

COULD EARLIER AVAILABILITY OF BOOSTERS AND PEDIATRIC VACCINES HAVE REDUCED IMPACT OF COVID-19?

Erik T. Rosenstrom
Julie S. Ivy
Maria E. Mayorga
Julie L. Swann

Department of Industrial and Systems Engineering
North Carolina State University
915 Partners Way
Raleigh, NC 27695, USA

ABSTRACT

The objective is to evaluate the impact of the earlier availability of COVID-19 vaccinations to children and boosters to adults in the face of the Delta and Omicron variants. We employed an agent-based stochastic network simulation model with a modified SEIR compartment model populated with demographic and census data for North Carolina. We found that earlier availability of childhood vaccines and earlier availability of adult boosters could have reduced the peak hospitalizations of the Delta wave by 10% and the Omicron wave by 42%, and could have reduced cumulative deaths by 9% by July 2022. When studied separately, we found that earlier childhood vaccinations reduce cumulative deaths by 2,611 more than earlier adult boosters. Therefore, the results of our simulation model suggest that the timing of childhood vaccination and booster efforts could have resulted in a reduced disease burden and that prioritizing childhood vaccinations would most effectively reduce disease spread.

1 INTRODUCTION

On November 1, 2021, the CDC/FDA approved the use of Pfizer COVID-19 vaccinations for children ages 5-11 (CDC 2021a), and on November 19, 2021, the CDC/FDA approved the use of Pfizer and Moderna booster vaccines for adults 20+ (CDC 2021b). These pharmaceutical interventions (PIs) for COVID-19 were made available after the Delta variant epidemic surge and roughly four weeks before the spread of the Omicron variant in the United States. As a result, the pandemic environment became increasingly complex in the second half of 2021. Examples of this complexity include age group-specific PIs with county specific-uptake (NC DHHS 2022), dynamic adherence to and changing guidelines for non-pharmaceutical interventions (NPIs) (Delphi Epidata API 2022), multiple variants of differing severity causing multiple epidemic waves (Wolter et al. 2022), immunity escape due to Omicron (Araf et al. 2021) and waning immunity for all recovered classes (Nordström et al. 2022). In this environment, it is not clear how the timing of PI rollout may impact disease spread, and with the great effort required to get PIs to market (Janse et al. 2021), it is essential to understand the tradeoffs associated with prioritizing PI rollout on disease spread. Through counterfactual scenarios, we aim to answer the two research questions: (i) what is the effect of the earlier distribution of PIs by age group under the pandemic environment of summer and fall of 2021, and (ii) which PI (childhood vaccination or adult booster) would more effectively reduce disease burden if rolled out sooner? We employ a stochastic agent-based simulation to create a data-driven agent population and adaptable disease model to answer these questions.

Previous work has found that the timing of NPIs can dramatically impact the outcome of an epidemic wave (Morris et al. 2020). The authors used a SIR model to derive robust NPI policies that minimized cases and found that performance was sensitive to NPI implementation timing. In Patel et al. (2021), the authors demonstrate that vaccines can do little to prevent additional waves presented by increases in transmission without a large enough portion of the population vaccinated. Other works have examined the best prioritization strategy for COVID-19 vaccine rollout under limited supply. They find that essential workers are an important group to receive vaccines, but they do not explicitly consider the timing of vaccine distribution relative to multiple forthcoming epidemic waves (Grauer et al. 2020; Mulberry et al. 2021; Rosenstrom et al. 2022a). Costantino et al. (2019) show that it is possible to reduce influenza cases by beginning vaccine distribution closer to the expected peak prevalence time. To our knowledge, no work has yet directly examined the impact of timing of COVID-19 vaccine availability and subsequent distribution in relation to the Delta and Omicron variant waves.

This study describes the simulation model designed to project the impact of the timing of childhood vaccine and adult booster availability on state-level hospitalization and deaths that captures the complexities of the pandemic context to represent underlying disease dynamics accurately. This simulation is a stochastic agent-based network model with an extended Susceptible-Exposed-Infected-Recovered (SEIR) disease model. The model has been expanded to include waning immunity of recovered agents, multiple pharmaceutical interventions uptake in multiple subpopulations with geographic variability, dynamic transmission rates to capture variants, and updated simulation seeding procedures. This simulation model has also been used to conduct several previous COVID-19 analyses on school closures, mask-wearing, lifting of non-pharmaceutical interventions, vaccine equity, and the impact of school policies on community spread (Oruc et al. 2021; Patel et al. 2021; Rosenstrom et al. 2021; Rosenstrom et al. 2022a; Rosenstrom et al. 2022b; Baxter et al. 2022).

2 METHODS

2.1 Model Overview

We employ a stochastic agent-based network model with an extended SEIR framework to define the progression of SARS-CoV-2 (Figure 1). Agents interact in groups via a time-varying interaction network composed of their household, peer group, and community (Figure 1). We use a generalized force of infection model to generate the time until the next infection by sampling an exponential distribution with a time-varying rate based on the number of susceptible and infected agents and agents' behavior within groups of the interaction network. The probability that a group is selected to generate the next infection is proportional to the total force of infection generated. Within a selected group, all susceptible agents are equally likely to be infected (Shi et al. 2010, Rosenstrom et al. 2022b). Once an agent is selected for infection, they progress through the extended SEIR framework. Using a stochastic agent-based model, we can generate multiple stochastic realizations to represent the uncertainty of disease.

Our simulation model is populated with census demographic data at the census tract level for the population of North Carolina (U.S. Census 2017). The agents' attributes captured are age (0-4, 5-9, 10-19, 20-64, 65+), and race/ethnicity (Hispanic/Non-Hispanic American Indian or Alaska Native, Asian, Black, multi-racial, Native Hawaiian or Other Pacific Islander, Other race or White), and household size. Additionally, we include diabetes by age and race/ethnicity as a proxy for comorbidities within the population. Older agents have an increased probability of transitioning to hospitalization and death than younger agents.

All agents are assigned to households ranging in size from 1-6. Households can be multigenerational. We assume that all agents within a household have the same race/ethnicity and that children (ages 0-19) do not live alone. Peer group interactions are age-dependent, representing the school for school-aged children (ages 5-19) and work for working-aged adults (ages 20-64). Agents interact within the same peer groups throughout the simulation. We assume that agents ages 0-4 and 65+ do not interact in

school/workplace peer groups. Community interactions occur among all agents in the census tract and are parameterized by a community infectious hazard parameter fitted during model calibration.

