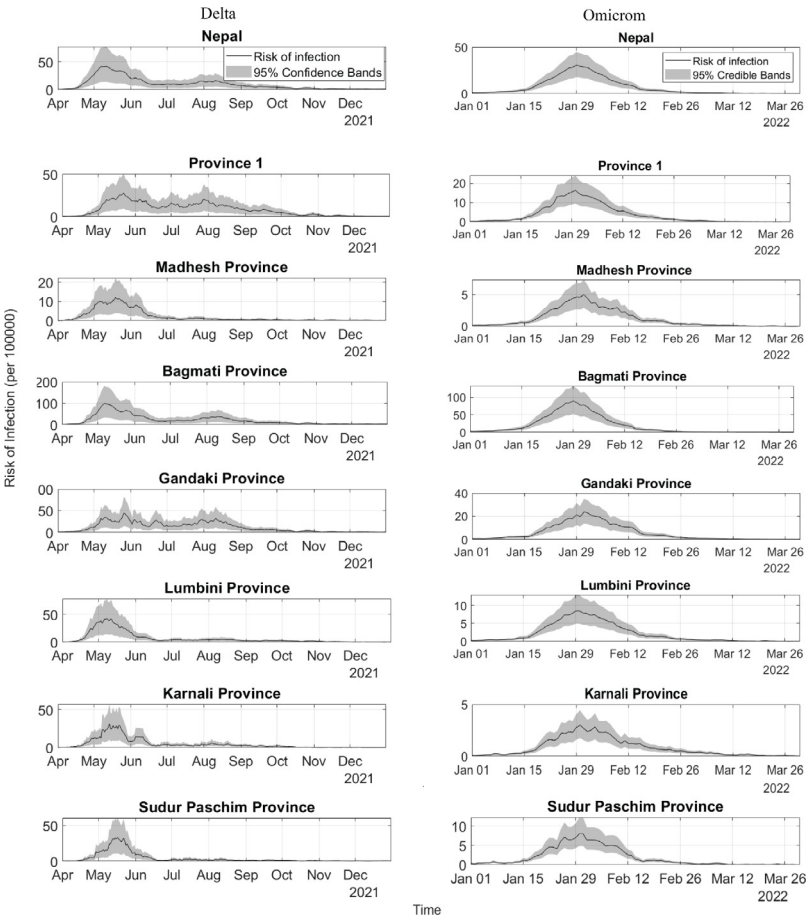


Fig. 3. Risk of infection (per thousand hundred) due to Delta and Omicron variants of Nepal and its seven provinces. The first column is the risk of infection during the Delta wave, and the second column is the risk of infection during the Omicron wave. The scaling on the y-axis differs depending on the province and wave.

Table 2
The maximum risk of infection and time of highest risk of COVID-19 during Delta and Omicron variant of Nepal and its seven provinces.

Risk of infection of Delta variant			
Regions	Risk of infection (per 100 000)	95% CrI	Time of highest risk
Nepal	42.19	[14.06, 77.33]	11 May, 2021
Province 1	27.49	[9.16, 50.40]	23 May, 2021
Madhesh	12.16	[4.05, 22.29]	19 May, 2021
Bagmati	98.94	[32.99, 181.31]	7 May, 2021
Gandaki	44.53	[14.84, 81.62]	26 May, 2021
Lumbini	42.89	[14.30, 78.63]	8 May, 2021
Karnali	31.16	[10.39, 57.13]	14 May, 2021
Sudur Paschim	33.26	[11.08, 60.97]	17 May, 2021
Risk of infection of Omicron variant			
Nepal	30.42	[17.61 46.43]	30 Jan, 2022
Province 1	16.30	[9.87, 24.03]	31 Jan, 2022
Madhesh	5.01	[2.63, 7.65]	1 Feb, 2022
Bagmati	89.62	[56.61, 132.05]	30 Jan, 2022
Gandaki	21.35	[13.48, 31.47]	1 Feb, 2022
Lumbini	8.46	[4.90, 12.47]	31 Jan, 2022
Karnali	3.00	[1.74, 4.43]	31 Jan, 2022
Sudur Paschim	8.03	[4.64, 11.83]	27 Jan, 2022

