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Ensemble forecast of COVID-19 for vulnerability assessment and policy interventions

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ABSTRACT

The COVID-19 pandemic necessitates forecasts to frame science-informed policies. An accurate forecast of the size and timing of future waves could help public health officials and governments to plan appropriate responses. An ensemble forecast by aggregating different scenarios and models makes the prediction robust and reliable. We present an ensemble forecast for Wave-3 of COVID-19 in the state of Karnataka, India, using the IISc Population Balance Model for infectious disease spread. The reported data of confirmed, recovered, and deceased cases in Karnataka from 1 July 2020 to 4 July 2021 are utilized to tune the model's parameters. An ensemble forecast is done from 5 July 2021 to 30 June 2022. The ensemble is built with 972 members by varying seven critical parameters that quantify the uncertainty in the spread dynamics (antibody waning, viral mutation) and interventions (pharmaceutical, non-pharmaceutical). The probability of Wave-3, the peak date distribution, and the peak caseload distribution are estimated from the ensemble forecast. Analysis of the ensemble forecast results shows that compliance to COVID-appropriate behaviour, daily vaccination rate, and emergence time of immune-escape new variants are the most significant causal factors that determine the timing and severity of COVID-19 Wave-3. We observe that when compliance to COVID-appropriate behaviour is similar to a lockdown-like situation, the emergence of new immune-escape variants beyond September 2021 is unlikely to induce a new wave. No or partial compliance to COVID-appropriate behaviour makes a new wave inevitable. However, increasing the vaccination rate reduces the active caseload at Wave-3's peak. If Wave-3 emerges, on average, the daily confirmed caseload of children (Age 0–17 years) could be up to seven times more than the corresponding caseload (4390) at Wave-2's peak. Therefore, large-scale surveillance, including genome sequencing for early detection of new variants and non-pharmaceutical interventions to improve COVID-Appropriate behaviour, is vital to prevent Wave-3 of COVID-19. Doubling the vaccination rate as of 4 July 2021 to 560K doses per day will reduce the daily confirmed cases even if Wave-3 arises. Consequently, hospitalizations, ICU, and Oxygen requirements can be decreased. Since vaccination is yet to start in children, it is essential to ramp up the public health facilities, including pediatric ICUs to treat MIS-C, by 5-9 times to handle the worst-case situation. From a modeling perspective, capturing the nonlinear dynamics induced by the uncertainties in the causal factors is the key to a successful forecast. Therefore, an effort should be made to build an ensemble forecast that contains multiple models and, more importantly, models that account for causal factor uncertainties.

Introduction

COVID-19 cases were first reported in India from February 2020, and the first nationwide lockdown was imposed on 25 March 2020 to contain the spread and improve preparedness. A graded nationwide reopening started in June 2020. After that, in the state of Karnataka, the Wave-1 began gradually building up, reaching a maximum daily confirmed caseload of 10K (7-day average) around 11 October 2020. Subsequently, the daily confirmed caseload reduced to less than 1K by December 2020 and stayed below 1K until mid-March 2021. From the 3rd week of March 2021, the caseload started increasing again, and a Wave-2 started raging, reaching a peak of 47.5K daily confirmed cases on 9 May 2021¹. Additionally, since 16 January 2021, vaccination against COVID-19 started in India with a rationing policy based on the recipient's age². Genome sequencing studies have shown that Wave-1 was caused by the B.1.1.7 (Alpha) variant and Wave-2 was caused by the B.1.617.2 (Delta) variant³⁻⁷. Despite timely NPIs (decentralized state-wise, city-wise, and community-wise lockdown), there was a widespread concern due to the high load on the medical infrastructure with reports of ICU and oxygen shortages during Wave-2.

Unfortunately, none of the mathematical models in use before Wave-2 could forecast the Wave-2⁸. Unaccounted uncertainties in human behaviour, mobility, implementation of policy at the local level, mutation, immune response, and anti-body waning could be one of the reasons for the forecast failure. For a successful forecast, an ensemble method that incorporates these uncertainties is needed. An ensemble forecast is built by aggregating predictions from different scenarios and models. Such an approach has been shown to perform well in different fields consistently⁹⁻¹². Particularly for COVID-19, a multimodel

ensemble approach that aggregates short-term model forecasts from individual modellers/groups was used in the USA and publicly released by the Center for Disease Control and Prevention (CDC) every week¹³. In Italy, there have been attempts to use ensemble forecasting for short-term projection of the ICU requirements¹⁴. Even though a multi-model ensemble was used, careful uncertainty quantification of the parameters, as mentioned earlier, was not included in these studies.

Several authors have analyzed the data of COVID-19 Wave-2 in India and ascribed causal factors¹⁵. The importance of mutation in the Wave-2 and¹⁶ the effect of immunity waning have been characterized¹⁷. The effect of non-pharmaceutical interventions like lockdowns^{18,19} and vaccine allocation strategies² has also been studied. Predictions for third-wave based on immunity waning, the emergence of an immune-escape new variant, and social distancing²⁰ have also been made. However, no comprehensive ensemble forecast considering all known causal factors has been reported in the literature.

