Supplementary Materials
Plausibility of a third wave of COVID-19 in India: A mathematical modelling based analysis

Model overview

We developed a deterministic, compartmental model of SARS-CoV-2 transmission, illustrated in Figure 1A (Main text). The model is stratified into three different age groups (<24 yr, 24-60 yr, and >60 yr). The model captures essential features in the natural history of SARS-CoV-2, including the role of asymptomatic infection, and the pronounced variations in disease severity, and mortality risk, by age (Table S1). To capture age-specific patterns of transmission (the 'age-mixing' matrix), we drew from recently published findings from a large contact tracing study in India[1]. As described below, we incorporated uncertainty in model parameters by defining plausible ranges for these parameters (Table S2), and then sampling from these ranges.

Model equations

In all equations that follow, state variables (*e.g.* U, E *etc*) denote the respective proportions of the total population in the corresponding states. Thus at time zero (prior to the epidemic), all state variables sum to 1. In this way, the model results can be applied to different settings within India, regardless of the actual population size involved. Accordingly, all model results are shown as population rates, *e.g.* symptomatic incidence per million population. Governing equations are as follows, where subscript j denotes age group:

Uninfected (U):

$$\frac{dU_j}{dt} = -\lambda_j U_j + w_a R_j$$

Exposed but not yet infectious (E):

$$\frac{dE_j}{dt} = \lambda_j U_j - \eta E_j$$

Asymptomatic and infectious (A):

$$\frac{dA_j}{dt} = \eta\left(1 - p^{(sym)}\right) E_j - \gamma A_j$$

Presymptomatic and infectious (P):

$$\frac{dP_j}{dt} = \eta\, p^{(sym)}\, E_j - r\, P_j$$

Symptomatic and infectious (S):

Table S1. List of state variables

State symbol	Meaning
U_j	Uninfected (j=1, 2, 3 indicating three age groups)
E_j	Exposed
A_j	Asymptomatic
P_j	Pre-symptomatic
S_j	Severe symptomatic
R_j	Recovered

Table S2. Parameters used in the model simulation

Parameter	Meaning	Values	Source/remarks
β	Transmission rate from symptomatic infection	0.06 for R_0=1.3 (Increases in proportion to R_0)	Calculated in order to yield assumed value of R_0 for different waves in India, by evaluating spectral radius of next-generation matrix (*e.g.* as described earlier[2])
η	Amongst those exposed, rate of developing infectiousness	(1/3-1/5)/day	Corresponds to an average latent period of 3-5 days: Together with the period of pre-symptomatic transmission (see *r* below), corresponds to an overall average incubation period of 4-6 days[3]
$p^{(sym)}$	Proportion developing symptoms	1/3-2/3	Wide variation noted in individual studies and meta-analysis[4-6]
k	Relative infectiousness of asymptomatic versus symptomatic infection	2/3-1	
r	Amongst those with pre-symptomatic infection, rate of developing symptoms	1/day	Assumption, corresponds to mean pre-symptomatic duration of one day
γ	Recovery rate	0.2/day	Assumption, corresponds to mean infectious period of five days[7]
w_a	Per-capita rate at which post-infection immunity wanes	(1/365-1/120)/day	Assuming mean duration of immunity lasts for four months to one year[8]

Parameter	Meaning	Age groups (yr)			Source/remarks
		<24	24-60	>60	
CFR_j	Case fatality rate in age Group I	0.1%	1.45%	10.9%	Represents proportion dying amongst those with symptoms. Drawn from a recent study from two Indian States[1]
μ_j	Mortality rate for severe cases	0.0002/day	0.0029/day	0.0245/day	Hazard rates of μ_i are calculated to yield case fatality rates, using: $CFR_i=\mu_i/(\mu_i+\gamma)$ Uncertainty in the mortality hazards are considered +/−25%
N_j	Population (India)	46%	44.5%	9.5%	Extrapolated from the Census of India 2011[9]
m_{ij}	Connectivity matrix between age Group I with age Group J	1.37 2.52 0.28	1.43 2.90 0.34	0.05 0.10 0.02	Drawn from reference[1]. Uncertainty in the each element of the contact matrix is considered +/−5%

There remains much uncertainty about parameters relating to SARS-CoV-2 natural history, *e.g.*, infectiousness of asymptomatic people relative to symptomatic ones and, duration of pre-symptomatic period, *etc*., In this study we adopted a range of parameter values to reflect this uncertainty in our model projections; we sampled uniformly from the parameter ranges shown here.

$$\frac{dS_j}{dt} = rP_j - (\gamma + \mu_j)S_j$$

Recovered and partially immune (R):

$$\frac{dR_j}{dt} = \gamma(A_j + S_j) - w_a R_j$$

A key parameter here is $p^{(sym)}$, the proportion of infected individuals developing symptoms.

