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Approval Sheet

Prioritization of Primary Versus Booster Vaccinations for the Prevention of COVID-19 Incidence and Hospitalizations

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Abstract Cover Page

Prioritization of Primary Versus Booster Vaccinations for the Prevention of COVID-19 Incidence and Hospitalizations

By

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Bachelor of Science
Colorado State University
2020

Thesis Committee Chair: Samuel M. Jenness, PhD

An abstract of
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Abstract

Prioritization of Primary Versus Booster Vaccinations for the Prevention of COVID-19 Incidence and Hospitalizations
By Kathryn Krupinsky

Background. Since their introduction at the end of 2020, COVID-19 vaccines have been instrumental tools in combating the pandemic. A year after becoming available to the general population, the proportion of the United States population that received primary and booster vaccinations remains low despite their high effectiveness. Given the limited public health resources for increasing vaccine uptake, there is a present need to determine whether more attention should be given to increasing the number of individuals who receive their primary vaccination series versus increasing the number of primary-vaccinated individuals who receive a booster vaccination dose.
Methods. For this study, we built upon a network-based mathematical model to include booster vaccination, waning immunity, multiple SARS-CoV-2 strains, and reinfection. This model was designed to represent the local epidemic in the state of Georgia, USA from approximately January 2021–December 2021 and was parameterized using published literature and Georgia Department of Public Health surveillance data. Multiple scenarios were run with higher and lower rates of primary and booster vaccine administration. Total incidence, symptomatic infections, and hospitalizations were recorded for the general and greater than 65 population.
Results. We found that increasing the rate of both primary and booster vaccination doses decreased the infection and hospitalization rates in both the general and greater than 65 population. However, the booster vaccination dose had a smaller impact on these rates compared to rates of primary vaccination. Sensitivity analysis showed that this minimal impact of the booster was likely due to booster dose timing relative to secondary waves of infection.
Conclusions. Our study suggests that prioritizing primary vaccinations would have a greater public health impact than prioritizing boosters among those with a primary vaccination. Booster vaccinations have the potential to be highly impactful; however, attention needs to be given to developing accurate forecasting tools so that vaccine distribution can be tailored to prevent subsequent waves of disease.

Cover Page

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BACKGROUND

SARS-CoV-2, the virus which causes COVID-19 disease, will become one of the defining health events of the 21st century. Just over two years since its declaration as a pandemic by the WHO, SARS-CoV-2 is estimated to have caused 80 million cases and 979,000 deaths in the United States alone, with countless more worldwide.[1] In the state of Georgia, as of April 2022, COVID-19 has also had a major impact, causing an estimated 1.9 million cases, 110,000 hospitalizations, and 31,000 confirmed deaths.[2] Further, the emergence of variants and the relaxation of public health restrictions has led to multiple waves of disease. There have been many non-pharmaceutical interventions (e.g., masking, social distancing) to combat the COVID-19. However, one of the most effective pharmaceutical interventions has been the development and distribution of highly effective vaccines.

The first COVID-19 vaccines began distribution within the US in late 2020 and consisted of a two-dose vaccination series administered 21–28 days apart.[3] After this primary series, it was estimated that individuals had up to a 97% reduction in risk of disease;[4] however, more recent data has suggested waning immunity.[5] Estimating the durability of vaccines is complicated by the emergence of novel SARS-CoV-2 strains, which have had varying infectivity, transmissibility, and severe disease risk.[6] These two factors prompted the development and introduction of a booster (third) vaccination, recommended to be administered at least 150 days (5 months) after the receipt of the complete primary vaccine series.[7]

Despite being available to the general population in the United States since May 2021, only 66% of the eligible US population has completed the complete primary vaccine series and 50% completed the booster vaccination dose.[1,8] This proportion is even lower in Georgia, with only 54.3% completing the primary series and 36.2% completing the booster.[1] Initial vaccine uptake rates were high; however, the rate of new vaccinations (both primary and booster series) has decreased drastically in the last months of 2021.[9] Given the high effectiveness of these vaccines and the limited public health resources for vaccine promotion and rollout, there is a present need to understand how resources can be used to maximize the number of cases and hospitalizations prevented. Specifically, there is a need to determine whether more attention should be given to increasing the coverage of primary vaccinations to COVID-19 vaccine-naive individuals or given to increasing the number of individuals who receive their booster vaccination dose after completing the primary vaccination series.

Dynamic transmission models have been instrumental throughout the pandemic in answering questions about the impact of non-pharmaceutical and pharmaceutical interventions. Models are particularly well suited to answer these questions because of their ability to quickly test multiple scenarios and represent complex community behavior. For COVID-19 vaccination, multiple studies have been done which examine the components relevant to postulating an optimal vaccination strategy. Moghadas et al. utilized an individual-based model to investigate the effects of delaying the second primary vaccinations; they found that understanding the waning immunity profile would influence when doses should optimally be administered. Other modeling studies have looked at the effects of different waning immunity assumptions, finding a wide range of results from no impact of inclusion or exclusion of waning immunity[10] to waning immunity being solely responsible for future waves of the pandemic.[11,12] Modeling studies looking at the impact of multiple strains[13,14] suggest booster vaccinations have a major impact on decreasing the overall number of cases but do not prevent additional waves from occurring altogether. Getz et al. utilized an individual-based model which investigated both waning immunity and multiple strains in combination; however, their model was not tailored to a specific population and did not including any mixing patterns.

In this study, we utilized a network-based dynamic transmission model of SARS-CoV-2 to understand how increasing rates of COVID-19 primary and booster vaccination dose administration impacts disease incidence and hospitalization for the total and older population. Specifically, we aimed to model the local epidemic in the state of Georgia while accounting for vaccine-induced immunity waning over time and for multiple strains to be in circulation. We aimed for this work to be informative in postulating the best scale-up strategy to optimally minimize the number of infections and hospitalizations accrued over a year-long period.

METHODS

Overview

In this study, we utilized a network-based model to represent SARS-CoV-2 transmission, natural disease progression, and vaccination behaviors of the population of Georgia, USA over a one-year period spanning approximately from January 2021 to December 2021. Our model was built and simulated using the EpiModel software platform.[15] This platform uses the statistical framework of temporal exponential random graph models (TERGMs) to estimate and simulate underlying contact patterns of the population. For this study, we built additional model components to permit for transmission and

tracking of a second SARS-CoV-2 strain, booster vaccinations, waning vaccine immunity, and reinfection. The model was run utilizing parameter sets that varied primary and booster vaccination administration rates. For all experimental scenarios, we calculated the number and percent of COVID-19 cases and hospitalizations averted relative to current vaccination rates for the general and over-65 population.

Baseline Model

Our model tracked 10,000 individuals (agents) who were assumed to represent the population of the state of Georgia, USA. Individual age was treated as a continuous variable with agents assigned at simulation start an initial age following a normal distribution (mean: 40, standard deviation: 21, range: 0, 99). Individuals were eligible to exit the model population at any time step through death with mortality rates varying by age. New individuals entered the model population exclusively through birth.

All modeled individuals were members of 3 distinct contact networks and transmission environments, representing the community, the workplace, and the home. For all three environments, the mean degree (average number of contacts per day) was held constant throughout each simulation at a value of 4, consistent with contact studies conducted during 2021.[16] This mean degree was assumed to represent the average community member and accounted for contact rate reductions influenced by the non-pharmaceutical interventions implemented throughout 2021. Each environment was represented with unique TERGMs to simulate contacts which occurred daily. These contacts were subsequently combined to create a multi-layer dynamic network used in the final simulations.