Our goal is to build a long-term ensemble forecasting system that includes all the causal factors with uncertainties. Such a system will enable policymakers to better prepare for all eventualities. Specifically, we aim to quantify the probability of a new COVID wave (Wave-3) in Karnataka, India, and determine the distribution of the date and age-wise caseload of Wave-3's peak. Further, we aim to determine the factors contributing to a new wave and recommend suitable interventions to reduce its likelihood and impacts.

Results

Ensemble forecast by varying control variables

Our IISc Spatio-temporal Infectious Disease Spread Model²¹, based on first-principles population balance equations, is used to build an ensemble of different scenarios for the spread of COVID-19 in Karnataka, India. To fit the model parameters with the dynamics of new waves and to build scenarios based on them, computations are performed from Jul 1, 2020, to Jun 30, 2022, where the actual data of the emergence of the second wave, that is, the data until Jul 4, 2021, is used. However, certain parameters cannot be directly estimated as data is unavailable or not accessible. Moreover, aspects of COVID-19 spread related to mutation and antibody waning are uncertain²⁰. To account for these uncertainties, we introduce the following control variables in the model.

1. Case-to-Infection Ratio (CIR): The reported district-wise CIR values in the first serological survey for Karnataka^{7,22,23} are used in our model. It has been reported that the average CIR in Karnataka was 40, and we denote this test case as CIR40. Further, to account for the uncertainty in the district-wise CIR estimate, we consider CIR50 as well, where the district-wise CIR is multiplied with a factor of 1.25.
2. The emergence of Immune-Escape New viral Variant (IENV): The emergence of immune-escape new viral variants is critical for the emergence of the new waves²⁴. The emergence of new variants and their transmission capability depends on the circulation of the existing variants and the antibody of the infected people. Further, we can observe that the duration between the peaks across the world is between nine and thirty-five weeks. In this study, we introduce the immune-escape new viral variant after (i) eight weeks (IENV-Jul21), (ii) sixteen weeks (IENV-Sep21), and (iii) twenty-four weeks (IENV-Nov21) of the second wave (May 2021) in Karnataka.
3. Reinfection due to Immune-Escape New Variant: We consider the transmission of immune-escape new viral variants in 33% (IENV-33P), 66% (IENV-66P), and 100% (IENV-100P) of the recovered population.
4. Antibody Waning (ABW) - Timescale and Population Fraction: The antibody waning could be a factor for reinfections and consequently induce new waves. A few studies show that the SARS-CoV-2 antibody wanes between five to twelve months^{25,26}. However, in the absence of unambiguous evidence, six scenarios by varying the timescale of antibody waning and the fraction of population for which antibody wanes are considered. Specifically, the antibody waning in 33% (ABW-33P), 66% (ABW-66P), and 100% (ABW-100P) of the recovered population in 150 (ABW-150) and 180 (ABW-180) days are considered.
5. Vaccination Rate: Vaccination is the key to contain the spread of the virus. In the absence of treatment, preventing the spread by vaccinating the entire population is the only solution to eradicate the virus. Nevertheless, with the present vaccination rate (as of 4 Jul 2021), people in the age group of 60 years and above, 45-59 years, 18-44 years, would be fully vaccinated by 9 Jul 2021, 21 Jul 2021, and 13 Dec 2021, respectively. In addition to the availability of the vaccines, the vaccine-hesitancy is also delaying the vaccination drive. Hence to study the effect of the vaccination rate on the emergence of new waves, three scenarios, (i) present rate, which is 280K vaccinations per day (VR-280K), (ii) 50% increase in the present rate (VR-420K), and (iii) double the present rate (VR-560K), are being considered.
6. COVID-appropriate behavior (CAB): COVID-appropriate behaviour (social distancing) plays a significant role in COVID spread, and it varies from region to region. Though the behaviour of individuals determines the social distancing, NPIs

Figure 1. The conditional probability of Wave-3 given a control variable (a) and two control variables (b) are depicted. The length of the arrows in (a) indicate the control variables' degree of influence on Wave-3. The values in the cells in (b) represent the conditional probability of Wave-3 given two control variables, whereas the color indicates the median of active cases at peak.

such as lockdowns, restrictions on mass gatherings, curfew, etc., will also affect the social distancing. To study the effect of different compliance of CAB on new waves, three scenarios (i) Good compliance (Good CAB): similar to the behaviour between Mar-May'21, (ii) Bad compliance (Partial CAB), and (iii) Worse compliance (No CAB), are considered.

We vary these influencing parameters to build a total of 972 scenarios. For each scenario we estimate the date of peak (if any) and the caseload at peak. A scenario without a peak is declared as a No-Wave (NW) scenario. The conditional probability of Wave-3 given a particular value for a parameter is then estimated, from only those scenarios with that chosen parameter value, as the ratio of scenarios leading to a Wave-3 to the total number of scenarios. The conditional probability given two parameter values is estimated by considering only those scenarios in which those chosen parameter values are used. All statistical quantities (mean, median, confidence interval, inter-quartile range, probability distribution function and scatter) are estimated from this ensemble forecast.

