# Supplemental Online Content

Linas BP, Xiao J, Dalgic OO, et al. Projecting COVID-19 mortality as states relax nonpharmacologic interventions. *JAMA Health Forum*. 2022;3(4):e220760. doi:10.1001/jamahealthforum.2022.0760

**eAppendix**

**eReferences**

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

# eAppendix.

## A1. Introduction

The *COVID-19 Policy Simulator* uses a mathematical model to simulate the COVID-19 pandemic at the national and state levels in the United States. The model is calibrated to historical trends in daily incident deaths and updated weekly as new data arises and the pandemic situation evolves. The online tool allows users to simulate the disease trajectory under different non-pharmaceutical interventions (NPIs) with varying timing and intensity. Forecasts are made for total cases, diagnosed cases, active cases, deaths, hospital bed occupancy, and ICU bed occupancy. Since May 2020, we have contributed weekly to the Centers for Disease Control and Prevention (CDC) COVID-19 Forecast Hub.[1]

## A2. Development Timeline

eTable 1 lists major model updates and the dates on which they were introduced.

*eTable 1. Major model updates.*

| Date | Update |
|---|---|
| February 2021 | Vaccine rollout |
| August 2021 | Age-stratification to incorporate age-stratified vaccine data and differential mortality of age groups |
| October 2021 | Lower vaccine effectiveness due to Delta variant from August 1, 2021 |
| December 2021 | Waning (natural and vaccine-conferred) immunity |
| January 2022 | Lower vaccine effectiveness due to Omicron variant from December 1, 2021 |

## A3. Model Overview

Our model is an extension of the traditional susceptible-infected-recovered (SIR) model,[2] which partitions a population into compartments representing mutually exclusive disease states. At any time $t$, the variables $S(t)$, $E(t)$, $I(t)$, $R(t)$, and $D(t)$ denote the number of people in the susceptible, exposed, infected, recovered, and deceased compartments respectively. The flow of people between compartments is assumed to obey a system of deterministic ordinary differential equations. We let $\Delta t = 1$ to be compatible with data sources reporting daily data.

*Age stratification*

We stratify the population into two age groups, <65 years (low-risk) and ≥65 years (high-risk), with the subscript $a \in \{L, H\}$. The total population in age group $a$, denoted by $N_a$, is assumed to be constant over the simulation period.

*Vaccination*

To reflect administration guidelines of the Pfizer-BioNTech and Moderna vaccines,[i] we stratify the disease states by vaccination status. The subscript $v \in \{0, 1, 2\}$ denote the number of vaccine doses received under the recommended two-dose regime. The third vaccine, Janssen, approved for a single-dose regime, is omitted from the model due to its accounting for only 3.7% of all administered doses in the U.S. as of October 31, 2021.[ii] Since there is no data on vaccination status at the time of infection, we assume doses are allocated proportionally to the susceptible and recovered compartments over the

historical time horizon,[iii] i.e., if $V_{a,1}(t)$ and $V_{a,2}(t)$ are the actual number of first and second doses administered to age group $a$ on day $t$, the proportion of the $v$-dose susceptible and recovered compartments, $v \in \{0, 1\}$, moving into the corresponding $(v+1)$-dose compartments on day $t$ is

$$\alpha_{a,v+1}(t) = \min\left\{1, \frac{V_{a,v+1}(t-12)}{S_{a,v}(t) + R_{a,v}(t)}\right\}.$$

The time lag of 12 days accounts for the delay between receiving a vaccine dose and the beginning of protection.[3] The implicit assumption is that a susceptible person does not become infected in the 12 days after receiving a dose. The vaccine reduces both susceptibility to infection and mortality risk. After $v$ vaccine doses, the probability of contracting the virus is reduced by $100 \times e_v^I\%$, with $0 = e_0^I \leq e_1^I, e_2^I \leq 1$; similarly, the infection fatality rate is reduced by $100 \times e_v^D\%$, with $0 = e_0^D \leq e_1^D, e_2^D \leq 1$.