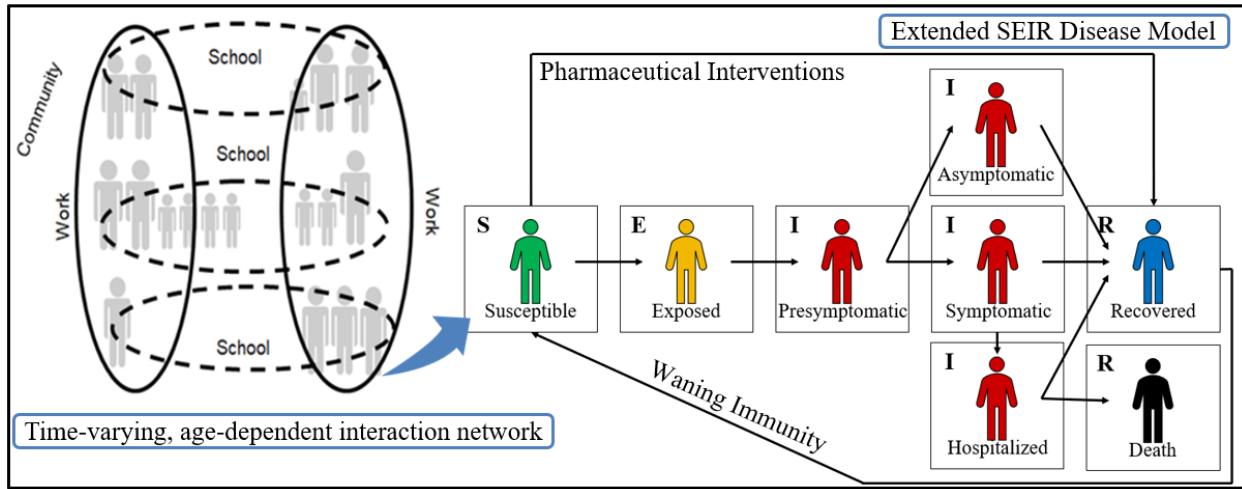


Figure 1: Interaction Network and Extended Susceptible-Exposed-Infected-Recovered Disease Model.

Figure 2 shows the simulation timeline. The impact of waning immunity is discussed in Section 2.2; the uptake of vaccination and boosters within the population is discussed in Section 2.3; the dynamic implementation of the COVID-19 variants is discussed in Section 2.4, and the dynamic masking and school-aged children peer group interactions are discussed in Section 2.5 as part of the model calibration.

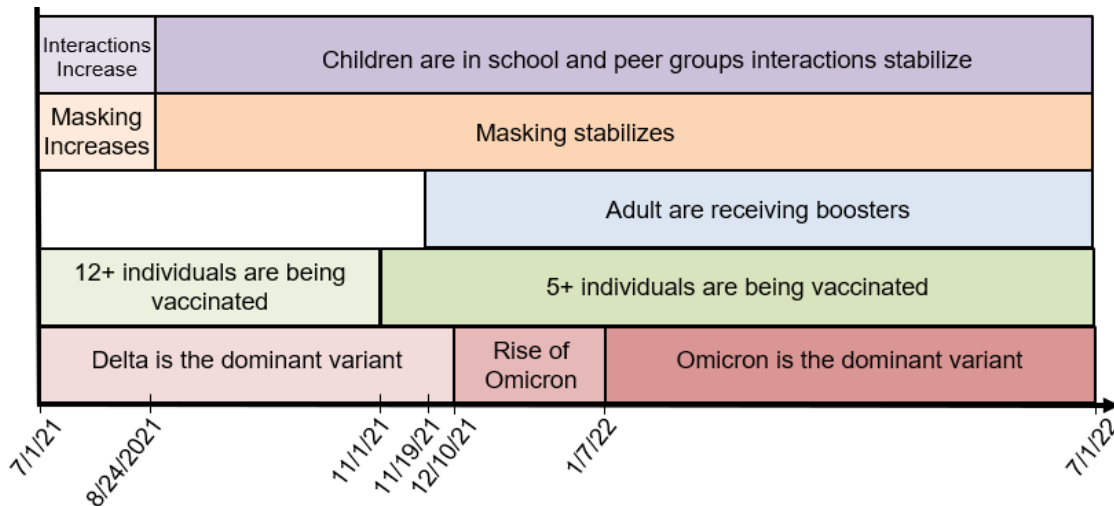


Figure 2: Simulation Timeline.

2.2 Waning Immunity

An agent entering the Recovered state (whether due to initial vaccination, subsequent doses, or disease-induced immunity) may return to susceptibility after a period of time. Our modeling assumptions are informed by literature, data analysis, and expert opinion through discussion with COVID-19 Scenario Modeling Hub (CSMH 2022). Here immunity wanes according to a shifted exponential distribution with a minimum value of two months and an overall median of 6 months (Nordström et al. 2022). We shift this

distribution as we account for vaccine efficacy before an agent enters the recovered state; therefore, we assume that all recovered agents are guaranteed two months of immunity. We assume that if an agent is vaccinated or boosted in the recovered state during the simulation, their immunity is extended by an additional time sampled from the same distribution. Finally, we assume that all immunity follows the same waning attributes regardless of an agent's attributes (e.g., age).

When agents transition from recovered to susceptible for the first time, a variable is activated, indicating that they have previous immunity. Having previous immunity reduces the probability of severe outcomes (Kojima and Klausner 2022). Here the probability of hospitalization for all age groups and the probability of death for all age groups is reduced by 85% and 95% relative to the risk without previous immunity. Hence the probability of severe outcomes remains dependent on age and chronic conditions.

2.3 Vaccine and Booster Distribution

Vaccine and booster uptake was obtained from the North Carolina Department of Health and Human Services (NC DHHS) COVID-19 Dashboard by county and age (NC DHHS 2022). The vaccine structure presented in Rosenstrom et al. (2022a) has been modified to distribute vaccines according to county-level uptake by age and accommodate children ages 5-19. In this structure, agents are determined to be vaccine-willing or not, using probabilities based on their age and county of residence. Selected agents are placed in the eligible vaccine-willing population. According to a number of available vaccine doses each day, agents are selected from this eligible vaccine-willing population to receive a vaccine. The eligible vaccine-willing population changes as agents receive a vaccine or are added according to age eligibility. A similar structure is implemented to distribute the second dose of vaccines and boosters. An agent must be a fully vaccinated adult to be eligible for a booster. As is shown in Figure 2, children ages 5-11 were not eligible for vaccination until November 1, 2021; adults were not eligible for boosters until November 19, 2021, and older youths (12+) were not given boosters during the simulation.

