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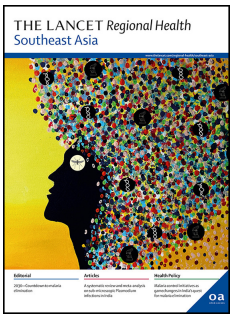

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Effect of hybrid immunity, school reopening, and the Omicron variant on trajectory of COVID-19 epidemic in India: A modelling study

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Abstract

Background: The course of the COVID-19 pandemic has been driven by several dynamic behavioral, immunological, and viral factors. We used mathematical modeling to explore how the concurrent reopening of schools, increasing levels of hybrid immunity, and the emergence of the Omicron variant affected the trajectory of the pandemic in India, using Andhra Pradesh (pop: 53 million) as an exemplar Indian state.

Methods: We constructed an age- and contact-structured compartmental model that allows for individuals to proceed through various states depending on whether they have received zero, one, or two doses of the COVID-19 vaccine. We calibrated our model using results from another model (ie, INDSCI-SIM) as well as available context-specific serosurvey data. The introduction of the Omicron variant is modelled alongside protection gained from hybrid immunity. We predict disease dynamics in the background of hybrid immunity coming from infections and an ongoing vaccination program, given prior levels of seropositivity from earlier waves of infection. We describe the consequences of school reopening on cases across different age-bands, as well as the impact of the Omicron (BA.2) variant.

Findings: We show the existence of an epidemic peak in India that is strongly related to the value of background seroprevalence. As expected, because children were not vaccinated in India, re-opening schools increases the number of cases in children more than in adults, although in all scenarios, the peak number of active hospitalizations was never greater than 0.45 times the corresponding peak in the Delta wave before schools were reopened. We varied the level of infection induced seropositivity in our model and found the height of the peak associated with schools reopening reduced as background infection-induced seropositivity increased from 20% to 40%. At reported values of seropositivity of 64% from representative surveys done in India, no discernable peak was observed. We also explored counterfactual scenarios regarding the effect of vaccination on hybrid immunity. We found that in the absence of vaccination, even at high levels of seroprevalence (>60%), the emergence of the Omicron variant would have resulted in a large rise in cases across all age bands by as much as 1.8 times. We conclude that the presence of high levels of hybrid immunity resulted in fewer cases in the Omicron wave than in the Delta wave.

Interpretation: In India, decreasing prevalence of immunologically naïve individuals of all ages was associated with fewer cases reported once schools were reopened. In addition, hybrid immunity, together with the lower intrinsic severity of disease associated with the Omicron variant, contributed to low reported COVID-19 hospitalizations and deaths.

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INTRODUCTION

The first confirmed case of COVID-19 in India was documented on Jan 30, 2020. The initial epidemic wave of COVID-19 in India peaked in September 2020. Thereafter, cases decreased gradually until the middle of February 2021, when a second wave, driven by the emergence of the Delta variant, led to a sharp increase in cases. At the apex of the second epidemic wave, daily reported cases were significantly higher than the previous wave. By late April 2021, India had surpassed 2.5 million active cases, overtaking Brazil as the country with the second highest number of confirmed COVID-19 cases in the world after the US.

Schools have remained mostly closed in India during the pandemic, in an attempt to slow or arrest transmission of the virus.[1] During the first epidemic wave, school closures together with broader lockdown measures (eg, travel restrictions) likely contributed to low levels of transmission. However, as travel restrictions and physical distancing measures were relaxed, the effectiveness of keeping schools closed in India was been widely discussed. Many have argued that the epidemiological benefits of keeping schools closed has been outweighed by the significant impact on cognitive and social development of children. Schools in many states reopened by Aug 2021, as the Delta wave ended.

India's COVID-19 vaccination drive began on Jan 16, 2021. Vaccinations were initially targeted at frontline workers (eg, police, revenue officials, local government officials) and health-care workers, but the target population was broadened a month later to include the elderly (ie, >60 years) and those older than 45 years with comorbidities (eg, diabetes mellitus, coronary heart disease, or hypertension). In later phases, younger age-groups became eligible for vaccines, until all adults older than 18 years were eligible for vaccination by May 1, 2021. From Jan 3, 2022, children between 15-18 years have been eligible for COVID-19 vaccination. A third dose was approved for those older than 18 years from April 10, 2022.

COVID-19 vaccines have been found to be extremely efficient in reducing severe cases, hospitalizations, and deaths.[2–10] Mathematical modeling has indicated that vaccinating in an age descending manner[11–13] is effective at reducing severe illness, hospitalizations, and deaths, even if the vaccine supply is limited. A major challenge with attaining high population vaccination coverage globally, has been vaccine hesitancy in some populations.[14] Studies found substantially higher willingness to receive COVID-19 vaccines in low- and middle-income countries, including India, relative to most other high-income countries.[15]

The trajectory of COVID-19 around the world has been marked by the appearance of multiple variants. On Nov 26, 2021, the World Health Organization (WHO) named a new variant of concern B.1.1.529, first discovered in South Africa, as the "Omicron" variant. The first case of Omicron (BA.1.1) in India was reported on Dec 3, 2021. By the beginning of January 2022, BA.1.1 accounted for 31% of reported sequences in the country. The BA.2.12.1 Omicron subvariant soon replaced BA.1.1 and was the dominant variant, with more than 90% of reported sequences in India in early 2022, largely due to its high transmissibility[16–18] and its immune escape potential.[19–21] As a result, even settings with high levels of immunity experienced Omicron-associated epidemic waves.