reached the highest level among provinces in a short period of time (3 weeks) around the fourth week of January 2022. During this time, we observed a considerable disparity in maximum risk of infection across Nepal and its provinces, ranging from 3.00, 95% CrI [1.74, 4.43] per hundred thousand in Karnali to 89.62, 95% CrI [56.61, 132.05] per hundred thousand in Bagmati. Furthermore, during the Delta surge, Madhesh province had a low (5.01, 95% CrI[2.63, 7.65] per hundred thousand) risk of infection at the peak time of the Omicron surge. The higher uncertainty, i.e., a larger width of credible intervals, for estimates may attribute to the fluctuation of the data set of new cases. The fluctuation of daily new cases may be due to the poor recording of daily testing and detected positive cases.

We found a considerable difference in the patterns of risk of infection between the two waves of COVID-19 in Nepal. The risk of infection during the Delta wave was abruptly increased, and with a complete lockdown, it took about one month to decline, but in the Omicron wave, it climbed and fell quickly without lockdown. Furthermore, during the Delta surge, the maximum risk of infection was slightly higher than the Omicron surge in Nepal (38.69%) and Bagmati province (10%) but significantly higher in Gandaki (108.57%), Lumbini (407%), Karnali (938.66%), and Sudur Paschim (314%) than that of the Omicron surge. The Bagmati province was the most vulnerable to both Delta and Omicron surges, while the rest of the provinces were more vulnerable to the Delta surge than the Omicron surge.

3.3. Risk of hospitalization

We calculated the risk of hospitalization using our model to the available data on active hospitalizations with COVID-19 in Nepal and its provinces. The results shown in Fig. 4 (left column) illustrate the risk that COVID-19 patients are admitted to hospitals in Nepal and its provinces during the Delta surge (1 May to 31 December 2021).

In Nepal, the risk of hospitalization of the Delta variant remains at 10% on average (min 7%, max 20%), and Province 1 shows a risk of hospitalization of 11% (min 6%, max 22%). Madhesh province had