2.4 Modeling Variants

Over the time horizon of the simulation, the Delta and, subsequently, Omicron variants became dominant (CDC 2022). These variants are more infectious than the ancestral strain (Liu and Rocklov 2021; Araf et al. 2021). We model variants with a dynamic transmission rate parameter, β , parameterized by empirical studies estimating the transmission of the respective variants and subsequently tuned to account for seasonality. Here the Omicron transmission rate is tuned via model calibration to be 1.33 times more infectious than Delta (see Section 2.7). To transition from Delta to Omicron dominance, changes in the transmission rate occurred weekly from December 10, 2021, to January 7, 2021, proportionally with variant prevalence in NC (CDC 2022), capturing the variant competition.

In the case of the Omicron variant, there was significant immunity loss likely due to the virus's genetic characteristics; this caused a large proportion of the population to become susceptible to Omicron (Araf et al. 2021). It was estimated via calibration that 50% of the immune population became susceptible to Omicron. This is implemented by adapting the existing waning immunity structure. From December 10, 2021, to January 7, 2022, 50% of agents that recovered prior to the onset of Omicron are assigned to transition to the susceptible state. Groups of agents transition weekly to the susceptible state, where the size of these groups increases proportionally with the prevalence of Omicron. The remaining 50% of agents are assigned to transition back to the susceptible state according to the standard implementation described in Section 2.2. We assume there is no immune escape for boosted individuals, and they follow the waning immunity described in Section 2.2.

Variants differ in the probability of causing severe outcomes. Omicron is calibrated as 50% less severe for all immunity classes than Delta (Wolter et al. 2022). As Omicron becomes the dominant strain from December 10, 2021, to January 7, 2022, the corresponding probabilities of hospitalization and death for all age groups incrementally change over weekly updates proportionally with the prevalence of Omicron until the probabilities of transitioning to hospitalization and death are reduced by 50% compared to Delta.

2.5 Simulation Seeding

The simulation is seeded to begin on July 1, 2021. We seed the agents into the susceptible, exposed, currently hospitalized, recovered, and dead states at the census tract level. All agents not seeded into exposed, hospitalized, recovered, or dead are seeded into the susceptible state. We use The New York Times data (NYT 2022) to seed cases, recoveries, and deaths at the county level following reported age distributions. We used North Carolina Department of Health and Human Services dashboard hospital region data (NC DHHS 2022) to seed the number of hospitalized people. We apportion region-level hospitalizations to counties according to the number of observed cases in each county six days prior.

To estimate the number of people recovered and actively infected, we estimate the cumulative number of cases that have occurred. Using an infection fatality rate of 0.5% (Hauser et al. 2020), we estimate the total number of cases required to generate the observed deaths. Assuming a time delay of two weeks from infection onset to recovery, the estimated infections two weeks prior to July 1, 2021, minus the total deaths as of July 1, 2021, approximate the total number of recovered. The estimated true cases minus the number of recovered, deaths, and hospitalizations yielded the number of active cases on July 1, 2021. We seed all active cases into the exposed state and do not assume an age distribution. Given these county-level values, we apportion them to census tracts according to population size.

The NC DHHS COVID-19 Dashboard provides the total number of fully vaccinated people by age and location, which are also seeded. We assume that the likelihood of someone being vaccinated and their current disease state are independent. If a susceptible agent is assigned vaccination, they move to the recovered state with a probability that their vaccination is still effective. This probability is age-group specific given the approximate times age groups were eligible for vaccination according to the North Carolina vaccine distribution plan (Dooling et al., 2021). All agents seeded into the recovered state through infection or vaccination begin immunity waning as described in Section 2.2 with one exception; when recovered individuals are vaccinated during seeding, we assume immunity is not additive.

2.6 Scenarios Description

We examine four scenarios that vary the timing of childhood vaccine and adult booster availability and subsequent distribution. For each PI, we test two availability start times, the observed start time and an earlier start time leading to 4 combinations. For childhood vaccination availability, these start times are 8/1/21 (shifted) and 11/1/21 (real), and for booster availability, these start times are 8/19/2021 (shifted) and 11/19/21 (real). Both early availability start times are shifted three months prior to their original release. For childhood vaccination, this represents beginning vaccination prior to the fall term of school in NC. For boosters, this represents closer to when other countries (e.g., Israel) began administering additional vaccine doses as boosters (Bar-On et al. 2021). In scenarios with early distribution start times, we shift observed uptake earlier in time, assuming the same uptake rate over the new period. We assume that there are no differences in vaccine efficacy or side effects due to vaccination in the earlier rollout scenarios. Simulation optimization was not used to identify these shifted start times.

2.7 Simulation Calibration

The simulation is calibrated using data from July 1, 2021, through March 14, 2022. The data used for calibration were the state-level hospitalizations over time and the cumulative state-level deaths, which were pulled from the NC DHHS COVID-19 Dashboard (NC DHHS 2022) and New York Times COVID-19 data repository (NYT 2022), respectively. The primary parameters tuned to calibrate the model are the transmission rate, β , over time, and probability of severe outcomes (hospitalization and death) associated with Delta. These parameters have values derived from the literature (Appendix Table 1) and are subsequently tuned as follows to capture the disease spread in North Carolina. The calibration of the time-varying transmission rate occurs first, where the transmission rate is constrained to be monotonic and to increase over the time window corresponding to the introduction of the Delta and Omicron variants in North Carolina. The parameter space is manually searched following standard metaheuristic techniques in

which good candidate solutions are incrementally changed for future iterations. The parameter space searched varied the transmission rate of Omicron from 1x to 1.5x the transmission rate of Delta. The parameter search concludes when the peaks associated with each epidemic wave are correctly timed. Next, ranges of severe outcome probabilities are searched manually to finetune the number of hospitalizations and deaths. The range of values searched is approximately $\pm 15\%$. Validation is stopped when observed data fall within the 10th and 90th percentiles of each outcome with an emphasis on the peak height and timing for current hospitalizations and the last three months of the validation window for cumulative deaths. The validations are reported in Figures 3 and 4 in the results.

