Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods.

Model Structure

We adapted an agent-based model of COVID-19 transmission to account for the waning of naturally acquired or vaccine-elicited immunity. 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.

To incorporate age-specific risk of hospitalizations and deaths, we stratified the model population into seven age groups of 0 to 4, 5 to 11, 12 to 17, 18 to 49, 50 to 64, 65 to 79, and 80+ years based on demographics of New York City. 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 individuals (eTable 1).

SARS-CoV-2 variants

We considered the spread of five variants, including Iota (B.1.526), Alpha (B.1.1.7), Gamma (P1), 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 the first diagnosis. Specifically, the Iota variant was introduced on October 25, 2020, with an estimated 35% higher transmissibility compared with the original Wuhan-I strain. We then introduced the Alpha variant on November 29, 2020, with a 50% higher transmissibility compared to the original strain. The Delta variant was inserted on February 10, 2021, with an elevated transmissibility of 30% compared with the Alpha variant. We introduced the Gamma variant on February 9, 2021, with 60% higher transmissibility compared to the original strain. Finally, we introduced the Omicron variant on November 15, 2021, based on the date of the first diagnosis of an NYC resident (November 22, 2021). We considered a 35% higher transmissibility of Omicron compared to Delta.

Distribution of disease stages and infectiousness

For previous variants (Original, Alpha, Gamma, and Iota), the incubation period for each infected individual was sampled from a log-normal distribution with a mean of 5.2 days.
proportion of infected individuals progressed to a pre-symptomatic stage\textsuperscript{14,15} with an infectious period which was sampled from a Gamma distribution with a mean of 2.3 days.\textsuperscript{14,16} 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.\textsuperscript{14,16} The infectious period of individuals who remained asymptomatic was sampled from a Gamma distribution with a mean of 5 days\textsuperscript{14,17}.

The incubation period for the Delta and Omicron variants were shorter.\textsuperscript{18–21} For Delta, the incubation period was sampled from a lognormal distribution with a mean of 4.3 days, and a pre-symptomatic duration of 2 days on average.\textsuperscript{19,21} The incubation period for Omicron was also sampled from a log-normal distribution, but with a mean of 3.3 days.\textsuperscript{20} The mean duration of the presymptomatic stage for Omicron was assumed to be the same as Delta with an average of 2 days.

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.\textsuperscript{16,22,23}

\textit{Disease outcomes}

We assumed that asymptomatic and mild symptomatic individuals recover without hospitalization. Self-isolation was implemented to start for symptomatic individuals after the onset of symptoms for a period of 10 days, reducing their number of daily contacts by an average of 74% (eTable 1). Severely ill individuals due to primary infection were hospitalized within 2-5 days of symptom onset,\textsuperscript{24,25} 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.\textsuperscript{26–28} The risk of hospitalization with the Delta variant was assumed to be 2.26 times higher than that due to infection with Alpha.\textsuperscript{28} 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.\textsuperscript{29,30} The risk of ICU admissions was reduced by 38.1% in severe patients of Omicron compared to those infected with Delta.\textsuperscript{31}

\textit{Vaccination and immune dynamics}

The number of vaccine doses per day and distribution of the first and second doses were parameterized with NYC vaccination data in different age groups (data provided by the NYC Department of Health and Mental Hygiene). We also implemented the booster vaccination with the daily distribution rates reported from August 13, 2021.\textsuperscript{32} We defined booster as all additional doses administered in NYC because the data did not distinguish between a third dose as part of the primary series (for specific individuals with risk factors) and a booster dose. 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.\textsuperscript{33}

We performed a literature review to derive the estimates of vaccine effectiveness 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 eTables 2, 3). We assumed the same degree of reduced protection in naturally-acquired immunity as vaccine-induced immunity (without booster) against Omicron. However, natural immunity was associated with 3.1 times (95% confidence interval: 1.4 – 4.8) lower risk of hospitalization compared to fully vaccinated individuals without a booster and no prior infection during the time period when Delta was the predominant variant.34

We considered both primary, booster, and hybrid immunity in the model. Although hybrid immunity from infection plus two to three vaccine doses is shown to increase vaccine effectiveness with longer durability47,48, we did not have any specific quantification of such effectiveness for the duration of the study. We therefore conservatively assumed that vaccination of those with a previous infection will lead to a protection estimated for the effectiveness of the second dose in the primary series or booster doses. To implement the waning immunity after vaccination, we fitted a Gaussian model to estimates of vaccine effectiveness over time,42,49–52, and determined the temporal relative effectiveness curves (eFigure 1). The relative effectiveness was used as a multiplicative factor in the effectiveness 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. The protection induced following natural infections was in the range of 56% to 92% against reinfections, and 69.4% to 100% against severe, critical, or fatal COVID-19 with different variants.53

Model implementation

We used confirmed and probable COVID-19 cases per 100,000 population in NYC to calibrate the model and determine the per-contact transmission probability of the original strain during the pre-symptomatic stage of the disease. Confirmed COVID-19 cases were classified by a positive molecular test. Probable cases were defined as individuals meeting any of the following criteria with no positive molecular test on record: (a) tested positive with an antigen test, (b) presented symptoms and following exposure to a confirmed COVID-19 case, or (c) died and their cause of death was listed as COVID-19.54

