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Supplementary appendix

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Responsive and agile vaccination strategies against COVID-19 in India

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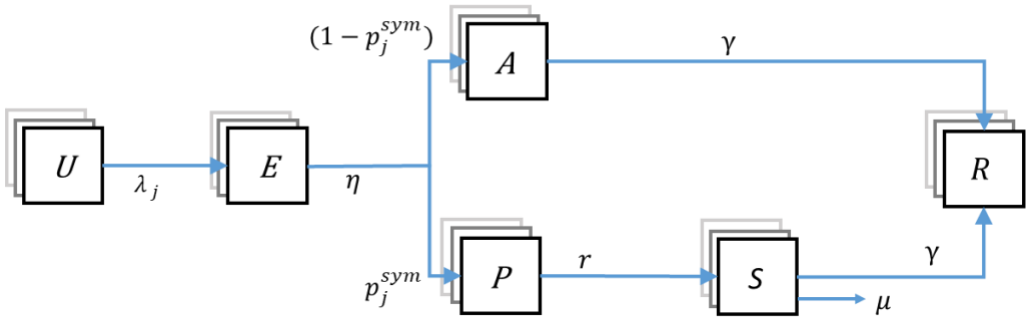
Appendix

Model overview

We developed a deterministic, compartmental model of SARS-CoV-2 transmission, illustrated in figure S1. The model is stratified by different age groups (<18 year, 18 – 60 year, and >60 year), and by vaccination status. On the latter, it can take three weeks for vaccine-induced protection to become effective [1]. We incorporated this delay into the model, assuming that during this period, a vaccinated individual essentially has no protective immunity. Accordingly, we stratified vaccination status into three categories: (i) non-vaccinated, (ii) vaccinated but who do not yet have vaccine-induced immunity, and (iii) having vaccine-induced immunity.

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 (see 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.[2] As described below, we incorporated uncertainty in model parameters by defining plausible ranges for these parameters (see table S2), and then sampling from these ranges.

A



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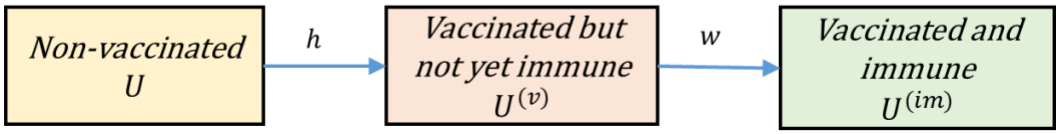

Figure S1. Schematic illustration of the model structure. (A) Overall model structure, with compartments as follows: U (Uninfected); E (infected, latent); A (asymptomatic); P (presymptomatic); S (symptomatic); and R (recovered). For each compartment, the 'layers' in the diagram illustrate stratification by age group (<18 yo, 18 – 60yo and 60yo+), and by vaccination status (unvaccinated, vaccinated but not yet immune, and vaccinated and immune). Superscripts (*j*) denote those parameters that depend on vaccination status (see panel B). Model parameters are as listed in Table S1. (B) Transitions between different strata of vaccination status. We assume that it takes three weeks on average following vaccination, to gain immunity; superscript (v) denotes those who have received vaccination, but are not yet immune (owing to the post-vaccination delay of three weeks for immunity to become effective), while superscript (im) denotes those who have gained vaccine-induced immunity. We assume different types of vaccine effect: a 'disease-preventing' vaccine (presented in the main text) is one that reduces the proportion of individuals who develop symptoms (hence also reducing mortality) without affecting susceptibility to infection. By contrast, an 'infection-preventing' vaccine is one that reduces susceptibility to infection without affecting the proportion symptomatic following infection.

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 districts within India, regardless of the actual population size involved. Accordingly, all model results are shown as population rates, e.g. deaths per 100,000 population.

Model compartments are listed in Table S1, and model parameters listed in Table S2. Governing equations are as follows, where subscript i denotes age group, and subscript j denotes vaccination status:

Uninfected (U):

Uninfected, unvaccinated ($U_{i,1}$)

$$\frac{dU_{i,1}}{dt} = -(1 - c_1)\,\lambda_i\,U_{i,1} - h_i U_{i,1}$$

Uninfected, vaccinated but not yet immune ($U_{i,2}$)

$$\frac{dU_{i,2}}{dt} = -(1 - c_2)\,\lambda_i\,U_{i,2} + h_i U_{i,1} - w_i U_{i,2}$$

Uninfected, vaccinated and immune ($U_{i,3}$)

$$\frac{dU_{i,3}}{dt} = -(1 - c_3)\,\lambda_i\,U_{i,3} + w_i U_{i,2}$$

In modelling vaccine uptake, we only model transitions between the uninfected compartments: in practice it is likely that infected individuals would receive vaccination as well (particularly those without symptoms), but we assume that any post-infection vaccine essentially occurs too late to have any effect on the natural history of infection.