Other epidemic context-specific parameters that impact calibration are the percent reduction in severity from Delta to Omicron (Wolter et al. 2022), and the probability of immune escape associated with Omicron (Araf et al. 2021), the masking parameters stratified by urban, suburban, and rural (Delphi Epidata API 2022), and school starting times in North Carolina (PHG 2021). Again we use literature and data to inform these parameter values. A constant value is chosen and held constant throughout the calibration process. A table of parameters can be found in the appendix.

Given the challenges of calibrating a large agent-based model, the major lesson learned is to ensure that the time-varying aspects of the simulation are captured prior to parameter tuning. These aspects are often components like subgroups of agents' behavior or dynamic properties of the epidemic environment like the emergence of variants. This lesson manifested in the calibration of the Delta wave, as initially, we had all kids starting school at the same time, which was an inaccurate assumption. This made the simulated epidemic peak occur sooner and higher than the observed epidemic peak. After accounting for the varying school start times in the model, we achieved the correct shape peak and subsequently tuned parameters to fit the observed epidemic wave. We indicate this with "increasing interactions" in Figure 2. It also manifested in the calibration of the Delta and Omicron waves. With multiple variants, it is essential to model the properties of competing variants, which here largely impacted the disease severity and transmissibility as described in Section 2.4.

2.8 Computational Information

The stochastic agent-based simulation model is implemented in C++ and is run on an HPC computing platform. Each scenario consists of 45 replications. Simulation replications run in parallel where each is allocated four cores of an Intel(R) Xeon(R) CPU E5-2640 v2 @ 2.00GHz processor. Each simulation replication runs approximately 6 hours and produces approximately 0.69 GB of output data. Simulation output processing is written in Python and is similarly run in parallel, with respect to scenarios, on four cores of the same processing units. Depending on the types and number of output file types to be processed, the runtime can vary from 30 seconds to 1+ hours.

3 RESULTS

3.1 Hospitalizations

Figure 3A-D shows the average number of people hospitalized over time through the simulation time horizon, with each subfigure showing one scenario. This labeling will be used to compare scenarios succinctly. It includes the observed hospitalizations from 7/1/2021 – 3/14/2022 (red lines) and the 10th and 90th percentiles of the simulation results (green shading).

Comparing Figures 3A to 3C (changes to pediatric vaccinations under observed booster start time) and 3B to 3D (changes to pediatric vaccinations under early booster start time), we observed that distributing childhood vaccines earlier leads to reduced peak hospitalization for the Delta wave by 423 and 392 hospitalizations, respectively and reduce the peak for the Omicron wave by 1,039 and 4,710 hospitalizations respectively. Comparing Figures 3C to 3D (changes to boosters under early childhood vaccination start time), earlier availability of boosters reduces the peak hospitalizations by 1,742 during Omicron. Comparing Figures 3A to 3B (changes to boosters under observed childhood vaccination start

time), earlier availability of boosters increases the peak hospitalizations by 2,197 during Omicron. Comparing 3A to 3D shows that distributing childhood vaccines and boosters earlier reduces the Omicron peak by 2,512 hospitalizations. There is considerable uncertainty generated due to the immunity loss and reinfections that reduce the statistical significance of these differences. We observed that childhood vaccinations are the main driver for lower peak hospitalizations during the Omicron wave.

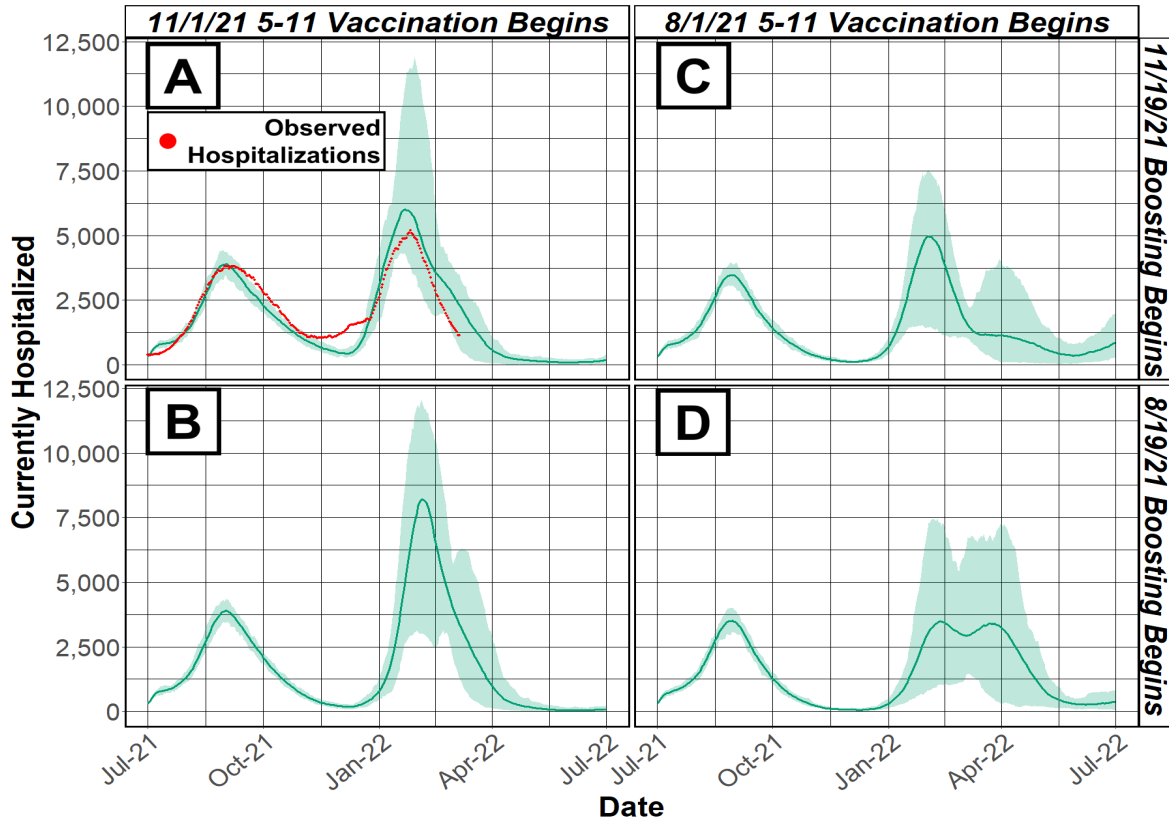


Figure 3: Impact of Booster and Childhood Vaccination Timing on Hospitalizations.