Each model scenario was initialized with 100 persons in the exposed (infected but not infectious) state. Each parameter set (scenario) consisted of 364 daily time steps, which we simulated 10 times each. Model parameters (Table 1) were drawn from existing literature and the Georgia Department of Public Health surveillance data.[17] For each scenario, parameters were not time varying and remained the same throughout all scenario-specific simulations.

Our model represented the natural history of COVID using a SEIRS framework (Figure 1). Individuals entered the model in one of two states: susceptible (Su) or exposed (E). Susceptible persons could be exposed at any time point after contacted an infectious person. Following exposure, individuals were stochastically assigned an asymptomatic pathway or symptomatic pathway with probability dependent on decade of age. If assigned to the symptomatic pathway, exposed individuals progressed through the

infectious pre-symptomatic (IpS) and infectious symptomatic (IS) states; if assigned the asymptomatic pathway, exposed individuals directly entered the asymptomatic state (A). In both cases, persons were considered infectious and, if encountering a susceptible (Su) individual, were able to transmit infection. If the infectious symptomatic (IS) state was reached, individuals could stochastically enter a hospitalized state (H) or the recovered state (R). Additionally, following reaching the asymptomatic (A) and hospitalized (H) states, individuals could progress to the recovered state (R). Once recovered, individuals stochastically reentered the susceptible population (Su) where they could be reinfected.

Multiple Strains

At model initiation, all exposed individuals were assigned one of the two SARS-CoV-2 strains. 90% of exposed individuals were assigned the primary strain; 10% of exposed individuals were assigned the secondary strain. If infected with the secondary strain, an increased relative infectivity, symptomatic case progression rate, and hospitalization rate was observed. Following a transmission event, newly infected individuals were recorded as having the same strain as the infected individual within the transmission event and exclusively transmitted that strain. In the case that an agent became reinfected, we assumed no immunity for either strain.

Vaccination Design

Individuals in the susceptible (Su) state were eligible for a first vaccination dose at any time point following the first time-step (day) of the simulation. Following receipt of the first vaccination dose, individuals were eligible to receive the second vaccination dose after 21 model days had elapsed. The booster vaccination dose could be received starting 150 days after the second vaccination dose was received. After each vaccination dose, 14, 7, and 7 days needed to elapse prior to the activation of vaccine provided preventative effects for the first, second, and third (booster) doses, respectively. Immunity waned starting after the onset of protective effects from the vaccine following an exponential decay pattern with a half-life of 80 days. Vaccination reduced the risk of initial infection, the risk of progression to symptomatic disease and the risk of eventual hospitalization. Vaccination efficacy was the same for both strains of SARS-CoV-2. Vaccination rates for both vaccination doses in the primary vaccination series and the booster vaccination dose were stratified by age groups. Age groups were based on currently available vaccination data with rates divided into five age-groups (under 5, 6–11, 12–17, 18–64, 65+) for the primary vaccination doses and into three age-groups (under 18, 19–50, 51+) for the booster dose.

Intervention Scenarios

A total of 16 scenarios were modeled. For the reference scenario, vaccination rates were assumed to be those currently observed in Georgia and were manually calibrated to the cross-sectional (as of April 2022) Georgia vaccine coverage levels stratified by age-group. Individuals, across age groups, were eligible to receive vaccination at all time points with lower rates used for the younger age-groups to account for the shorted amount of time for which the vaccine has been approved for younger persons. For the remaining scenarios, the calibrated rates of primary and booster vaccinations were multiplied by 1.3, 1.7, and 2.0 to represent relative increases in vaccination rates by 30%, 70%, and 100%. All four primary administration rates (reference, 30%, 70%, and 100% increase) were simulated in combination with all four potential booster administration rate scenarios (reference, 30%, 70%, and 100% increase), for a total of 16 scenarios. A complete list of vaccination scenarios is provided in Table 2.

Sensitivity Analyses

We conducted further exploratory analysis to better understand how the timing and magnitude of vaccination impacted disease incidence and hospitalizations. Additional scenarios included runs with lower primary vaccination and booster vaccination rates (relative to the reference rates), decreased mean number of contacts per day, and a delay in initiation of vaccination to day 90.

Model Output

For each model run, we tracked the prevalent and incident number of individuals in each state, including each vaccination state. For individuals over 65 years of age, total numbers of incident symptomatic infections, asymptomatic infections, and hospitalizations were recorded. Summary metrics in the form of cumulative infections, hospitalizations and vaccination were calculated for each individual run and each tested scenario. The number and percent of hospitalizations averted were calculated by comparing experimental scenarios against the mean reference scenario value and 50% simulation intervals were calculated by comparing the experimental scenario's lower and upper bounds with the mean reference scenario value.

RESULTS

Table 3 shows the vaccination coverage from the model at one year. Under current uptake rates for the primary and two booster vaccinations (reference scenario), the model produced an end-cross-sectional

coverage of 66.4% (50 SI: 66.1%, 66.5%), 52.6% (50 SI: 52.3%, 53.7%), and 31.7% (50 SI: 31.3%, 32.1%) for the first, second, and third doses, respectively, which closely reproduced observed vaccination coverage of Georgia in February 2022. As vaccination rates increased for both the primary and booster series of vaccination doses, the cumulative coverage increased, with the most ideal vaccination rates considered in this model yielding a coverage of 79.7% (50 SI: 79.4%, 79.9%), 73.9% (50 SI: 73.6%, 74.2%), and 62.6% (50 SI: 62.1%, 62.8%) for the first, second, and third doses, respectively.

For the reference scenario, total infections occurred at a rate of 16,679 cases per 10,000 PY (50 SI: 16669, 16705). Symptomatic infection occurred at a rate of 7,986 per 10,000 PY (50 SI: 7905, 8080) and made up 48.0% (50 SI: 47.5%, 48.4%) of total cases. Hospitalizations occurred at a rate of 1,138 per 10,000 PY (50 SI: 1060, 1202) (Table 4). As the primary vaccination rates increased, we observed a lower cumulative incidence (Figure 2). The number and percentage of symptomatic infections remained approximately the same regardless of vaccination rate (Table 5). Under current booster vaccination rates, 48.0%, 48.1%, 47.6%, and 47.5% of total infections were symptomatic with primary vaccination rates at current, 1.3-fold, 1.7-fold, and 2-fold higher than current rates, respectively (Table 5). High variability in the number of hospitalizations was seen for all scenarios (Table 6). For both infection and hospitalizations, changes in booster rates had minor impacts on the cumulative infection rate; meanwhile, changes in the primary vaccination rates had more substantial impacts (Figure 3). Under current booster vaccination rates, increasing the primary vaccination rates by 30%, 70%, and 100% above current rates led to the prevention of 1.2%, 1.5%, and 2.2% of infections and 4.2%, 2.9%, and 13.4% of hospitalizations, respectively (Table 4, Table 6). Alternatively, under current primary vaccination rates, increasing the booster vaccination rates by 30%, 70%, and 100% led to the prevention of 0.3%, 1.1%, and 0.1% of infections and 5.7%, 2.4%, and -2.7% of hospitalizations, respectively (Table 4, Table 6).

