Colorado COVID-19 Mathematical Model Documentation

Prepared by the Colorado COVID-19 Modeling Group

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We use a deterministic, age-structured susceptible, exposed, infected, recovered (SEIR) model to estimate the impact of interventions and behavioral changes on COVID-19 transmission to date as well as to project the number of people with COVID 19, those needing hospitalization and critical care and the number of deaths in Colorado under different scenarios. The model has been calibrated to Colorado-specific demographics and Colorado-specific COVID-19 data. Site-specific model parameters are fit to Colorado COVID-19 hospitalization data, and time-varying parameters are updated weekly. This documentation describes the model, data sets used, and key assumptions.

Key model updates

The model has been updated to reflect our changing death rates and assumptions about vaccination.

Death Rates

Age-specific death rates among COVID-19 patients have changed over time, with the highest death rates seen early in the pandemic. During the summer, when prevalence was low, death rates appeared to have dropped substantially, however these rates have risen substantially since that time. We have simplified the model, instead of including death as a time-varying parameter, we now simply take a weighted average of death rates over time (Table 4).

Vaccine

Two vaccines became available in Colorado on December 15th, 2020. As of 02/16/21, 686,231 individuals have received at least one dose, and 308,294 have received two doses. Both vaccines require two doses per individual and are being distributed in phases (https://covid19.colorado.gov/covid-19-vaccine-development-and-planning). There is limited evidence that some individuals are immune after the first dose, and we have incorporated the assumption that the vaccines are 33% efficacious 14 days after the first dose. The vaccines are assumed to become fully effective (90%) 32 days from time of receipt of first vaccine dose [1, 2]. To account for vaccination in the model, we have added a vaccination compartment to the SEIR model (Figure 1, bottom). Individuals are assumed to receive vaccine regardless of previous infection status, but the vaccine is only assumed to have an effect among individuals in the susceptible or recovered compartments. Utilizing data from CDPHE, vaccinations are distributed in the model to reflect data on the age-distribution of vaccinations in Colorado in the past (Appendix Table A2). Vaccination is introduced into the model as the number of individuals receiving their first dose of

vaccine each day. This value is multiplied by vaccine efficacy (33% 14 days after vaccination and 90% 32 days after vaccination) and by the proportion of the population vaccinated among whom it is likely to have an effect (Susceptible + Recovered / (Total Population – (Vaccinated + dead + hospitalized))). Vaccination rates have increased steadily overtime and will continue to be updated in the model to reflect current vaccination rates in Colorado. Projections of current vaccination depend on estimates and projections of future vaccine availability from CDPHE. Vaccination is assumed to be transmission blocking when effective, while it is currently uncertain if this is true, we choose to model the best-case scenario here to show the maximum possible effect of vaccination at this point. Vaccination is assumed to be highly immunogenic, as duration is currently unknown. For these simulations immunity due to vaccination is assumed to last two years. Individuals will move from the vaccinated compartment back into the susceptible compartment with an exponential distribution with a mean of 730 days.

Model structure

In the model, exposed individuals incubate infections for 4.2 days before becoming infectious. This is based on evidence that the incubation period for SARS-CoV-2 (the time between infection and symptom onset) is approximately 5.2 days [3-5], and that individuals are infectious before symptom onset [6-9]. Presymptomatic infectiousness is currently thought to be greatest in the day before symptom onset [10] and thus we assume 1 day of presymptomatic infectiousness among individuals who become symptomatic. Infected individuals can be either symptomatic or asymptomatic. The infectious period is the same regardless of symptoms and lasts for 9 days [8, 10]. Both the latent period and infectious period are exponentially distributed in the model. The model accounts for evidence that asymptomatic individuals are probably less infectious than symptomatic individuals [11], including includes a ratio of transmission probability for symptomatic vs. asymptomatic individuals which is estimated via model fitting (described below).

We developed an age-structured model with four separate age compartments (0-19, 20-39, 40-64, and 65+) based on evidence that the probability an infected individual develops symptoms [12] and the probability a symptomatic individual is hospitalized [13-15] are age-dependent. We used Colorado demographic data for 2016 from the US Census to define age and population structure and adjusted for a 9% relative population increase since 2016 based on current estimates of population growth in Colorado. Age-dependent probabilities that an infected individual is symptomatic were generated from the literature, estimating the product of the age distribution of Colorado within each age-compartment and the age-group-specific symptomatic fraction as shown in Table 1 ([12], personal communication). Table 1 also shows the probability of hospitalization and ICU need among symptomatic individuals for each age group. These were estimated using Colorado COVID-19 hospitalization and intensive care unit (ICU) data and model fitting techniques, described below. Symptomatic cases that require hospital care are moved into either a non-ICU hospitalized, or ICU compartment 8 days after the onset of symptoms [5]. We assume that the average length of hospital stay is dependent on both age and whether or not critical care is required. These values, shown in Table 2, are based on hospital data for COVID-19 patients in Colorado through the end of September. With growing evidence that length of stay has declined since the beginning of the pandemic, we estimate two values for each age group: mean length of stay for March – April, and mean length of stay May – present. Data on length of stay by age and

month are shown in Appendix Table 1. In the model, no further transmission occurs once the patient enters the hospital.