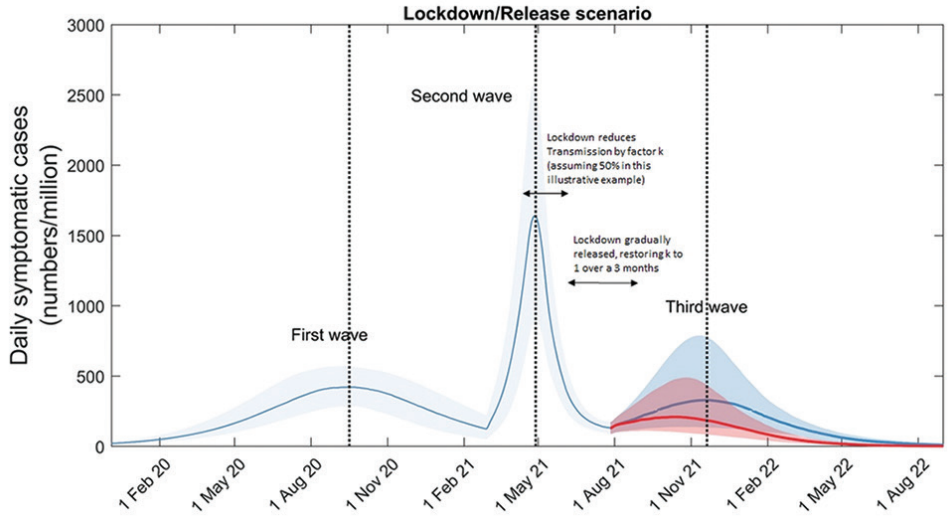

Fig. S1. Illustrative results for the impact of vaccination on a third wave in a lockdown/release scenario. Using the same parameters as for Fig. 5A in the main text, the red curve shows a vaccine ramp-up scenario where 40 per cent of the population has received two doses within three months of the second wave peak, and further that the effect of vaccination is (conservatively) to reduce severity of to infection by 60 per cent. Results illustrate how vaccination could substantially reduce the overall burden during the third wave.

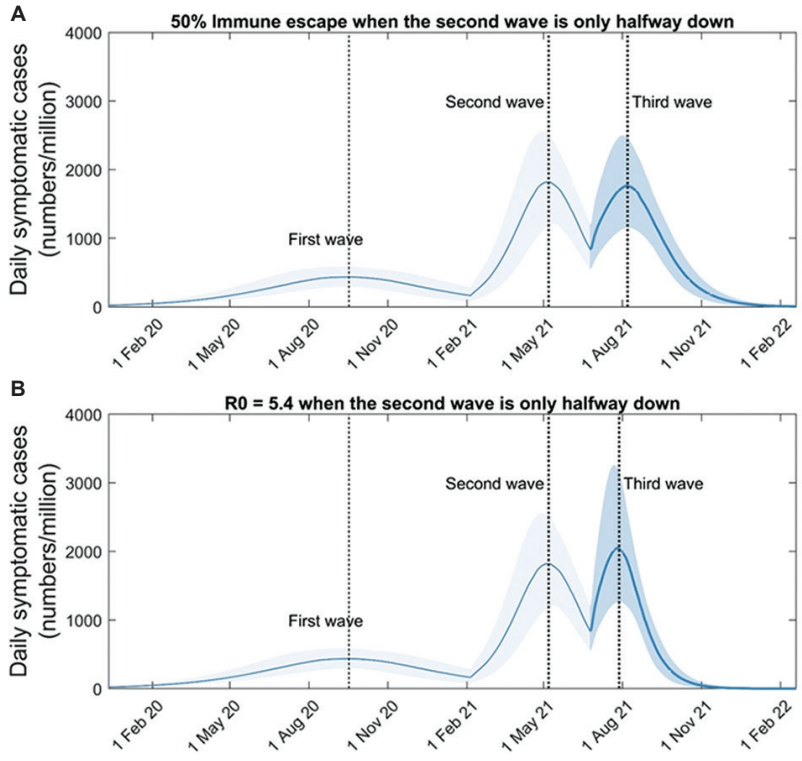

Fig. S2. Illustrative implications for early emergence of a variant. In the main text we assume, for simplicity and ease of exposition, that any variant causing a third wave would emerge only after the second wave has fully resolved. Here we show illustrative examples where emergence occurs while infection levels are still high, during the second wave. (**A**) illustrates early emergence of an immune escape variant (analogous to Fig. 3), (**B**) illustrates early emergence of a more-transmissible variant (analogous to Fig. 4). Both cases show the potential for overlapping second and third waves.

For the force-of-infection experienced by individuals in age group j, we have:

$$\lambda_j = \sum_{k,l} \beta m_{jk} \left[S_{kl} + k\left(A_{kl} + P_{kl} \right) \right]$$

Overall, the value of the basic reproduction number (R_0) for this model is proportional to the value of β, the rate-of-infection attributable to symptomatic individuals (noting that k acts as an adjustment for a/pre-symptomatic individuals). As described below, we controlled for R_0 by adjusting the value of β accordingly.

Uncertainty

We assumed plausible ranges for model parameters relating to the natural history of SARS-CoV-2, as listed in Table S1. Using latin hypercube sampling, we drew 250 sets of parameter values from within these ranges. For each resulting set of parameter values, we simulated the model as described above, to yield an ensemble of 250 model projections. On this ensemble, we estimated 95 per cent uncertainty intervals by calculating the 2.5th and 97.5th percentiles.

References

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