Appendix S1

Estimating the Impact of Vaccination on Reducing COVID-19 Burden in the United States: December 2020 to March 2022

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This Online Supplementary Document provides details of the model structure and parameterizations for the results reported.

Model structure

We employed our previous agent-based model of COVID-19 transmission[1] and expanded its dynamic structure to account for waning of naturally-acquired or vaccine-elicited immunity, as well as booster vaccination. The model implemented natural history of COVID-19 with epidemiological classes of individuals as susceptible; latently infected (not yet infectious); asymptomatic (and infectious); pre-symptomatic (and infectious); symptomatic (and infectious) with either mild or severe illness; recovered; and dead.

The population was stratified into seven age groups of 0 to 4, 5 to 11, 12-17, 18 to 49, 50 to 64, 65 to 79, and 80+ years based on the US demographics,[2] and incorporated age-specific risk of hospitalizations and deaths, contact patterns. Daily contacts between individuals were sampled from age-specific negative-binomial distributions with parameters that accounted for the effect of interventions such as isolation of symptomatic cases (Table S1).

Table S1. Mixing patterns and the daily number of contacts derived from empirical observations.[3,4] Daily numbers of contacts were sampled from negative binomial distributions for different scenarios.

Age group	Proportion of contacts between age groups					No. of daily contacts Mean (SD)	No. of daily contacts for isolated individuals Mean (SD)
	0-4	5-19	20-49	50-65	65+		
0-4	0.24	0.18	0.42	0.11	0.05	10.21 (7.65)	2.86 (2.14)
5-19	0.02	0.59	0.28	0.08	0.03	16.79 (11.72)	4.70 (3.28)
20-49	0.03	0.16	0.62	0.14	0.05	13.79 (10.50)	3.86 (2.95)
50-65	0.02	0.11	0.48	0.27	0.12	11.26 (9.59)	3.15 (2.66)

65+	0.02	0.11	0.40	0.22	0.25	8.00 (6.96)	2.24 (1.95)

SARS-CoV-2 variants

We considered the spread of four variants, including Iota (B.1.526), Alpha (B.1.1.7), Delta (B.1.617.2), and Omicron (B.1.1.529), in addition to the original Wuhan-I SARS-CoV-2 strain. All variants were introduced in the model at a date corresponding to twice the average duration of their incubation period before the date of identification reported in the GISAID database.[5] Specifically, the Iota variant was introduced on October 25, 2020, with an estimated 35% higher transmissibility compared with the original Wuhan-I strain.[6] We then introduced the Alpha variant on November 29, 2020, with a 50% higher transmissibility compared to the original strain.[7,8] The Delta variant was inserted on February 10, 2021, with an elevated transmissibility of 30% compared with the Alpha variant.[9,10] Finally, we introduced the Omicron variant on November 15, 2021, with a 35% higher transmissibility of Omicron compared to Delta.[11]

Distribution of disease stages and infectiousness

The incubation period for each infected individual was sampled from a log-normal distribution with a mean of 5.2 days.[12] A proportion of infected individuals progressed to a pre-symptomatic stage[13,14] with an infectious period which was sampled from a Gamma distribution with a mean of 2.3 days.[13,15] The symptomatic disease following the pre-symptomatic stage had an average infectious period of 3.2 days, which was also sampled from a Gamma distribution.[13,15] The infectious period of individuals who remained asymptomatic was sampled from a Gamma distribution with a mean of 5 days.[13,16]

Infectiousness was assumed to be highest during the pre-symptomatic stage. The transmissibilities during asymptomatic, mild symptomatic, and severe symptomatic stages were 26%, 44%, and 89%, respectively, relative to the pre-symptomatic stage.[15,17,18]