Causal factors for a new COVID wave in Karnataka, India

Among the 972 scenarios, Wave-3 is observed in 648. In the event of Wave-3, the conditional probability (likelihood) of Wave-3 given a control variable is presented in Fig. 1 (a). Even though the Case-to-Infection ratio and the antibody waning could impact the emergence of new COVID waves, we see that these factors do not influence the probability of Wave-3 significantly. Variations in the emergence and reinfection from new immune-escape variant, vaccination rate, and compliance to NPI (CAB norms) significantly influence the emergence of a new COVID wave. In fact, the timing of the new immune-escape variant influences the probability of Wave-3 more than its reinfection percentage. Therefore, we characterize the timing of the new immune-escape variant, vaccination rate, and NPI (CAB norms) as the primary causal factors and further analyze its influence on the Wave-3.

To investigate the pair-wise combined effect of the primary causal factors on Wave-3, the conditional probability of Wave-3 given pairs of these causal parameters is presented in Fig. 1 (b). All scenarios where Good CAB is followed have the lowest probability of Wave-3. On the other hand, Wave-3 will definitely emerge (probability=1) in all scenarios where No CAB is followed. Even increasing the vaccination rate or delayed mutation do not reduce the probability when No CAB is followed. This analysis reveals that NPIs in the form of CAB norms are significant to control Wave-3. Early emergence of IENV, i.e., scenarios with IENV-Jul21 have high probabilities for Wave-3 since the fraction of vaccinated population is low. Only exception is the scenarios with Good CAB. Even though July 2021 has passed at the time of submission of this article, these results are still significant to forewarn how other infectious diseases may spread or even if a vaccine-escape mutation of SARS-CoV-2 emerges.

Wave-3 peak date and active caseload

The quantities of interest for policymaking are the peak date and active caseload at peak. Fig. 2 shows a scatter plot between the date of Wave-3's peak and active caseload at peak for different scenarios corresponding to the primary causal factors being present. A special axis entry for No Wave (NW) is used to depict the scenarios that do not show a new wave. The arrangement and color of scatter markers in the figure help us visualize the joint-effect of adherence to CAB by the public, IENV emergence and reinfection fraction, vaccination rate, and CIR in the population on caseload and date of peak. Each panel (a-i) in Fig. 2 shows only those scenarios in which the variable mentioned in the column (CAB) and the row (IENV emergence time) are active. For example, panel (a) shows all the scenarios where the CAB is set to "Good" level and IENV emergence time is set to July 2021. Within the panel, each point represents a particular scenario. Each scenario is colored by the vaccination rate, marked by a marker that represents the IENV reinfection fraction, and the border is colored by the CIR.

Figure 2. Scatter plot of active cases at the peak of Wave-3 v/s the date of peak for different scenarios of CAB and timing of the immune-escape variant with different vaccine rates.

First, we see that for scenarios with Good CAB (panels a,d,g), the active case at the peak is lower. Significantly, scenarios with Good CAB and IENV emergence time beyond September 2021 (panels d,g) do not see a new wave. In panel (a), we see a peak only when IENV causes reinfection in 100% of the previously infected and recovered population. This result further emphasizes that Good CAB is the primary intervention strategy for preventing COVID waves. However, in reality, the financial and livelihood requirements to reopen economies will result in a relaxation of CAB norms, and only a partial CAB is likely to be followed. In those scenarios with partial CAB (panels b,e,h), if an immune escape new variant emerges in July 2021 or September 2021, Wave-3 is inevitable in Karnataka. Moreover, we see that vaccination rate is the key governing factor that reduces the active caseload at peak. Crucially, reaching a vaccination level of 580K per day in Karnataka will ensure no Wave-3 if no immune escape new variant starts spreading in the population before November 2021. A higher CIR (meaning lower reported cases during Wave-2) will result in a delayed peak but at the same active caseload as seen by the clustering among the same color and marker shapes.

To complete the analysis, we look at the scenarios with no CAB. Under these scenarios, we expect the highest levels of the

caseload at peak and an assured emergence of new COVID waves in Karnataka. Fortunately, we see that vaccination reduces the caseload. The reinfection fraction significantly affects the caseload in the No CAB, IENV-Jul'21 scenarios (panel c). Here, we see a wide distribution in the caseload at the peak but a narrow distribution in the peak date. Such a situation is characteristic of the underlying populations immunity which vaccines improve.

Figure 3. The probability of the predicted date of peak and the number of active cases on the day of peak for different vaccination rates and timing of emergence of immune-escape new variants, i.e., in Jul'21, Sep'21 and Nov'21.

To further understand Wave-3 properties from the perspective of vaccination, Fig. 3 shows the probability distribution function of peak date and active cases at peak for different vaccination rates. Here, we only look at the scenarios resulting in a Wave-3 and ignore those that do not lead to a Wave-3. We see that almost all the distribution curves are multi-modal, indicating the joint-effects of CAB and IENV reinfection rates. It is evident from Fig. 3 that the emergence of a new immune-escape variant is likely to be followed by a third wave within 45 to 60 days. In most cases, a higher vaccination rate helps to bring down the active caseload at its peak. Doubling the daily vaccination rate (VR-560K, Fig. 3(c),(f)) results in fewer scenarios with Wave-3 despite the emergence of an immune-escape new variant in November. The critical contribution of increased vaccination rate is that more of the susceptible population are protected up to the vaccine efficacy levels.

As a ready reference for policymaking, Table 1 shows a summary of the median peak date, inter-quartile range of peak date and the minimum and maximum active caseload during this period of inter-quartile range for scenarios with specific combinations of IENV emergence time and vaccination rates. This table summarizes the information presented in the graphs above.