Attempts to understand the trajectory of the COVID-19 pandemic in India, across multiple waves of the disease, have spurred the development of a number of compartmental models.[12,22–25] Earlier models were constructed so as to be appropriate to immunologically naïve populations. However, preexisting levels of infection-associated seroprevalence as well as the relatively high population coverage of the vaccination program (eg, >80), mandate that current models now accommodate additional complexity. Using mathematical models, we aim to answer two specific questions: (1) why did India not see a large increase in cases following the reopening of schools in many states? and (2) why did the Omicron-associated third epidemic wave not have a significant impact on the population despite higher transmissibility and immune escape potential? We use data from the southern Indian state of Andhra Pradesh to address these two questions here.

METHODS

Model

Our approach extends the INDSCI-SIM model [insert reference here for *PLOS Comp Bio* paper once published]. Briefly, INDSCI-SIM is an age-stratified, contact-structured nine-compartment epidemiological compartmental model that has been used to provide a detailed analysis of the first wave of COVID-19 in India. The set of compartments that describes unvaccinated individuals in the model presented here is identical to that in the INDSCI-SIM model. In the original INDSCI-SIM model, a small number of parameters were chosen to vary with time while others were fixed. Time-dependence was extracted using Bayesian methods. To address undercounting, a bias factor, relating actual numbers of infected to those detected each day, was also incorporated into the INDSCI-SIM model. The numerical values of the constant parameters are shown in Tables 1-3.

In our generalized model (Fig 1), individuals progress to different compartments based on whether they are unvaccinated, vaccinated with one dose, or vaccinated with two doses. Unvaccinated individuals progress through nine compartments upon infection: Susceptible (S) individuals who are infected move to the Exposed (E) compartment from which they can either become Asymptomatic Infected (IA) and then Recover (R), or become Pre-symptomatic Infected (IP), meaning that they will eventually exhibit symptoms. A certain fraction of Pre-symptomatic Infected individuals become Mildly Infected (IM) before recovering, while the remainder become Severely Infected (IS) and are eventually Hospitalized (H). A fraction of Hospitalized individuals eventually dies, moving to the Decedent (D) compartment, while the remaining recovers.

The progression for vaccinated individuals is similar: individuals who have been Vaccinated but have not contracted the disease (V) can nevertheless be infected (ie, breakthrough infection) and move to the Vaccinated Exposed compartment (VE), from which they can either move to the Vaccinated Asymptomatic (VA) or Vaccinated Symptomatic (VS) compartments. The Vaccinated Asymptomatic, as well as a large fraction of the Vaccinated Symptomatic, recover. However, our model allows for a small fraction of Vaccinated Symptomatic individuals to die depending on age. A distinction is made between individuals who received their vaccine after having contracted the disease (the Recovered Vaccinated; RV) and those who contracted the disease after being vaccinated (the Vaccinated Recovered; VR) to account for the different levels of protection these trajectories might offer, especially where reinfections exist. Separate pathways of compartments exist for both one and two doses of the vaccine. Vaccine efficacy is reflected in the differential rates at which vaccinated individuals can get infected compared to unvaccinated individuals. Additionally, the fraction of infected individuals who progress to symptomatic or severe disease is lower for those in the vaccinated compartments. The parameters governing the disease progression are shown in Tables 1-3. We have used parameter values from the INDSCI-SIM model.[26]

The population is divided into age bands grouped into 10-year intervals: 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+ years. Contacts between different age bands are differential, reflecting the social structure of the population. An age-specific contact matrix is used to account for the impact of non-pharmaceutical interventions, including lockdowns and school closures. The contact matrix C_{ij} ultimately governs the force of infection on each age-band i due to the age-band j.

The parameter β, which governs the force of infection for every susceptible individual, is assumed to be the same for all individuals, independent of their vaccination status. The value of β was obtained from simulations of the INDSCI-SIM model, where it is estimated using a Bayesian approach to match daily reported cases and deaths of Andhra Pradesh. This approach gives us a likely value of β, as well as a confidence interval. Our simulations are run for a range of β within this interval, providing a band of potential disease trajectories. In addition, this quantity is further modulated by the relative intensity of

contacts between susceptible and different kinds of infectious individuals whose effect is simply specified here through factors of ϵ. These values are obtained from the INDSCI-SIM simulations, and are held constant throughout the Delta wave. At the onset of Omicron, these values are reset to 1, indicating that both asymptomatic and symptomatic individuals are equally likely to infect susceptible individuals during the Omicron wave.

To estimate the undercounting of daily cases, a bias factor of 11 and 22 is used for Andhra Pradesh before and after the Omicron wave, respectively. The first factor is taken from the INDSCI-SIM predictions for July 2021, while the second is an assumption based on the reduced levels of testing in the Omicron wave, where a good fraction of the population chose to remain untested or their test results were not reported, as home-based rapid antigen tests were more accessible to much of the population.[27–29]

Initial conditions

We begin all simulations of our model from Aug 1, 2021. The initial conditions for our simulation were obtained by running the INDSCI-SIM model from March 1, 2020, to Aug 1, 2021. Values in each compartment were then used as the initial condition for our vaccination model. India's vaccination drive began on Jan16, 2021. From March 1, 2020 individuals above older than 60 years and individuals older than 45 years with comorbidities were eligible for vaccination, and on the 1st of April, this was relaxed to include all individuals above the age of 45. On the 1st of May, all individuals above the age of 18 were eligible for vaccination. Since the original INDSCI-SIM model did not implement vaccinations, it was necessary to estimate the number of individuals who had been vaccinated with either one or two doses. These numbers are obtained from covid19india.org.