Disease outcomes

We assumed that asymptomatic and mild symptomatic individuals recover without hospitalization. Self-isolation was implemented to start within 24 hours of symptom onset for all symptomatic individuals, reducing their number of daily contacts by an average of 74% (Table S1). Severely ill individuals due to primary infection were hospitalized within 2-5 days of symptom onset, [19,20] and therefore effectively excluded from the chain of disease transmission. The model was parameterized with rates of intensive care unit (ICU) and non-ICU admissions. [21–23] The risk of hospitalization with the Delta variant was assumed to be 2.26 times higher than that due to infection with Alpha.[23] We considered a 75.2% (95% confidence interval: 72.0% – 77.0%) risk reduction of hospitalization for severe disease due to infection by Omicron compared to Delta.[24,25] The risk of ICU admissions was reduced by 38.1% in severe patients of Omicron compared to those infected with Delta.[26]

Vaccination and immune dynamics

The number of vaccine doses per day and distribution of the first and second doses were parameterized with reported vaccination data in different age groups.[27] The booster eligibility

was set to a 6-month period elapsed since the last dose of vaccine in fully vaccinated individuals. On January 3, 2022, this timeline was reduced to 5 months.[28]

We performed a literature review to derive the efficacy estimates following each dose of vaccine against infection, symptomatic disease, and severe disease for all variants in the model. Estimates of vaccine effectiveness for different SARS-CoV-2 variants in the model are summarized in Tables S2, S3. We assumed the same degree of reduced protection in naturallyacquired immunity as vaccine-induced immunity (without booster) against Omicron.

To implement the waning immunity after vaccination, we fitted a Gaussian model to estimates of vaccine effectiveness over time,[29–32] and determined the temporal relative effectiveness curves (Figure S2). The relative effectiveness was used as a multiplicative factor in the efficacy of vaccines after the second dose to determine the temporal immunity of individuals against infection and severe disease for each variant. We applied the same relative effectiveness for waning of naturally-acquired immunity.

Table S2. Estimated vaccine efficacies (%) and their 95% confidence intervals from published studies for Pfizer-BioNTech vaccines. Booster dose restored or increased the protection efficacy of two doses.

Vaccine efficacy (%)	**Timelines**		**Reference**
Original strain and Iota variant	1 week after the second dose	1 week after the booster dose	[33,34]
Infection	86.1 (82.4, 89.1)	86.1 (82.4, 89.1)	
Symptomatic disease	93.0 (88.0, 95.0)	93.0 (88.0, 95.0)	
Severe disease	98.0 (90.0, 99.0)	98.0 (90.0, 99.0)	
Gamma variant			[34,35]
Infection	75 (70.5, 78.9)	75 (70.5, 78.9)	
Symptomatic disease	82.0 (65.0, 91.0)	82.0 (65.0, 91.0)	
Severe disease	96.0 (68.0, 99.0)	96.0 (68.0, 99.0)	
Alpha variant			[34,35]

Infection	89.5 (85.9, 92.3)	89.5 (85.9, 92.3)	
Symptomatic disease	89.0 (87.0, 90.0)	89.0 (87.0, 90.0)	
Severe disease	96.0 (94.0, 97.0)	96.0 (94.0, 97.0)	
Delta variant			34,36
Infection	85.0 (79.0, 90.0)	85.0 (79.0, 90.0)	
Symptomatic disease	92.0 (90.0, 94.0)	92.0 (90.0, 94.0)	
Severe disease	97.0 (96.0, 98.0)	97.0 (96.0, 98.0)	
Omicron variant			37,38
Infection	33.0 (31.0, 35.0)	76.0 (72.0, 79.0)	
Symptomatic disease	69 (62.0, 75.0)	82.0 (79.0, 84.0)	
Severe disease	81.0 (65.0, 90.0)	90.0 (80.0, 94.0)	

Table S3. Estimated vaccine efficacies (%) and their 95% confidence intervals from published studies for Moderna vaccines. Booster dose restored or increased the protection efficacy of two doses.