*Transmission*

For a susceptible individual in age group $a$ who has received $v$ vaccine doses, the rate of exposure to the virus is given by

$$\lambda_{a.v} = (1 - e_v^I)\mathcal{R}(t)\gamma \sum_{a' \in \{L,H\}} c_{a,a'} \frac{I_{a',0}(t) + I_{a',1}(t) + I_{a',2}(t)}{N_{a'}},$$

where $\mathcal{R}(t)$ is the time-varying effective reproduction number. We model $\mathcal{R}(t)$ as a step function with breakpoints at the beginning of each calendar month over the historical time horizon to capture the effect of NPIs enforced during this period. The coefficients $c_{a,a'}$ are the elements of the contact matrix with row sums normalized to 1, so that $c_{a,a'}$ is the proportion of contacts per day of age group $a$ that are with age group $a'$. When a susceptible individual contracts the virus, they enter the exposed state and remain there for the duration of the latent period with a mean of $1/\kappa$ days. After that, they transition to the infected state and remain there for the duration of the infectious period with a mean of $1/\gamma$ days. Finally, the infected individual will either die with probability $\delta_{a,v} = (1 - e_v^D)\delta_a$, where $\delta_a$ is the baseline infection fatality rate for age group $a$, or recover with probability $\left(1 - \delta_{a,v}\right)$.

*Waning immunity*

An individual who has recovered from natural infection ($R_{a,v}$) enjoys a period of natural immunity with a mean of $1/\omega_n$ days before transitioning back into the susceptible state ($S_{a,v}$). A fully vaccinated susceptible individual ($S_{a,2}$) is protected for the duration of vaccine-conferred immunity with a mean of $1/w_v$ days before transitioning back into the partially susceptible state ($S_{a,1}$). Finally, since individuals with natural immunity who are subsequently vaccinated have been reported to exhibit "unusually potent immune responses",[4] a fully vaccinated recovered individual ($R_{a,2}$) is assumed to possess two 'layers' of immunity, shedding first their natural immunity then their vaccine-conferred immunity.

*Booster shots*

It is assumed that, once vaccinated, an individual will never shed their immunity completely (within the time frame of the simulation), and a fully vaccinated individual who has shed their vaccine-conferred

immunity is indistinguishable from a partially vaccinated individual. Thus, the model differentiates between the subpopulation that is willing to receive booster shots and the subpopulation that is unwilling to be vaccinated. Fully vaccinated individuals wane into the partially vaccinated state and are 'boosted' back into the fully vaccinated state.

*Differential equation formulation*

In summary, our model is described by the following system of equations, where $(t)$ has been dropped for notational simplicity:

$$
\begin{aligned}
\dot{S}_{a,0} &= -(\lambda_{a,0} + \alpha_{a,1})S_{a,0} + \omega R_{a,0},\\
\dot{E}_{a,0} &= \lambda_{a,0}S_{a,0} - \kappa E_{a,0},\\
\dot{I}_{a,0} &= \kappa E_{a,0} - \gamma I_{a,0},\\
\dot{R}_{a,0} &= (1-\delta_{a,0})\gamma I_{a,0} - (\alpha_{a,1} + \omega)R_{a,0},
\end{aligned}
$$

$$
\begin{aligned}
\dot{S}_{a,1} &= -(\lambda_{a,1} + \alpha_{a,2} + \alpha_{a,3})S_{a,1} + \alpha_{a,1}S_{a,0} + \omega(R_{a,1} + \alpha'_{a,3}S_{a,2}),\\
\dot{E}_{a,1} &= \lambda_{a,1}S_{a,1} - \kappa E_{a,1},\\
\dot{I}_{a,1} &= \kappa E_{a,1} - \gamma I_{a,1},\\
\dot{R}_{a,1} &= (1-\delta_{a,1})\gamma I_{a,1} + \alpha_{a,1}R_{a,0} - (\alpha_{a,2} + \alpha_{a,3} + \omega)R_{a,1},
\end{aligned}
$$

$$
\begin{aligned}
\dot{S}_{a,2} &= -\lambda_{a,2}S_{a,2} + (\alpha_{a,2} + \alpha_{a,3})S_{a,1} + \omega\alpha'_{a,3}(R_{a,2} - S_{a,2}),\\
\dot{E}_{a,2} &= \lambda_{a,2}S_{a,2} - \kappa E_{a,2},\\
\dot{I}_{a,2} &= \kappa E_{a,2} - \gamma I_{a,2},\\
\dot{R}_{a,2} &= (1-\delta_{a,2})\gamma I_{a,2} + (\alpha_{a,2} + \alpha_{a,3})R_{a,1} - \omega\alpha'_{a,3}R_{a,2},
\end{aligned}
$$

$$
\dot{D} = \delta_{a,0}\gamma I_{a,0} + \delta_{a,1}\gamma I_{a,1} + \delta_{a,2}\gamma I_{a,2}.
$$

The initial conditions are $\left(I_{a,0}(0),\ S_{a,0}(0)\right) = \left(I_{a,0}^{\text{init}},\ N_a - I_{a,0}^{\text{init}}\right)$ and zero for all other variables. eTables 2 and 3 display the values or ranges for all model parameters and their references.