The INDSCI-SIM simulation provides a background infection-induced seropositivity of roughly 64%, close to the actual seropositivity measured in the serosurvey conducted from June to July 2021.[30] When we use the term "seropositivity" in this paper to refer to our initial condition on Aug 1, 2021, we refer to the population prevalence of antibodies induced by infection, rather than both from infection and vaccination, a reasonable approximation at low levels of vaccination.

In order to study the effect of different initial seropositivity levels, we also conducted simulations in which we adjusted the number of individuals in the susceptible and recovered compartments so that the total number of recovered matched the infection-induced seropositivity levels for which we aimed. For example, for seropositivity levels lower than 64%, an appropriate number of individuals was transferred from the recovered to the susceptible compartment, while the inverse was done for seropositivity levels greater than 64%.

A constant fraction of the susceptible and recovered individuals, based on the vaccine coverage in our study region, were transferred from the Susceptible compartment to the Vaccinated (V1, V2) and Recovered Vaccinated (RV1, RV2) compartments, representing the fraction of people who had received vaccines by the simulation start date. These numbers were then divided among the first (V1, RV1) and second dose (V2, RV2) vaccine compartments based on the details of the vaccine coverage by the date of the simulation's start. For example, 30% of the population of the state of Andhra Pradesh was vaccinated with at least one dose, and 10% with the second dose, by the Aug 1, 2021. Thus, we move 20% of all susceptible individuals to the V1 compartment and 10% to the V2 compartment. This is repeated for individuals in the recovered compartment, moving them to the RV1 and RV2 compartments, respectively. We ignore the number of individuals who were infected at the time of vaccination, as we expect this number to be very low.

Reopening schools

Our simulation, like the INDSCI-SIM model, uses contact matrices to model the contacts between individuals of different age-bands.[31] In our simulations, we consider all individuals below the age of 20 to

be children. This age-band (technically 0-18, but we ignore this minor discrepancy) is not eligible to receive vaccines. The remaining population is considered to be adult. The contact matrix method allows us to model the effects of social structures such as those arising from household and work contacts. This method can therefore also be used to model the effects of non-pharmaceutical interventions like lockdowns and restrictions on public transport. In particular, these contact matrices (Table 4) can be used to model the reopening of schools, by introducing more contacts between the children, as well as between children and adults.

We use contact matrices that are a weighted average over the contributions from different types of "locations" (eg, home, workplace, school).[26,31] The weights may vary with time, appropriate to the interventions implemented at that point in time, and are described in Table 4.

In the INDSCI-SIM simulation, which we use to obtain the initial conditions for the hybrid-immunity model, we assume that schools are closed, and that physical interactions due to public transport and social gatherings are minimized. As a result, the contribution to the contact matrices of household contacts is 1 and work contacts is 0.5. Both school and public gathering contacts were assumed to be 0. In the hybrid immunity model proposed in this paper, we allow for the existence of many more interactions. We assume the existence of "other" physical interactions like public transport and social gatherings, and add a contribution of 0.5 to the contact matrices for the first fifteen days, while keeping schools closed. Home and work contact contributions were left unchanged. These choices can of course be varied to represent other intervention scenarios.

Reopening schools was modeled by gradually increasing the corresponding values of the contact matrices in intervals of 20 days. School interactions were thus ramped up from 0% to 50% over roughly 120 days, which corresponds to Dec 15, 2021. This coincides with the onset of the Omicron wave in India, and therefore, we further assume all schools to be closed from Dec 15, 2021 until the end of the simulation in March 2022.

Emergence of Omicron variant

The Omicron variant of concern was first detected in South Africa, before spreading to more than 90 countries. To describe the epidemiology of the Omicron variant, we calibrated our model with data from South Africa (See Supplementary Material), using daily reported cases to estimate its growth rate.

We simulated the growth of cases associated with the Omicron variant in South Africa from Nov 15, 2021. Given that by then, the total vaccinated population in South Africa was 27% and 22% for the first and second doses, respectively, we use this input in our calculations. We initially assume a seropositivity of 60% and assume that the effects of a prior infection can be taken to be equivalent to that of a single vaccination, 20% of the population from the recovered compartment were moved to the V1 compartment from where they can be infected.

The weight factors multiplying the home and work contact matrices were taken to be 1, while the weight factors of schools and "other" were taken to be 0.5, assuming that no strict restrictions were implemented in South Africa during the Omicron wave. The population was vaccinated at a low vaccination rate. All parameters for the unvaccinated except β are the same as used in the INDSCI-SIM model. We have chosen a value of β such that the increase in number of daily cases matches the reported daily cases. To account for case-undercounting, a bias factor of 15 is used to best fit the South African data for cases and deaths accounting for the fact that many symptomatic patients chose not to be tested. This factor was further optimized to fit the Indian data, based on the expected seroprevalence and the test positivity.

Vaccine allocation

The rate at which individuals receive the first vaccine dose depends only on the number of individuals eligible for a first dose. The same is true for the second dose. Additionally, any excess first doses are used to vaccinate the individuals eligible for second doses. The same process is repeated for the second dose, with any excess doses being used to vaccinate eligible unvaccinated people. This process ensured that all available vaccines were used, whenever possible. The details of our calculations can be found in the Supplementary Material.

We study the possible outcomes for different background seroprevalence levels of 20%, 40%, and 80% in order to assess the importance of hybrid immunity.