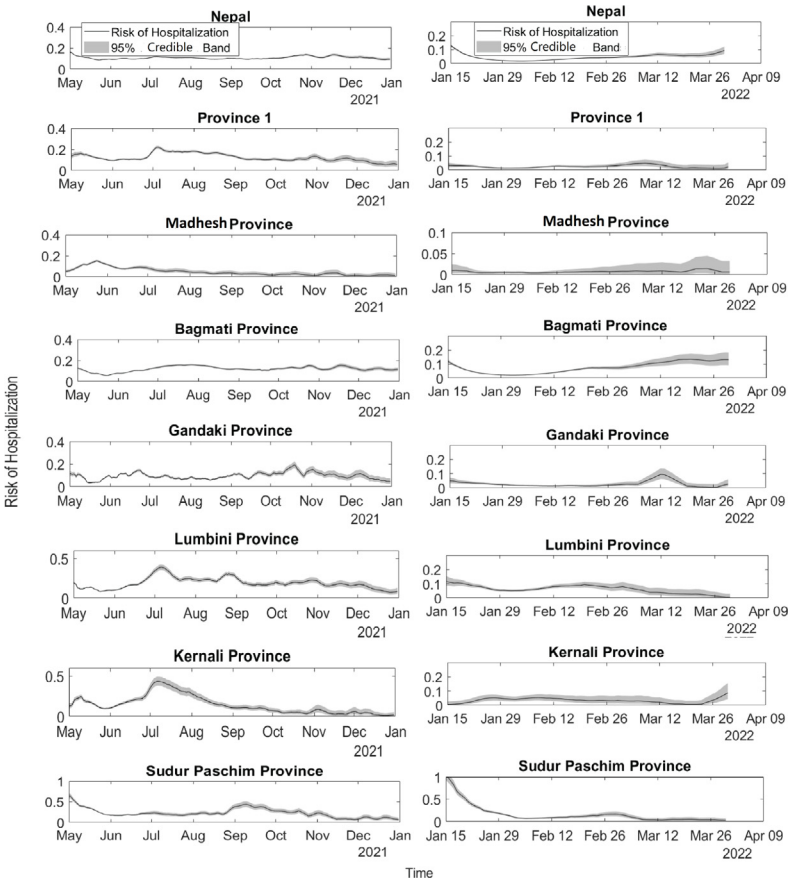


Fig. 4. Risk of hospitalization during Delta and Omicron wave in Nepal and its provinces. The left column is the risk of hospitalization during the Delta wave, and the right column is the risk of hospitalization during the Omicron wave. The scaling on the y-axis differs depending on the province and the wave.

the lowest risk of hospitalization at 6% (min 5%, max 14%). Although many actual hospitalization cases are in the Bagmati province, the risk of hospitalization is 11% (min 10%, max 15%), similar to other regions. Besides the Madhesh province, Gandaki province also has a lower risk of hospitalization of 9.5% (min 5%, max 18%). The risk of hospitalization in both Lumbini and Karnali provinces is high [Lumbini: 19% (min 7%, max 38%); Karnali: 14% (min 3%, max 42%)]. In Sudur Paschim, the risk of hospitalization was initially high (68%) but later on around 21% (min 6%, max 43%). The initial higher risk of hospitalization in Sudur Paschim could be due to the high volume of returnees migrant workers from India.

The Omicron surge had substantially lower hospitalization rates than the Delta surge. The results in Fig. 4 (right column) show that the risk of hospitalization was 2.5% during the peak time of the Omicron wave in Nepal. At the end of March 2022, the hospitalization rate was again raised in Nepal as well as in Bagmati province. Sudur Paschim province had an extremely high risk of hospitalization during the mid of January, which could be due to the inclusion of the institutional isolation of returnee migrant workers in the data. Our estimates show that compared to the Delta wave (Fig. 4, left column), the hospitalization risk in Nepal and its provinces is significantly lower during the Omicron wave (Fig. 4, right column), falling to even less than 1% in some provinces (Nepal: 1.8%, 95% CrI [1.7%, 1.9%], Province 1: 1.2%, 95% CrI [1%, 1.5%], Madhesh: 0.38%, 95% CrI [0.17%, 0.7%], Bagmati: 2%, 95% CrI [1.9%, 2.1%], Gandaki: 1.3%, 95% CrI [0.97%, 1.75%], Lumbini: 1.3%, 95% CrI [0.29% 4.29%], Karnali: 0.6%, 95% CrI [0.022%, 3.18%], Sudur Paschim: 2.9%, 95% CrI [0.92%, 7.15%]). At the end of March 2022, the risk of hospitalization increased in Nepal and Bagmati province.

3.4. Impact of Non Pharmaceutical Interventions (NPIs) on reducing the risk of COVID-19 infection

NPIs are known to play an important role in the mitigation of COVID-19. In general, restricting of mobility through NPIs, such as lockdown, reduces the contact rate, thereby reducing the risk of infection. Here, we used our model to quantify the impact of NPIs implemented by the Government of Nepal on reducing the risk of COVID-19. In Fig. 5, we present the maximum risk of infection during the Delta wave with different control levels. In Bagmati province (the province with the highest risk), the maximum risk would have increased by 216.32% if the lockdown was not implemented during the Delta surge. Similarly, Madhesh province (a province with the lowest risk) would have increased by 216.61% if the lockdown was not implemented.

The results in Fig. 6 show the trend of risk of infection during the Delta wave under different control levels. Our model estimates that if the lockdown had not been implemented during the Delta surge in Nepal, there would have been three times more new infections (Fig. 6). We also observed a similar impact of control strategies on the trend of risk of infection during the Omicron wave as in the Delta wave. For example, the risk of infection is reduced by about two-thirds due to the reduction of contact rate by 70% (Nepal: 30.42, 95% CrI [17.61, 46.43] to 9.6, 95% CrI [1.60, 17.61], Province 1: 16.30, 95% CrI [9.87, 24.03] to 5.15, 95% CrI [1.71, 9.44] per hundred thousand).