*eTable 2. Estimates of fixed and calibrated parameters.*

| Parameter | Estimate | Reference and notes |
|---|---|---|
| *Fixed parameters* | | |
| $N_L$ | State-dependent | U.S. Census Bureau: SC-EST2020-AGESEX-CIV: POPEST2019_CIV |
| $N_H$ | | |
| $[c_{L,L}, c_{L,H}; c_{H,L}, c_{H,H}]$ | [0.93, 0.07; 0.48, 0.52] | [5] Aggregate columns and rows into age groups <65 years and ≥65 years, then normalize so that rows sum to 1. |
| $\kappa$ | 1/5.5 | [6] |
| $\gamma$ | 1/10 | [7] |
| $\omega_n, w_v$ | 16 months | [8] |

| | | |
|---|---|---|
| | | Reinfection by endemic SARS-CoV-2 is expected to occur between 3 months and 5 years after peak antibody response, with a median of 16 months. |
| *Calibrated parameters* | | |
| $\mathcal{R}(t)$ | 0.5–6.0 | [9, 10, 11, 12]<br>Widely varying by location and SARS-CoV-2 variant. |
| $I^{\text{init}}$ | 100–10,000 | Divided proportionally into:<br>• $I_L^{\text{init}} = \frac{N_L}{N_L+N_H} I^{\text{init}}$,<br>• $I_H^{\text{init}} = \frac{N_H}{N_L+N_H} I^{\text{init}}$. |

*eTable 3. Evolution of estimates of variant-dependent parameters.*

| Parameter | Estimate | Reference and notes |
|---|---|---|
| *Baseline values* | | |
| $\delta_L$ | 0.001 | Based on this meta-analysis. These values chosen to approximate the CDC's "Estimated Total Infections". |
| $\delta_H$ | 0.030 | |
| $1 - e_1^I$ | 0.54 | [13]<br>Table 2: "Documented Infection" at "14 to 20 days after first dose": $(1 - \text{RR})\% = 46$.<br>Derivation: $1 - e_1^I = 1 - 0.46$. |
| $1 - e_2^I$ | 0.08 | [13]<br>Table 2: "Documented Infection" at "7 days after second dose to end of follow-up": $(1 - \text{RR})\% = 92$.<br>Derivation: $1 - e_2^I = 1 - 0.92$. |
| $1 - e_1^D$ | 0.52 | [13]<br>Table 2: "Death" at "14 to 20 days after first dose": $(1 - \text{RR})\% = 72$.<br>Derivation: $(1 - e_1^I)(1 - e_1^D) = 1 - 0.72$. |
| $1 - e_2^D$ | 0.63 | Vaccine clinical trials report 95% efficacy against death.<br>Derivation: $(1 - e_2^I)(1 - e_2^D) = 1 - 0.95$.<br>Note that it is the *conditional probability* of death that is higher after the second dose than after the first dose. If a fully vaccinated individual contracts a breakthrough infection despite 92% reduction in susceptibility, it is plausible that they are particularly vulnerable and have a smaller reduction in mortality risk *conditional on infection* compared to a partially vaccinated individual who contracts a breakthrough infection. |
| *Delta variant (parameter values change at a linear rate as the variant saturates over August 2021)* | | |
| $1 - e_2^I$ | 0.13 | [14]<br>"Two dose vaccine effectiveness was 86.7% (95% confidence interval 84.3% to 88.7%) against infection with the delta variant, ..."<br>Derivation: $(1 - e_2^I) = 1 - 0.87$. |
| $1 - e_1^I$ | 0.90 | Scaled up proportionally to $e_2^I$.<br>Derivation: $1 - e_1^I = 0.54 \times (0.13/0.08)$. |
| $\delta_L$ | 0.0023 | [15]<br>"Increased risk with the Delta variant was more pronounced at ... 133% (95% CI 54%–231%) for death."<br>Derivation: $\delta_L = 0.001 \times 2.33$.<br>Derivation: $\delta_H = 0.030 \times 2.33$. |
| $\delta_H$ | 0.0700 | |