Effect of Wave-3 on different age-groups

The data until 10 June 2021 shows that 4.2%, 5%, 53.2%, 23% and 14.645 % of the people in the age groups 0–11, 12–17, 18–44, 45–59, and above 60 years were infected with COVID-19. However, India started an age-dependent vaccination drive, with no widespread vaccine availability for children (0–17 years). As such, for Wave-3, we expect a higher contribution to the daily confirmed caseload from children. To estimate this impact on different age groups, we analyze the age-wise daily confirmed caseload at Wave-3 peak and compare it with the corresponding numbers at Wave-2. Table. 2 shows the statistics of the ratio between the 7-day average of daily confirmed cases of Wave-3 (predicted by our model) and Wave-2 peaks. The first line in each cell shows the ensemble mean with the 95% confidence interval and the second line shows the ensemble median.

Table 1. Statistics for total active cases and the date of the peak at various vaccine rates, and COVID-appropriate behaviour. The first value in the cell is the median date of peak and the mean value of active cases on the median date of peak, followed by the first and third quartile values for the date of peak, and the minimum and the maximum number of active cases in the inter-quartile range.

Vaccination rate per day	Emergence of IENV	Good CAB	Partial CAB	No CAB
280K	Jul'21	15-Oct'21 (36K) 14-Oct'21, 21-Oct'21 36K – 48K	21-Sep'21 (173K) 05-Sep'21, 10-Jan'22 144K – 207K	27-Aug'21 (451K) 22-Aug'21, 10-Sep'21 451K – 2M
	Sep'21	No Wave-3	05-Jan'22 (220K) 10-Dec'21, 02-Feb'22 207K – 229K	08-Nov'21 (674K) 02-Nov'21, 24-Nov'21 527K – 766K
	Nov'21	No Wave-3	21-Feb'22 (189K) 19-Feb'22, 24-Feb'22 179K – 197K	22-Dec'21 (7M) 20-Dec'21, 24-Dec'21 616K – 11M
420K	Jul'21	27-Sep'21 (23K) 26-Sep'21, 08-Oct'21 23K – 26K	23-Sep'21 (119K) 06-Sep'21, 28-Jan'22 89K – 134K	29-Aug'21 (1M) 23-Aug'21, 08-Sep'21 370K – 1M
	Sep'21	No Wave-3	23-Jan'22 (114K) 23-Dec'21, 26-Feb'22 112K – 117K	13-Nov'21 (479K) 05-Nov'21, 02-Dec'21 377K – 529K
	Nov'21	No Wave-3	27-Mar'22 (38K) 24-Mar'22, 31-Mar'22 37K – 43K	27-Dec'21 (1M) 26-Dec'21, 29-Dec'21 460K – 3M
560K	Jul'21	12-Sep'21 (16K) 11-Sep'21, 24-Sep'21 15K – 16K	25-Sep'21 (79K) 08-Sep'21, 04-Feb'22 57K – 88K	28-Aug'21 (225K) 23-Aug'21, 31-Aug'21 17K – 656K
	Sep'21	No Wave-3	03-Feb'22 (23K) 02-Jan'22, 03-Mar'22 23K – 25K	17-Nov'21 (340K) 06-Nov'21, 11-Dec'21 288K – 406K
	Nov'21	No Wave-3	No Wave-3	05-Jan'22 (529K) 04-Jan'22, 08-Jan'22 296K – 792K

We see that the children (0-17 years) are more affected than other age groups, primarily due to the unavailability of vaccines. In the worst case, with VR-280K and IENV-Nov21, the daily confirmed cases of children (0–11 years) at the Wave-3 peak will be on average twenty times more than that of the daily confirmed cases at Wave-3 peak. Overall, our ensemble forecast indicates that the average impact of Wave-3 on children (0–17 years) could be seven times more than that of Wave-2.

Active Cases During May'21 - Jun'22

Fig. 4 shows the ensemble forecast of active cases in Karnataka from May 2021 to June 2022. Each panel shows the scenarios given a pair of CAB and IENV emergence-time control variables. The colored solid line is the mean value of the ensemble of active cases, and the shaded zone in the region of uncertainty (each color corresponds to a particular vaccination rate). The rows in Fig. 4 represent the good, partial, and no CAB, whereas the columns represent the emergence of IENV in Jul'21, Sep'21, and Nov'21, respectively.

These plots confirm the observations from our analysis above, but now showing a time series of the active caseload distribution. As mentioned earlier, the scenarios with Partial CAB (middle row in Fig. 4) are likely to be followed due to the reopening of the economy including offices and educational institutions. The impact of the new wave will be more when it emerges early (Fig. 4 (d)). At the peak of the new wave, the active caseload will be very high with the present vaccination rate,

Table 2. Predicted impact of Wave-3 on different age groups with different vaccination rates. The first value in the cell is the mean with the confidence interval of ratios of the 7-day average of confirmed cases at Wave-3 peak and Wave-2 peak, followed by the median.