Exposed but not yet infectious (E_{ij}):

$$\frac{dE_{ij}}{dt} = \left(1 - c_j\right)\lambda_i\,U_{ij} - \eta E_{ij}$$

Asymptomatic and infectious (A_{ij}):

$$\frac{dA_{ij}}{dt} = \eta\left(1 - \left(1 - d_j\right)p^{(sym)}\right)E_{ij} - \gamma A_{ij}$$

Presymptomatic and infectious (P_{ij}):

$$\frac{dP_{ij}}{dt} = \eta\left(1 - d_j\right)p^{(sym)}\,E_{ij} - r\,P_{ij}$$

Symptomatic and infectious (S_{ij}):

$$\frac{dS_{ij}}{dt} = rP_{ij} - \mu_{ij}\, S_{ij}$$

Recovered and partially immune (R_{ij}):

$$\frac{dR_{ij}}{dt} = \gamma(A_{ij} + S_{ij})$$

For the force-of-infection experienced by individuals, we have:

$$\lambda_i = \sum_{k,l} \beta\, m_{ik} \left\{[S_{kl} + k\,(A_{kl} + P_{kl})] + [{S^v}_{kl} + k\,({A^v}_{kl} + {P^v}_{kl})] + \left[{S^{im}}_{kl} + k\left({A^{im}}_{kl} + {P^{im}}_{kl}\right)\right]\right\},$$

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.

State symbol	Meaning
U_{ij}	Uninfected (i = 1, 2, 3 indicating three age groups) (j = 1, 2, 3 indicating vaccination status)
E_{ij}	Exposed
A_{ij}	Asymptomatic
P_{ij}	Pre-symptomatic
S_{ij}	Severe symptomatic
R_{ij}	Recovered

Table S1 List of state variables

Modelling test positivity rate

We modelled testing at sentinel sites as sampling at random from a symptomatic population, only some having SARS-CoV-2, and the remainder (a proportion *n*) having non-COVID-related respiratory diseases. We modelled test positivity rate through time as:

$$TPR(t) = \frac{\sum_{ij} S_{ij}(t)}{\sum_{ij} S_{ij}(t) + n},$$

where (as defined above) S_{ij} is the number of symptomatic individuals with COVID-19 from age group *i* and vaccination status *j* at time t. To fix *n*, we modelled a first wave of SARS-CoV-2 using the governing equations above. We then estimated the value of *n* in order to yield a TPR of 10% at the epidemic peak, in agreement with test data from that period[3].

Modelling the second wave

For a given sample of model parameters (see 'uncertainty' below), we chose the rate-of-infection β in such a way as to fix the basic reproduction number, R_0, as follows: in this model, R_0 is proportional to β. For a given set of parameter values, we calculated R_0 as the spectral radius of the next generation matrix, arising from the governing equations shown above, and assuming no prior immunity in the population. We then adjusted the value of β in order to yield the required value of R_0 (we show results for 2, and 2.5).

As initial conditions, we assumed that 25% of the population has already been infected in the first wave, and occupies the recovered compartment[4] (because we are not modelling reinfection on these timescales, the dynamics are unchanged when allowing for mortality, rather than recovery, in the first wave). We then initiated the second wave by introducing a single infected, infectious individual in this population, and simulating forwards in time.

To simulate vaccination, we monitored model-based TPR as described above. We assumed that the vaccination effort would be initiated as soon as TPR exceeds 0.5%, and further that vaccination is implemented in such a way that over-18-year-olds are subject to a per-capita 'hazard' of vaccination of $-\frac{1}{30}\log(1-p)$. This results in a vaccination coverage of p being reached after 1 month; we assumed no further vaccination beyond this point.

To simulate non-pharmaceutical interventions, we assumed further that β is reduced by 25% for the duration of vaccination, and that it is restored to its pre-intervention value immediately upon completion of the vaccination drive, after 1 month.

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 500 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 500 model projections. On this ensemble, we estimated 95% uncertainty intervals by calculating the 2.5^{th} and 97.5^{th} percentiles.

Table of parameters

Parameter	Meaning	Values	Source/Remarks
β	Transmission rate from symptomatic infection	0.09 – 0.14	Calculated in order to yield assumed value of R_0 for second wave in India, by evaluating spectral radius of next-generation matrix (e.g. as described in [5]). Value shown here is to yield R0 = 2 – 3.
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 presymptomatic transmission (see r below), corresponds to an overall average incubation period of 4-6 days [6]
$p^{(sym)}$	Proportion developing symptoms	1/3 – 2/3	Wide variation noted in individual studies and meta-analysis [7–9]
k	Relative infectiousness of asymptomatic vs symptomatic infection	2/3 – 1	
r	Amongst those with presymptomatic infection, rate of developing symptoms	1 /day	Assumption, corresponds to mean pre-symptomatic duration of 1 day

γ	Recovery rate	0.2 /day			Assumption, corresponds to mean infectious period of 5 days[10]
	Age groups	<18 year	18-60 year	>60 year	
CFR_i	Case fatality rate in age group *i*	0.08%	1.17%	10.9%	Drawn from a recent study from two Indian States.[2]
μ_i	Mortality rate for severe cases	0.0002 /day	0.002 4 /day	0.024 5 /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_i	Population (India)	36.5%	54%	9.5%	Extrapolated from the Census of India 2011[11]
m_{ij}	Connectivity matrix between age group i with age group j	1.35 2.50 0.28	1.43 2.91 0.34	0.04 0.10 0.02	Drawn from ref.[2] Uncertainty in the each element of the contact matrix is considered +/- 5%.
h	Per capita rate of vaccination	0	0.046 /day	0.046 /day	Rate to cover 75% of adult population in 30 days
w	Per capita rate of vaccine induced immunity	0.0476 /day			Assumption, mean duration to develop vaccine induced immunity three weeks