Table 7 shows the model output for the 65+ year-old population. In the reference scenario, total infections occurred at a rate of 16,484 (50 SI: 16358, 16678) cases per 10,000 PY. Symptomatic infection occurred at a rate of 12,115 per 10,000 PY (50 SI: 11,921, 12,071) and made up 73.7% (50 SI: 72.8%, 74.1%) of total cases. Hospitalizations occurred at a rate of 4,133 (50 SI: 3817, 4275) per 10,000 PY. The symptomatic infection and hospitalization rates for older subpopulations are higher than those for the general population (7,986 and 1,138 per 10,000 PY, respectively) and the overall infection rate was slightly lower than that of the general population (16,676 per 10,000 PY) under the same conditions. The

percentage of symptomatic infections was higher for the greater than 65 population with, for the reference scenario, 73.7% (50 SI: 72.8%, 74.1%) of infections being symptomatic compared to 48.0% (50 SI: 47.5%, 48.4%) observed with the general population under the same conditions. Like the general population, increasing the primary vaccination rate had a more pronounced impact on model output rates than increasing booster vaccination rate (Figure 4).

To further assess the impact of booster vaccination rates, we conducted additional scenarios with no booster and booster administration decreased by 90%, 75%, and 50% (relative to reference rates) under a consistent primary vaccination rate. Additional scenarios showed an approximately linear decrease in infection rate as booster rate scaled from no booster to current rates (Figure 5). Additional examination showed a time dependent effect with booster coverage reaching a high level prior to a small secondary peak under all scenarios at or above current administration rates (Figure 6). This contrasts with lower booster administration rates in which booster coverage does not reach high levels of coverage at a time prior to additional cases occurring or the end of the simulation (Figure 6).

DISCUSSION

In our study, we used a network-based mathematical model simulated over a one-year period to investigate how increasing the rates of COVID-19 primary and booster vaccination impacted disease incidence and hospitalization for the general population and elderly adults. Our model was unique in that it was tailored to the epidemic in the state of Georgia and accounted for contacts within three distinct transmission environments, waning vaccine-induced immunity, and multiple SARS-CoV-2 strains. We found that compared to increasing booster vaccination rates, increasing the primary vaccinations led to a greater decrease in the overall disease incidence, symptomatic disease incidence, and disease-specific hospitalizations. We additionally showed that the impact of increased booster vaccination rates was dependent on the timing of booster roll-out relative to subsequent waves of SARS-CoV-2 infections. These results suggest that, to maximize impact of booster vaccinations, there is a need to develop tools which can accurately forecast future waves of the epidemic.

Our model showed that primary and booster COVID-19 vaccinations are successful and play an important role in decreasing overall COVID-19 infections and hospitalizations. In all tested scenarios, we found that increased vaccination rates and cumulative vaccination coverage led to a lower general infection, symptomatic infection, and hospitalization rate for both the general and greater than 65 population. This result is consistent with other COVID-19 modeling studies, which found decreases in

cases, hospitalizations, and deaths following increased coverage of the primary[13,14] and booster[12] vaccination doses. Our result contrasts with the results of Gumel et al. who saw minor increases in deaths with increased vaccination rates[10]; however, because we did not track infection-specific deaths, this may have been an unobserved trend in our output data. In conjunction with existing studies, our study suggests that continued support for vaccination distribution programs is crucial to effectively mitigating the infections and hospitalizations caused by COVID-19 disease.

We found that any increase in the primary or booster vaccination rate led to decreases in the infection and hospitalization rates; however, the magnitude of impact for the booster dose was highly dependent on the scale-up timing relative to waves of disease. This result suggests that the timing of booster administration is crucial for optimal impact of boosters on disease outcomes. Our model showed that when booster vaccinations are set to current or above-current rates, little to no changes in overall infection rate was observed. Conversely, when booster vaccinations were set to less-than-current rates, there were notable differences in infection rates. When booster coverage was examined in conjunction with daily exposure rates (Figure 6), a potential explanation for this pattern emerged. For scenarios where booster rates were at current or above current levels, booster coverage surpassed the exposure rate just after the peak of the second wave of infection. Alternatively, at lower-than-current booster vaccination rates, there was variation in timing of booster coverage relative to peak of the second wave of infection. This pattern suggested that the timing of booster vaccine scale-up was an important consideration when looking for optimal impact on the pandemic. Further, this finding was consistent with previous work which looked at the impact of a delayed administration of the second dose of the primary series. In a study on this topic conducted by Moghadas et al., it was found that, when waning immunity was considered, a delayed-dose-strategy potentially led to an increase in cases because of secondary infection surges during the gap between doses.[18] Our model demonstrates that the timing of booster vaccination introduction relative to waves of disease is critical and shows that findings about the timing of the second vaccination dose can be applied to the booster vaccination dose.

Given current knowledge about COVID-19 vaccinations, their long-term immunity profile, and the timing of previous waves of infection, primary vaccination should be prioritized over booster vaccination. Our model showed that increasing the primary vaccination rate led to the greatest change in the number of infections and hospitalizations averted with a doubled rate leading to an aversion of 13.4% of infections. This result is in line with a previous study whose model predicted that 15% of mortality could be averted

if the primary vaccination rate was doubled.[10] Our study additionally showed that the booster vaccination dose has little effect on the number and percent of infections averted. As described previously, this was due to the timing of scale-up relative to disease waves. This result contrasts with a previous study that saw a large impact of the booster dose after introduction.[12] Our study provides an additional perspective and, until further evidence can be accrued about the impact of boosters, the majority of attention should continue to be placed on increasing primary vaccination rates.

Limitations

First, due to the presently limited information on the nature of waning vaccine-induced and natural-infection-induced immunity, our model was a simplification of actual immunological processes. For our model, we represented waning immunity as an exponential decay process based off the half-life of serum antibody levels post-vaccination. This was a potentially flawed methodology given the possibility for a T-cell mediated response to play a role in the disease response and to persist long after detectable antibody levels have cleared[19]. Given this assumption, our model likely overestimated disease frequency among vaccinated individuals because vaccine-derived protection likely has a longer half-life than observed through antibody studies. Our model also did not account for heterogeneity in duration of waning immunity which prior studies have shown to be caused by age, disease severity, and some underlying individual comorbidities[20–22]. This likely led to an underestimation of disease frequency given the age distribution, number of severe cases requiring hospitalization, and the number of comorbidities within the Georgia population[1,23]. Nonetheless, we believe that our model is still valid given that the factors are individual-based and likely have a negligible effect when looking at the overall population-level immunity profile. Second, our model was limited by the inclusion of only two SARS-CoV-2 strains and the limited treatment of those strains. The emergence of novel strains can change the landscape of the epidemic rapidly and without warning. While some previous models have accounted for this using complex evolutionary models paired with epidemic models[24], our study did not include such models and therefore was unable to reproduce the specific observed strain-specific dynamics and produces an underestimation of cases near the end of the simulation. Third, our model overestimated infection rates and, therefore, is limited in application to reality. This overestimation was most likely due to an assumption that the same mean degree can be used for all three transmission environments in the model. This assumption led to an abundance of network connections for each individual and more potential transmission events than would be expected. While inaccurate, this likely led to a more

extreme scenario of infection waves and allows for smaller, intervention-driven effects to be amplified for our study.

Conclusions

Overall, we found that, given our current understanding of COVID-19 immunity and pathogen evolution, energy should be focused on increasing administration rates for the primary vaccination series rather than on increasing administration rates of booster vaccinations. However, booster vaccinations have the potential to greatly impact the progression of the epidemic if used in a way and at a time where they are needed most. With waning immunity and novel strain emergence, there is an urgent need for a better understanding and development of forecasting tools so that future waves of the epidemic can be anticipated and prevented with vaccinations and other interventions.