RESULTS

Figure 2 shows the daily number of cases, aggregated over all age-bands for Andhra Pradesh, along with the three other scenarios involving different background seroprevalence levels. The results for adults and children can be found in the Supplementary Material.

Figure 2A shows that the absence of a noticeable rise in the daily number of cases or deaths, in both older and younger age-bands when schools were reopened, can be explained by the fact that the background seroprevalence was sufficiently high.

For example, had the seroprevalence been lower (eg, 20%) we would have expected to see a sharp rise in cases with a high peak around the end of September 2021, as can be seen in the Figure 2B. Our simulations indicate that this peak would have affected children, who were unvaccinated, much more than adults. For example, in the case where the seropositivity was 20%, it was found that the height of the school reopening peak relative to the Delta wave's peak was roughly 2.8 times for children, while it was only 1.3 times for adults. If the background seroprevalence had been close to 40%, the height of the school reopening peak would have been around 0.9 times the Delta peak for children, while the height relative to the Delta peak would have only been 0.3 times for adults.

Once the seroprevalence crosses 60%, the school-reopening-associated epidemic peak is completely washed out, indicating that the level of immunity attained through the combination of both vaccination and prior infection is sufficient to curtail the spread of the disease. Even when the seroprevalence was 20%, while a sharp rise in daily cases was observed, these cases were mostly asymptomatic or mild, with the number of severe cases remaining quite low in comparison to numbers in the Delta wave. Our simulations found these cases to occur mainly among the adult population who had more of a chance of severe illness than children.

The introduction of Omicron – modeled by an increase in β which was calibrated by the data from South Africa – causes an upswing in the number of cases across all age-bands, as expected. As described in the Methods section, the possibility of reinfection by Omicron is modeled by moving a constant fraction of 20% of the recovered individuals to the "single-dose-vaccinated'' compartment V1. The locations of the peak of the Omicron wave in our simulations match actual data reasonably well. However, the duration of the wave in our simulations appears to be larger. A larger value of β would have allowed us to match the observed width.

Figure 3 shows the counterfactual scenario where our simulation was run for a seropositivity of 64% (Figure 2A) but without incorporating the effects of vaccination. As can be seen, while this would not have affected school reopening, a much higher peak could have been expected during the Omicron wave. Both children and adults would have fared similarly during this wave, as is to be expected given that both groups are now unvaccinated. This would have resulted in a rise in the number of severe cases (and,

consequently, deaths) over all age-bands that would have been much larger than the numbers observed during the Delta wave.

DISCUSSION

We are not aware of other transmission dynamic models, at the time of preparing this manuscript, that incorporate hybrid immunity into discussions of the COVID-19 trajectory of India, and to assess its specific impact on school reopening and the Omicron case trajectory. The model contains multiple interacting time-varying components, all of which are essential to understanding the dynamics of the disease across the Delta and Omicron waves. Our model includes a two-dose vaccine and differential levels of protection from these doses, across different age-bands. Our results are specific to Andhra Pradesh. However, given that other states in India reported similar key model parameters, including seroprevalence, our results can be largely generalized to other settings in the country. Some states (eg, Kerala) reported lower seroprevalence after the second wave and therefore we would caution against extrapolating our findings to such settings.

Our results explain why cases from the Delta wave continued to decline even as schools were reopened across the state of Andhra Pradesh. Given that seroprevalence levels in adults and children were largely comparable following the second epidemic wave, we conclude that the impact of school reopening on case-load was substantially reduced by the fact that a large fraction of the population had already been infected. Our simulations indicate that at the levels of seropositivity at which schools were reopened (ie, approximately 60%), infection-induced immunity was the primary factor in curtailing the spread of SARS-CoV-2. However, it should be noted that vaccination remains important for providing protection to those who have not been exposed to the virus that causes COVID-19 and for providing additional protection in those who have been exposed. We show, through model calculations at different levels of seropositivity, that low seropositivity values would have led to a much more substantial effect on infections in school-going children.

Next, we showed that the impact of the Omicron trajectory was reduced in India for two reasons: the high background seropositivity from infection and the high vaccine coverage, in addition to the overall reduced severity of disease caused by this variant. While we chose conservative values for the extent of reinfections as well as for break-through infections, our model can easily account for larger numbers if other, more aggressively immune-evading variants, were to emerge.

We draw multiple lessons from this work. At large background seropositivity levels, especially if background prior infection levels in children are comparable to those in adults, schools can and should be reopened. This should have only a marginal impact on cases. Further, our model suggests that increased immune evasion leading to an effectively larger susceptible population can lead to cases increasing sharply, indicating that the immune escape potential of new variants should be carefully tracked. Finally, given that variants of the original Omicron strain appear to be dominant across the world currently, the development of new vaccines that target Omicron variants should be a priority.

Our study has limitations. First, our model is calibrated against reported numbers of daily infections. We attempt to account for underreporting using bias factors from the INDSCI-SIM model and an assumption based on reduced testing and reporting during the Omicron wave. Otherwise, we do not account for time-varying undercounting of reported cases. This is particularly evident in the calibration of beta (i.e., force of infection) from South African data shown in Supplementary Material A3. Anecdotal and newspaper reports suggest that due to the relative mildness of the disease associated with the Omicron variant, those infected may have chosen to not get tested. Additionally, certain variables in our model are not known empirically, most notably rates between compartment among vaccinated individuals (ie, either one or two doses). We made reasonable estimates for these rates in the absence of widely accepted values. Such values may also vary between sub-variants of Omicron variants and we do not explicitly account for this.