Vaccine Rate	Emergence of IENV	0-11 Years	12-18 Years	18+ Years
280K	Jul'21	10.17 ± 5.1 1.92	7.88 ± 3.96 1.29	2.36 ± 1.27 0.24
	Sep'21	6.18 ± 1.64 3.22	4.66 ± 1.26 2.33	0.96 ± 0.29 0.44
	Nov'21	21.12 ± 8.72 4.68	15.78 ± 6.57 3.34	2.76 ± 1.18 0.54
420K	Jul'21	8.69 ± 4.42 1.06	6.75 ± 3.42 0.85	1.77 ± 0.96 0.13
	Sep'21	5.01 ± 1.3 2.88	3.66 ± 0.97 2	0.51 ± 0.16 0.23
	Nov'21	11 ± 3.73 3.65	8.06 ± 2.79 2.55	0.88 ± 0.31 0.27
560K	Jul'21	7.4 ± 3.76 0.79	5.79 ± 2.96 0.61	1.34 ± 0.75 0.07
	Sep'21	4.05 ± 1.21 3.11	2.91 ± 0.88 1.98	0.3 ± 0.1 0.15
	Nov'21	8.85 ± 1.32 7.61	6.42 ± 1.05 5.41	0.38 ± 0.06 0.32

around 350K, when a new variant emerges before September 2021. If we assume that there is no antibody waning at least for 180 days, then, a new wave is predicted only at the beginning of next year, even if a new variant emerges before September 2021. In this case, the impact will be minimal. The benefits of increasing the vaccination rate can clearly be seen in Fig. 4 (e). Though a new wave is predicted in some scenarios, the active caseload is less with the doubled vaccination rate. Crucially, if a new variant does not emerge until the end of October 2021, then a new wave can be suppressed by doubling the vaccination rate (Fig. 4 (f)). In this case, our forecast shows that the active caseload will be as high as 200K with the present vaccination rate. This finding emphasizes the necessity of vaccinating the entire population by December 2021.

Discussion

Among the three most important causal factors of Wave-3, viz., emergence of IENV, NPI (CAB norms) and vaccination rate, only the latter two are human controlled factors. NPIs such as mobility restriction, masking, physical distancing mandates, and crowd control measures must be enforced to ensure that the general public practice CAB. Public education programs and reminders are required for strict compliance. Ensuring a smooth supply chain for vaccine and enhanced production can increase the vaccination rates to the required level so as to vaccinate the entire population before a new immune escape variant emerges. Genome sequencing and large-scale surveillance measures are required to identify the emergence of an immune escape new variant and alert the public and government.

If lockdown-like restrictions are imposed to ensure Good CAB, emergence of new variants beyond September 2021 is unlikely to induce new waves. We recognize that it is practically impossible to have continued imposition of lockdown-like restrictions. Nevertheless, our modeling shows that extreme caution while rolling back restrictions is required. Our results indicate that the key weapon to open up economies is increasing the vaccination rates. Even if a third wave is imminent due to the inability to enforce NPIs for Good CAB, increasing the vaccination rate will reduce the peak active caseload. This reduction is significant as vaccination will reduce severe cases that require hospitalization, ICU, and Oxygen. Specifically, the scenario with a vaccination rate of 560K per day (twice the average vaccination rate as of 4 July 2021) would have a lower probability of Wave-3 than other scenarios when Good CAB is not enforceable. The state can prepare the vaccination logistics based on this rate. Apart from arranging the vaccine doses, the state has to strengthen the micro planning and ensure better social

Figure 4. Time series of mean of active cases with 95% confidence interval.

mobilization to enhance the vaccination speed and coverage.

A longstanding worry among pediatricians and policymakers is the impact of COVID-19 on non-vaccinated children²⁷. The ensemble forecast estimates that the daily confirmed cases of children (Age 0-11 and 12-17 years) at peak could be on average seven times more than the corresponding daily confirmed cases at Wave-2 peak. Based on the predicted increase in daily confirmed caseload of children in a potential Wave-3 compared to data of Wave-2, the policymakers can plan pediatric facilities for children with COVID-19. Further, it is crucial to set up a registry of infected children to monitor for short- and long-term consequences, including Multisystem Inflammatory Syndrome in Children (MIS-C). Evidence from a study in the USA²⁸ suggests that MIS-C incidence is 5.1 (95% CI, 4.5-5.8) persons per 1 million person-months. As such, we can expect 129 cases of MIS-C in one month during the peak. However, they also report that 316 MIS-C infections per 1 million COVID infections in children can occur. Thus, based on our results, we expect an estimated 514 children (on average) in Karnataka to

suffer from MIS-C if a Wave-3 occurs. The best policy intervention would be to strengthen the healthcare services for children, including opening new pediatric ICUs. We recommend such an approach even if the reality is less severe than estimated (due to differences in India and the USA), as the facility can strengthen the country's pediatric healthcare.

In short, policies to ensure at least partial compliance of CAB from the public, increased vaccination rates, surveillance for mutations and enhanced pediatric facilities are crucial to fight a new COVID-19 wave in Karnataka. Though the estimated Wave-3 numbers are for the state of Karnataka, the dynamics of the ensemble forecast will apply to all other states of India. Therefore, our recommendations can be contextualized for the policy interventions in the rest of the country.

Our projections were computed on 4 July 2021²⁹. At the time of submission of this article, July 2021 has passed and there is no evidence for emergence of a immune-escape new variant so far. As predicted by scenarios without IENV-Jul21, no Wave-3 emerged in the month of September. The IENV-Jul21 scenarios are still significant for future planning when vaccine-escape variants emerge.

