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Determining Safe NPI Relaxation Strategy in India During the Delta and Omicron Waves of COVID-19: Findings from a Two-Strain COVID-19 Transmission model

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Abstract

Determining Safe NPI Relaxation Strategy in India During the Delta and Omicron Waves of COVID-19: Findings from a Two-Strain COVID-19 Transmission model

By Ting-Hsuan Wu

The use of non-pharmaceutical interventions (NPIs) has been a critical strategy to slow and prevent the spread of SARS-CoV-2 during the COVID-19 pandemic. Dynamic transmission models have been developed to project the course of the pandemic under various assumptions. This study aimed to validate model-projected COVID-19 cases and deaths for the Delta wave to assess model performance and project the course of the pandemic during the time period where transmission is driven by the Omicron variant. We updated the parameters of a two-strain SEIR model and compared model-projected and reported COVID-19 cases and deaths in India over 180 days starting from July 27th, 2021. The difference (projected – reported) and percent error were calculated to assess the degree of agreement between model projections and the reported data. Following external validation, we updated model parameters with the best estimates corresponding to the Omicron wave and projected the number of COVID-19 cases and deaths over 180 days beginning from November 26th, 2021. When NPI relaxation is delayed for at least 180 days, model-projected cases for the Delta wave aligned with reported number of cases in India. Between days 30 and 75, the Onam holiday was celebrated, and model projections underestimated the number of reported cases during this time. If the Onam spike is excluded, model-projected cases closely aligned with reported data, with a mean error of 1.7% and -2.0% for the 12-week and 24-week (full SDE) inter-dose intervals, respectively. The model projected 518 deaths per million after 150 days, which overestimated the 352 deaths per million reported in India. Projections for the Omicron wave suggest that cases will peak earlier than they did in the Delta wave, with a smaller second peak occurring later during the simulation period. External validation of the two-strain SEIR model suggests that the model was consistent with cases in India and that NPIs continued to reduce transmission throughout the six-month period, but validation work must continue as more data on the characteristics of the Omicron variant become available.

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Table of Contents

Introduction

In December of 2019, a cluster of pneumonia cases of unknown etiology was reported in Wuhan, China. In less than a month, a novel coronavirus, SARS-CoV-2, was isolated as the causative agent. Approximately three months after the first cases of COVID-19 were reported, COVID-19 was declared a pandemic by the World Health Organization (WHO). As of April 14, 2022, over 500 million cases and 6 million deaths have been reported globally (1). Surges in COVID-19 cases and the demand for oxygen supplies have overwhelmed healthcare capacity across the world.

Variants of Concern, Non-pharmaceutical Interventions (NPIs), and Vaccines

As SARS-CoV-2 spread rapidly across the world, variants have been isolated and identified in multiple countries. Five variants in particular, Alpha, Delta, Gamma, Beta, and Omicron, have been named Variants of Concern (VOC). The Alpha variant, first detected in the U.K. in September 2020, is 50% more transmissible than earlier strains and was linked to an increase in COVID-19 cases and hospitalizations among younger people aged 20 to 59 (2–4). The Delta variant was first documented in India in October 2020 and has been reported to be up to 60% more transmissible than the Alpha variant (5,6), partly due to an increase in viral load during infection (7). The Delta variant dominated transmission worldwide from July to December of 2021 and was also linked to increased hospitalizations and transmissibility (8–11). The Beta variant was first documented in South Africa in May 2020 and has been estimated to be more transmissible than non-VOCs but less transmissible than the Alpha and Delta variants (6). The Gamma variant, first detected in Brazil in November 2020, was found to be more transmissible than non-VOCs but has not competed well against the Alpha or Delta variants (12). Lastly, the Omicron variant was first reported to the WHO by South Africa in November 2021. Since being designated a VOC, the

Omicron variant has spread to countries in all six WHO regions (13). Preliminary studies have demonstrated a shorter doubling time of the Omicron variant relative to the previous variants (14), giving the Omicron variant a substantial growth advantage. Rapid transmission of this variant within populations with high levels of immunity has been observed (15–17), and an early analysis estimated the Omicron variant to be up to two times more transmissible than the Delta variant (18,19). Despite the increase in transmission, the hospitalization rate among cases during the Omicron-dominated period is lower than the hospitalization rates among cases during the Beta- and Delta-dominated periods, indicating a potential decrease in disease severity of infection caused by the Omicron variant (20–22).

Non-pharmaceutical interventions (NPIs), including face covering, social distancing, lockdowns, school closures, and travel bans, have been critical parts of the global response to reduce SARS-CoV-2 spread in the absence of effective COVID-19 vaccines and treatments. NPIs were implemented to reduce viral spread, prevent healthcare systems from being overwhelmed, and to give time to achieve herd immunity through vaccination and are still partially in place in many parts of the world. India's implementation of various NPIs including case surveillance, testing, social distancing, travel restrictions, and lockdowns early in the pandemic delayed SARS-CoV-2 spread (23) and averted many deaths, even with imperfect compliance (24).

Although NPIs have been effective in reducing transmission, prolonged NPI mandates have negative economic, psychological, physical, and social impacts (25–28). Thus, the development of a safe and efficacious vaccine was critical in the fight against the pandemic, with the hope that widespread vaccination might enable these non-pharmaceutical interventions to be safely relaxed. Of 107 vaccine candidates (29), adenoviral vector vaccine ChAdOx nCoV-19 (AstraZeneca), developed at the University of Oxford, became the first non-profit COVID-19

vaccine aimed to increase equity and global supply to LMICs (30,31). The AstraZeneca vaccine also became the first viral vector vaccine candidate to publish promising efficacy and safety data. Blinded, randomized, controlled trials across the U.K., Brazil, and South Africa revealed that the efficacy of the AstraZeneca vaccine against symptomatic disease from the wildtype strain is 64.1% after one dose and 70.4% after two doses (32), with an additional 37% protection against hospitalization within the first two weeks of a positive COVID-19 test (33). Vaccine efficacy against emergency department visits is 94.8% (34), indicating that the vaccine provides substantial protection against severe disease caused by the wildtype. Vaccine efficacy increased from 70.4% to 81.3% following an increase in the inter-dose interval to 12 weeks and longer (35).

As VOCs became more prevalent, concerns regarding immune escape prompted sub-analyses to evaluate how well vaccines protected against disease caused by the VOCs. In general, studies have shown that the full two dose series seem to remain highly effective against emerging variants, particularly for more severe disease. Analysis revealed that the full two dose series had similar effectiveness against symptomatic infection for the Alpha (VE=60; 95%CI: 41-73 to 74.5%; 95%CI: 68.4-79.4 (33,36)), Delta (67%; 95%CI: 61.3-71.8 (37)) and Gamma strains (VE=77.9%; 95%CI: 69.2-84.2 (38)) compared with the initial wildtype strain (VE=70.4%; 95%CI: 54.8-80.6 (32)). Protection was also similar against the most severe disease for the Delta variant, with an estimated efficacy against hospitalization of 86% and 91% against severe disease (39). However, a single dose was less effective against some variants, with one dose providing 49% protection against the Alpha variant, 30% against the Delta variant, and 41% against the Gamma variant (compared with 64.1% for the wildtype) (32,37,40). In contrast, a single dose appeared to be highly protective against hospitalization with the Beta/Gamma variant (40). However, efficacy against

mild or moderate disease from the Beta variant is much lower, with one study estimating an efficacy of only 10.4% (41).

Concerns about immune evasion have been returned with the emergence of the Omicron variant. Several studies have observed considerable evasion of the Omicron variant to antibody neutralizing activities from vaccination or natural infection (42–44), partially explaining the rapid spread of the Omicron variant in populations with high immunity levels. Vaccine efficacy against infection by the Omicron variant is still undergoing investigation, but studies have found the AstraZeneca vaccine to provide little to no protection against infection caused by the Omicron variant 15-20 weeks after the second dose (45,46). Other preliminary studies have found 33-50% relative reduction in the protection from primary vaccine series against infection caused by the Omicron variant compared with the Delta variant (19,47). In contrast, vaccine efficacy against severe diseases caused by the Omicron variant remained high, with primary series doses reducing hospitalization following infection by the Omicron variant by 63% (48) With the progression in vaccine development, the focus on mitigation strategy shifted towards mass vaccination programs and safe relaxation of NPIs. The difference in vaccine distribution and rollout rates by country requires the assessment of the safest NPI relaxation strategy best suited for each country.

While these vaccines have been helpful, NPIs remain important as vaccine supply and accessibility are limited in low- and middle-income countries (LMICs) and as variants emerge. Global vaccine distribution is highly unequal, with 80% of the population receiving only 5% of the total COVID-19 vaccines in the world as of March 31, 2021. (49). The WHO Strategic Advisory Group of Experts on Immunization (SAGE) stated on May 27th of 2021 that high-income countries have administered 69 times more doses than LMICs per inhabitant (50). Inequity in

global vaccine distribution forces LMICs to rely on prolonged NPIs before populations reach the herd immunity threshold.