Since we are using a compartmental model, we implicitly assume our population is homogeneously mixed. This is partially addressed by using age-dependent contact matrices; however, network and agent-based models may provide more detailed insights into the effects of heterogeneous mixing. Last, we have chosen to not include a third-dose for our vaccine, since very few third doses were distributed during our period of study (ie, March 1, 2021 to March 1, 2022). While booster doses were administered beginning Jan 10, 2022, these were only administered to individuals older than 60 years with comorbidities and frontline workers. It was only after April 8, 2022 that booster doses became available to all eligible adults. Future models could be updated to account for third doses.

We conclude that Andhra Pradesh did not see a large rise in cases among the unvaccinated individuals, who were predominantly children as they were not yet eligible for vaccines, after schools began reopening because of high background levels of seropositivity. To further address this claim, we experimented with various counterfactual scenarios to show that a rise in cases would have been expected with lower levels of prior seropositivity. Our discussion of the Omicron wave illustrates that even with its higher transmissibility, the impact of this variant was blunted by high levels of hybrid immunity. We verify this through the construction of a number of counterfactual scenarios where we can alter the balance of infection- and vaccination-induced seroprevalence.

CONTRIBUTORS

FM, PC, and BW did the literature search. BW, SK, and GIM designed the study. Analyses were interpreted by all authors. FM and PC wrote the original draft of the manuscript which was reviewed and edited by all other authors (SK, BW, and GIM). All authors (FM, PC, SK, BW, and GIM) had full access to all the data. BW and GIM had final responsibility for the decision to submit for publication.

DECLARATION OF INTERESTS

We declare no competing interests.

DATA SHARING

Aggregated case and vaccination data are available www.covid19india.org and www.covid19bharat.org.

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TABLES

Table 1: Transition rates and branching parameters for disease progression

Parameter	Value day^{-1}		Description	Reference
β	**Delta wave** day^{-1} [0.075, 0.097]	**Omicron wave** day^{-1} 1.74 × [0.075,0.097]	Rate at which infected individuals can infect the susceptible population	**Delta:** INDSCI-SIM (on Aug 1, 2021). **Omicron:** value calibrated from South African data (see Supplementary Material)
γ	0.5 day^{-1}		Exposed individuals become asymptomatic or pre-symptomatic after an average of $1/\gamma = 2$ days	INDSCI-SIM
λ_A	0.1428 day^{-1}		Asymptomatic individuals recover after an average of $1/\lambda_A = 7$ days	
λ_P	0.5 day^{-1}		Pre-symptomatic individuals develop symptoms after an average of $1/\lambda_P = 2$ days	
$\lambda_{\mathfrak{I}}$	0.1428 day^{-1}		Mildly infected individuals recover after an average of $1/\lambda_{\mathfrak{I}} = 7$ days	
λ_{IS}	0.1736 day^{-1}		Severely infected individuals are hospitalized after an average of $1/\lambda_{IS} = 6$ days	
ρ	0.068 day^{-1}		Hospitalized individuals either recover or die after an average of $1/\rho = 15$ days	
α_i	See Table 2		Fraction of exposed individuals who move to the asymptomatic compartments. These fractions are age-stratified (as indicated by the index i).	INDSCI-SIM (on Aug 1, 2021)
α_{v1i}	0.989		Fraction of *vaccinated* exposed (single and two-shot)	

α_{v2i}	0.999	individuals who move to the asymptomatic compartments. These fractions are the same for all ages, although this can be simply generalized.	
μ_i	See Table 2	Fraction of pre-symptomatic individuals who develop mild symptoms.	INDSCI-SIM (on Aug 1, 2021)
δ_i	See Table 2	Rate at which individuals transition from the hospitalized compartment to the dead compartment. δ_i takes different values for the Delta and Omicron waves.	**Delta:** INDSCI-SIM (on Aug 1, 2021). **Omicron**: Value of δ_i is reset to the original value used INDSCI-SIM on March 2021.
η_{v1i}	$\frac{\rho \times \delta_i}{10}$	Rate at which individuals move from the symptomatic vaccinated compartments to the dead compartments. This number is assumed to be $(\rho \times \delta_i)/10$ and $(\rho \times \delta_i)/50$ for the first and second-shot vaccine cases respectively, for each age-band.	
η_{v2i}	$\frac{\rho \times \delta_i}{50}$		

Table 2: Age-stratified branching parameters for disease progression

Age band	α_i	μ_i	δ_i **(Delta wave)**	δ_i **(Omicron wave)**
0-9	0.5	0.999	0.00308	0.0185
10-19	0.45	0.997	0.00311	0.0187
20-29	0.4	0.988	0.00238	0.0143
30-39	0.35	0.968	0.00276	0.0166
40-49	0.3	0.951	0.00566	0.034
50-59	0.25	0.898	0.00833	0.05
60-69	0.2	0.834	0.0161	0.097
70-79	0.15	0.757	0.035	0.21
80+	0.1	0.727	0.0366	0.22

Table 3: Contact parameters that modulate the interactions between susceptible and infected individuals

Contact intensity parameter	Value (Delta wave)	Value (Omicron wave)	Description
ϵ_{IA}	0.410	1	Relative intensity of contacts for asymptomatic individuals.
ϵ_{IS}	0.383	1	Relative intensity of contacts for severely infected individuals
ϵ_{IP}	0.383	1	Relative intensity of contacts for pre-symptomatic
ϵ_{IM}	0.383	1	Relative intensity of contacts for mildly infected