One of the limitations of our modeling is that we have not considered the possibility of new variants infecting the vaccinated population. However, we have considered a fixed efficacy of 70% for the vaccinated population that can partially offset the limitation. Further, the recovery rate is fitted to the data from July 2020 to May 2021; however, it could be more due to vaccination or less due to new variants.

From a modeling perspective, capturing the nonlinear dynamics induced by the uncertainties in the causal factors ensures a successful forecast. A national effort to build an ensemble forecast that contains multiple models, including models such as ours that account for causal factor uncertainties can strengthen the response to future waves.

Materials and Methods

IISc-COVID Model

The IISc Spatio-temporal Infectious Disease Spread COVID model proposed in²¹ is employed to compute all estimates using our in-house finite element package^{30,31}. The model consists of an unknown scalar function describing the dynamics of the infected population in a six-dimensional space. In particular, the active infected population is distributed in space, infection severity, duration of the infection, and age of the infected people. Let T_∞ be a given final time, $\Omega := \Omega_x \otimes \Omega_\ell$ be the spatial domain, and $\Omega_\ell := L_v \times L_d \times L_a$ be the internal domain. Here, L_v , L_d and L_a denote the infection severity, duration of infection, age of the people, respectively. Then, the dynamics of the infected population $I(t, \mathbf{x}, \ell) \in (0, T_\infty] \times \Omega_x \otimes \Omega_\ell$ is described by the population balance equation

$$\begin{aligned} \frac{\partial I}{\partial t} + \nabla \cdot (\mathbf{u}I) + \nabla_\ell \cdot (\mathbf{G}I) + (C_R + C_{ID})I &= F & \text{in } (0, T_\infty] \times \Omega_x \times \Omega_\ell, \\ I(t, \mathbf{x}, \ell) &= g_n & \text{in } (0, T_\infty] \times \partial\Omega_x^- \times \Omega_\ell, \\ I(t, \mathbf{x}, (\ell_v, 0, \ell_a)) &= B_{nuc} & \text{in } (0, T_\infty] \times \Omega_x \times L_v \times L_a, \\ I(t, \mathbf{x}, (0, \ell_d > 0, \ell_a)) &= 0 & \text{in } (0, T_\infty] \times \Omega_x \times L_d \times L_a, \\ I(0, \mathbf{x}, \ell) &= I_0 & \text{in } \Omega_x \times \Omega_\ell. \end{aligned}$$

The movement of the population within the spatial neighbourhood can be incorporated through $\mathbf{u}$. The internal growth $\mathbf{G} = (G_{\ell_v}, G_{\ell_d}, G_{\ell_a})^T$, the recovery rate C_R , and infectious death rate C_{ID} rate are described in our previous paper²¹.

Adding to the base model, our current implementation includes antibody waning, vaccination, breakthrough infections, new immune escape variants, case-to-infection ratio (CIR) (unreported cases), social distancing, lockdown/unlock policies. In the model, all these factors affect the new infection, i.e, the nucleation of COVID cases B_{nuc} .

Let us first consider the modeling of antibody waning. Let N be the total number of people and N_{ab} be the number of people with antibodies. Suppose there is no antibody waning, then the susceptible ratio is defined as

$$S_R = \frac{N - N_{ab}}{N}.$$

To introduce antibody waning, we use the cumulative distribution function for the Weibull distribution

$$W(t) = 1 - \exp(-t/\lambda)^k, \quad t > 0.$$

Now define the antibody waning susceptible ratio as

$$S_R^w(t) = \frac{N - N_{ab}^w}{N}, \quad N_{ab}^w = (1 - W(t)) * N_{ab}.$$

Here, $k = 5.67$ defines the shape of the curve, λ is the duration of antibody retention, and t is the time. Next, the vaccinated population must be removed from the susceptible population. Moreover, the efficacy of the vaccine should also be considered. Suppose N_v is the total number of vaccinated people with 70% efficacy, then the vaccinated population is added to N_{ab}^w , i.e.,

$$N_{ab}^w = (1 - W(t)) * N_{ab} + 0.7N_v.$$

Serological surveys indicate that CIR varies between 20 and 60 or even more³². For instance, the first serological survey report of Karnataka shows $CIR = 40$ in Karnataka³³; that is, there are 39 unreported cases for every reported case in Karnataka during the first wave. CIR has to be incorporated into the model since CIR will significantly influence the nucleation. In our model, we included the CIR as follows:

$$N_{ab}^w = CIR N_{ab}^w + 0.7N_v.$$

Vaccine-dependent fatality is another critical feature in our model. The straightforward approach is to define the infectious rate as a function of the vaccinated population ratio. Alternatively, vaccine-dependent fatality can also be incorporated in the nucleation when the model accounts for the severity of the infection. In particular, the newly infected but vaccinated population must be added into the model with less severity. Since one of the internal variables in our model is infection severity ℓ_v and the infectious death rate is zero for $\ell_v < 0.64$, the newly infected but vaccinated population is distributed within $\ell_v < 0.64$.