TABLES AND FIGURES

Table 1. Model Parameters

Population Mixing Parameters	
Infection Probability	0.129[25]
Average Contacts per Day	4[16]
Proportion Symptomatic[26]	
0-9-year-olds	0.40
10-19-year-olds	0.25
20-29-year-olds	0.37
30–39-year-olds	0.42
40–49-year-olds	0.51
50-59 years old	0.59
60-69-year-olds	0.72
70+-year-olds	0.76
Proportion Hospitalized**	
0-9-year-olds	0.033
10-19-year-olds	0.017
20-29-year-olds	0.030
30-39-year-olds	0.059
40-49-year-olds	0.092
50-59-year-olds	0.014
60-69-year-olds	0.014
70+-year-olds	0.29
Natural History	
Time-from-Exposed-to-Asymptomatic (days)	5.2[27]
Time-from-Asymptomatic-to-Recovered (days)	7.8[28]
Time-from-Exposed-Infectious-to-Pre-Symptomatic (days)	5.5[27]
Time-from-Infectious Pre-Symptomatic-to-Infectious Symptomatic (days)	1.4[27]
Time-from-Infectious Symptomatic-to-Recovered (days)	8.6[29]*
Time-from-Infectious Symptomatic-to-Hospitalized (days)	4[30]
Time-from-Hospitalized-to-Recovered (days)	4**
Time-from-Recovered-to-Susceptible (days)	390[31]+
Infection Probability Asymptomatic Relative Risk	0.27[32]
Testing	
PCR Sensitivity	0.8[33]
Diagnosis Rate – Symptomatic	0.1[34]
Diagnosis Rate – Other	0.01[34]
Vaccination	
Time Vaccination Starts	1 (assumed)
Base First Vaccination Rate (days)	
0-4-year-olds	0[1,35–38] ++
5-11-year-olds	0.001[1,35–38] ++
12-17-year-olds	0.02[1,35–38] ++
18-65-year-olds	0.11[1,35–38] ++
65+-year-olds	0.43[1,35–38] ++

Table 1. **Model Parameters (cont.)**

Vaccination (cont.)	
Base Second Vaccination Rate (days)	
0-4-year-olds	0[1,35–38]++
5-11-year-olds	0.0005[1,35–38]++
12-17-year-olds	0.0006[1,35–38]++
18-65-year-olds	0.008[1,35–38]++
65+-year-olds	0.0075[1,35–38]++
Base Third Vaccination Rate (days)	
0-17-year-olds	0[1,38–40]++
18-49-year-olds	0.01[1,38–40]++
50-64-year-olds	0.05[1,38–40]++
65+-year-olds	0.043[1,38–40]++
Half-Life of Vaccine Immunity (days)	80[5]
Interval between 1st and 2nd Vaccine (days)	21[3]
Interval between 2nd and 3rd Vaccine (days)	150[3(p19)]
Time-to-Immunity – 1st Vaccine (days)	14[41]
Time-to-Immunity – 2nd Vaccine (days)	7[41]
Time-to-Immunity – 3rd Vaccine (days)	7[42]
Peak Relative Risk of Infection – 1st Vaccine	0.324[43]
Peak Relative Risk of Infection – 2nd Vaccine	0.112[43]
Peak Relative Risk of Infection – 3rd Vaccine	0.12[42]++
Peak Relative Risk of Symptomatic Disease – 1st Vaccine	0.40[4]
Peak Relative Risk of Symptomatic Disease – 2nd Vaccine	0.09[4]
Peak Relative Risk of Symptomatic Disease – 3rd Vaccine	0.09[42]++
Peak Relative Risk of Hospitalization – 1st Vaccine	0.30[4]
Peak Relative Risk of Hospitalization – 2nd Vaccine	0.02[4]
Peak Relative Risk of Hospitalization – 3rd Vaccine	0.07[42]++
Population Demographics	
Arrival Rate (per day)	0.00016[44]
Arrival Age (years-old)	0
Mortality Rate (by days)	Stratified by years-old [45]
Mortality Disease Multiplier	180[34]
Additional Strain	
Prevalence of Strain 2 at Initialization (per 10,000 individuals)	0.001[46]
Strain 2 Infectivity Multiplier	2.01[25]
Strain 2 Symptomatic Progression Multiplier	1.04[47]*
Strain 2 Hospitalization Multiplier	2.26[48]

*calculated value **derived from primary data (all of GA March 2020 – March 2021) ***infection probability intervention, act rate intervention, act rate diagnosis intervention, and act rate symptomatic intervention currently set at start time infinity. +this estimate is possibly on the lower end; 390 days was the upper limit of the period assessed ++manually calibrated

Table 2. **Model Scenarios**

		Booster Vaccination Rate			
		Current	Current + 30%	Current + 70%	Current + 100%
Primary Vaccination Rate	Current	Scenario 1	Scenario 2	Scenario 3	Scenario 4
	Current + 30%	Scenario 5	Scenario 6	Scenario 7	Scenario 8
	Current + 70%	Scenario 9	Scenario 10	Scenario 11	Scenario 12
	Current + 100%	Scenario 13	Scenario 14	Scenario 15	Scenario 16

Table 3. Proportion of Population Vaccinated at End-of-Simulation, General Population. *This table shows the proportion of the general population that has received the first, second, and booster doses after one year of the simulation. For each combination of primary and booster rates, 10 simulations were run.*

Administration Rate		Percent Coverage (50% Simulation Intervals)		
Primary Vaccination Rates	Booster Vaccination Rates	First Dose	Second Dose	Third (Booster) Dose
Current	Current	66.4 (66.1,66.5)	52.6 (52.3,53.7)	31.7 (31.3,32.1)
	Current + 30%	66.6 (66.0,67.1)	52.8 (52.3,53.4)	33.5 (33.0,34.1)
	Current + 70%	66.7 (65.8,66.8)	52.8 (52.1,53.2)	34.6 (34.1,35.1)
	Current + 100%	66.9 (66.6,67.3)	53.0 (52.3,53.6)	35.5 (35.0,35.7)
Current + 30%	Current	72.1 (71.8,72.6)	62.1 (61.3,62.8)	41.6 (40.9,42.1)
	Current + 30%	72.3 (71.8,73.0)	62.4 (61.7,63.0)	43.8 (43.1,44.5)
	Current + 70%	72.4 (71.7,72.9)	62.3 (61.7,62.7)	45.2 (44.7,45.8)
	Current + 100%	72.1 (71.8,72.4)	62.2 (61.7,62.5)	45.8 (45.2,46.4)
Current + 70%	Current	77.1 (76.6,77.4)	70.1 (69.5,70.5)	52.1 (51.6,52.5)
	Current + 30%	77.2 (76.5,77.7)	70.1 (69.5,70.7)	54.5 (54.0,55.2)
	Current + 70%	77.1 (76.7,77.2)	70.1 (69.6,70.6)	55.9 (55.3,56.2)
	Current + 100%	76.9 (76.6,77.2)	69.9 (69.5,70.1)	56.4 (56.1,56.6)
Current + 100%	Current	79.6 (79.4,79.8)	73.8 (73.6,74.1)	58.2 (57.8,58.8)
	Current + 30%	80.0 (79.8,80.2)	74.4 (73.9,74.6)	60.9 (60.6,61.5)
	Current + 70%	79.9 (79.7,80.2)	74.3 (73.8,74.7)	62.5 (61.9,63.1)
	Current + 100%	79.7 (79.4,79.9)	73.9 (73.6,74.2)	62.6 (62.1,62.8)