Table 4: Weights used for age-specific contact matrices

Model	Home	School	Work	Others
INDSCI-SIM model (from March 1, 2020 to July 31, 2021)	1	0	0.5	0
Hybrid immunity model (Before school open, Aug 1, 2021 to Aug 15, 2021)	1	0	0.5	0.5
Hybrid immunity model (After school open, Aug 16, 2021 to Dec 15, 2021)	1	0 to 0.5	0.5	0.5
Hybrid immunity model (Omicron, South Africa)	1	0.5	1	0.5
Hybrid immunity model (Omicron, Andhra Pradesh & district, from Dec 16, 2021)	1	0	0.5	0.5

Weights used to create the contact matrices that simulate social contacts and mixing within the population. Four different locations (Home, School, Work, and Others) were used to address the contacts between different age groups. At home all age groups have contacts with each other with equal weights. The same is true for the "Others" location, but with half the weight as the Home location. In schools, children in the below 20 age-bands have high contact with each other, while teachers (age-bands 20 and above) have moderate contact with each other as well as with the children. See Prem et al. and Hazra et al. for more details.

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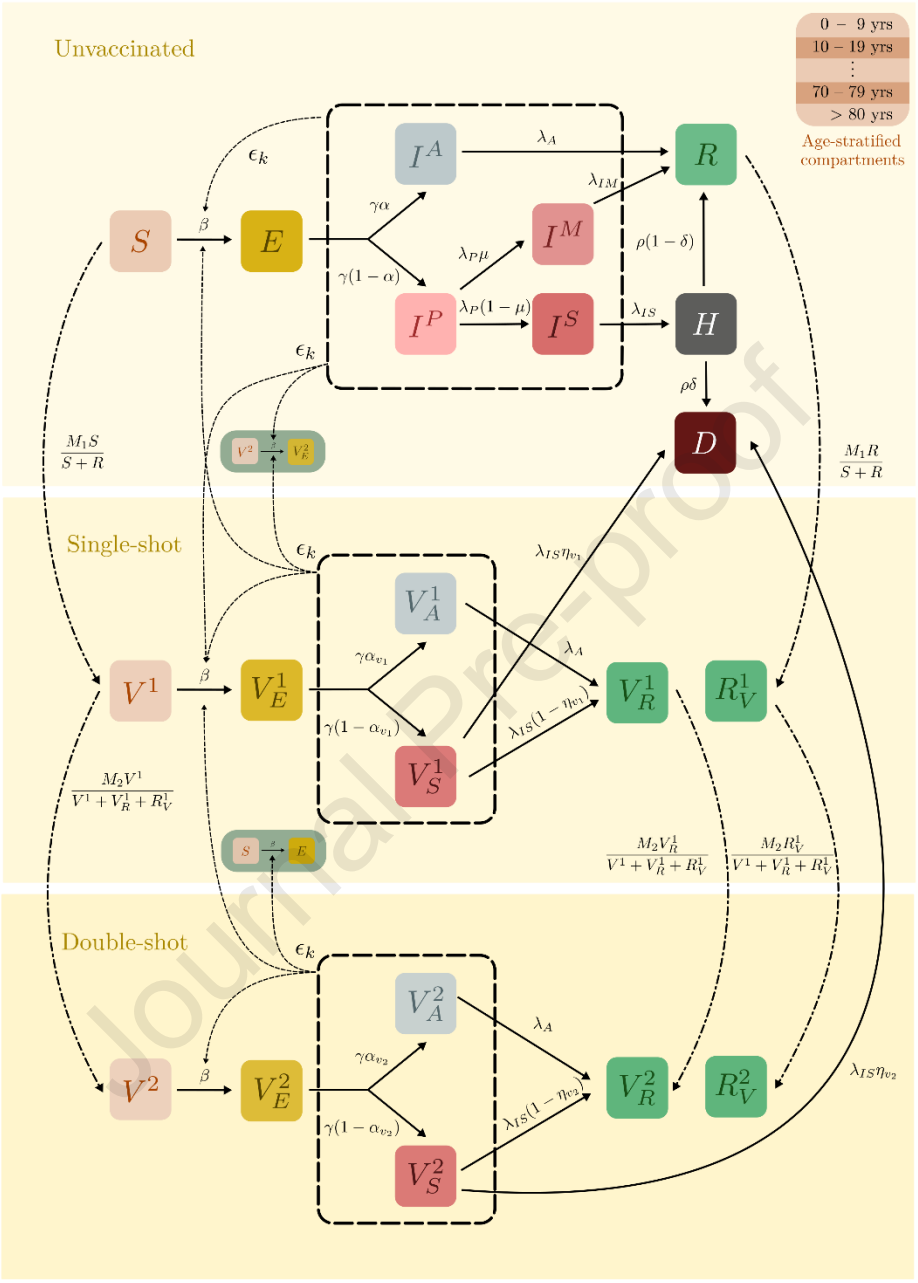
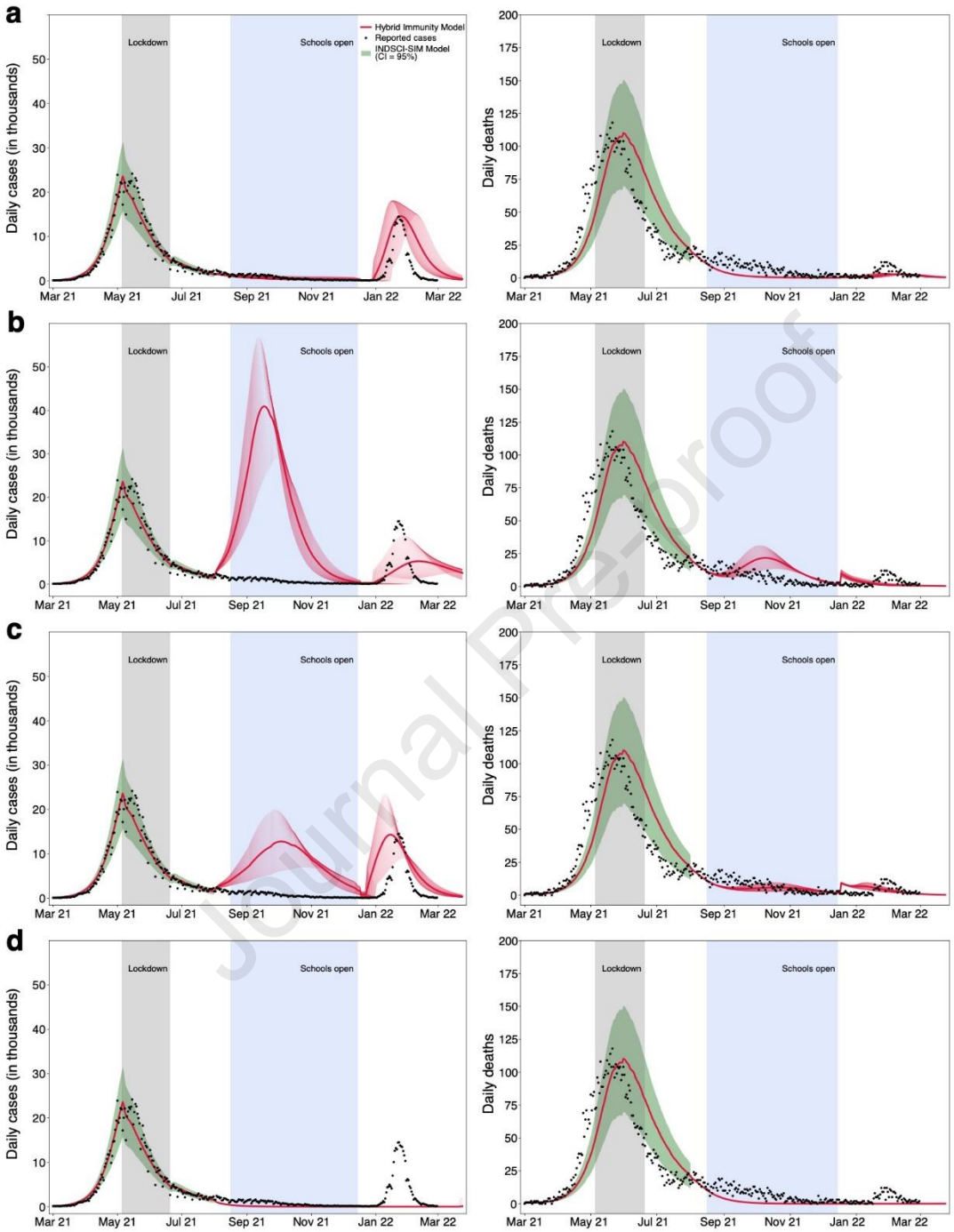
Figure 1: Schematic of model for unvaccinated, one-dose vaccinated, and two-dose vaccinated individuals