We also estimated the risk of infection under the closure of school/colleges and working places only during the Delta and Omicron waves (Fig. 7). We observed that closing schools and colleges (i.e., restriction of mobility of school/college age groups) and workplaces (i.e., restriction of mobility of the adult groups of age 25–59) can reduce the risk of infection by 26.30% while a complete lockdown reduces the

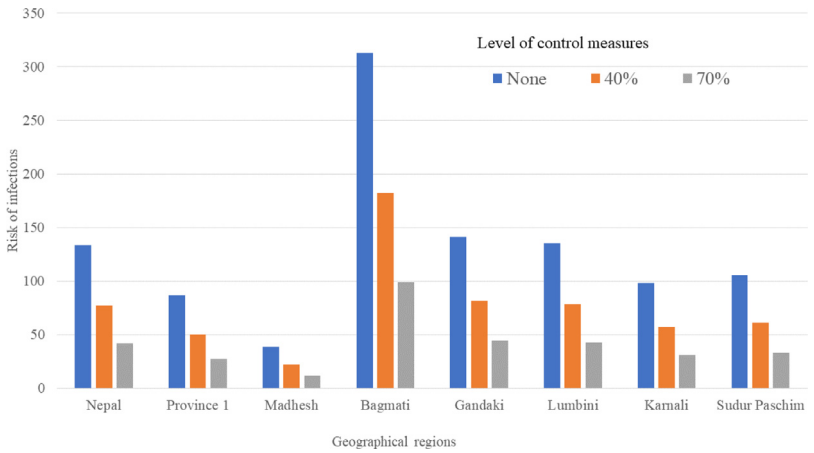


Fig. 5. The maximum risk of infection under different control levels during the Delta wave in Nepal and its provinces.

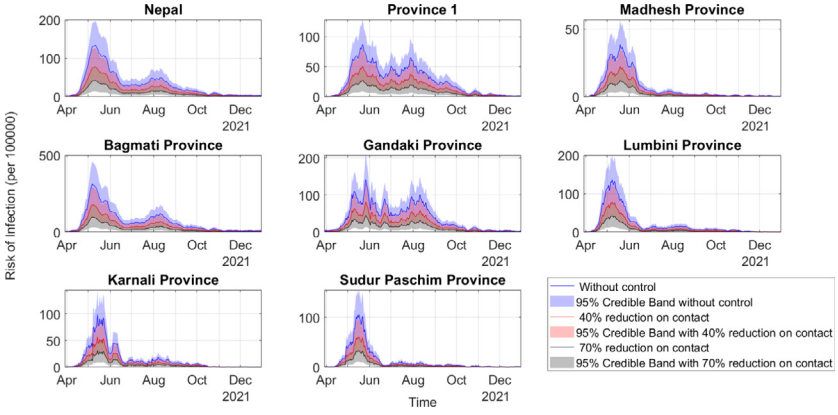


Fig. 6. Effect of control measures on a reduction of risk of infection during the Delta wave. Here, for a baseline computation, we took the average contact rate of 5.65 contacts per person per day during the Delta wave and assumed that lockdown reduces the contact rate by 70% (Coburn et al., 2009). To observe the impact of the lockdown, we used our model to estimate the risk of infection for 70% (5.79 contacts per person per day), 40% (11.58 contacts per person per day), and 0% (19.31 contacts per person per day) reduction of contact rate.

risk of infections by 68.42% (during the Delta, none: 133.54, 95% CrI [77.33, 196.74], school/college closed: 98.42, 95% CrI [49.22 147.59], working place closed: 98.42, 95% CrI [56.25, 154.61], lockdown: 42.17, 95% CrI [14.06, 77.33]; during the Omicron wave, none: 30.42, 95% CrI [17.61, 46.43], schools/colleges closed: 22.41, 95% CrI [11.21, 33.62], working places closed: 22.42, 95% CrI [12.81, 36.82], lockdown: 8.00, 95% CrI [1.60, 17.61] per hundred thousand).