Next, we discuss the modeling of new immune escape variants, which are the primary source for new waves. Suppose $N_{ab}(t)$ be the total antibody population on the day t of the introducing a new immune escape variant. Let us assume a fraction of the antibody population, $F_{nv} * N_{ab}$, where $0 \leq F_{nv} < 1$, is still immune to the new variant of SARS-CoV-2. Then, the antibody population with a new immune-escape variant is redistributed as

$$N_{ab}^{nv}(t) = ((1 - F_{nv}) + F_{nv}(1 - W(t))) N_{ab}(t)$$

with $k = 2.67$ and $\lambda = 15$. Incorporating all these models, the nucleation is given by

$$B_{nuc}(t, \mathbf{x}, \ell) = R(t) \int_{\Omega_\ell} [1 - \gamma_Q] I(t, \mathbf{x}, \ell) d\ell,$$

where

$$R(t) = R_0 S_R^w(t) f_1(t, S_D) f_2(\ell_v),$$

$$\gamma_Q = \frac{1}{1 + \exp(-(\ell_v - 0.4)/0.1)} \frac{1}{1 + \exp(-(\ell_d - 5.1)/2)}.$$

Here, $\gamma_Q \in [0, 1]$ is the fraction of the infected population in quarantine, and it depends on testing, isolation, and comorbidity of the susceptible population. Further,

$$f_1(t, S_D) = \left[1 - \frac{1}{1 + \exp(-(S_D(t) - 0.5)/0.1)} \right],$$

$$f_2(\ell_v) = \begin{cases} 3\sqrt{\frac{2}{\pi}} \exp\left(\frac{-(\ell_v - 0.4)^2}{2(0.4/3)^2}\right) & 0 \leq \ell_v < 0.4, \\ 3\sqrt{\frac{2}{\pi}} \exp\left(\frac{-(\ell_v - 0.4)^2}{2V_R((1-0.4)/3)^2}\right) & 0.4 \leq \ell_v \leq 1. \end{cases}$$

The $S_D \in [0, 1]$ in the function $f_1(t, S_D)$ is a social distancing parameter, where $S_D = 1$ implies a perfect social distancing and $R \rightarrow 0$. Hence, S_D is a key parameter to forecast lockdown and unlock phases. Next, the function $f_2(\ell_v)$ is used to distribute the newly infected population as a function of vaccine-dependent severity. Here, the vaccinated ratio is defined as

$$V_R = \frac{N - N_{Vac}}{N},$$

where N_{Vac} is the total number of vaccinated people.

Data of Infected, Recovered and Deceased

Crowd sourced data from www.covid19india.org³⁴ is utilized for fitting the model, as well as comparing the model forecast with data from the day the fit is completed. Only three time-series data, viz., infected, recovered and deceased are utilized. Active is calculated as Infected-Recovered-Deceased. The range of values for other parameters in the model are fixed from literature as described in the modeling section.