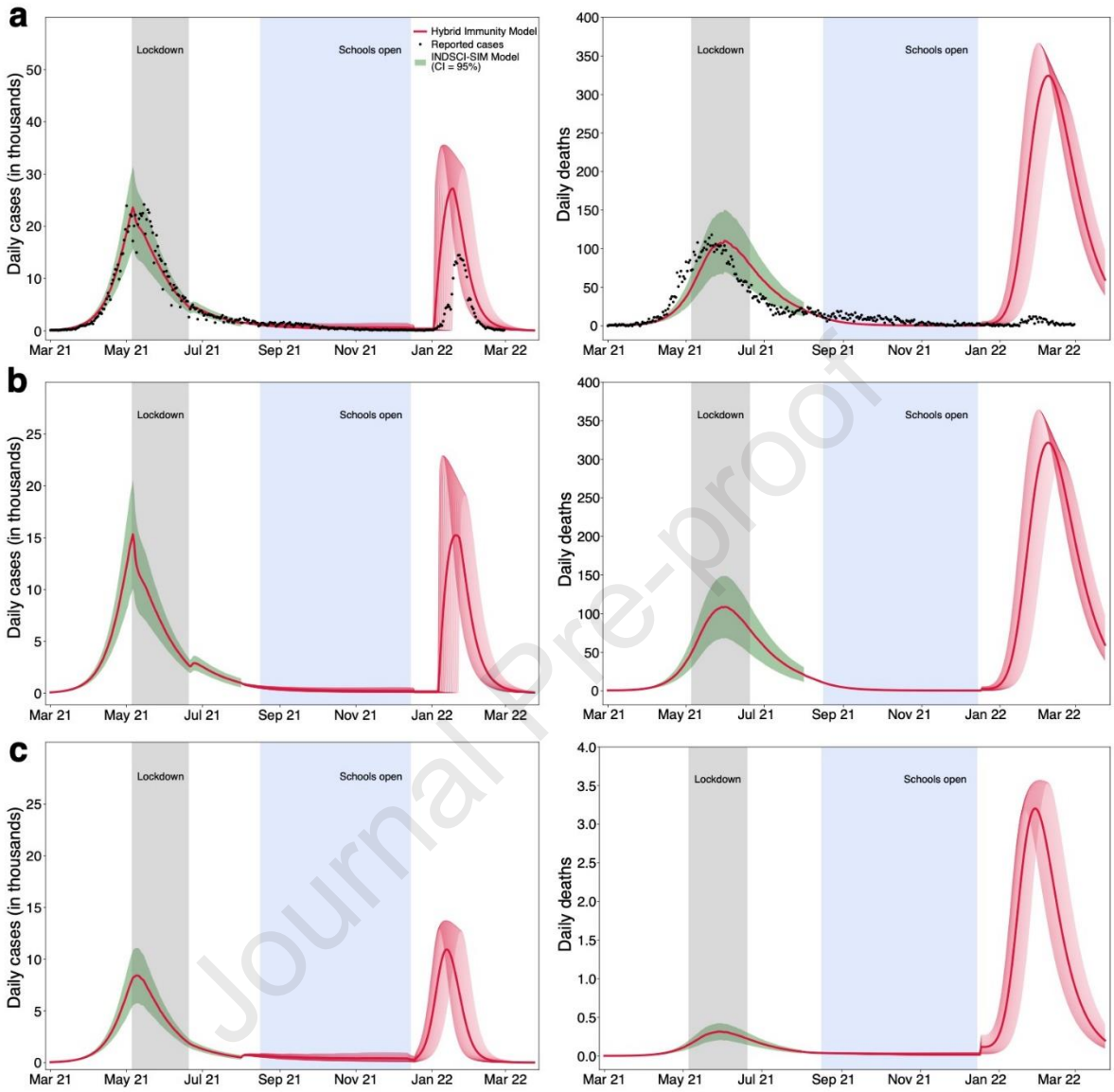
Model compartments are each stratified by 10-year age intervals. S = susceptible, E = exposed, IA = asymptomatic infected, IP = pre-symptomatic infected, IM = mildly infected, IS = severely infected, R = recovered, H = hospitalized, D = decedent, V = vaccinated, VE = vaccinated exposed, VA = vaccinated asymptomatic, VS = vaccinated symptomatic, VR = vaccinated recovered, RV =recovered vaccinated. Transition rates and parameters are provided in Tables 1-3. To decrease visual clutter, some compartments are shown twice (as small insets). These duplicates correspond to the same single compartment. Dashed lines point to the parameter that is modified by contact matrices and contact parameters. Dash-dotted lines indicate vaccination.