| | | |
|---|---|---|
| | | We assume that the increased mortality of Delta is a consequence of higher IFR only, not lower vaccine effectiveness against death after infection. |
| *Omicron variant (parameter values change at a linear rate as the variant saturates over December 2021)* | | |
| $1 - e_2^I$ | 0.30 | UKHSA Report: Figure 2B |
| $\delta_L$ | 0.0008 | UKHSA Report: "The risk of hospital admission from emergency departments with Omicron was approximately one-third of that for Delta (Hazard Ratio 0.33, 95% CI: 0.30 to 0.37)." |
| $\delta_H$ | 0.0233 | Same as above. |

## A4. Calibration and Numerical Solution

We calibrate the model to historical daily incident deaths. The system of ordinary differential equations is solved numerically using Euler's method (R package `deSolve`).[16] The calibration method is generalized simulated annealing (R package `GenSA`) with the sum of squared errors as the objective function.[17] To account for uncertainty in the calibrated values, we repeat the calibration process 100 times with different initial solutions, resulting in 100 unique sets of parameter values and fitted curves. At each time point, we take the median as the point estimate and compute the 90% coverage simulation band.

eTable 4 displays our input data and their references.

*eTable 4. Input data.*

| Data | Source | Reference |
|---|---|---|
| COVID-19 cases and deaths | JHU CSSE | [18] |
| Vaccine administration | Our World in Data and CDC | [19] and CDC |

## A5. Forecasting

We make forecasts by allowing the model to continue running past the historical time horizon. Diagnosed cases and hospital and ICU occupancy are not accounted for in the SEIR model. We estimate these in a post-processing step as follows.

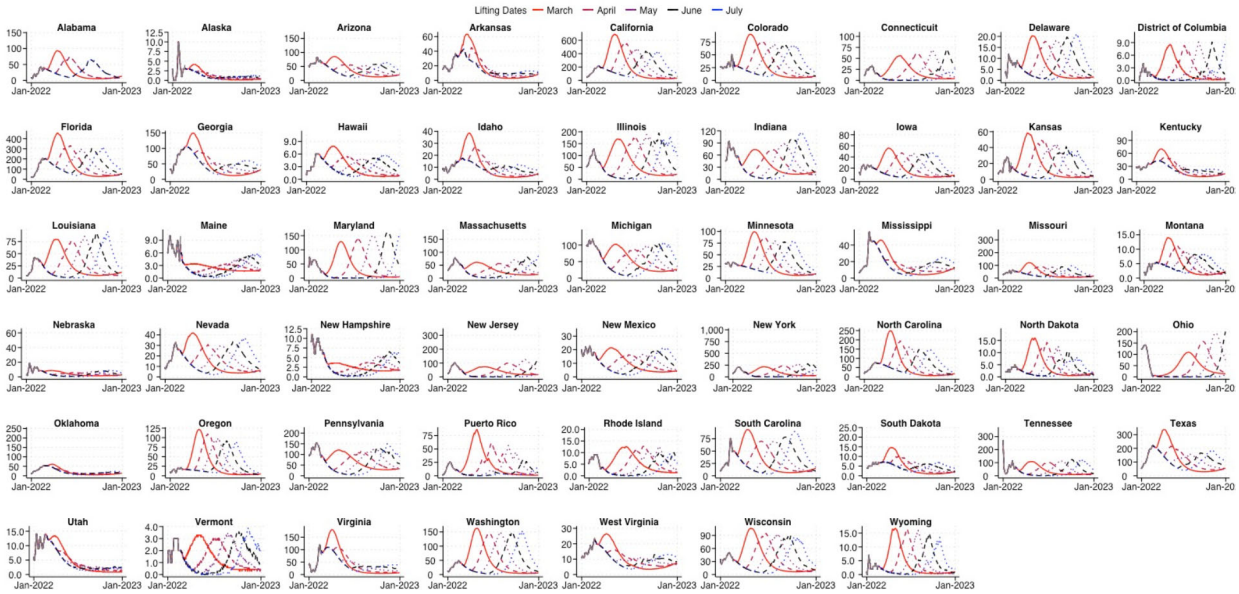
*Diagnosed cases*
We assume the future diagnosis rate remains at the latest estimated value, i.e., the number of incident diagnosed cases on the last day of data divided by the number of incident total cases on the last day of data.