4. Discussion

The timely assessment of the epidemic trend and its potential burden is essential to minimize the epidemic disaster and manage the healthcare facilities. In order to allocate resources and design health policies during the early stages of a pandemic, it is necessary to estimate the risk of infection and risk of hospitalization. Generally, the risk of hospitalization remains the same throughout the transmission period for the same kind of strain. However, the pattern of hospitalization may vary depending on the geographic region, cultural background, level of education, way of life, access to medical services, and population group among which the disease is circulating (Jackson et al., 2021; Athavale et al., 2021). Even when more infections result in more patients being admitted to hospitals, the risk of hospitalization may not be constant over time.

The effective reproduction number is widely used to track the transmission rate during epidemics. However, due to variations in the size of the susceptible population, the number of actively infected individuals, and the population's pattern of contact, two regions with the same effective reproduction number may have different levels of vulnerability (risk) throughout the pandemic. To track the trend of an epidemic more precisely by including the most vital factors of disease transmission, we developed data-driven mathematical models which provide a timely estimation of the risk of infection and the risk of hospitalization during a pandemic. Our mathematical model of risk of infection considers the susceptible population, active infectious population, and contact pattern of the people in addition to the effective reproduction number. Similarly, our hospitalization risk model uniquely utilizes active hospitalized cases to describe the temporal pattern of hospitalization trends. We implemented our models to the unique data sets of new COVID-19 cases and hospitalized cases in Nepal and its provinces. Furthermore, our models also allow us to determine how the implemented control strategies could effectively control the disease.

The seven provinces of Nepal have a range of population contact patterns due to their diverse geographic locations, distinctive lifestyles, cultural traditions, economic conditions, and level of urbanization (Pantha et al., 2021). The recorded COVID-19 cases also varied throughout provinces (MoHP, 2022). Despite huge discrepancies among provinces, the reproduction numbers of COVID-19 of the Delta and Omicron waves across Nepal and its provinces are not considerably

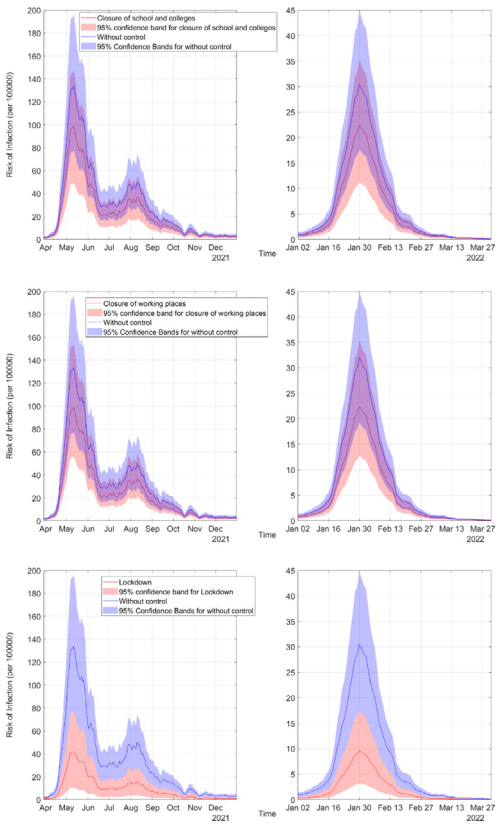


Fig. 7. Effect of closures of school colleges, working places, and lockdown on reducing the risk of infection during the Delta and Omicron waves. The left column is for the Delta wave, and the right column is for the Omicron wave. The first row represents the impacts of the closure of schools and colleges, the second row represents the effects of closing working places, and the third row represents the effects of lockdown.

different (Fig. 2), indicating that reproduction numbers alone may not fully capture the disease trend. A noticeable difference in reproduction number between the Delta and Omicron surges regarding the non-pharmaceutical interventions is that the total lockdown was needed to be implemented during the Delta wave, while during Omicron wave, partial closure of schools and colleges were enough for the reproduction number to fall below the threshold value one. In some provinces (Madhesh, Lumbini, Karnali, and Sudur Paschim), we noticed a wider range of credible intervals for the estimated R_t at the end of March 2022. This increased variability may be due to the fact that there were fewer reported new cases, with more fluctuations.