Figure 2: Effect of infection-induced seropositivity on school reopening



The daily number of cases (left panels) and the daily number of recorded deaths (right panels) for all age-groups, for the entire state of Andhra Pradesh, as well as three scenarios that demonstrate a variation in background seroprevalence. The top-most panels represent a background seroprevalence of 64%, while the remaining are for 20%, 40%, and 80% seroprevalence respectively. The black dots represent the recorded daily numbers obtained from covid19bharat.org, while the confidence intervals are obtained from the INDSCI-SIM simulation. The initial part of the graph follows the INDSCI-SIM prediction until Aug 1, 2021. Schools are gradually opened, as described in the Methods section, over a period of 120 days. The numbers are scaled by an appropriate bias factor to account for daily undercounting of cases.

Figure 3: Role of vaccination in hybrid immunity



Results of a counterfactual simulation with no vaccination coverage, to demonstrate the effect that the absence of vaccination has on the disease trajectory. All panels represent results for a seropositivity of 64%, close to the reported value from serosurvey data. The panels on the left show the daily number of cases, while those on the right show the daily number of deaths. a. shows the results for all age groups, b. the results for adults (above 20) and c. the results for children (below 20). Our simulations indicate that a much higher Omicron peak could have been expected if a smaller fraction of the population had been vaccinated, as can be seen by comparing Figures 3a and 2a.

RESEARCH IN CONTEXT

Evidence before this study

We searched the PubMed and preprint archives for articles published from December 1, 2021 to May 31, 2022 to identify modeling studies that attempted to integrate hybrid immunity (i.e., vaccine- and infection-derived immunity) and emerging variants of concern with immune escape potential using the search terms "coronavirus", "COVID-19", "SARS-CoV-2", "variant", "VOC", "Alpha", "Iota", "Delta", "Gamma", "Omicron", "Alpha", "vaccin*", "immuni*", "hybrid immunity", and "hybrid". We identified several studies that demonstrate the protection provided by hybrid immunity and multiple agent-based and compartmental models that simulate the trajectory of SARS-CoV-2 infection; however, no published modeling studies attempted to integrate hybrid immunity and emerging variants of concern. The available evidence suggesting additional protection provided by hybrid immunity, including in the presence of variants of concern, supports the inclusion of these factors into transmission models.

Added value of this study

We constructed a model that incorporates both infections and a vaccination program. We used this model to explore the consequences of hybrid immunity in the context of school reopening as well as the Omicron variant, in a model Indian state. In our age-stratified compartmental model, we have differentiated between individuals who were infected before or after vaccination. We have therefore been able to estimate disease trajectories in the context of emerging variants of concern.

Implications of all the available evidence

The findings of our study support the notion that decreasing prevalence of immunologically naïve individuals in many settings is associated with a reduction in the number of reported cases. This remains true even as some critical non-pharmaceutical interventions are relaxed, especially reopening of schools. Our study also suggests that the decrease in hospitalizations and deaths since the Omicron variant emerged is likely due to two factors: increasing levels of hybrid immunity in the population and the intrinsic lower severity of disease associated with the Omicron variant relative to previous variants (eg, the Delta variant).