3.2 Deaths

Figure 4A-D shows the average number of cumulative deaths over the simulation time horizon, with each subfigure showing one scenario. As before, observed values are shown in the red lines, while the green shaded areas show the 10th and 90th percentiles of the simulation results.

Comparing Figures 4A to 4C (changes to pediatric vaccinations under observed booster start time) and 4B to 4D (changes to pediatric vaccinations under early booster start time), we observed that distributing childhood vaccines earlier leads to 2,615 and 2,170 fewer cumulative deaths at the end of the time horizon, respectively. Comparing Figures 4A to 4B (changes to boosters under observed childhood vaccination start time) and 4C to 4D (changes to boosters under early childhood vaccination start time), earlier availability of boosters reduces cumulative deaths by 6 and 451 at the end of the time horizon, respectively. Comparing 4A to 4D, distributing both childhood vaccines and booster earlier reduces the number of cumulative deaths by 2,164 at the end of the time horizon. Again we observe that earlier childhood vaccination is a primary driver for reducing cumulative deaths, though as can be seen by the wide percentile ranges, there is considerable uncertainty associated with waning immunity during the Omicron wave.

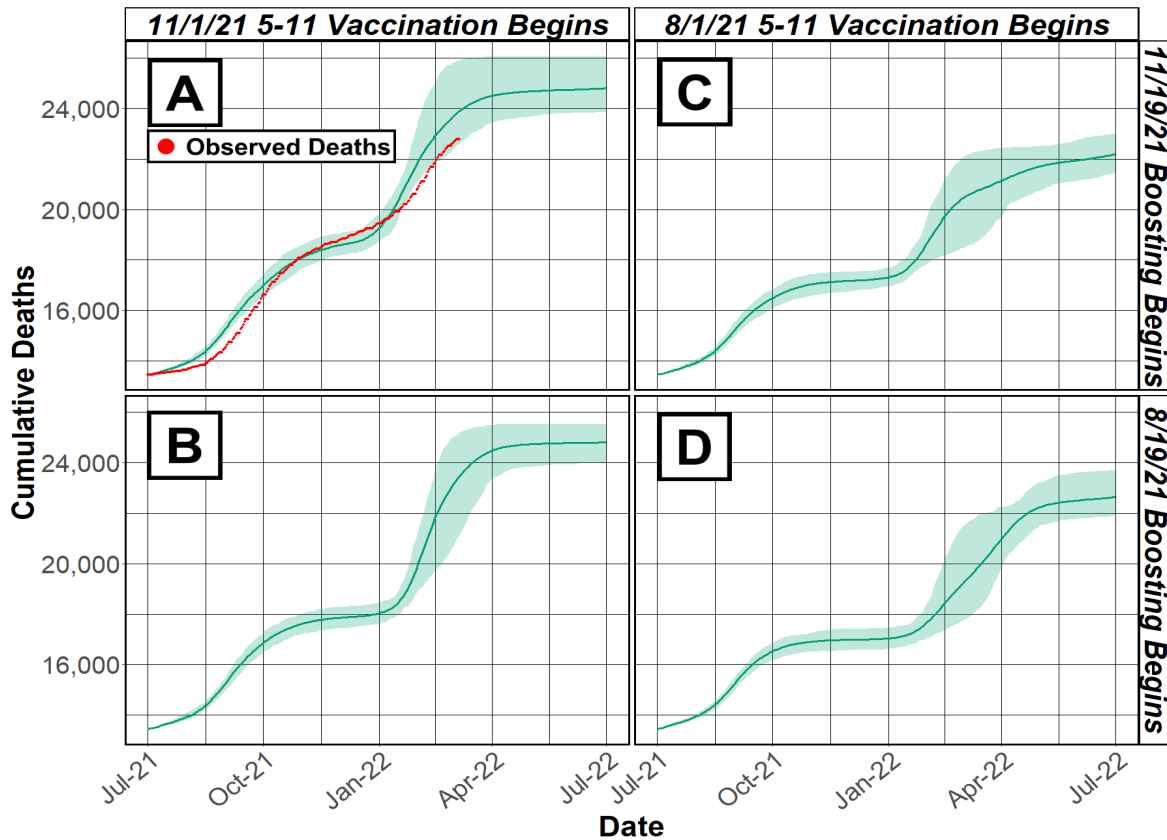


Figure 4: Impact of Booster and Childhood Vaccination Timing on Cumulative Deaths.

4 DISCUSSION

In this analysis, we used a stochastic agent-based extended SEIR disease model with multiple types of PIs, waning immunity, and parameterized to Delta and Omicron variants to retrospectively answer the two research questions: (i) what is the effect of the earlier distribution of PIs by age group under the pandemic environment of summer and fall of 2021, and (ii) which PI (childhood vaccination or adult booster) would more effectively reduce disease burden if rolled out sooner? In the four scenarios, the simulation suggests that earlier availability of childhood vaccinations reduces the peak hospitalizations and cumulative deaths when controlling for booster availability start time. This analysis highlights that children's behavior directly impacts the adults and elderly, who make up the majority of hospitalizations and deaths. In this pandemic context, they are a driver of disease spread as they are largely susceptible with only immunity from infection. Increasing the immunity of this age group through PIs decreases disease outcomes for the entire population. We found that booster timing can also impact peak hospitalizations positively and negatively given the childhood vaccination setting but ultimately did not impact the number of cumulative deaths. Given booster eligibility requirements and the protection from severe disease associated with previous immunity, it is sensible that boosters have little impact on cumulative deaths. However, we observe that the timing of the boosters impacts the amount of immunity present during waves of the pandemic leading to increases in cases and hospitalizations in some cases. With the early availability of boosters, immunity waning had started to occur in recovered agents by the time Omicron became prevalent.

While the distribution of the childhood vaccination is non-trivial to speed up due to FDA regulatory procedures and clinical trials, these works suggest a prioritization of childhood vaccination above booster rollout in the allocation of PI rollout policy. Children have a larger impact on statewide disease spread due to their limited cumulative immunity prior to PI availability. Given the impact of waning immunity we observed, it is likely that even earlier PI distribution rollout plans may be suboptimal compared to the observed PI rollout start time. This work motivates future work to identify an optimal time to distribute PIs before multiple epidemic waves with immunity loss. With the now existing COVID-19 vaccine and epidemic forecasting infrastructure, optimal timing should be considered in future PI efforts to reduce the disease burden.