Models

The uncertainty surrounding the future of the ongoing COVID-19 pandemic has shed light on the usefulness of dynamic transmission models to inform policy makers and guide public health safety recommendations. Dynamic transmission models incorporate disease-specific parameters to reflect disease transmission and are useful for projecting long-term epidemiologic outcomes and potential impacts if certain components of disease transmission (such as contact rates) are modified. It is important to distinguish between forecasting and projection as the two components of model prediction. Forecasting attempts to quantitatively predict future events, while projections attempt to describe what happens given certain assumptions and hypotheses (51). In Kenya, an age-structured compartmental model projected that COVID-19 severity and deaths are reduced with a reduction in contacts, and this reduction is greater when contacts are reduced for 190 days compared with 60 days (52). Vardavas et al. developed a COVID-19 transmission population-based model (PBM) to compare the impact of NPIs on health and economic outcomes and found that, if compliance is high, a periodic strategy where periods of strict NPI implementation followed by periods of relaxation can achieve similar health outcomes as a stringent fixed NPI implementation at lower social welfare cost (53).

As vaccine candidates reached phase III clinical trials with promising results, many studies utilized dynamic transmission models to assess vaccine allocation strategies under various vaccine efficacy and coverage scenarios on country-specific scales and global scales. For instance, Moore et al. used an age stratified SEIR model and supported prioritization of elder individuals as the optimal vaccine strategy in the United Kingdom (54). Hogan et al. extended a SEIR model that

explored SARS-CoV-2 transmission across different countries to assess vaccine allocation strategies and found that equitable global vaccine allocation is projected to be the optimal strategy (55).

Models are useful when they accurately reflect our current understanding of the topic and use valid and reliable data. Failure to do so will compromise model outputs and create misleading interpretations. The COVID-19 forecasting model developed by the Institute of Health Metric and Evaluation (IHME) (56), although highly influential and widely cited by policy makers, has received heavy criticism due to the unstable nature of its forecasts. The IHME model fitted a statistical curve and failed to account for the features of COVID-19 and the regional variation in pandemic responses (57,58), resulting in forecasts that were both too optimistic and too pessimistic (59,60). To produce forecasts that are generalizable to the population for which they are intended, models must ensure that reliable and representative data and assumptions are used for model development.

The early phases of an epidemic, when knowledge of the pathogen is limited, surveillance is imprecise, and testing is incomplete, drive models to make many assumptions. Changes in disease transmission dynamics over time due to behavior modification and ongoing pathogen evolution require continuous updates of the model structure and parameters. As more data become available, it is essential to validate models to explore their limitations and strengths and understand how to appropriately apply and interpret the results.

Model Verification and Validation

Model validation is a critical process to ensure model projections used to inform policy and guide recommendations are trustworthy. Model validation is used to evaluate the accuracy of outputs by assessing the degree of agreement between model outputs and observed/reported data

or the outputs from other models aiming to answer similar research questions so that decision makers can reliably incorporate model outputs in their decisions. Continuous validation allows for models to be revised to accurately reflect the data and reveals whether model projections under- or overestimate the observed outcomes. There are several model validation methods, but not all methods must be used for a model's output to be valid and useful. For instance, if a model's primary objective is to predict future events, then the researchers may focus on predictive validity over other forms of validity. Validation methods can be categorized into face validity, internal validity, external validation, predictive validation, and cross-model validation (61). External validation compares empirical observations and model outputs to evaluate model performance in calculating actual outcomes, while predictive validation determines the model's ability to predict or reproduce outputs similar to observed data not available during model development (61,62).

Objective/Aim

With an efficacious vaccine, NPIs can be potentially relaxed safely in LMICs. To identify the vaccine coverage level needed for safe NPI relaxation without straining the healthcare systems in LMICs, a two-stain SEIR-like model was developed by Kraay et al. (63). This study aims to evaluate the external validity of that model's projected COVID-19 cases and deaths in India. Kraay et al. Initially, the projected cases and deaths in India for the Delta wave was for different hypothetical NPI and vaccination scenarios, so this validation study also aims to determine which NPI relaxation strategy was most consistent with the observed incidence data. Following model validation, this paper aims to project COVID-19 cases and deaths for the Omicron-dominant wave.

Method

SEIR Model Structure

We used a two-strain SEIR-like model (Figure 1) with strain 1 representing the wild-type strain and strain 2 representing the average VOC characteristics to (1) identify the level of vaccine coverage needed to safely relax NPIs without straining the healthcare systems and (2) investigate how prevalence of VOCs and inter-dose interval of AstraZeneca vaccine impact safe NPI relaxation (63). Individuals enter a latent, non-infectious period (*E*) following exposure to strain 1 or 2 and will progress to either infectious and symptomatic (*I*) or infectious and asymptomatic (*A*). A portion of symptomatic individuals will become hospitalized (*H*), and all individuals who are not hospitalized are assumed to recover (*R*). A portion of hospitalized individuals will die (*D*), and the rest will recover (R). We assume that homotypic immunity does not wane during the simulation, but heterotypic immunity wanes and individuals can be re-infected by the strain that did not infect them previously. This model is stratified by vaccination status (unvaccinated, vaccinated with one dose, vaccinated with 2 doses), risk group (high risk and low risk), and age (<20, 20-65, and ≥65 years). Protection from the vaccine is assumed to begin as soon as vaccine doses are administered, with the level of protection differing for one vs. two doses. Four inter-dose intervals are considered:

1. 12-week interval as recommended for AstraZeneca vaccine
2. 24-week interval without additional waning of protection during the second 12 weeks
3. 24-week interval with 80% overall protection than what is observed for 12 weeks during the 24-week waiting period
4. No second dose administered, with the overall protection by a single dose to be 50%

This model was applied to six WHO member states: Ecuador, India, Yemen, Malaysia, South Africa, and Serbia. For each scenario, this model's outputs include deaths, symptomatic COVID-

19 cases, and hospitalizations over a 180-day period. In this study, we limit our analysis to India and consider two time periods for the simulations: the Delta-dominated period begins on July 27th, 2021, and the Omicron-dominated period begins on November 26th, 2021, which corresponds to the beginning of the transmission wave driven by the Omicron variant.

Model Parameters

Model parameters are shown in Table 1 (63). Overall, the model parameters can be broken down into three categories: calibrated, fixed, and varied. Calibrated parameters by country are calibrated to the country-specific incidence data. To update the fixed parameters, a systematic search was conducted on PubMed and medRxiv for current best estimates. Varied parameters are used to project how different vaccine allocation, vaccine efficacy, and strain dynamics might change simulation outputs. Our model incorporates two SARS-CoV-2 strains, with strain 1 reflecting characteristics of the wildtype strain, and strain 2 reflecting characteristics averaged across the VOCs. For Delta-variant simulations, we assume that strain 2 is 50% more transmissible than strain 1 (ψ). We also assume that individuals can only be infected by each strain once. Following infection by one strain, individuals cannot be infected by a different strain until immunity has waned ($1/\epsilon$), reflecting a period of complete cross-protection. Upon exposure, movement from the *S* compartment to the *E* compartment is governed by the transmission rate (b). Movement from the *E* compartment to the *I* or *A* compartments are governed by the latent period and the probability of symptomatic infection ($1/\sigma * \nu$) or the latent period and the complement of the probability of symptomatic infection ($1/\sigma * (1-\nu)$), respectively. The movement from the *I* compartment to the *H* compartment is governed by the probability of hospitalization (ϕ), which differs between age groups of <20, 20-64, and 65+ years. Similarly, the movement from the *H* compartment to the *D* compartment is governed by the probability of death (ρ) and varies between

age groups as well. A proportion of those in the *H* compartment will recover and move to the *R* compartment, which is governed by the complement of the probability of death ($1-\rho$). All individuals in the *A* compartment are assumed to recover and move to the *R* compartment. Individuals in the *R* compartment are assumed to have immunity that wanes over time, effectively moving them to the second *S* compartment, in which they are susceptible to the strain that did not cause the first infection. All individuals not in the *I* or *H* compartments are eligible to get vaccinated given that they are not fully vaccinated already. Vaccine efficacy varies by strain in protection against infection and hospitalization (63). Single dose efficacy (SDE) is lower than two doses (TDE), with single dose VE against strain 2 lower than single dose VE against strain 1. Table 2 outlines 64 scenarios considered and reported by Kraay et al. We assume that vaccine coverage among the eligible population will not exceed 80% (the maximum possible coverage in our simulations), corresponding to 48% of the overall population of India. We assumed high initial variant transmission (70%) and excluded the scenario with immediate NPI relaxation, as these were not consistent with either policy decisions or the incidence data (not shown).