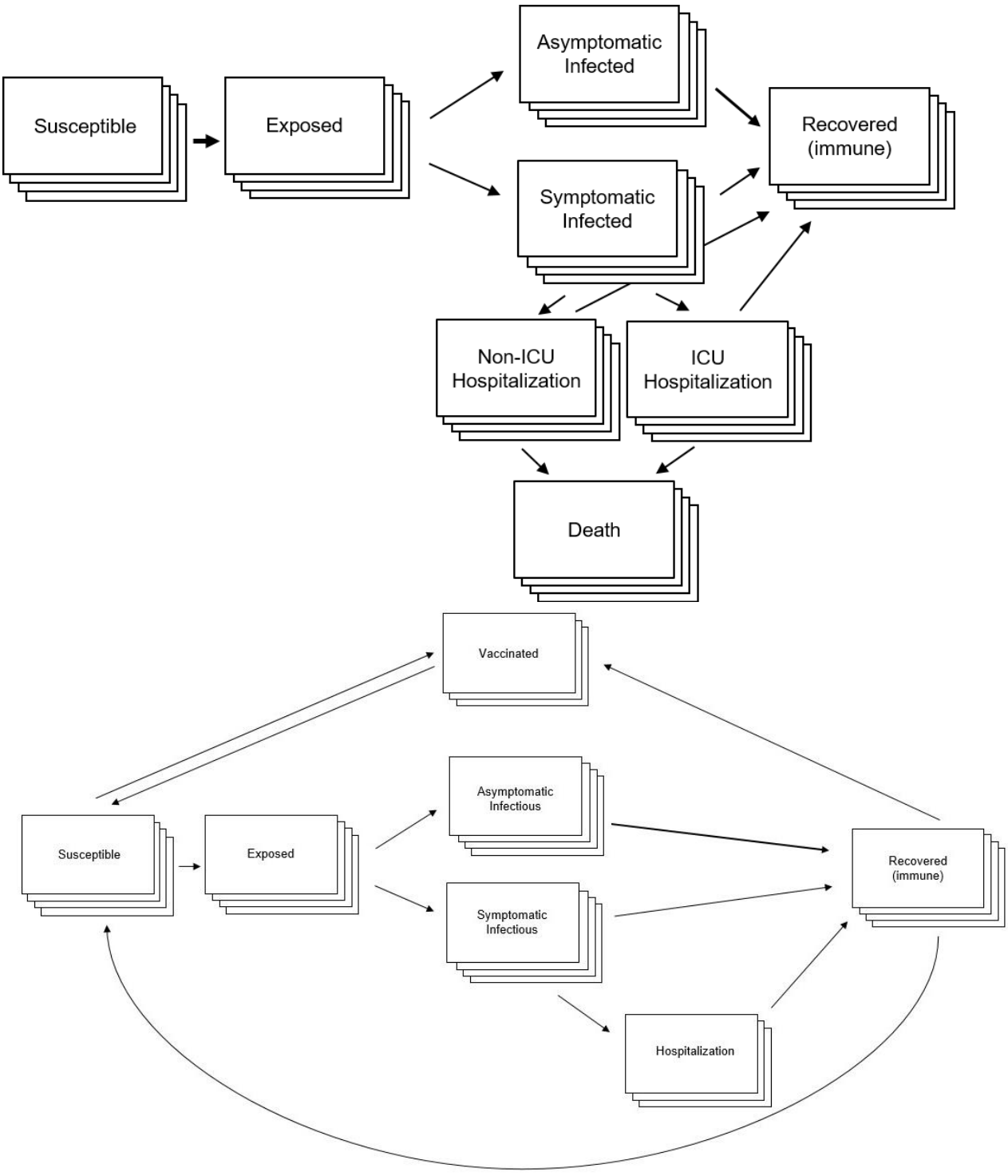

Figure 1. The base structure of the SEIR model (top). The model is age-stratified, with separate compartments for each of four age groups 0-19, 20-39, 40-64, and 65+. The symptomatic infected compartment includes a 1-day period where individuals are infectious but not yet symptomatic. The model structure including functionality for

varying immunity duration and vaccination (bottom), hospitalization is still broken into ICU/non-ICU and deaths are still modeled but are not shown in the figure for ease of visualization.