Table 4. Infection Rate at End-of-Simulation, General Population. *This table shows the cumulative infection rate of the general population after one year of the simulation. For each combination of primary and booster rates, 10 simulations were run.*

Administration Rate		Outcome (50% Simulation Interval)		
Primary Vaccinations	Booster Vaccination	Infection Rate (per 10,000 PY)	Number of Infections Averted (per 10,000 PY)	Percent Infections Averted
Current rates	Current rates (ref)	16676 (16669, 16705)	--	--
	Current + 30%	16624 (16522, 16724)	52.5 (-48.3, 154.6)	0.32 (-0.2, 0.0)
	Current + 70%	16490 (16551, 16698)	186.3 (-21.6, 125.4)	1.1 (-0.3, 0.9)
	Current + 100%	16652 (16554, 16692)	24.1 (-15.9, 121.8)	0.14 (-0.1, 0.8)
Current + 30%	Current	16476 (16366, 16609)	200.1 (66.9, 310.6)	1.2 (0.4, 1.9)
	Current + 30%	16484 (16396, 16607)	192.6 (69.0, 280.1)	1.2 (0.4, 1.7)
	Current + 70%	16524 (16482, 16579)	152.1 (97.6, 193.6)	0.91 (0.6, 1.2)
	Current + 100%	16544 (16506, 16580)	132.4 (96.2, 170.2)	0.79 (0.6, 1.0)
Current + 70%	Current	16418 (16360, 16504)	258.2 (172.4, 316.0)	1.5 (1.0, 1.9)
	Current + 30%	16226 (16322, 16447)	450.1 (229.1, 353.4)	2.7 (1.4, 2.1)
	Current + 70%	16331 (16201, 16404)	345.2 (272.5, 474.9)	2.1 (1.6, 2.8)
	Current + 100%	16394 (16320, 16508)	282.6 (168.6, 356.4)	1.7 (1.0, 2.1)
Current + 100%	Current	16310 (16225, 16407)	365.9 (268.8, 451.0)	2.2 (1.6, 2.7)
	Current + 30%	16295 (16175, 16426)	381.4 (249.7, 501.3)	2.3 (1.5, 3.0)
	Current + 70%	16333 (16276, 16404)	343.1 (272.3, 400.3)	2.1 (1.6, 2.4)
	Current + 100%	16258 (16159, 16323)	418.0 (352.7, 517.1)	2.5 (2.1, 3.1)

Table 5. Symptomatic Infection Rate at End-of-Simulation, General Population. *This table shows the cumulative symptomatic infection rate of the general population after one year of the simulation. For each combination of primary and booster rates, 10 simulations were run.*

Administration Rate		Outcome (50% Simulation Interval)			
Primary Vaccinations	Booster Vaccination	Symptomatic Infection Rate (per 10,000 PY)	Percent Total Infections	Number Symptomatic Infections Averted (per 10,000 PY)	Percent Symptomatic Infections Averted
Current	Current (ref)	7986 (7905,8080)	48.0 (47.5,48.4)	--	--
	Current + 30%	7972 (7903,8022)	48.1 (47.8,48.3)	14.4 (-26.4,83.0)	0.2 (-0.5,1.0)
	Current + 70%	7865 (7875,7931)	47.8 (47.5,48.1)	120.7 (55.5,111.4)	1.5 (0.7,1.4)
	Current + 100%	7964 (7868,8032)	48.0 (47.6,48.2)	22.4 (-46.1,117.6)	0.28 (-0.6,1.5)
Current + 30%	Current	7902 (7832,7941)	48.1 (47.5,48.5)	84.3 (45.0,154.2)	1.1 (0.6,1.9)
	Current + 30%	7809 (7766,7857)	47.5 (47.1,47.8)	177.5 (129.1,219.7)	2.2 (1.6,2.8)
	Current + 70%	7877 (7789,8010)	47.8 (47.5,48.3)	109.3 (-23.7,196.9)	1.4 (-0.3,2.5)
	Current + 100%	7889 (7798,7934)	47.8 (47.3,48.2)	97.1 (51.9,188.5)	1.2 (0.7,2.4)
Current + 70%	Current	7786 (7724,7886)	47.6 (47.1,47.9)	199.8 (100.5,261.8)	2.5 (1.3,3.3)
	Current + 30%	7660 (7664,7760)	47.3 (47.1,47.5)	325.7 (226.3,322.0)	4.1 (2.8,4.0)
	Current + 70%	7803 (7701,7898)	47.9 (47.5,48.2)	183.2 (87.9,284.6)	2.3 (1.1,3.6)
	Current + 100%	7844 (7724,7962)	48.0 (47.4,48.4)	142.2 (24.3,262.0)	1.8 (0.3,3.3)
Current + 100%	Current	7730 (7614,7818)	47.5 (47.0,47.8)	256.0 (168.5,371.9)	3.2 (2.1,4.7)
	Current + 30%	7674 (7564,7817)	47.2 (47.0,47.6)	312.4 (168.7,421.7)	3.9 (2.1,5.3)
	Current + 70%	7741 (7688,7847)	47.5 (47.0,48.1)	244.8 (139.5,298.2)	3.1 (1.7,3.7)
	Current + 100%	7695 (7621,7788)	47.5 (47.0,48.9)	291.5 (197.8,364.7)	3.7 (2.5,4.6)

Table 6. Hospitalization Rate at End-of-Simulation, General Population. *This table shows the cumulative hospitalization rate of the general population after one year of the simulation. For each combination of primary and booster rates, 10 simulations were run.*

Administration Rate		Outcome (50% Simulation Interval)		
Primary Vaccinations	Booster Vaccination	Hospitalization Rate (per 10,000 PY)	Number of Hospitalizations Averted (per 10,000 PY)	Percent Hospitalizations Averted
Current	Current (ref)	1138 (1060, 1202)	--	--
	Current + 30%	1073 (1023, 1090)	65.0 (48.7, 115.3)	5.7 (4.3, 10.1)
	Current + 70%	1111 (943, 1218)	27.1 (-79.3, 195.3)	2.4 (-7.0, 17.2)
	Current + 100%	1169 (1051, 1289)	-30.4 (-150.3, 87.9)	-2.7 (-13.2, 7.7)
Current + 30%	Current	1091 (925, 1217)	47.6 (-78.4, 213.5)	4.2 (-6.9, 18.8)
	Current + 30%	1071 (948, 1217)	67.1 (-78.9, 190.5)	5.9 (-6.9, 16.7)
	Current + 70%	1050 (998, 1115)	88.9 (23.2, 140.0)	7.8 (2.0, 12.3)
	Current + 100%	1064 (951, 1213)	74.2 (-75.0, 187.2)	6.5 (-6.6, 16.4)
Current + 70%	Current	1106 (1039, 1202)	32.8 (-63.8, 99.8)	2.9 (-5.6, 8.8)
	Current + 30%	964 (918, 1022)	174.6 (116.2, 220.6)	15.3 (10.2, 19.4)
	Current + 70%	1030 (914, 1149)	109.0 (-10.6, 224.4)	9.6 (-0.9, 19.7)
	Current + 100%	1064 (1021, 1092)	74.4 (46.2, 117.6)	6.5 (4.1, 10.3)
Current + 100%	Current	986 (867, 1108)	152.1 (30.6, 271.6)	13.4 (2.7, 23.9)
	Current + 30%	940 (886, 1021)	198.4 (118.0, 252.9)	17.4 (10.4, 23.9)
	Current + 70%	985 (918, 1040)	153.3 (98.0, 220.4)	13.5 (8.6, 19.4)
	Current + 100%	987 (924, 1005)	151.7 (133.5, 214.8)	13.3 (11.7, 18.9)