*Hospital and ICU bed occupancy*
We back-calculate hospital and ICU bed occupancy from incident deaths assuming an average time to death from hospital and ICU admission of 16 and 10 days respectively.[20] Starting in August, we forecast occupancy data provided by the U.S. Department of Health and Human Services. Note that the data does not include all hospitals in any given state so our forecasts do not estimate the total demand for hospital and ICU beds.

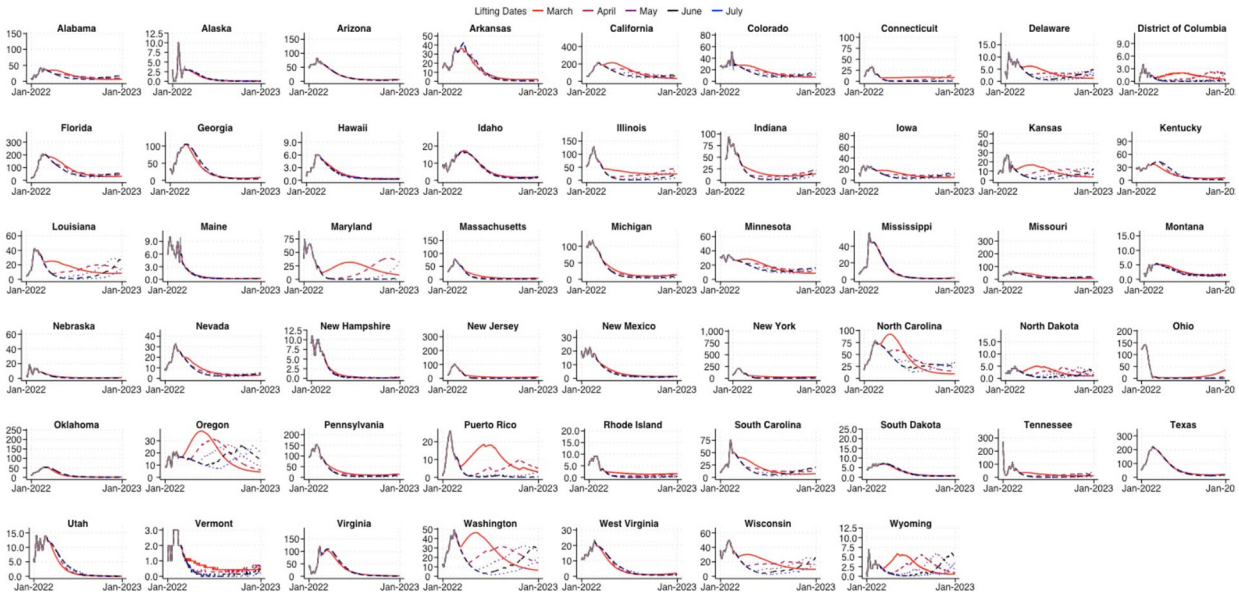
## A6. Non-Pharmaceutical Interventions

The *Simulator* offers four types of non-pharmaceutical interventions:

1. *Current interventions:* The effective reproduction number remains at the latest calibrated value.
2. *Lockdown:* The effective reproduction number is 0.3, the estimated value in Wuhan during the strict lockdown of the city starting in March 2020.[21]
3. *Stay-at-home orders:* The effective reproduction number is the lowest calibrated value attained during the period from March to July 2020.
4. *Minimal restrictions:* The effective reproduction number is the basic reproduction number, which changes with the proportions of the circulating variants of concern.




*(a)*




*(b)*

*eFigure 1. Model-based projections of COVID-19 deaths following the lifting of NPIs in each state, assuming an effective reproduction number of 5.0 (eFigure 1a) and 3.0 (eFigure 1b).*

## eReferences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[i] See https://www.cdc.gov/coronavirus/2019-ncov/vaccines/second-shot.html for details.
[ii] See https://ourworldindata.org/grapher/covid-vaccine-doses-by-manufacturer?country=~USA for details.
[iii] The CDC advises against vaccination while under active infection. See https://www.cdc.gov/coronavirus/ 2019-ncov/vaccines/faq.html for details.