References

1. Government of India. COVID-19 dashboard, DOI: <https://www.mygov.in/covid-19> (2021). Last accessed on Aug 26, 2021.
2. Foy, B. H. *et al.* Comparing COVID-19 vaccine allocation strategies in India: A mathematical modelling study. *Int. J. Infect. Dis.* **103**, 431–438, DOI: <https://doi.org/10.1016/j.ijid.2020.12.075> (2021).
3. Samarasekera, U. India grapples with second wave of COVID-19. *The Lancet Microbe* **2**, e238 (2021).
4. Cherian, S. *et al.* Convergent evolution of SARS-CoV-2 spike mutations, L452R, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. *BioRxiv* (2021).
5. Budhiraja, S. *et al.* Differentials in the characteristics of COVID-19 cases in Wave-1 and Wave-2 admitted to a network of hospitals in North India. *medRxiv* (2021).
6. Asrani, P., Eapen, M. S., Hassan, M. I. & Sohal, S. S. Implications of the second wave of COVID-19 in India. *Lancet Respir. Med.* (2021).
7. Babu, G. R. *et al.* The burden of active infection and anti-sars-cov-2 igg antibodies in the general population: Results from a statewide sentinel-based population survey in Karnataka, India. *Int. J. Infect. Dis.* **108**, 27–36 (2021).
8. Agrawal, M., Kanitkar, M. & Vidyasagar, M. <https://pib.gov.in/PressReleasePage.aspx?PRID=1715485>. *Press. Inf. Bureau* (2021).
9. Viboud, C. *et al.* The RAPID Ebola forecasting challenge: Synthesis and lessons learnt. *Epidemics* **22**, 13–21 (2018).
10. Johansson, M. A. *et al.* An open challenge to advance probabilistic forecasting for dengue epidemics. *Proc Natl Acad Sci India* **116**, 24268–24274 (2019).
11. Reich, N. G. *et al.* A collaborative multiyear, multimodel assessment of seasonal influenza forecasting in the United States. *Proc. Natl. Acad. Sci.* **116**, 3146–3154 (2019).
12. Leutbecher, M. & Palmer, T. N. Ensemble forecasting. *J. Comput. Phys.* **227**, 3515–3539, DOI: [10.1016/j.jcp.2007.02.014](https://doi.org/10.1016/j.jcp.2007.02.014) (2008).
13. Ray, E. L. *et al.* Ensemble forecasts of coronavirus disease 2019 (covid-19) in the us. *MedRxiv* (2020).
14. Farcomeni, A., Maruotti, A., Divino, F., Jona-Lasinio, G. & Lovison, G. An ensemble approach to short-term forecast of COVID-19 intensive care occupancy in Italian regions. *Biom. J.* **63**, 503–513 (2021).
15. Ranjan, R., Sharma, A. & Verma, M. K. Characterization of the Second Wave of COVID-19 in India. *medRxiv* (2021).
16. Chen, J., Wang, R., Wang, M. & Wei, G.-W. Mutations strengthened SARS-CoV-2 infectivity. *J. Mol. Biol.* **432**, 5212–5226 (2020).
17. Adiga, A. *et al.* Strategies to Mitigate COVID-19 Resurgence Assuming Immunity Waning: A Study for Karnataka, India. *medRxiv* DOI: [10.1101/2021.05.26.21257836](https://doi.org/10.1101/2021.05.26.21257836) (2021).
18. Salvatore, M. *et al.* Comprehensive public health evaluation of lockdown as a non-pharmaceutical intervention on COVID-19 spread in India: national trends masking state-level variations. *BMJ Open* **10**, e041778 (2020).
19. Ray, D. *et al.* Predictions, role of interventions and effects of a historic national lockdown in India's response to the COVID-19 pandemic: data science call to arms. *Harv. data sci. rev.* **2020** (2020).
20. Mandal, S., Arinaminpathy, N., Bhargava, B. & Panda, S. Plausibility of a third wave of COVID-19 in : A mathematical modelling based analysis. *Ind J Med Res.* DOI **10** (2021).
21. Ganesan, S. & Subramani, D. Spatio-temporal predictive modeling framework for infectious disease spread. *Sci Rep* 6741, DOI: [10.1038/s41598-021-86084-7](https://doi.org/10.1038/s41598-021-86084-7) (2021).
22. Lau, E. H. *et al.* Neutralizing antibody titres in SARS-CoV-2 infections. *Nat. Commun.* **12**, 1–7 (2021).
23. Muecksch, F. *et al.* Longitudinal Serological Analysis and Neutralizing Antibody Levels in Coronavirus Disease 2019 Convalescent Patients. *J. Infect. Dis.* **223**, 389–398, DOI: [10.1093/infdis/jiaa659](https://doi.org/10.1093/infdis/jiaa659) (2020).
24. Cherian, S. *et al.* SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. *Microorganisms* **9**, 1542 (2021).
25. Choe, P. G. *et al.* Waning antibody responses in asymptomatic and symptomatic sars-cov-2 infection. *Emerg. infectious diseases* **27**, 327 (2021).
26. Hamady, A., Lee, J. & Loboda, Z. A. Waning antibody responses in covid-19: what can we learn from the analysis of other coronaviruses? *Infection* 1–15 (2021).

27. Children and adolescents deeply impacted by COVID-19 pandemic, PAHO director asserts, DOI: <https://www.paho.org/en/news/15-9-2021-children-and-adolescents-deeply-impacted-covid-19-pandemic-paho-director-asserts> (2021).
28. Incidence of Multisystem Inflammatory Syndrome in Children Among US Persons Infected With SARS-CoV-2, author=Payne, Amanda B and Gilani, Zunera and Godfred-Cato, Shana and Belay, Ermias D and Feldstein, Leora R and Patel, Manish M and Randolph, Adrienne G and Newhams, Margaret and Thomas, Deepam and Magleby, Reed and others. *JAMA Netw. Open* **4**, e2116420–e2116420 (2021).
29. Belagere, C. "If new variant emerges, Karnataka may see 20 lakh cases between August 22 and September 10: IISc". *The New Indian Express* 09 Aug. 2021. www.newindianexpress.com/states/karnataka/2021/aug/09/if-new-variant-emerges-karnataka-may-see-20-lakh-cases-between-august-22-and-september-10-iisc-2342092.html.
30. Ganesan, S. *et al.* An object oriented parallel finite element scheme for computations of PDEs: Design and implementation. *2016 IEEE 23rd Int. Conf. on High Perform. Comput. Work. (HiPCW)* 2–11, DOI: [10.1109/HiPCW.2016.023](https://doi.org/10.1109/HiPCW.2016.023) (2016).
31. Wilbrandt, U. *et al.* ParMooN – a modernized program package based on mapped finite elements. *Comput. Math.* **74**, 74–88, DOI: [10.1016/j.camwa.2016.12.020](https://doi.org/10.1016/j.camwa.2016.12.020) (2016).
32. Murhekar, M. V. *et al.* SARS-CoV-2 antibody seroprevalence in India, August–September, 2020: findings from the second nationwide household serosurvey. *Lancet Glob. Heal.* **9**, e257–e266 (2021).
33. Murhekar, M. V. *et al.* Prevalence of SARS-CoV-2 infection in India: Findings from the national serosurvey, May–June 2020. *Indian J. Med. Res.* **152**, 48 (2020).
34. COVID-19 India dashboard, DOI: <https://www.covid19india.org/> (2021). Last accessed on Aug 26, 2021.

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Author contributions statement

SG and DS developed the computational model and designed the experiments in consultation with GRB. SG implemented the model in the in-house finite element package ParMooN. SG, DS, TA, DG and GRB analysed the data and arrived at the conclusions. TA and DG produced the plots, tables for the data analysis. All authors contributed to preparing the manuscript and proof reading.