The risk of infection varies widely among provinces in both the Delta and Omicron waves despite the similar reproduction number. The ability of our model to capture the discrepancies among the provinces highlights the risk of infection as a critical indicator of the disease trend. Our results show a similar risk of infection in Nepal and in Bagmati province during the Delta and Omicron surges. However, in the case of other provinces, the risk of infection is less during the Omicron surge than during the Delta surge. Less risk of the Omicron is in contrast to what has been observed in other regions of the world, where the Omicron wave had a higher risk of infection than the Delta wave (Liu and Rocklöv, 2022; Du et al., 2022; Ito et al., 2022). Note that 36% of Nepalese people were fully vaccinated, and 49% were vaccinated with at least one dose by 4 January 2022 (Ritchie et al., 2020). Because of the low severity of the Omicron variant (Bhatia and Klausner, 2020; Wan et al., 2020), and the high coverage of vaccines, there were presumably fewer reported cases during the Omicron surge, which could be attributed to the low risk of infection as estimated by our model. During the Delta wave, infection risk rapidly increased and declined slowly. In contrast, during the Omicron wave, it rose and fell quickly, which may be due to the burnout of the susceptible population during previous waves or vaccinations, resulting in a faster climb and decline of cases compared to the Delta wave.

A substantial strength of our models also lies in their ability to describe the discrepancies among provinces in the pattern of the risk of hospitalization. We observed these discrepancies throughout Nepal and its provinces (for example, 6% in Madhesh province and 21% in Sudur Paschim) during the Delta surge (Fig. 4). The disparities in the risk of hospitalization reflect the unequal distribution of healthcare facilities and the different living standards of the people in different provinces (Cao et al., 2021; Saito et al., 2016). For example, Madhesh province shares the border with Province 1, which has relatively better and larger hospitals. Therefore, many people from Madhesh province go to the hospitals of Province 1, causing a higher hospitalization rate in Province 1 than in Madhesh province. Bagmati province contains Kathmandu, the capital city, and other major cities such as Lalitpur, Bhaktapur, Bharatpur, Hetauda, and Dhulikhel, comprising the major hospitals of Nepal. Among the reported hospitalized cases ~48%, were in this province (MoHP, 2022), which may have included the hospitalization of people from other provinces as well.

Despite the fewer number of new cases and hospitalized cases, the rate of hospitalization in Karnali and Sudur Paschim was estimated to be high. Madhesh province, on the other hand, has a low risk of hospitalization and low reported new cases. Our model estimates a four times higher risk of hospitalization during the Delta surge than the Omicron surge in Nepal and most provinces (Fig. 4), consistent with the higher hospitalization during the Delta surge found in other studies (Bhatia and Klausner, 2020; Wan et al., 2020; Centre for Disease Control and Prevention (CDC), 2022). The unusual risk of hospitalization seen in the Sudur Paschim is likely due to the data set. For example, on 1st January 2022, there were four new cases while seven persons were in hospital. From 1st to 12th January 2022, only 330 new cases were reported, but 395 active hospitalized cases were reported on 12th January, indicating more than 100% risk of hospitalization, as revealed in the model prediction. The higher active hospitalized cases of Sudur Paschim, compared to the new cases, could be due to the inclusion of the institutional isolation of returnee migrant workers in the data of active hospitalized cases.