The model calibration started on October 1, 2020 with a pre-existing immunity against COVID-19 that was included in the model using a probability distribution function, based on the seropositivity in different age groups (eTable 4).55 Specifically, at the start of calibration, we used the mean of weighted percent seropositivity estimated for different age groups as the fraction of individuals that have been exposed to the virus. In order to account for waning immunity, we used the ratio of the number of reported cases on each day to the cumulative number of cases as the probability of infection on that day within the time period prior to October 1, 2020. This distribution was used to determine the time of infection for individuals, and their level of immunity was adjusted according to a Gaussian fit described in section Vaccination and immune dynamics above.
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 age-specific 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). We derived model outcomes for symptomatic infections, hospitalizations, and deaths, and calculated the PYLL to estimate the VLS lost and parameterize the ROI analysis.
eTable 1. Mixing patterns and the daily number of contacts derived from empirical observations.\textsuperscript{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 | 5-19 | 20-49 | 50-65 | 65+ |
| 0-4       | 0.23 | 0.18 | 0.42  | 0.11  | 0.054 | 10.21 (7.65) | 2.86 (2.14) |
| 5-19      | 0.03 | 0.59 | 0.29  | 0.06  | 0.03  | 16.79 (11.72) | 4.70 (3.28) |
| 20-49     | 0.04 | 0.15 | 0.63  | 0.14  | 0.05  | 13.79 (10.50) | 3.86 (2.95) |
| 50-65     | 0.02 | 0.11 | 0.49  | 0.27  | 0.11  | 11.27 (9.59)  | 3.15 (2.66) |
| 65+       | 0.02 | 0.11 | 0.41  | 0.21  | 0.24  | 8.00 (6.96)   | 2.24 (1.95)  |
**eTable 2.** Estimated vaccine efficacies (%) and their 95% confidence intervals from published studies for Pfizer-BioNTech vaccines. Booster dose restored or increased the effectiveness of two doses.

| Vaccine effectiveness (%) | Timelines                      | Reference |
|----------------------------|-------------------------------|-----------|
| Original strain and Iota variant | 1 week after the second dose | 1 week after the booster dose | 35,36 |
| 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              |                               |           | 36,37 |
| 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              |                               |           | 36,37 |
| 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) | |
|                       | Delta variant                                                                 | Omicron variant                                                                 |
|-----------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                       | 96.0 (94.0, 97.0)                                                             | 96.0 (94.0, 97.0)                                                              |
| **Severe disease**    |                                                                               |                                                                               |
|                       | 96.0 (94.0, 97.0)                                                             | 96.0 (94.0, 97.0)                                                              |
| **Delta variant**     |                                                                               |                                                                               |
| **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**   |                                                                               |                                                                               |
| **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)                                                              |
|                       |                                                                               |                                                                               |

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### eTable 3. Estimated vaccine effectiveness (%) and their 95% confidence intervals from published studies for Moderna vaccines. Booster dose restored or increased the effectiveness of two doses.

| Vaccine effectiveness (%) | Timelines                  | Reference |
|---------------------------|----------------------------|-----------|
| **Original strain and Iota variant** | 1 week after the second dose | 1 week after the booster dose | 36,43 |
| 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**         |                            |           |   |
| Infection                 | 77.0 (63.0, 86.0)          | 77.0 (63.0, 86.0) | 36,44 |
| 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**         |                            |           | 36,43 |
| 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**         |                            |           | 36,39,40,45 |
| 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) |   |
|                      | Omicron variant |                     |
|----------------------|-----------------|---------------------|
| Severe disease       | 98.0 (93.0, 99.0) | 98.0 (93.0, 99.0)   |
| 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, 90.4)   |
**eFigure 1.** Temporal relative effectiveness of vaccines against infection and severe disease derived from Gaussian fit to data of vaccine effectiveness after the second dose prior to Omicron.
**eTable 4.** Percentage of seropositivity estimated in different age groups by October 1, 2020.

| Age group   | 0 to 17 years | 18 to 44 years | 45 to 64 years | 65+ years |
|-------------|---------------|----------------|----------------|-----------|
| Percentage  | 20%           | 26.4%          | 25%            | 15.1%     |
eFigure 2. Model fit to probable and confirmed cases of COVID-19 in NYC and projections of cases per 100,000 population in NYC with and without vaccination (counterfactual scenario) from October 1, 2020 to January 31, 2022. Reported incidence of confirmed and probable cases were obtained from the NYC Department of Health and Mental Hygiene.56

Model fit and projected outcomes
**eTable 5.** Reported (Pandemic Burden in NYC During Vaccination Campaign) and Simulated (Without Vaccination) Deaths and Hospitalizations From December 14, 2020 to January 31, 2022

| Scenario                              | Deaths (95% CrI) | Hospitalizations (95% CrI) | Data type                        |
|---------------------------------------|------------------|---------------------------|----------------------------------|
| NYC vaccination                       | 14,368           | 82,316                    | Actual counts reported           |
| Counterfactual (without vaccination)  | 62,376           | 387,236                   | Derived from model simulations   |
|                                       | (58,614 to 66,098) | (365,281 to 407,687)      |                                  |
eFigure 3. Estimated potential years of life lost (PYLL).
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