Table 7. Infection, Symptomatic Infection and Hospitalization Rates at End-of-Model-Simulation, 65 and Over Population. *This table shows the cumulative infection, symptomatic infection, and hospitalization rate of the elderly population after one year of the simulation. For each combination of primary and booster rates, 10 simulations were run.*

Administration Rate		Outcome (50% Simulation Interval)		
Primary Vaccinations	Booster Vaccination	Infection Rate (per 10,000 PY)	Symptomatic Infection Rate (per 10,000 PY)	Hospitalization Rate (per 10,000 PY)
Current	Current	16484 (16358, 16678)	12115 (11921, 12331)	4133 (3817, 4275)
	Current + 30%	16286 (16120, 16472)	11784 (11507, 12071)	3576 (3357, 3718)
	Current + 70%	16230 (16134, 16476)	11788 (11584, 11974)	3841 (3344, 4416)
	Current + 100%	16230 (16095, 16367)	11766 (11554, 12016)	3922 (3634, 4191)
Current + 30%	Current	16156 (15997, 16367)	11765 (11322, 12142)	3803 (3065, 4276)
	Current + 30%	16146 (16014, 16226)	11556 (11431, 11621)	3607 (3203, 4193)
	Current + 70%	16326 (16133, 16539)	11789 (11530, 11957)	3513 (3226, 3854)
	Current + 100%	16313 (16180, 16423)	11712 (11252, 12045)	3580 (3202, 4084)
Current + 70%	Current	16331 (16217, 16506)	11660 (11573, 12002)	3757 (3430, 4109)
	Current + 30%	15968 (15837, 16295)	11358 (10997, 11679)	3205 (2888, 3479)
	Current + 70%	16126 (16010, 16234)	11591 (11378, 11875)	3283 (2886, 3908)
	Current + 100%	16271 (16123, 16363)	11762 (11659, 11962)	3497 (3369, 3721)
Current + 100%	Current	16131 (16150, 16201)	11438 (11275, 11610)	3328 (2965, 3693)
	Current + 30%	16028 (15823, 16220)	11277 (10964, 11595)	3094 (2731, 3486)
	Current + 70%	16204 (16017, 16323)	11527 (11244, 11951)	3297 (2980, 3463)
	Current + 100%	16149 (15928, 16288)	11526 (11190, 11780)	3354 (3010, 3557)

Figure 1. **Model Flow Diagram.** *The model schematic represents the pathway through which all individuals progress. Individuals enter the model as either susceptible (Su) or exposed (E). Once exposed (E), individuals are assigned either the symptomatic or asymptomatic pathway. If assigned the symptomatic pathway, individuals progress through the infectious pre-symptomatic (IpS) and infectious symptomatic (IS) states; if assigned the asymptomatic pathway, individuals simply enter the asymptomatic state (A) and progress to the recovered state (R). If the infectious symptomatic state is reached, individuals will potentially enter the hospitalized state (H) and recovered state (R) or progress immediately to the recovered state (R). Once recovered, individuals stochastically re-enter the susceptible state (Su) where they become re-eligible to repeat the entire infection cascade.*

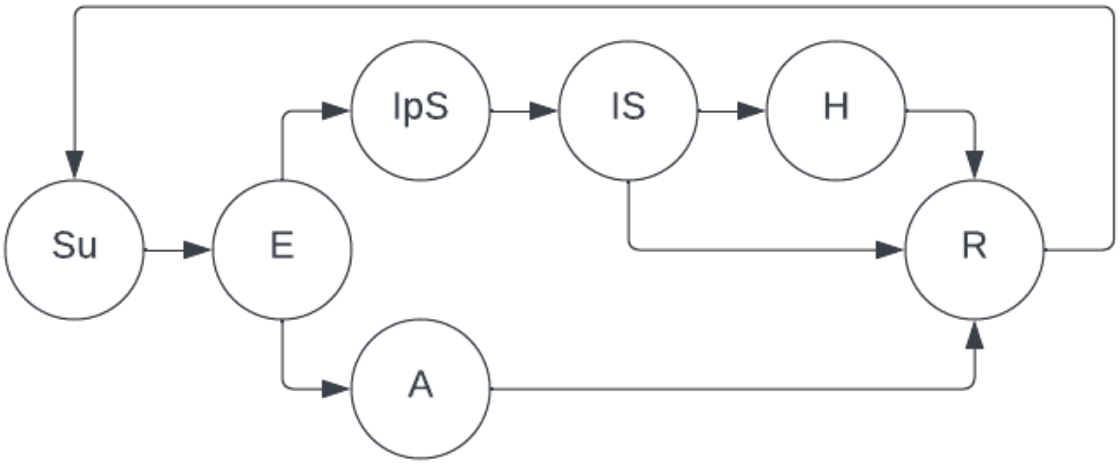


Figure 2. Model Output – Median Rates Across All Scenarios, General Population. *Infection, symptomatic infection, and hospitalizations rates calculated for each individual simulation using the same parameter sets and median value was taken thereafter for use within plots. Outcomes and person-time contributed by all individuals in model at each time step.*