We highlight the components and considerations required to analyze this type in the current pandemic context. Using a stochastic agent-based model provides the flexibility to directly model various aspects of human behavior. Here we model age group-specific PIs with county-specific uptake, dynamic adherence to non-pharmaceutical interventions (NPIs), multiple variants causing multiple epidemic waves, dynamic severity due to variants, immunity escape due to Omicron, and waning immunity for all recovered classes.

4.1 Limitations

The large age grouping forming the working-age adult population is limited in our model. As a result, we do not model differences in behavior that arise due to age within age buckets. This limits how we model comorbid conditions within the population and differing levels of social activity. Similarly, we consider 65+ as non-working-age adults. Thus, they do not have a workplace peer group that may not represent the populations given a geographic location. As a result, we may be underestimating cases, hospitalizations, and deaths for this age group, although in previous simulations, we have found results for this age group validated well. Additionally, we only illustrate the effect of high-risk chronic conditions within the population with diabetes. This would lead to a potential underestimation of hospitalizations and deaths. Additionally, we do not consider coupling effects such as resource limitations or changes in uptake behavior that may arise due to the shifted PI start times.

The attributes of COVID-19 immunity are not well understood (Perez-Alos et al. 2021; Ferdinands et al. 2022). Given our assumption of additive immunity, we could overestimate the effectiveness of vaccines and boosters, leading to underestimating the disease burden. We also assume that protection from severe disease outcomes does not wane over time. This may also be overestimating the immune protection and therefore underestimating the disease burden. It is unclear how an individual's age, the different timing, and the combinations of immunity impact an individual's immunity in the future. This is complicated further by immunity escaping variants. Our implementation assumes that all immunity behaves the same regardless of immune history and age. This may impact the parameterization of the Delta and Omicron waves and, therefore, the reported hospitalizations and deaths.

The final limitation pertains to model calibration. Given the large number of parameters derived from data and literature, each with some uncertainty, and the limited number of outcome metrics to fit models, there are likely multiple possible parameter combinations that would yield a valid fitting. This may impact the results presented beyond the validation period and reduce the generalizability of the modeling results to other geographies. Additionally, we combine disease parameters sourced from multiple studies, which may yield biases due to differences in disease spread or population composition.

5 CONCLUSION

We have demonstrated with our stochastic agent-based simulation model that the timing of vaccine and booster availability with respect to the emergence of new variants can be impactful. Particularly, earlier availability of childhood vaccines could have reduced hospitalizations and deaths associated with the Delta and Omicron waves. In the future, PI distribution plans will need to carefully consider the immunity landscape and the future emergence of variants when choosing the optimal timing.

A Appendix

Table 1 : Simulation Parameters.

PARAMETER	ESTIMATES	REFERENCES
Exposed (E) Duration	Weibull with mean 4.3 days	Grant et al. (2022)
Pre-symptomatic (IP) Duration	0.5 days	Ferguson et al. (2020)
Hospitalized (H) Duration	Exponential with mean 7.3 days	Iuliano et al. (2022)
Symptomatic (S) Duration	Exponential with mean 2.9 days	Hauser et al. (2020)
Symptomatic-Asymptomatic Duration Ratio	1.5	Ferguson et al. (2020)
Probability of Symptomatic (from IP)	0.66	Mizumoto et al. (2020)
Probability of Hospitalization (from IS)	0.005 for age 0-19;	Twohig, K.A., et al. (2022) and calibration
	0.032 for age 20-64;	
	0.191 for age 65+	
Probability of Death (from H)	0 for age 0-19;	Bast et al. (2021) and calibration
	0.0464 for age 20-64;	
	0.3161 for age 65+	
R0	5	Liu and Rocklov (2021)
β transmission rate of Delta	2.085	Liu and Rocklov (2021) and calibration
ω (proportion infections by IA)	0.24	Ganyani et al. (2020) and Keskinocak et al. (2020)
γ (proportion of transmission that occur outside households)	30%	Ekici et al. (2014) and Keskinocak et al. (2020)
δ (proportion of infections outside households that occur in community)	0.23	Keskinocak et al. (2020)
μ (import rate)	7.36 E-6	Keskinocak et al. (2020)

REFERENCES

Araf, Y., F. Akter, Y. dong Tang, R. Fatemi, M. S. A. Parvez, C. Zheng, and M. G. Hossain. 2021. "Omicron Variant of SARS-CoV-2: Genomics, Transmissibility, and Responses to Current COVID-19 Vaccines". *Journal of Medical Virology* 94(5):1825–1832.

Bar-On, Y. M., Y. Goldberg, M. Mandel, O. Bodenheimer, L. Freedman, N. Kalkstein, B. Mizrahi, S. Alroy-Preis, N. Ash R. Milo and A. Huppert. 2021. "Protection of BNT162b2 Vaccine Booster Against Covid-19 in Israel". *New England Journal of Medicine* 385(15):1393–1400.

Bast, E., F. Tang, J. Dahn, and A. Palacio. 2021. "Increased Risk of Hospitalisation and Death with the Delta Variant in the USA". *The Lancet Infectious Disease* 21(12):1629–1630.

Baxter, A., B. E. Oruc, P. Keskinocak, J. Asplund, and N. Serban. 2022. "Evaluating Scenarios for School Reopening Under COVID19". *BMC Public Health* 22:1–10.

Center for Disease Control and Prevention. 2021. "CDC Recommends Pediatric COVID-19 Vaccine for Children 5 to 11 Years". CDC.

Center for Disease Control and Prevention. 2021. "CDC Expands Eligibility for COVID-19 Booster Shots to All Adults". CDC.

Center for Disease Control and Prevention. 2021. "Variant Proportions". CDC. <https://covid.cdc.gov/covid-data-tracker/#variant-proportions>, accessed 1st March 2022.