Immunity

We incorporate temporary immunity into the model by allowing individuals recovered from infection (in the R compartment) to transition back into the susceptible (S) compartment at the rate of:

$$\frac{pS_i}{deltaI} + \frac{1 - pS_i}{deltaA}$$

Where pS_i is the proportion of infections symptomatic for a given age group and *deltaI* indicates the modeled duration of immunity for symptomatic (I) and *deltaA* asymptomatic (A) infections. The duration of immunity can be varied and is allowed to be either the same for symptomatic and asymptomatic infection or to be longer after symptomatic infections [16]. Given the structure of the model, movements between compartments (from the R to the S compartment, in this case) occur with an exponential distribution.

The duration of immunity is currently unknown, we have elected to be conservative and assume immunity is seasonal, as in other human seasonal coronaviruses. We assume *deltaI* = 360 days and *deltaA* = 180 days.

Table 1. Probabilities of symptoms and hospitalization by age group. The probabilities of hospitalization need are Colorado-specific estimates, derived from fitting age-specific hospitalization curves from the model to COVID-19 hospitalization data with onset date on or before August 31. COVID-19 hospitalization data sources and model fitting methods are described, below.

Age Category	Proportion of infected individuals that develop symptoms from [12]	Probability of non-ICU hospitalization given symptomatic
0-19	0.11	0.0174
20-39	0.36	0.0291
40-64	0.56	0.0321
65+	0.77	0.0501

Table 2. Probability of needing ICU care given symptomatic by age group over time. The probabilities of ICU need are Colorado-specific estimates, derived from fitting age-specific hospitalization curves from the model to COVID-19 hospitalization data with onset date on or before November 11. COVID-19 hospitalization data sources and model fitting methods are described, below.

Age Category	Probability of needing ICU before June 18th	Probability of needing ICU June 18th - Sep 13th	Probability of needing ICU after Sep 13th
0-19	0.00528	0.00528	0.00528
20-39	0.007474	0.00838	0.00591
40-64	0.01866	0.01785	0.012226
65+	0.02885	0.02234	0.02020

Table 3. Length of stay by age category and ICU vs non-ICU hospitalization from Colorado-specific COVID-19 hospitalizations based on Colorado COVID-19 patients hospitalized through September 2020. Source data are described in the Appendix.

Age Category	Estimates for patients before May 1		Estimates for patients on or after May 1st	
	Mean length of non-ICU hospitalization (days)*	Mean length of ICU stay (days)	Mean length of non-ICU hospitalization (days)*	Mean length of ICU stay (days)
0-19	4.0	7.0	5.0	4.0
20-39	5.5	9.9	3.6	4.4
40-64	7.4	13.5	5.3	8.5
65+	10.0	10.8	7.6	8.0

*Mean length of ICU stay is the mean time a COVID-19 ICU patient spends in the ICU. As ICU patients spend some time in the non-ICU as well, we account for this as follows. Non-ICU length of stay was calculated as non-ICU patient's length of stay plus the difference between total length of stay and ICU length of stay for ICU patients, multiplied by the proportion of hospitalized patients that enter the ICU.

Mortality is based on the probability of death based on age and hospitalization status (Table 3) and ICU capacity. We estimated probability of death for hospitalized COVID-19 patients based on hospital data for COVID-19 patients in Colorado from COPHS. Mortality among non-hospitalized COVID-19 cases was calculated as the proportion of all non-hospitalized cases with onset date on or before December 31, 2020 who died, by age, then adjusted for assumed case detection rate at the time of death, using reported COVID-19 case data in Colorado through December 31. We estimate additional mortality will occur if hospital capacity is reached. We assume that once available ICU beds are full, all cases requiring ICU in excess of availability will die. ICU bed capacity is set at 1325 beds, a number provided by CDPHE.

Table 4. Probability of death for Colorado COVID-19 case reports through February 5th, 2021 provided by CDPHE.

Age Category	Probability of death among hospitalized patients that don't need ICU care	Probability of death among hospitalized patients requiring ICU-care	Probability of death among non-hospitalized reported cases*
0-19	0.0000	0.0224	0.00002
20-39	0.0017	0.0702	0.00008
40-64	0.0065	0.1763	0.00062
65+	0.0831	0.3610	0.02080

* Using CDPHE COVID-19 data as of February 8th, non-hospitalized mortality was calculated as the proportion of all non-hospitalized cases with symptom onset date on or before December 31st who died, by age strata, then adjusted for assumed case detection rate at the time of death.