Parameter Validation

As the pandemic continues to evolve and new variants emerge, parameter values were validated by sourcing up-to-date literature. We sourced *Our World in Data (OWID)* for data on incidence, deaths, hospitalizations, healthcare capacity (defined by the total numbers of staffed beds and ICU beds), and current vaccination rollout rate in India (64). We sourced literature for country-specific seroprevalence data to estimate the age-stratified cumulative incidence and the proportion immune at baseline for each age group. Reporting rates were calculated using age-stratified cumulative incidence estimates and reported cumulative cases were sourced from *OWID*. Vaccine efficacy data were sourced from updated clinical trial literature (32,33,36,37).

External Validation

Model parameter values were updated before model simulation, and the projected numbers of COVID-19 cases and deaths over a 180-day period are compared with the reported numbers of cases and deaths for India. Since the Omicron wave is still ongoing as of April 2022, we conducted external validation on simulation results for the Delta-dominated period only (i.e., 180 days since July 27th, 2021). Reported cases for India are scaled using the reporting rate calculated from seroprevalence data to account for under-reporting, and reported cases are calculated to include all active infected cases on a given day (i.e., cases on day 7 were calculated to include cases from day 1 to day 7). Due to the lack of COVID-19 hospitalization data available for India, we focus our external validation analysis on COVID-19 cases and deaths for the Delta variant period, comparing model estimates with reported data for the same period.

Plots of the number of COVID-19 cases and deaths were generated using the "ggplot2" package (65) for visual comparison of model outputs and reported data. The first deviation metric was the differences between model outputs and reported data, and negative/positive values indicate that the model underestimated or overestimated the number of cases and deaths. To measure how well the model outputs fit the reported data, the percent error, $e = \frac{observed\ value - expected\ value}{expected\ value} \times 100\%$, was calculated using simulated and reported cases and deaths for India. Lastly, the mean percent error, $\frac{100\%}{n}\frac{\sum_{i=1}^{n} o_i - e_i}{o_i}$, was calculated to quantify the difference between model projection and reported data. We proceed with validation analyses for the scenario where single dose efficacy (SDE) for strain 1 and 2 are similar and focus our validation analyses on all four inter-dose intervals when NPI relaxation occurs after the maximum vaccine coverage is reached, as these scenarios had errors less than +/-100%. Additionally, because maximum vaccine coverage is not achieved in our simulation, projections are identical between NPI scenarios where relaxation is

delayed until maximum vaccine coverage is achieved and when NPI relaxation occurred after the duration of the simulation. Thus, we present only the scenario where NPI relaxation occurred after maximum vaccine coverage is achieved.

Omicron Simulation

Following external validation, we updated model parameters using current best estimates for the Omicron variant. We projected the number of COVID-19 cases and deaths in India over a 180-day period, beginning from November 26th, 2021, when the WHO designated the Omicron variant as a VOC (66). In addition to the relaxation at maximum coverage scenario, we also considered scenarios where NPIs were relaxed once 25% vaccine coverage was reached among the total population. We expect the maximum vaccine coverage to be achieved during the Omicron wave, so we also include scenario where NPIs were maintained throughout the simulation.

Results

Parameter Validation

Overall, the model parameters considered in the model by Kraay et al. (63) were consistent with current literature (Table 1). Initial states for the model were updated using seroprevalence data collected in India from June to July of 2021 to better reflect the baseline prevalence at the start of the simulation period (July 27th, 2021). The basic reproductive number R_0 used in the model was consistent with existing literature and meta-analysis. Relative transmissibility for strain 2 was updated from 1.5 to 2 to reflect the relative transmissibility of the Delta variant ($R_0 = 5.08$) compared with the wildtype ($R_0 = 2.5$). Additional literature sourced after model development confirmed that the values used for latent period and hospital length of stay were consistent with current best estimates for the Delta variant. In the original model, hospital length of stay for infection caused by the Delta variant was sourced from U.S. data, but the value was consistent

with data published for India. Vaccine efficacy values used in the original model were consistent with clinical trial data against the Delta variant but were reduced for the simulations for the Omicron wave.

Parameter values were then updated to model vaccine impact on cases and deaths during the Omicron wave (Table 1). The value of relative transmissibility of the Omicron variant compared with the wildtype strain increased to 4 (19,67). Hospital length of stay was reduced to 3 days (68), and the probability of symptomatic infection was reduced from 0.6 to 0.43 (69). The probabilities of hospitalization for each age group were updated to reflect a decrease in disease severity caused by the Omicron variant compared with the Delta variant (70). Similarly, the probabilities of death among hospitalized patients by age group were also decreased (68). Baseline conditions (i.e., the proportion of the population recovered, currently infected, and hospitalized by age group) for this simulation were updated and the proportion of individuals partially and fully vaccinated by age and risk groups were incorporated at the start of the simulation period (November 26th, 2021).

External Validation for the Delta Wave

The increase in reported cases after 150 days is consistent with the surge corresponding with the Omicron wave (Figure 2). We note that maximum vaccine coverage was not reached during our simulation, so all simulations used for validation assume NPIs are constant throughout the simulation. In general, model predictions were broadly consistent with incidence case data during the Delta wave (Figure 3L). Between days 30 and 75, during the Onam spike where cases increased as a result of large gatherings and festivals for the Onam celebration, all inter-dose interval scenarios underestimate reported cases (negative difference), with 24-week inter-dose interval (full SDE) underestimating the number of cases to the greatest extent (Figure 3R). From

approximately days 75 to 150, the difference between model-projected cases and reported cases fluctuated above 0, and the scenario of a 24-week (SDE) inter-dose interval produced the least overestimation. Model-projections across the modeled scenarios generally slightly underestimated cases, except for the scenario with no second dose, which overestimated the number of cases. Underestimation of cases across all inter-dose intervals are due to the Onam spike. The mean percent error of the projected number of cases is the smallest with a 24-week inter-dose interval (80% relative efficacy) at -2.9% and is the largest without a second dose at 8.2% (Table 2). Excluding the Onam spike, the mean percent error is the smallest for the 12-week inter-dose interval at 1.7% and largest without a second dose at 19%. The model-projected number of deaths per million after 150 days (December 24th,2021), overestimated the actual reported number of deaths per million across all inter-dose interval scenarios (Figure 5). Model scenario with a 24-week (full SDE) inter-dose interval projected 518 deaths per million by December 24th, 2021, while India reported a total of 352 deaths per million. There were minute differences between a 12-week and 24-week (80% and full SDE) inter-dose intervals, each projecting 524, 537, and 518 deaths per million, respectively. Without a second dose, the model projected 599 deaths per million, the highest of all inter-dose intervals.

Omicron Projections

Consistently across different inter-dose interval scenarios, NPI relaxation at 25% vaccine coverage had higher peaks of cases than when relaxation was delayed until maximum coverage was achieved or until after at least 180 days. The first peaks of cases occurred during similar time points, between days 50 and 70 (January 15th - February 4th, 2022) for these three NPI relaxation scenarios across all dosing scenarios (Figure 6). Additional simulation for 360 days after November 26th, 2021, showed that while the projected numbers of cases declined rapidly and

remained close to 0 following the first peaks for most inter-dose interval and NPI relaxation scenarios, the number of cases reached a lower second peak when NPIs were relaxed, regardless of the inter-dose interval used (S1). The timing of this NPI relaxation and the resultant second wave depended on the inter-dose interval used and the coverage at which NPIs were relaxed. Without a second dose and with delayed relaxation until maximum coverage was achieved, relaxation occurred around day 95 (March 1st, 2022) which triggered a follow-up transmission wave that peaked around day 125 (March 31st). The same NPI relaxation scenario resulted in delayed second waves of cases with 24-week inter-dose -interval scenarios around day 200 (June 14th, 2022) and a 12-week inter-dose interval around day 250 (August 3rd, 2022). The height of the second wave is the highest without a second dose, followed by 12-week and 24-week inter-dose intervals that have similar peaks. Finally, the number of deaths per million after 180 days (May 25th, 2022) is the lowest with a 12-week inter-dose interval and the highest without a second dose in every NPI relaxation scenario (Figure 7). Across all inter-dose interval and NPI relaxation scenarios, our model projected at most 2.8 deaths per million and at least 1.3 deaths per million in India by May 25th, 2022. Maximum vaccine coverage occurs around day 90 (February 24th, 2022) without a second dose, day 125 (March 31st, 2022) with a 24-week inter-dose interval, and day 150 (April 25th, 2022) with a 12-week inter-dose interval (Figure 8).