- COVID-19 Scenario Modeling Hub. 2022. “Round 13 Projections”. COVID-19 Scenario Modeling Hub (CSMH). <https://covid19scenariomodelinghub.org/viz.html>, accessed 1st March 2022.
- Costantino, V., M. Trent, and C. R. MacIntyre. 2019. “Modelling of Optimal Timing for Influenza Vaccination as a Function of Intraseasonal Waning of Immunity and Vaccine Coverage”. *Vaccine* 37:6768–6775.
- Delphi Epidata API. 2022. “Covidcast”. Delphi Group. <https://github.com/cmu-delphi/delphi-epidata>, accessed 1st February 2022.
- Dooling, K., M. Marin, M. Wallace, N. McClung, M. Chamberland, G. M. Lee, H. K. Talbot, J. R. Romero, B. P. Bell, and S. E. Oliver. 2021. “The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Janssen COVID-19 Vaccine — United States, February 2021”. *MMWR Surveillance Summaries* 70(9):329–332.
- Ekici, A., P. Keskinocak, and J. L. Swann. 2014. “Modeling Influenza Pandemic and Planning Food Distribution”. *M&SOM Manufacturing & Service Operations Management* 16(1):11-27.
- Ferdinands, J. M., S. Rao, B. E. Dixon, P. K. Mitchell, M. B. DeSilva, S. A. Irving, N. Lewis, K. Natarajan, E. Stenehjem, S. J. Grannis, J. Han, C. McEvoy, T. C. Ong, A. L. Naleway, S. E. Reese, P. J. Embi, K. Dascomb, N. P. Klein, E. P. Griggs, D. Konatham, A. B. Kharbanda, D. H. Yang, W. F. Fadel, N. Grisel, K. Goddard, P. Patel, I. C. Liao, R. Birch, N. R. Valvi, S. Reynolds, J. Arndorfer, O. Zerbo, M. Dickerson, K. Murthy, J. Williams, C. H. Bozio, L. Blanton, J. R. Verani, S. J. Schrag, A. F. Dalton, M. H. Wondimu, R. Link-Gelles, E. Azziz-Baumgartner, M. A. Barron, M. Gaglani, M. G. Thompson, and B. Fireman. 2022. “Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022”. *MMWR Recommendations and Reports* 71(7):255–263.
- Ferguson, N., D. Laydon, G. Nedjati-Gilani, N. Imai, K. Ainslie, M. Baguelin, S. Bhatia, A. Boonyasiri, Z. Cucunubá, G. CuomoDannenburg, A. Dighe, I. Dorigatti, H. Fu, K. Gaythorpe, W. Green, A. Hamlet, W. Hinsley, L. Okell, S. van Elsland, H. Thompson, R. Verity, E. Volz, H. Want, Y. Wan, P. Walker, C. Walters, P. Winskill, C. Whittaker, C. Donnelly, S. Riley, and A. Ghani. 2020. “Impact of Non-pharmaceutical Interventions (NPIs) to Reduce COVID19 Mortality and Healthcare Demand”. Report No. 9, Imperial College of London.
- Ganyani, T., C. Kremer, D. X. Chen, A. Torneri, C. Faes, J. Wallinga, and N. Hens. 2020. “Estimating the Generation Interval for Coronavirus Disease (COVID-19) Based on Symptom Onset Data”. *Eurosurveillance* 25(17):12-9.
- Grant, R., T. Charmet, L. Schaeffer, S. Galmiche, Y. Madec, C. Von Platen, O. Ch’eny, F. Omar, C. David, A. Rogoff, J. Paireau, S. Cauchemez, F. Carrat, A. Septfons, D. Levy-Bruhl, A. Mailles, and A. Fontanet. 2022. “Impact of SARS-CoV-2 Delta Variant on Incubation, Transmission Settings and Vaccine Effectiveness: Results From a Nationwide Case-control Study in France”. *The Lancet Regional Health - Europe* 13:1–12.
- Grauer, J., H. L’öwen, and B. Liebchen. 2020. “Strategic Spatiotemporal Vaccine Distribution Increases the Survival Rate in an Infectious Disease like Covid-19”. *Scientific Reports* 10:1–10.
- Hauser, A., M. J. Counotte, C. C. Margossian, G. Konstantinoudis, N. Low, C. L. Althaus, and J. Riou. 2020. “Estimation of SARS-CoV-2 Mortality During the Early Stages of an Epidemic: A Modeling Study in Hubei, China, and Six Regions in Europe”. *PLoS Medicine* 17(7):1–17.
- Iuliano, A. D., J. M. Brunkard, T. K. Boehmer, E. Peterson, S. Adjei, A. M. Binder, S. Cobb, P. Graff, P. Hidalgo, M. J. Panaggio, J. J. Rainey, P. Rao, K. Soetebier, S. Wacaster, C. E. Ai, V. Gupta, N. A. M. Molinari, and M. D. Ritchey. 2022. “Trends in Disease Severity and Health Care Utilization During the Early Omicron Variant Period Compared with Previous SARS-CoV-2 High Transmission Periods — United States, December 2020–January 2022”. *MMWR Recommendations and Reports* 71(4):146–152.
- Janse, M., T. Brouwers, E. Claassen, P. Hermans, and L. van de Burgwal. 2021. “Barriers Influencing Vaccine Development Timelines, Identification, Causal Analysis, and Prioritization of Key Barriers by KOLs in General and Covid-19 Vaccine RD”. *Frontiers in Public Health* 9:1–16.
- Keskinocak, P., B. E. Oruc, A. Baxter, J. Asplund, and N. Serban. 2020. “The Impact of Social Distancing on COVID19 Spread: State of Georgia Case Study”. *PLoS One* 15 (10): 1-16.
- Kojima, N., and J. D. Klausner. 2022. “Protective Immunity After Recovery From SARS-CoV-2 Infection”. *The Lancet Infectious Diseases* 22(1):12–14.
- Lui, Y., and J. Rocklov. 2021. “The Reproductive Number of the Delta Variant of SARS-CoV-2 is Far Higher Compared to the Ancestral SARS-CoV-2 Virus”. *Journal of Travel Medicine* 3(27):584–586.
- Mizumoto, K., K. Kagaya, A. Zarebski, and G. Chowell. 2020. “Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases On Board the Diamond Princess Cruise Ship, Yokohama, Japan, 2020”. *Eurosurveillance* 25(10):1–5.
- Morris, D. H., F. W. Rossine, J. B. Plotkin, and S. A. Levin. 2021. “Optimal, Near-optimal, and Robust Epidemic Control”. *Communications Physics* 4:1–8.
- Mulberry, N., P. Tupper, E. Kirwin, C. McCabe, and C. Colijn. 2021. “Vaccine Rollout Strategies: The Case for Vaccinating Essential Workers Early”. *PLoS Global Public Health* 1:1–14.
- Nordström, P., M. Ballin, and A. Nordström. 2022. “Risk of Infection, Hospitalisation, and Death up to 9 Months After a Second Dose of COVID-19 Vaccine: a Retrospective, Total Population Cohort Study in Sweden”. *The Lancet* 399(10327):814–823.
- North Carolina Department of Health and Human Services. 2022. “North Carolina COVID-19 Dashboard”. North Carolina Department of Health and Human Services (NC DHHS). <https://covid19.ncdhhs.gov/dashboard>, accessed 14th March 2021.