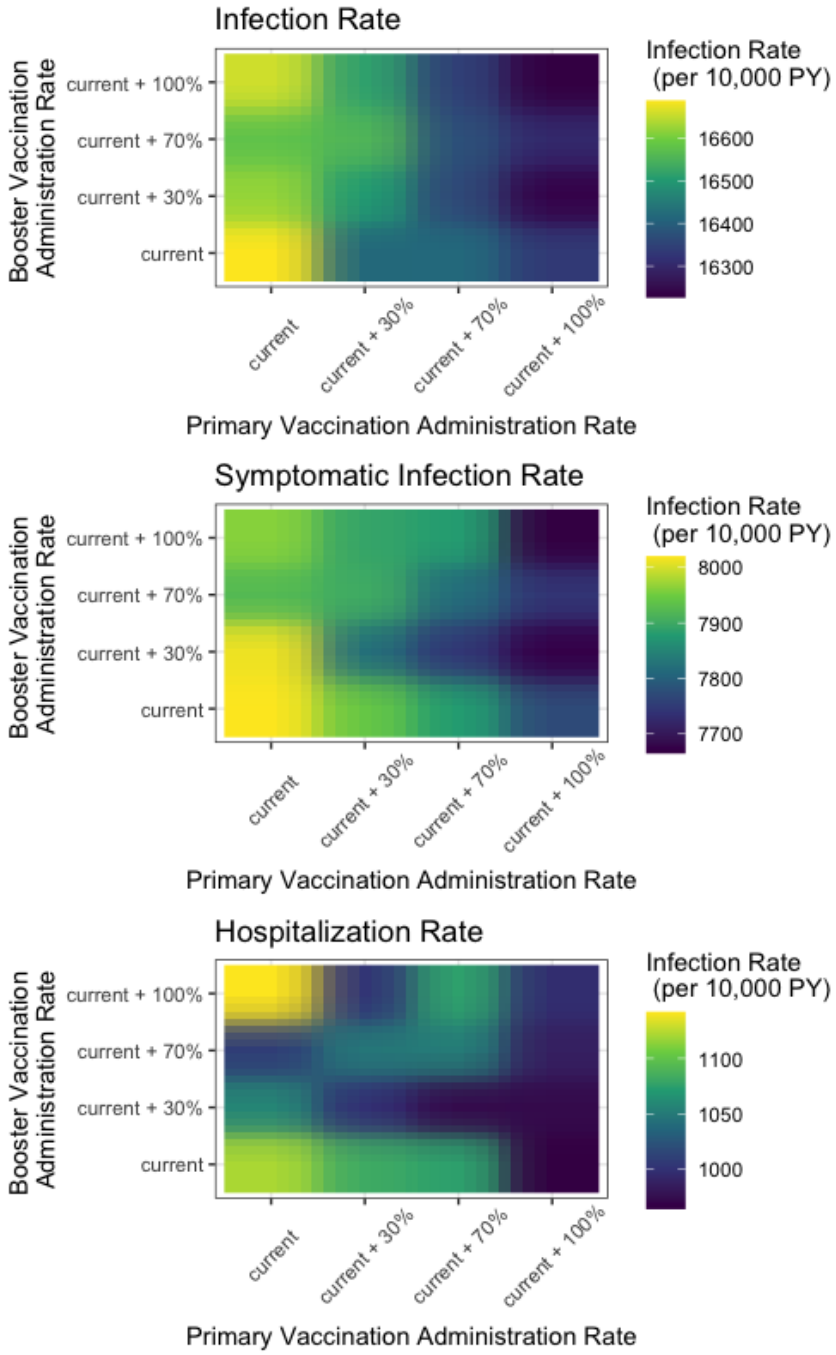


Figure 3. Cumulative Incidence per 10,000 PY, All Model Scenarios. *Cumulative infection rate per 10,000 person-years across all scenarios run. Plots were trimmed and excluded some lower outlier values.*

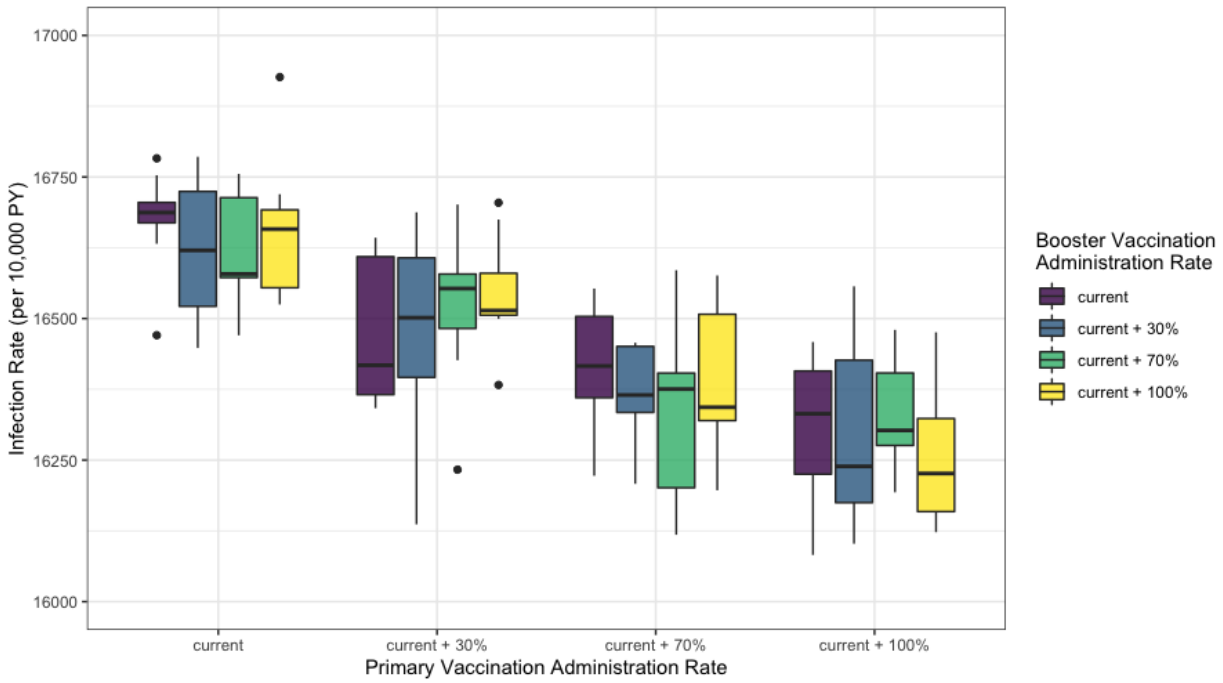


Figure 4. Model Output – Median Rates Across All Scenarios, Greater than 65. *Infection, symptomatic infection, and hospitalizations rates calculated for each individual simulation using the same parameter sets and median value was taken thereafter for use within plots. Population was restricted to individuals greater than sixty-five at time of event of interest and person-time contributed was exclusively those greater than sixty-five.*