Vaccine efficacy (%)	**Timelines**		**Reference**
Original strain and Iota variant	1 week after the second dose	1 week after the booster dose	34,39

Infection	96.4 (91.2, 98.5)	96.4 (91.2, 98.5)	
Symptomatic disease	96.0 (85.0, 99.0)	96.0 (85.0, 99.0)	
Severe disease	97.0 (78.0, 100.0)	97.0 (78.0, 100.0)	
Gamma variant			34,40
Infection	77.0 (63.0, 86.0)	77.0 (63.0, 86.0)	
Symptomatic disease	89.0 (21.0, 98.0)	89.0 (21.0, 98.0)	
Severe disease	95.0 (63, 99)	95.0 (63, 99)	
Alpha variant			34,39
Infection	98.4 (96.9, 99.1)	98.4 (96.9, 99.1)	
Symptomatic disease	92.0 (88.0, 95.0)	92.0 (88.0, 95.0)	
Severe disease	95.0 (92.0, 97.0)	95.0 (92.0, 97.0)	
Delta variant			34,41
Infection	86.7 (84.3, 88.7)	94.0 (92.3, 95.4)	
Symptomatic disease	95.0 (91.0, 97.0)	95.0 (91.0, 97.0)	
Severe disease	98.0 (93.0, 99.0)	98.0 (93.0, 99.0)	
Omicron variant			41,42

Infection	42.8 (33.8, 50.7)	67.7 (65.5, 69.7)	
Symptomatic disease	69 (62.0, 75.0)	82.0 (79.0, 84.0)	
Severe disease	81.0 (65.0, 90.0)	90.0 (80.0, 94.0)	

Direct healthcare costs

We used estimates of COVID-19 symptomatic infections and hospitalizations from the projections of our agent-based model to calculate direct costs associated with COVID-19 illness and hospitalizations (Table S4). Costs of health outcomes were stratified into outpatient visits for symptomatic infection, hospitalizations with or without intensive care, emergency medical services (EMS) calls, and emergency department (ED) visits. We assumed that, on average, 50% of symptomatic, non-hospitalized patients seek outpatient care. We also assumed that each non-hospitalized patient with severe COVID-19 accounts for one ED visit during the course of illness. We calculated the total number of EMS calls to be 2.5 times the number of hospitalized patients.[43]

Table S4. Direct costs (in 2021 US dollars) associated with health outcomes due to COVID-19 illness.

Outcomes of COVID-19 illness	Estimated costs	Range	Reference
Outpatient treatment per visit	$893	$586 —$1,337	[44]
Hospitalization without ICU (average per patient)	$25,188	$10,979 —$34,896	[44]
Hospitalization with ICU (average per patient)	$70,098	$41,046 —$102,524	[44]
ED care (average per visit)	$2200	$623 —$3,102	[45,46]
EMS transportation	$1,005	$712 —$1,546	[47]

Indirect effects and costs of vaccination and health outcomes

Indirect costs of vaccination included workdays lost for visiting vaccination clinics and loss of productivity due to adverse reactions to vaccines (Table S5) Published estimates were used for

the prevalence of adverse effects following vaccination. We also considered workdays lost due to isolation of symptomatic cases or hospitalization of severe cases (Table S6) Costs related to workdays lost were estimated by considering the percentage of vaccinated adults who are employed (i.e., ~66.5%, calculated based on the unemployment rate in 2021 and the coverage of fully vaccinated adults) and per capita gross domestic product of $69,288 for 2021 in the US.[48]

Table S5. Indirect effects of vaccination.

Effect	Estimate	Source
Workdays lost to receive vaccination	0.5	[49]
Percentage of Spikevax (Moderna vaccine) recipients with adverse reactions		[50]
After the first dose	51.7%	
After the second dose	74.8%	
Percentage of Comirnaty (Pfizer-BioNTech vaccine) recipients with adverse reactions		[50]
After the first dose	48.0%	
After the second dose	64.2%	
Percentage of Adenovirus-based (Janssen vaccine) recipients with adverse reactions	76%	[51]
Lost workdays due to adverse reactions		[52]
After the first dose	1.66 days	
After the second dose	1.39 days	

Table S6. Indirect effects of health outcomes.