- Oruc, B. E., A. Baxter, P. Keskinocak, J. Asplund, and N. Serban. 2021. "Homebound by COVID19: the Benefits and Consequences of Non-pharmaceutical Intervention Strategies". *BMC Public Health* 21(1):1–8.
- Patel, M. D., E. T. Rosenstrom, J. S. Ivy, M. E. Mayorga, P. Keskinocak, R. Boyce, K. Hassmiller Lich, R. Smith, K. Johnson, P. Delamater, and J. L. Swann. 2021. "Association of Simulated COVID-19 Vaccination and Nonpharmaceutical Interventions with Infections, Hospitalizations, and Mortality". *JAMA Network Open* 4:1–14.
- Perez-Alos, L., J. J. A. Armenteros, J. R. Madsen, C. B. Hansen, I. Jarlhelt, S. R. Hamm, L. D. Heftdal, M. M. Pries-Heje, D. L. Møller, K. Fogh, R. B. Hasselbalch, A. Rosbjerg, S. Brunak, E. Sørensen, M. A. H. Larsen, S. R. Ostrowski, R. Frikke-Schmidt, R. Bayarri-Olmos, L. M. Hilsted, K. K. Iversen, H. Bundgaard, S. D. Nielsen, and P. Garred. 2022. "Modeling of Waning Immunity After SARS-CoV-2 Vaccination and Influencing Factors". *Nature Communications* 13(1):1–11.
- Public Holidays Global. 2021. "North Carolina School Calendar 2021 and 2022" Public Holidays Global (PHG). <https://publicholidays.com/us/school-holidays/north-carolina/>, accessed 1st November 2021.
- Rosenstrom, E. T., B. E. Oruc, J. S. Ivy, M. E. Mayorga, P. Keskinocak, and J. L. Swann. 2021. "High-quality Masks Reduce COVID-19 Infections and Death in the US". In *Proceedings of the 2021 Winter Simulation Conference*, edited by S. Kim, B. Feng, K. Smith, S. Masoud, Z. Zheng, C. Szabo, and M. Loper, 1–11. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.
- Rosenstrom, E. T., J. Mele, J. S. Ivy, M. E. Mayorga, M. D. Patel, K. Hassmiller Lich, K. Johnson, P. Delamater, P. Keskinocak, R. Boyce, R. Smith, and J. L. Swann. 2022. "Can Vaccine Prioritization Reduce Disparities in COVID-19 Burden for Historically Marginalized Populations?". *PNAS Nexus* 1:1–9.
- Rosenstrom, E. T., J. Mele, J. S. Ivy, M. E. Mayorga, M. D. Patel, K. Hassmiller Lich, P. Delamater, R. Smith, and J. L. Swann. 2022. "Vaccinating Children Against COVID-19 is Essential Prior to the Removal of Non-Pharmaceutical Interventions". *PNAS Nexus* 3:1-8.
- Shi, P., P. Keskinocak, J. Swann, and B. Lee. 2010. "The Impact of Mass Gatherings and Holiday Traveling on the Course of an Influenza Pandemic: a Computational Model". *BMC public health* 10(778):1-12.
- The New York Times. 2021. "covid-19-data". The New York Times (NYT). <https://github.com/nytimes/covid-19-data>, accessed 14th March 2021.
- Twohig, K. A., T. Nyberg, A. Zaidi, S. Thelwall, M. A. Sinnathamby, S. Aliabadi, S. R. Seaman, R. J. Harris, R. Hope, J. Lopez-Bernal, E. Gallagher, A. Charlett, D. De Angelis, the COVID-19 Genomics UK (COG-UK) consortium, A. M. Presanis, and G. Dabrera. 2022. "Hospital Admission and Emergency Care Attendance Risk for SARS-CoV-2 Delta (B.1.617.2) Compared with Alpha (B.1.1.7) Variants of Concern: a Cohort Study". *The Lancet Infectious Diseases* 22(1):35–42.
- U.S. Census Bureau. 2018. "American Community Survey 5-year Estimates 2017". U. S. Census Bureau. data.census.gov, accessed 1st July 2020.
- Wolter, N., W. Jassat, S. Walaza, R. Welch, H. Moultrie, M. Groome, D. G. Amoako, J. Everatt, J. N. Bhiman, C. Scheepers, N. Tebeila, N. Chiwandire, M. du Plessis, N. Govender, A. Ismail, A. Glass, K. Mlisana, W. Stevens, F. K. Treurnicht, Z. Makatini, N. yuan Hsiao, R. Parboosing, J. Wadula, H. Hussey, M.-A. Davies, A. Boulle, A. von Gottberg, and C. Cohen. 2022. "Early Assessment of the Clinical Severity of the SARS-CoV-2 Omicron Variant in South Africa: a Data Linkage Study". *The Lancet* 399(10323):437–446.

AUTHOR BIOGRAPHIES

ERIK ROSENSTROM is an Operations Research Ph.D. student at North Carolina State University. His research interests include decision making under uncertainty as applied to improving health policy. He led the simulation implementation and analysis on this project. His email address is erosens@ncsu.edu. His website is <https://www.or.ncsu.edu/people/erosens/>.

JULIE IVY is a professor in the Department of Industrial and Systems Engineering at North Carolina State University. She received her Ph.D. in Industrial and Operations Engineering from University of Michigan. Her research interests are mathematical modeling of stochastic dynamic systems with an emphasis on statistics and decision analysis as applied to health systems.. Her email address is jsivy@ncsu.edu. Her website is <https://www.ise.ncsu.edu/people/jsivy/>.

MARIA MAYORGA is a Professor of Personalized Medicine in the Department of Industrial and Systems Engineering at North Carolina State University. She received her Ph.D. in Industrial Engineering and Operations Research from University California Berkeley. Her research interests include predictive models in health care and health care operations management. Her email address is memayorg@ncsu.edu. Her website is <https://www.ise.ncsu.edu/people/memayorg/>.

JULIE SWANN is department head of the Department of Industrial and Systems Engineering at North Carolina State University. She received Ph.D. in Industrial Engineering and Management Sciences from Northwestern University. Her research interests are using analytics and system approaches to enable health care and supply chains to become more efficient, effective, or equitable. Her email address is jlswann@ncsu.edu. Her website is <https://www.ise.ncsu.edu/people/jlswann/>.