Discussion

This study demonstrated that the COVID-19 cases projected by the two-strain SEIR model developed by Kraay et al. (63) are generally consistent with reported data from India during the Delta wave. Model projections suggest that the Omicron surge is likely to be short-lived, with a return to lower levels of transmission during the spring months. Moreover, we predict that

subsequent surges in transmission will be less likely to cause a large increase in deaths due to the lower severity of the Omicron variant.

External Validation

Overall, the model-projected number of COVID-19 cases in India 150 days after July 27th, 2021, aligned well with reported cases. A slight increase in reported cases around day 30 corresponds to the "Onam spike," which was anticipated by Indian government and public health officials with festivals and gatherings that occurred during that time period for the Onam celebration (71). The sharp increase in the number of reported cases after 150 days corresponds to the increase in transmission driven by the Omicron variant, thus the time after 150 days was excluded from the external validation analyses. Model projections were able to project that when NPI relaxation was delayed until maximum vaccine coverage was achieved or for at least 180 days, the difference between 12-week and 24-week inter-dose intervals is minimal. This suggests that the effects of standard vs. longer dosing intervals are similar when NPI use is prolonged, but these predictions could diverge after NPIs relax if long-term efficacy is lower for longer inter-dose intervals. Although activity levels have fluctuated over the course of the pandemic, partial NPI use has continued in India even after vaccine development. Between July 27th, 2021, and January 27th, 2021, the COVID-19 stringency index (includes school/workplace closures and travel bans) remained largely above 50 (100 = strictest), with the highest value of 81.94 and lowest value of 37.50 (72,73). Thus, our findings that the reported number of cases in India align closely with model scenarios where NPI relaxation is delayed is consistent with observed patterns of social interaction in India during the Delta wave. Overall, our model was able to capture NPI usage and vaccination rollout rate in India to project the number of cases that were broadly consistent with reported cases over a period of 6 months.

When NPI relaxation is delayed until maximum vaccine coverage is reached, the projected number of deaths per million overestimated the reported number of deaths per million in India 150 days after July 27th, 2021, regardless of the dosing scenario. The overestimation in model-projected deaths could partially be due to under-reporting of COVID-19 deaths and varying reporting quality between states in India. Many deaths occur in rural areas lack medical certification as they often occur without medical attention (74), and the differences in social, behavioral, and biological risk factors and distribution of chronic diseases (75) may exacerbate the variation between states in COVID-19 mortality. In addition, structural limitation as well as uncertainty of the model parameters may increase the gap between projected and reported deaths.

Omicron Simulation

Based on the model simulation, we expect cases to peak in January across all inter-dose interval and NPI relaxation scenarios and the number of cases to exceed the number of cases for the Delta wave. Our findings are broadly consistent with other studies, which projected cases in India to peak around January and extend into March or April of 2022 (76,77). A second smaller wave of cases projected to begin towards the end of the simulation period may be due to the relaxation of NPIs as adequate vaccine coverage level is reached for each scenario. Our projections suggest that delaying NPI relaxation until after 80% vaccine coverage is reached can reduce caseload and reduce deaths. The projected number of deaths per million after 180 days is substantially lower than the numbers projected for the Delta-period, with no more than three deaths per million projected during the Omicron wave compared with over 500 deaths per million projected for the Delta wave. The drastic decrease in the number of deaths per million projected during the Omicron wave may be due to a lower probability of hospitalization upon infection caused by the Omicron variant, a lower probability of death upon hospitalization for infections

caused by the Omicron variant compared with the Delta variant, and a higher starting vaccine coverage for the Omicron simulation than for the Delta simulation. The probabilities of hospitalization and death are estimated based on early preliminary studies, and additional studies are needed for more reliable estimates.

Limitation

Although the model projections were broadly consistent with the reported data in India, this study has some limitations. For external validation, we were unable to evaluate how the model-projected hospitalizations performed against reported data for India as this information is unavailable. For the simulation during the Omicron-dominant period, we did not account for the booster doses given to high-risk populations in India beginning in January. Due to limited data on the VE of AstraZeneca against infections caused by the Omicron variant, we used relative reduction from preliminary studies to estimate the VE incorporated in our model. Finally, under-reporting of deaths due to COVID-19 infections in India may be due to the lack of consistent infrastructure to report COVID-19 deaths appropriately. Future studies should aim to understand the social, biological, and behavioral factors that contribute to underreporting to develop methods for more precise excess mortality estimates.

Implications and Future Directions

External validation of dynamic transmission models allows us to identify the strengths and weaknesses of the models. It reveals potential biases of the model or how aspects of the real world that are not accounted for by the model will impact model projections. Based on the model projections from the Omicron simulation, we recommend continuing to delay NPI relaxation until the majority of the population is vaccinated. Much is unknown regarding the nature of immunity and cross-strain dynamics; more data is required to better estimate the effect of protection from

prior infection on the course of the pandemic as new variants emerge. Finally, given that VE is reduced against infections caused by the Omicron variant, future studies should focus on estimating the effect of booster doses on safe NPI relaxation strategies in India.

Tables and Figures

Figure 1

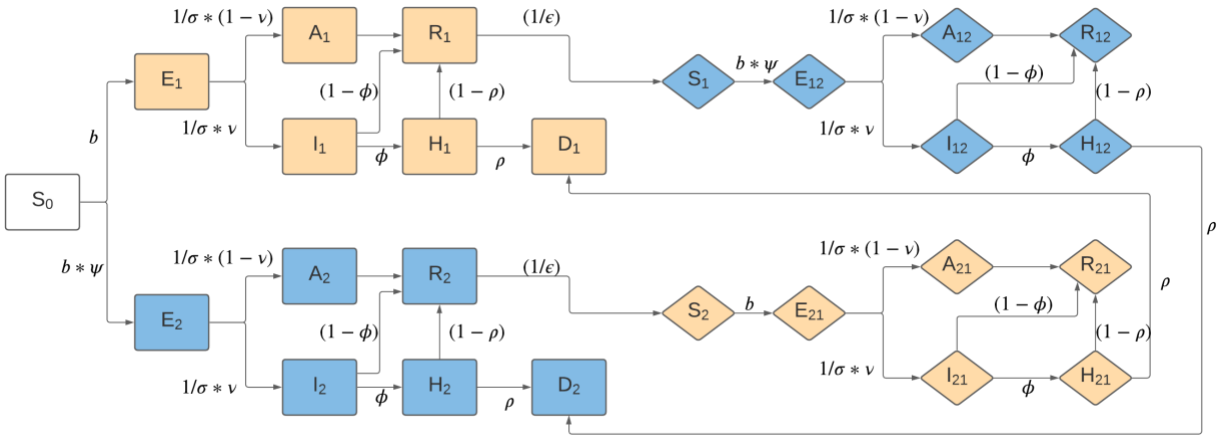

Figure 1: Flow diagram of SEIR model for an age and risk group under a single vaccine scenario. Yellow compartments represent infection by strain 1 (wild type) and blue compartments represent infection by strain 2 (VOCs). Squares represent first infection and diamonds represent re-infection by the strain that did not cause the first infection. The clear box represents susceptibility to both strains. Individuals in the *S*, *E*, *A*, or *R* are eligible to be vaccinated given that they have not been fully vaccinated already. Individuals in the *I* or *H* compartments are not eligible to receive a vaccine. Parameters are defined in Table 1.

Table 1

		Delta	Omicron	Sources
Calibrated Parameters				
R_0	Basic reproductive number	2.5	2.5	(78–80)
b	Transmission rate	0.0186	0.0186	Calibrated
κ	Reporting rate for clinical cases (fraction)	0.75	0.75	Calibrated
$sd(0)$	Proportion of social contacts maintained relative to pre-pandemic levels	0.45	0.45	Calibrated
Fixed Parameters				
$1/\sigma$	Latent period (days)	5.5	3*	(81–84); (85)
ν	Probability of symptomatic	0.6	0.43*	(86–88); (69)
$1/\gamma I$	Infectious period, symptomatic (days)	7	5*	(89)
$1/\gamma A$	Infectious period, asymptomatic (days)	7	5*	(89)
$1/\gamma H$	Hospital length of stay in the U.S. (days)	5	3*	(90,91); (68)
ϕ	Probability of hospitalization (<20)	0.0075	0.00054*	(92,93); (70)
	Probability of hospitalization (20-64)	0.15	0.0027*	(92,93); (70)
	Probability of hospitalization (65+)	0.45	0.024*	(92,93); (70)
ρ	Probability of death (<20)	0	0	(68)
	Probability of death (20-64)	0.0465	0.0018*	(68)
	Probability of death (65+)	0.266	0.014*	(94); (68)
λ	Vaccination dose available per day	0.33%	0.33%	Calibrated
Varied Parameters				
$vax_{e,h}$	Fraction of first dose received (65+, high risk)	40%	40%	Assumption
$vax_{e,l}$	Fraction of first dose received (65+, low risk)	30%	30%	Assumption
$vax_{a,h}$	Fraction of first doses received	20%	20%	Assumption
$vax_{a,l}$	Fraction of first doses received	10%	10%	Assumption
vax_{max}	Maximum vaccine coverage in any age group	80%	80%	Assumption
VE_I	VE against infection	70%	70%	
VE_P	VE against hospitalization	66%	66%	
α_I	Relative VE against infection for strain 2 compared with strain 1	0.5-1	0.46*	(47)
α_P	Relative VE against hospitalization for strain 2 compared with strain 1	0.25-1	0.44*	(47)
ψ	Relative transmissibility for strain 2 compared with strain 1	2*	4*	(19,67)
$1/\epsilon$	Duration of immunity	1 year	1 year	