	Vaccination status	Non-vaccinated	Received vaccination, but are not yet immune	Gained vaccination induced immunity	
c_j	Relative risk of infection associated with vaccination status j	0	0	0.6	For infection preventing vaccine
				0	For disease preventing vaccine
d_j	Relative risk of symptomatic disease/death associated with vaccination status j	0	0	0	For infection preventing vaccine
				0.6	For disease preventing vaccine

Table S2: Parameters used in the model simulation. 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.

Additional model results

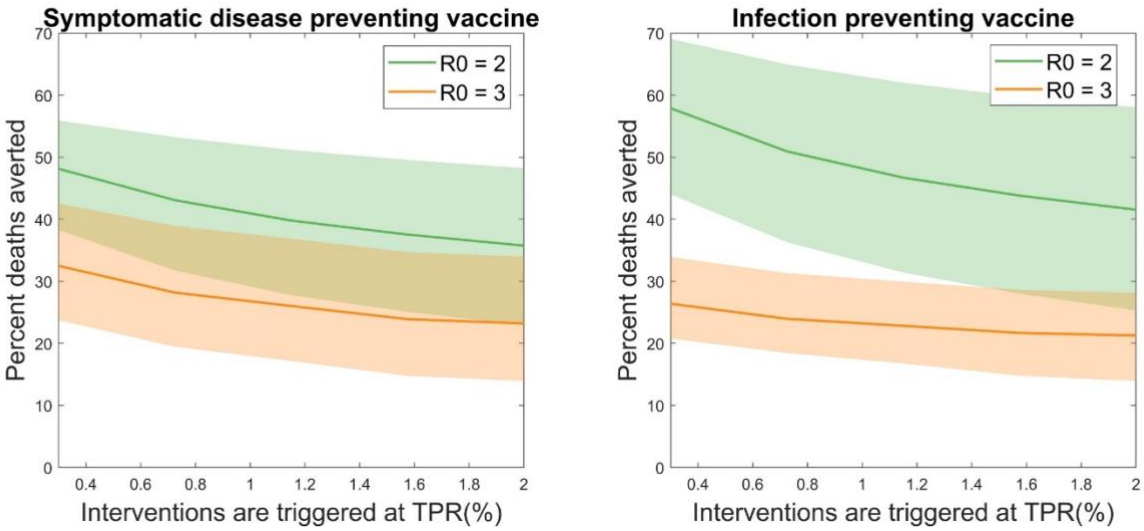

Figure S2. How the impact of responsive vaccination and NPIs varies with threshold TPR. Shown on the x-axis is the test positivity rate (TPR) at which interventions are triggered; as in Figure 1B (green curve), we assume that interventions include vaccination of 75% of over-18s within one month, concomitantly with non-pharmaceutical interventions to reduce transmission by 25% over this same duration. Shown are two scenarios for vaccine effect, as follows: (A) Assuming a vaccine having 60% efficacy at preventing severe disease and mortality but no effect on acquisition of infection, (B) Conversely, assuming a vaccine having 60% efficacy at reducing infection but no effect on severe disease or mortality, following infection.

Table S3. Summary of epidemiological impact (cumulative symptomatic incidence and deaths averted) under the different intervention scenarios for R_0 = 2.

Vaccination is triggered by a TPR of 0.5%	Symptomatic disease preventing vaccine		Infection preventing vaccine	
	Percent cases averted	Percent deaths averted	Percent cases averted	Percent deaths averted
with responsive vaccine alone	26% (CI 12 - 35)	37% (CI 21 - 50)	32% (CI 12 - 48)	42% (CI 18 - 59)
with responsive vaccine + NPI	32% (CI 24 - 39)	45% (CI 32 - 54)	44% (CI 29 - 56)	55% (CI 36 - 66)

Table S4. Summary of sensitivity analyses under alternative scenarios.

Sensitivity analysis	Symptomatic disease preventing vaccine, percent deaths averted	
	$R_0 = 2$	$R_0 = 3$
Threshold TPR of 0.5% (main text results)	45% (CI 34 – 54)	30% (CI 21 – 41)
Threshold TPR reduced from 0.5% to 0.3%	48% (CI 38 – 56)	33% (CI 24 – 43)
Vaccine efficacy reduced from 60% to 30%	26% (CI 21 – 31)	18% (CI 15 – 22)
Post-dose delay to gaining vaccine-induced immunity reduced from 3 weeks to 2	49% (CI 35 – 56)	35% (CI 25 – 43)

Data sharing

The model code and dataset are publicly available at https://github.com/sandipccmb/Responsive-and-agile-vaccination-strategies-.

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