We also used our model to evaluate the effectiveness of control strategies in suppressing infection rates. For the purpose of demonstration, we assumed different levels of control interventions (0%, 40%, and 70% reduction in contact rates) and estimated the corresponding risk of infection during the Delta surge (Figs. 5 & 6). Our results indicate that the risk of infection of COVID-19 would have been three times more if there were no lockdown (i.e., a lack of 70% reduction in contact) during the Delta surge. We also found that school/college closures have a greater impact on the reduction of risk of infection (Fig. 7), supporting the Nepal government's strategy of closing schools and colleges first during the peak of the Omicron surge (Kathmandu Post, 2022). Our model supports that the effectiveness of the control strategy is linearly translated to the risk of infection (Fig. 5). Other studies (Tian et al., 2020; Kraemer et al., 2020; Ferguson et al., 2020; Adhikari et al., 2021) have also reported that travel restrictions and non-pharmaceutical interventions have major impacts on the control of COVID-19 surges.

We acknowledge some limitations of our study. Although the population has a varied mixture pattern, we consider a homogeneous mixture in our model for estimating the risk of hospitalization so that every infected person has an equal probability of hospitalization. There are some uncertainties in the data used to compute the risk of infection and hospitalization. Underestimation and temporal inaccuracy (time lag between the time of infection/hospitalization and observation (record)) of the data also are two major factors that reduce the quality of the data we used. The better quality of data enhances the accuracy of the results of this study. Our model also does not consider the temporal

variation in under-reporting, which might otherwise be interpreted as a variation in the risk of infection. Reported COVID-19 cases include only those individuals who were tested and confirmed to be positive.

Several studies (Adhikari et al., 2021; Pullano et al., 2021; Adhikari et al., 2022; Saito et al., 2021) have found asymptomatic or undiagnosed COVID-19-infected individuals who can significantly spread the virus. The detection of COVID-19 cases in Nepal is low (Adhikari et al., 2022), implying that the actual risk of infection might be quantitatively different from our estimations. A Hidden Markov Model (HMM) could be an extension of our model to account for the imperfect observation process of undiagnosed cases. Hospital admission is nonspecific because it does not necessarily specify the reason and might cover a wide range of severity. Individuals infected with SARS-COV-2 may be hospitalized, but not necessarily as a result of COVID-19. A study (Clark et al., 2020) estimated that 17 billion (UI 10–24) individuals, or 22% (UI 15–28) of the world's population, have at least one underlying condition that increases their chance of developing severe COVID-19 if they become infected (range from 5% of those younger than 20 years to > 66% of those who are 70 years or older). Also, a study (Bastola et al., 2021) shows that among the COVID-19 patients hospitalized in Sukraraj Tropical and Infectious Disease Hospital of Nepal from January 2020 to January 2021, 64% had two or more comorbidities. Identifying an accurate number of hospitalized cases due to COVID-19 is necessary to accurately estimate the risk of hospitalization. Due to the unavailability of data regarding the number of new cases caused by the Delta and Omicron variants in mixed disease dynamics, we did not consider the mixed diseases model.

In summary, we developed data-driven mathematical models to estimate the risk of infection and the risk of hospitalization during the pandemic. As demonstrated by the applications of these models to a unique data set of Nepal and its provinces, the risk of infection and hospitalization can capture critical features of epidemic trends. Our model can also be used in other places and for outbreaks of other infectious diseases. Real-time quantification of the risk of infection and hospitalization is essential to develop ideal policy guidelines and appropriate control strategies for bringing society out of the devastating pandemic.

CRediT authorship contribution statement

Khagendra Adhikari: Formal analysis, Investigation, Methodology, Numerical simulation, Writing – original draft. **Ramesh Gautam:** Formal analysis, Review and editing. **Anjana Pokharel:** Formal analysis, Review and editing. **Kedar Nath Uprety:** Formal analysis, Supervision, Review and editing. **Naveen K. Vaidya:** Conceptualization, Formal analysis, Supervision, Review and editing.

Declaration of competing interest

None.

Data availability

The compiled data and codes that are analyzed will be available in the request of readers.

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