Table 1: Parameter values and sources for the model simulation corresponding to the Delta-wave and the Omicron-wave adapted from Kraay et al. (63). Baseline VE values are sourced from updated clinical trial data for AstraZeneca and parameter values are sourced from existing and

updated literature. Green texts correspond to estimates for the Delta variant, blue texts correspond to estimates for the Omicron variant. Black texts are sources for both Delta and Omicron variants. *Value was updated from the original report by Kraay et al to reflect current best estimate for the Delta-dominant wave.

Table 2

NPIs relax at	Relative two dose VE for VOC	Inter-dose interval	Relative SDE for VOC
0% coverage 25% coverage of 1+ doses among the total population 80% coverage of 1+ doses among target population No relaxation	Equal Reduced by 50% for both mild and severe disease	12 weeks 24 weeks, equal efficacy 24 weeks, 80% relative efficacy No second dose offered, 50% relative efficacy	100% 61%

Table 2: Scenarios considered for model simulation and external validation, adapted from Kraay et al. (63).

Figure 2

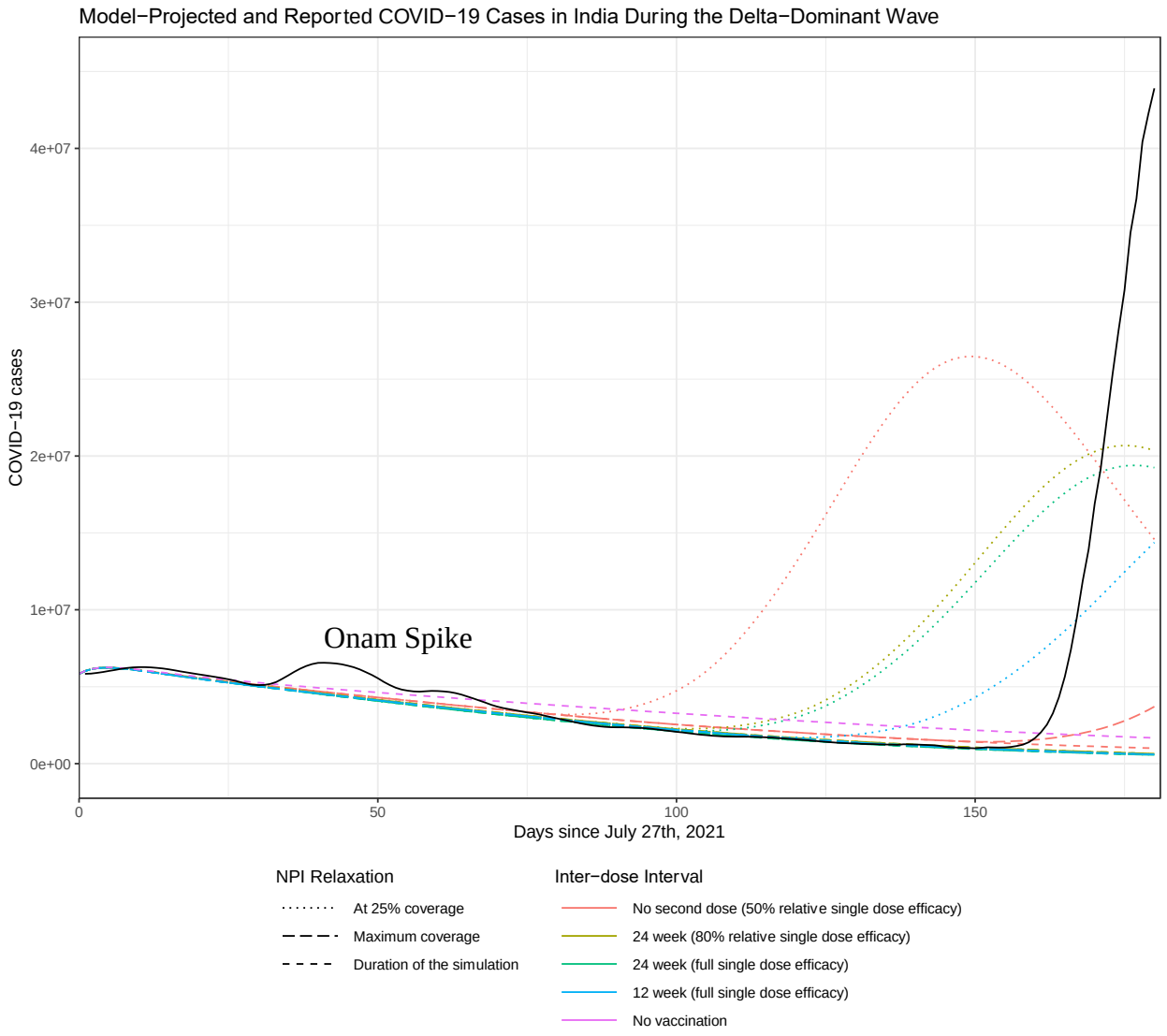

Figure 2: Number of cases in India over the 180-day simulation period, beginning from July 27th, 2021. Black solid line represents reported COVID-19 cases by India starting from July 27th, 2021. The increase in reported cases at around day 30 is associated with the "Onam spike" which resulted from large gatherings and festivals during the Onam celebration.