Effect	Estimate	Reference
Workdays lost for symptomatic, nonhospitalized cases	10 days	[53]
Symptomatic days of prior to hospitalization	3.5 days	[54–56]
Median duration of hospital stay without ICU for non-Omicron patients	6 days	
Median duration of hospital stay with ICU for non-Omicron patients	15 days	

Median duration of hospital stay without ICU for Omicron patients	3 days	
Median duration of hospital stay with ICU for Omicron patients	7 days	

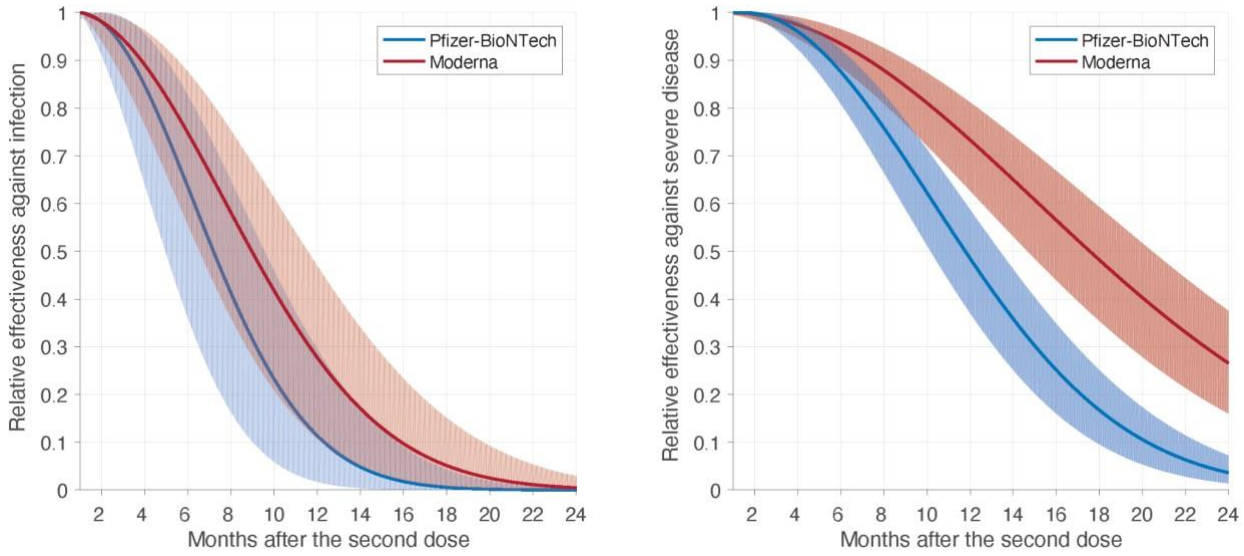

Figure S1. Temporal relative effectiveness of vaccines against infection and severe disease with 95% confidence intervals derived from a Gaussian fit to estimated effectiveness after the second dose of vaccines.[29–31]

Model implementation

With the transmission probability derived from the calibration process, we fitted the model to incidence per 100,000 population from October 1, 2020 to January 31, 2022. For fitting, the agespecific contact rates were adjusted throughout the simulations to minimize the difference between the temporal cumulative incidence predicted by the model and the cumulative reported cases, implicitly accounting for the change and effect of various non-pharmaceutical measures. Simulations were averaged over 500 independent Monte-Carlo realizations, and 95% credible intervals were derived using a bias-corrected and accelerated bootstrap method (with 500 replications), which corrects for bias and skewness in the distribution of bootstrap estimates when scaled from the per capita to the entire US population. We derived model outcomes for symptomatic infections, hospitalizations, and deaths, and calculated the years of life lost (YLL) using the age at death and life expectancy table. The model was implemented in Julia, and simulation codes are available at:
https://github.com/thomasvilches/USomicron/tree/national_estimation

Sensitivity analysis

To account for the range of direct costs (Table S4), we used the Latin Hypercube Sampling technique[57] to generate samples of size 1000 in which each outcome parameter was treated as a random variable and assigned a probability function. The parameters were uniformly distributed and sampled within their respective ranges. We then used these samples to estimate averted costs with outcomes derived from 500 bootstrap replicates of Monte-Carlo simulations.

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