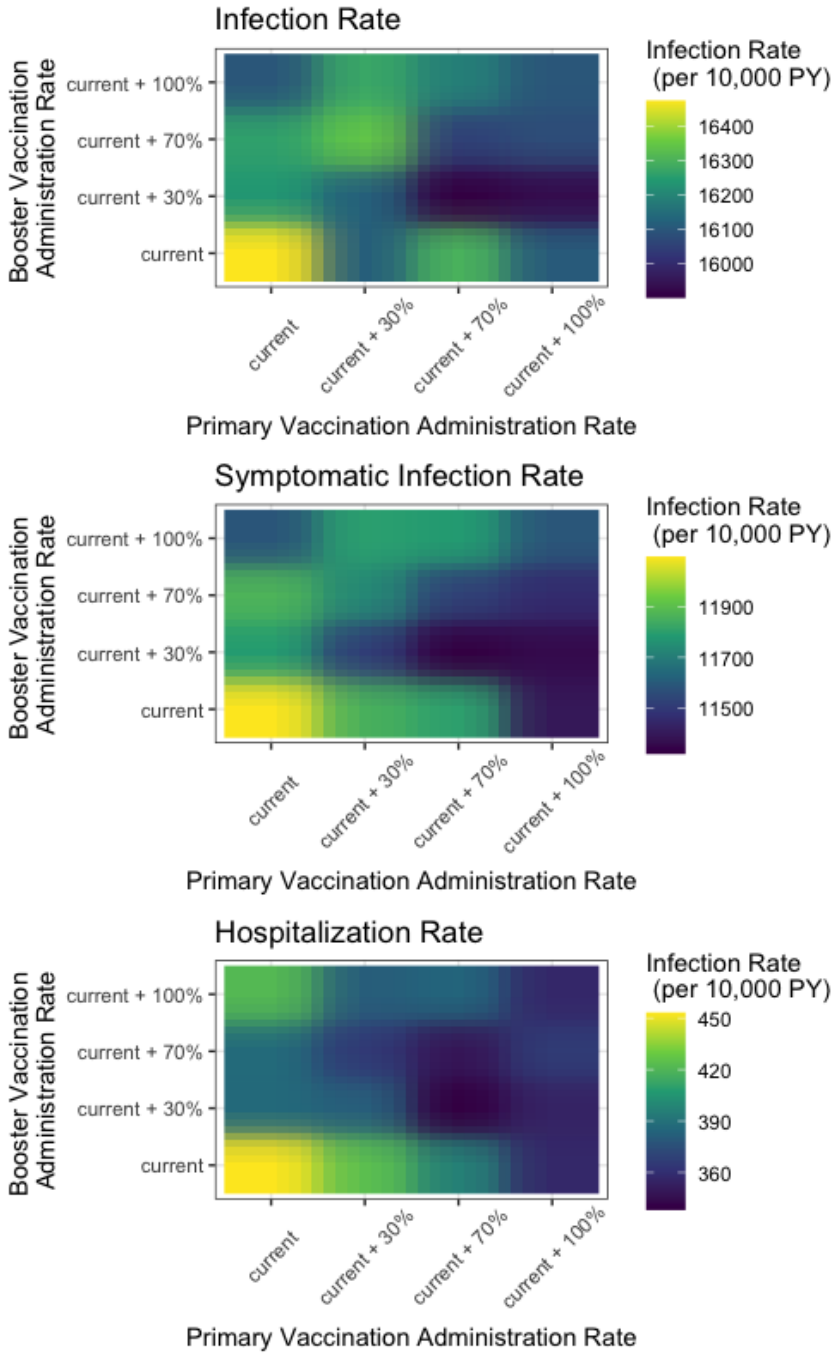


Figure 5. Cumulative Infection Rate Under Current Primary Vaccination Administration Rates.
Cumulative infection rate per 10,000 person-years across scenarios run with current primary vaccination dose administration rates and multiple booster administration rates. Plots were trimmed and excluded some lower outlier values.

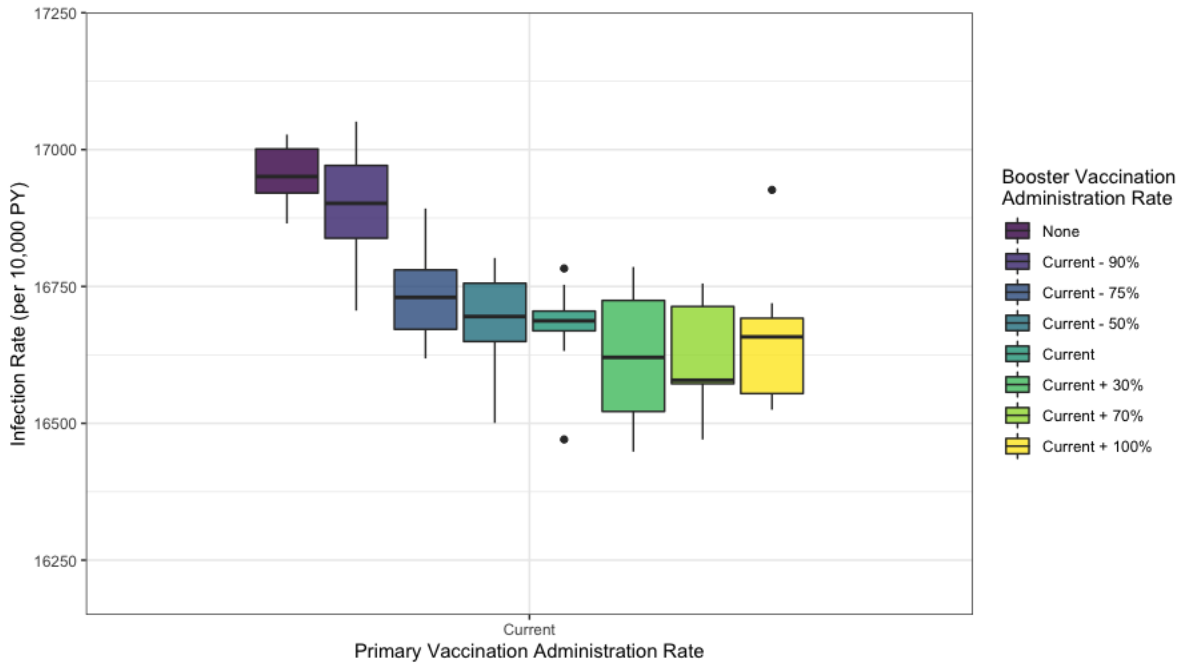
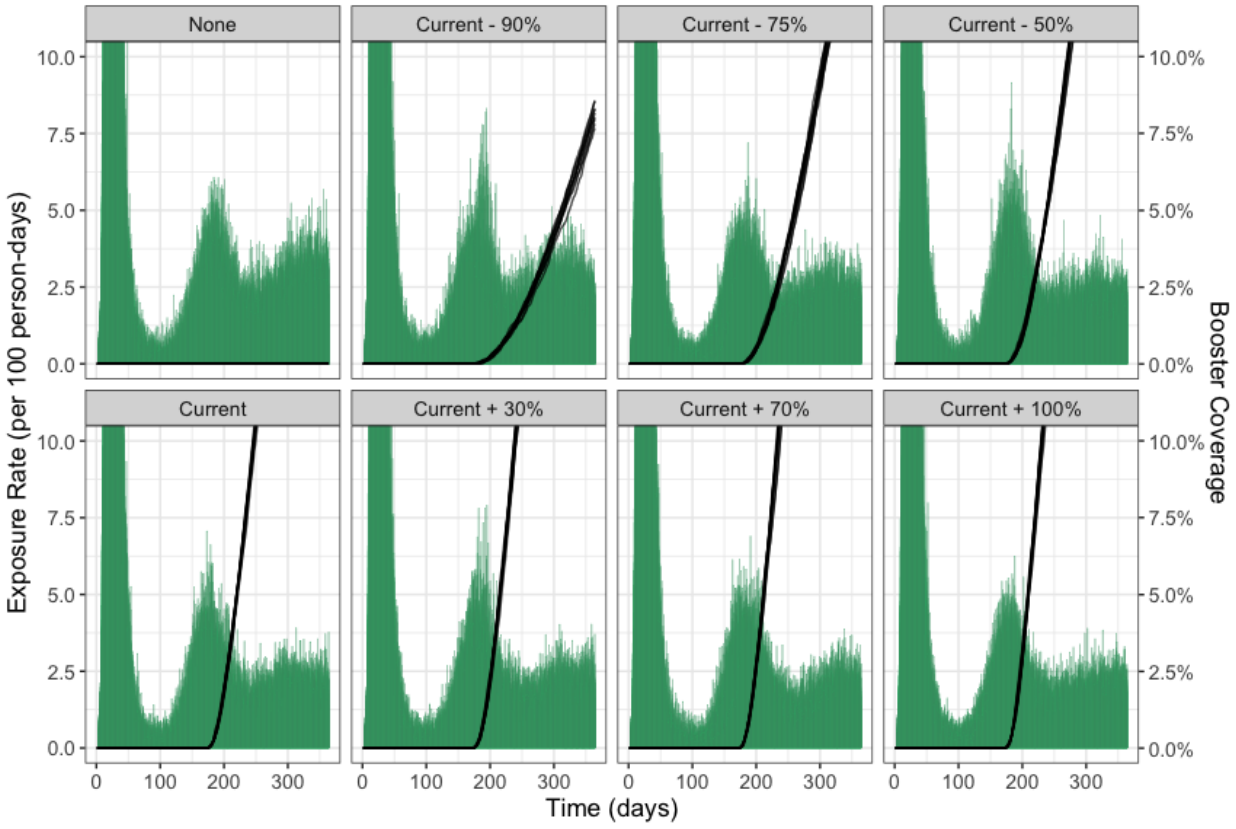


Figure 6. Exposure Rate Prevalence and Booster Prevalence Over Time. *Simulated daily exposure rate is represented by green bars and the cumulative booster vaccination dose is represented by the black line. All scenarios were run using currently observed primary vaccination dose administration rates with varying booster vaccination dose administration rates. All simulations run for each scenario (parameter set) is shown in each plot.*



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