Figure 3

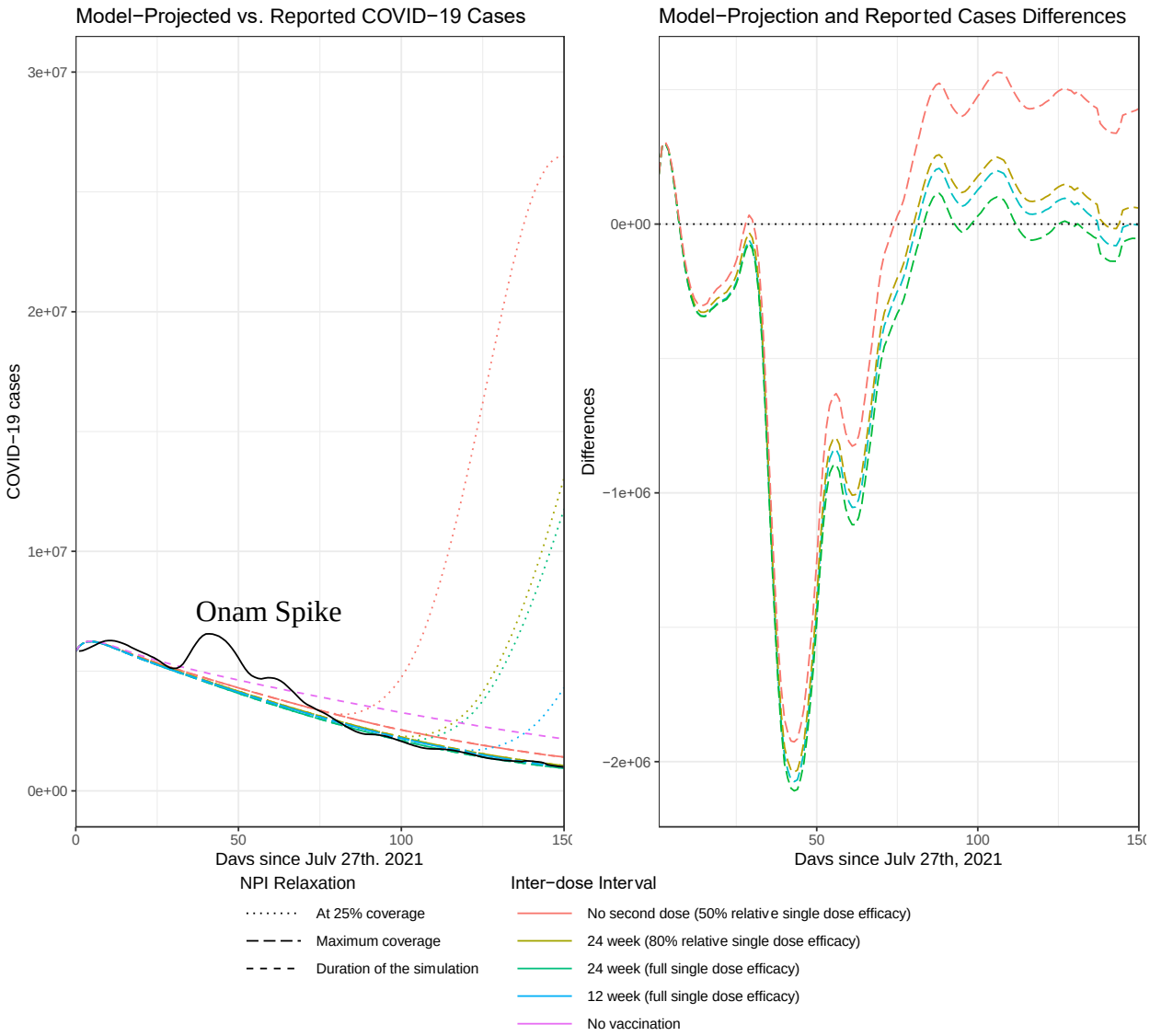

Figure 3: Left panel (L) shows the number of model projected COVID-19 cases up to 150 days from July 26th, 2021, across three NPI relaxation scenarios. The black solid line represents the reported number of COVID-19 cases from India. Right panel (R) shows the differences between the number of model-projected COVID-19 cases and the number of reported COVID-19 cases in India 150 days from July 27th, 2021. Dotted black horizontal line represents complete agreement between model projections and reported data. Only the scenario where NPI relaxation occurred after maximum coverage was considered. The Onam spike occurred around day 30.

Figure 4

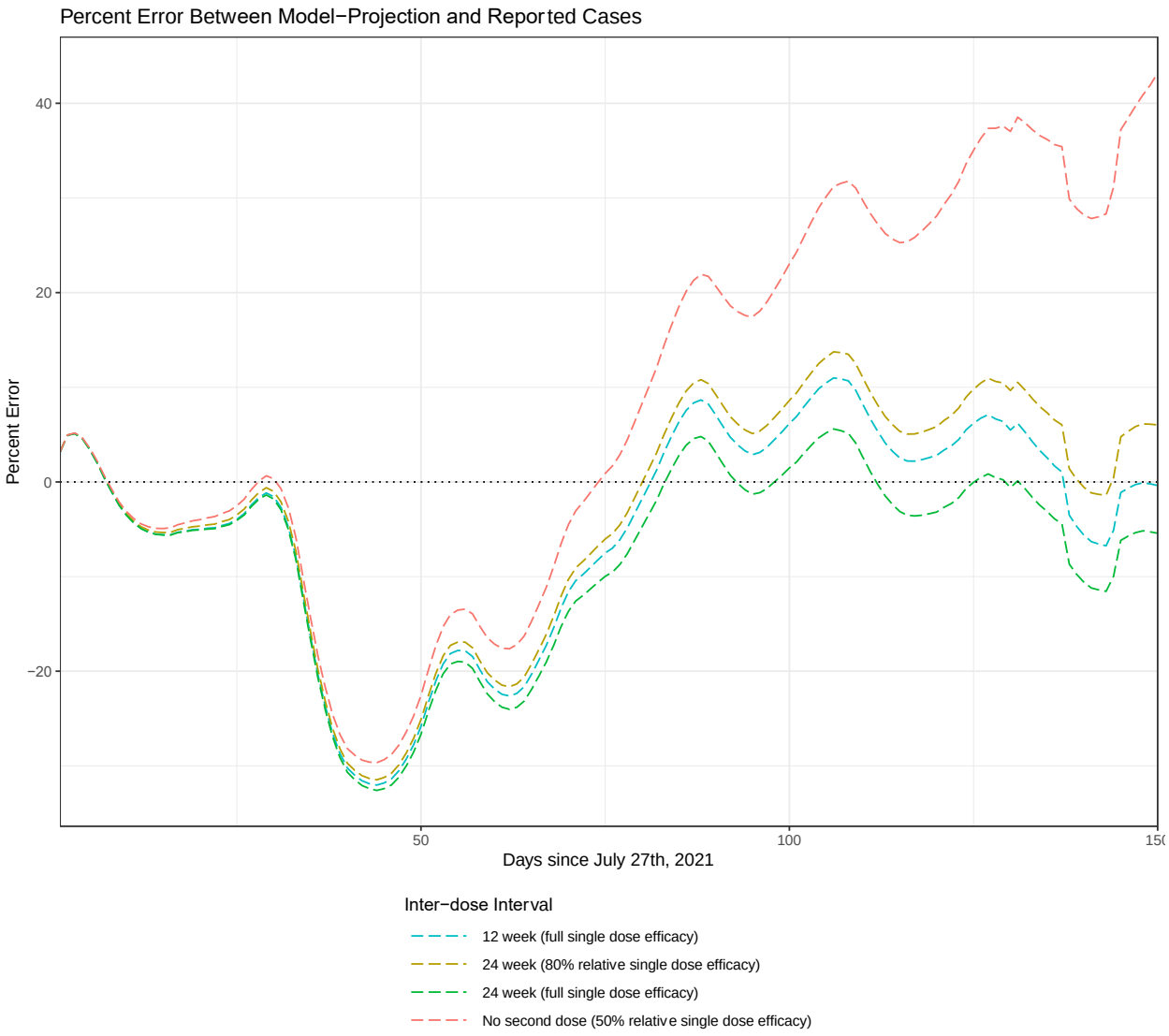

Figure 4: Percent error of model-projected number of COVID-19 cases in India 150 days after July 27th, 2021. Dotted black horizontal line represents complete agreement between model projections and reported data. Only the scenario where NPI relaxation occurred after maximum coverage was considered. The Onam spike occurred around day 30.

Table 3

NPI Factor	Inter-Dose Interval	*Mean PE	Mean PE	Minimum PE	Maximum PE
Maximum coverage	12-week (full SDE)	1.7	-4.9	-32	11
	24-week (80% relative SDE)	4.2	-2.9	-32	14
	24-week (full SDE)	-2.0	-7.7	-33	5.6
	No second dose (50% relative SDE)	19	8.2	-30	43

Table 3: The minimum, maximum, and average percent error of model-projected COVID-19 cases from July 26th, 2021. *Mean percent error without the Onam spike.

Figure 5

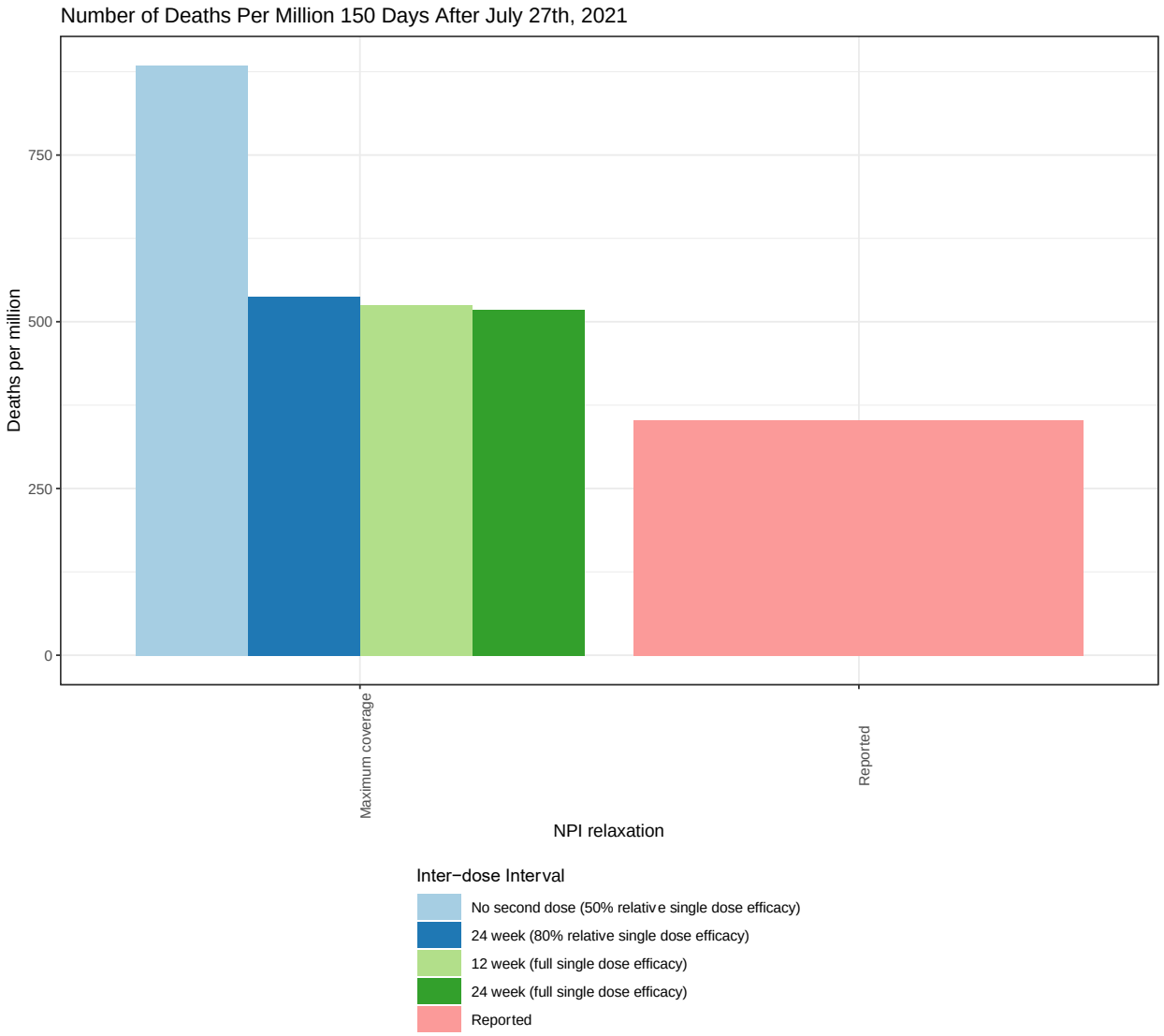

Figure 5: The number of COVID-19 deaths per million in India 150 days after July 27th, 2021.

Figure 6

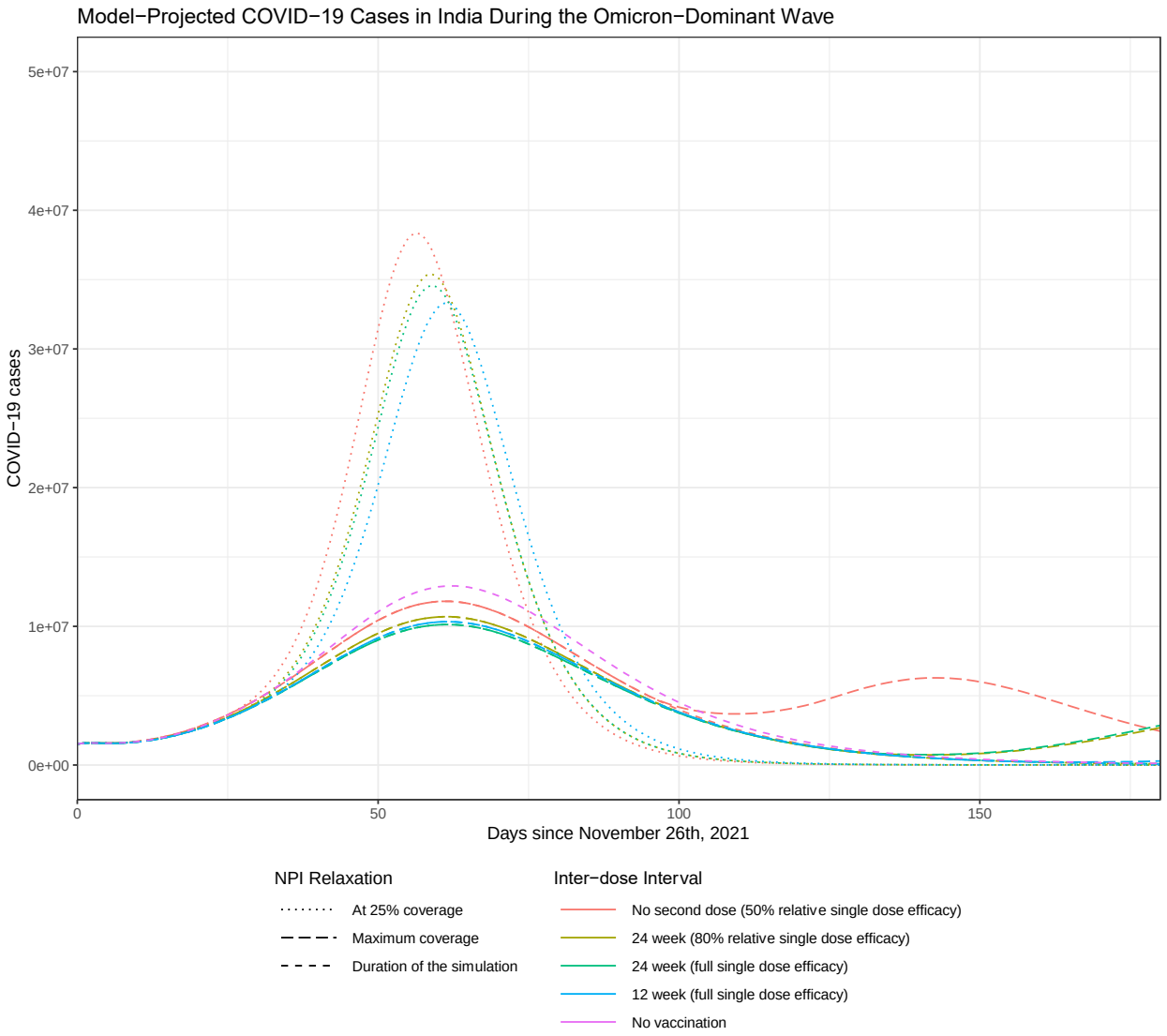

Figure 6: Model-projected COVID-19 cases in India over the 180-day period starting from November 26th, 2021.

Figure 7

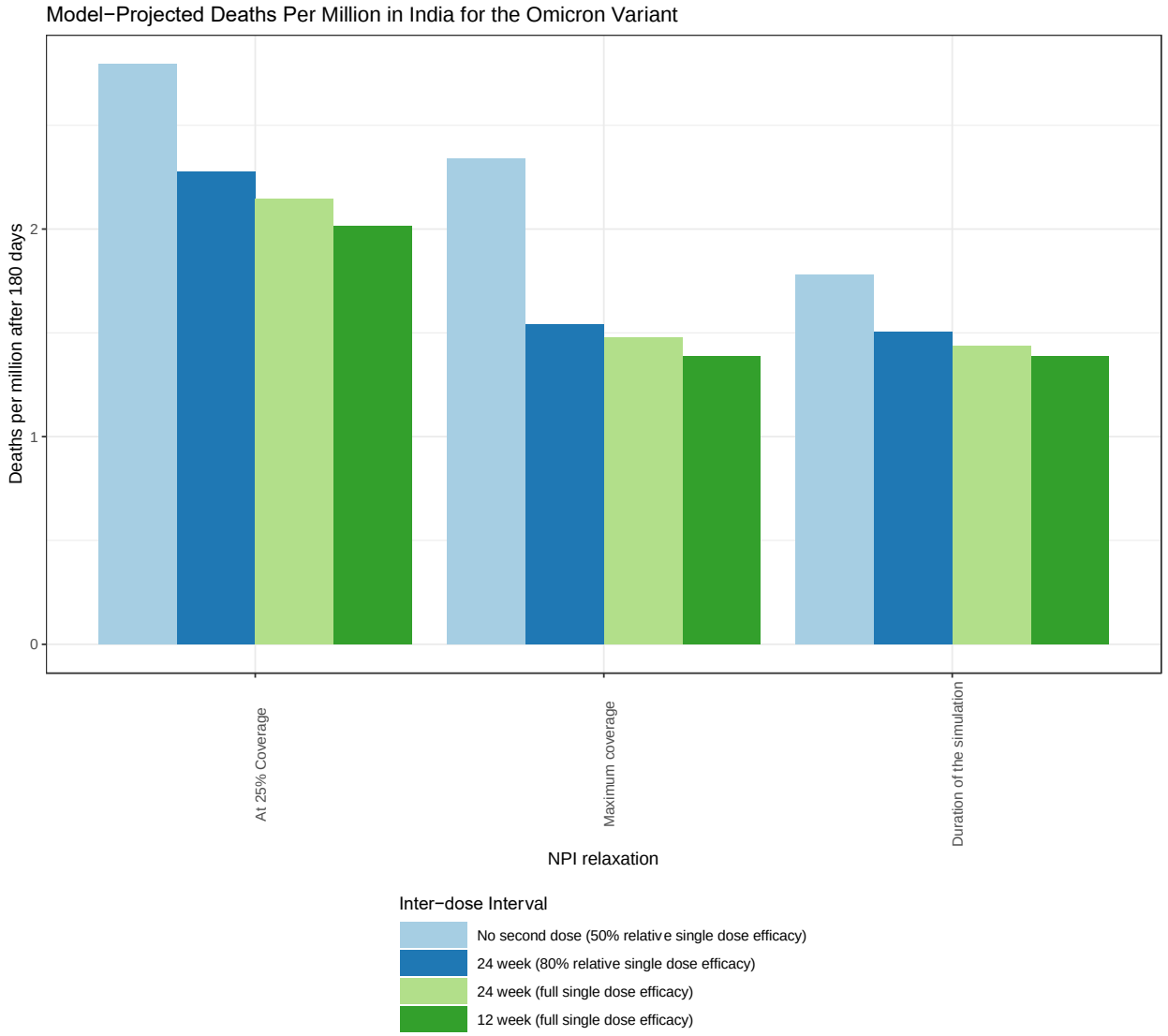

Figure 7: Model-projected number of COVID-19 deaths per million in India 180 days from November 26th, 2021 (Omicron-dominant wave).

Figure 8

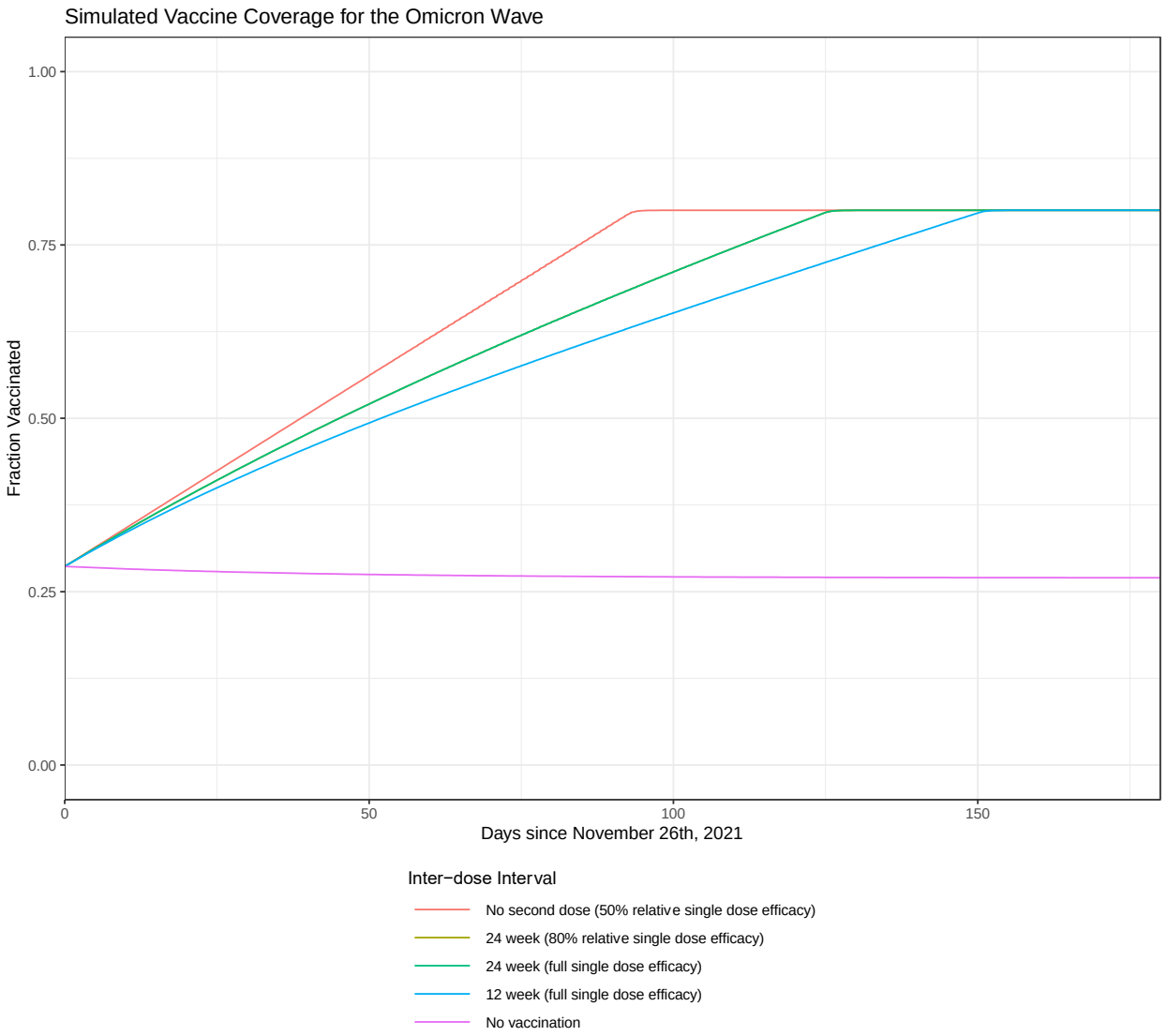

Figure 8: Simulated vaccine coverage for the Omicron simulation.

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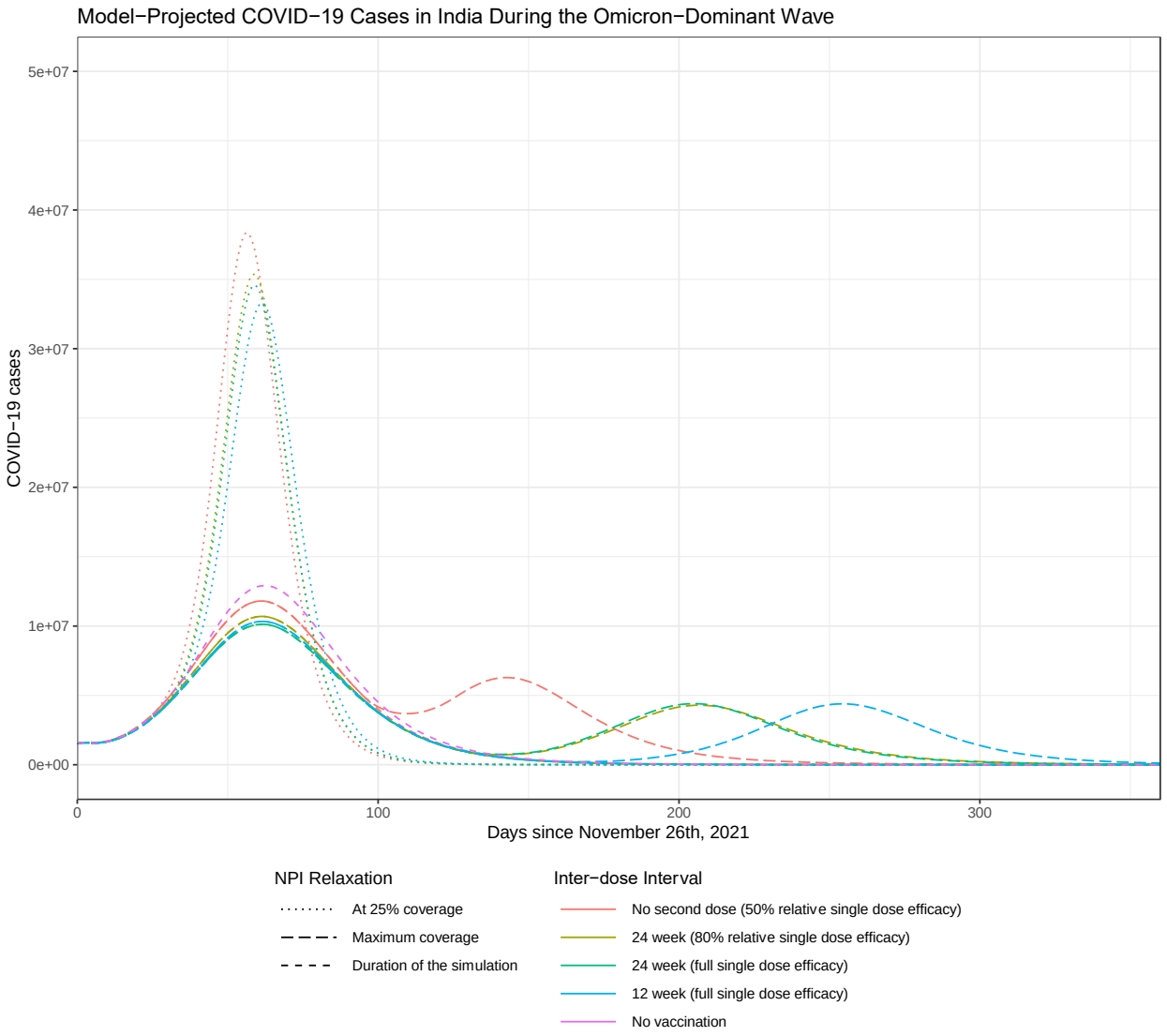
Supplementary Materials

S1



S1: Omicron simulation for 360 days after November 26th, 2021.