We assume random population mixing, and that infection probability does not vary by age or sex. The model assumes a single introduction event occurring on January 24, which we extrapolated from the first reported cases in Colorado and estimates of under-reporting in early stages of the outbreak. There are no additional importations, migration, or non-COVID-19 related deaths in the system.

Parameter estimation and source data

We use model fitting methods to estimate the parameter values which may vary regionally and/or for which there is considerable uncertainty in the current literature. The model-fitting process involves comparing model outputs to observed COVID-19 data in Colorado in order to infer parameter values.

Hospitalization data. We use hospitalization data to fit our overall model as this is seen as a more stable indicator of COVID-19 transmission than case data and is not sensitive to changes in testing capacity. The total hospitalizations (ICU + non-ICU) as predicted by the model are compared to Colorado COVID-19 hospitalization data provided by CDPHE and the EMResource hospital census of hospitalizations. The time series of COVID-19 hospitalizations in Colorado is based on hospitalization data provided by CDPHE through April 7 and the EMResource hospital census of hospitalizations starting 04/08 (EMResource hospital census appeared to undercount COVID-19 hospitalizations before that date). EMResource provides a daily census count of hospitalized patients on a given day and is assumed to have no built-in data lags. Because the EMResource provides an aggregate count of all hospitalized patients but does not offer information on the age distribution of COVID-19 patients, we additionally used CDPHE resource utilization data ("COPHS") which provides counts of hospitalized patients by age group to estimate age-specific hospitalization rates, as described below. The COPHS data also provides information on the length of hospital stay for each COVID-19 patient.

Case data. SARS-CoV-2 reported case data are obtained from CDPHE's Colorado Electronic Disease Reporting System (CEDRS). These data are used to estimate age-group specific levels of transmission reduction over time. Reporting of case data is lagged due to lags between onset date and report as well as lags between reporting and data entry, we account for this by truncating data at 10 days before export date.

Model fitting. Best-fitting parameter values were identified via a least squares cost function minimizing the comparison between the estimated model output and the observed data. For example, the number of hospitalizations estimated in the model is compared to the observed number of COVID-19 hospitalizations in Colorado. The cost function is minimized using a two-stage fitting algorithm in R, first applying a pseudo-random optimization algorithm [17] to find a region of minimum difference between the model and the data. The second phase used least squares optimization applying the Levenberg-Marquardt algorithm [18].

Primary time-fixed parameter estimates. The rate of infection (beta) and the proportionate increase in transmission comparing symptomatic to asymptomatic infections (lambda) were fit using data on hospitalizations from the early phase of the epidemic (up to March 27). Given the parameter values for beta and lambda, we estimated age-specific hospitalization and ICU rates, fitting the curves to the initial phase of the epidemic for CDPHE COPHS data with onset date on or before March 27. Priors for hospitalization rates came from [11]. These estimates were aligned to the age groupings in the model: 0-19, 20-39, 40-64, and 65+.

Estimating transmission control (TC). Model fitting using the same algorithms described above is used to estimate the level of total transmission control for each two-week period from March 1, the date of the first recorded COVID-19 hospitalization in Colorado, up to the current date. The transmission control parameter describes the estimated percent decrease in transmission-relevant

contacts compared to an uncontrolled baseline. TC folds all reductions in transmission relevant contact due to policies and behaviors and seasonality into a single parameter. TC is incorporated in the model in the equation: beta*(1 – TC), as an effective decrease in contact between susceptible and infectious individuals. Due to the average lag time between exposure and hospitalizations (~13 days), estimates of transmission control for a given period reflect contact rates approximately two weeks prior to the date estimated.

Estimating transmission control for distinct age groups. In order to examine differences in transmission control by age-group, we have augmented our methods using case data. Case data are particularly necessary to examine transmission control in the youngest age groups, for whom hospitalization data is sparse. In order to fit models to case data, assumptions about detection rate must be made. The detection rate was first assumed to follow the state-wide rates estimated from the total hospitalizations model (described below) and model-fitting measures were used. Preliminary estimates of age specific transmission control parameters were estimated by comparing age-specific incidence curves to age-specific reported case data using the same methods applied above. To capture age-group specific differences in detection rates, we then fit the age-specific TC model to age-specific hospitalizations, allowing us to estimate the daily number of infections by age group. We then compared that to the reported cases in order to estimate age-group differences in detection rate. With age-group specific detection rates, we were then able to compare the model estimated cases to age-specific cases detected by CEDRS. We then used the age-group specific cases to estimate age-specific TC to account for low hospitalization rates among younger age groups. Initially, retrospective age-specific transmission reduction levels were estimated using data up to October 12th, and then estimates were refit weekly for the next three biweekly parameters. Each week, the last three biweekly parameters are re-estimated.

Estimating the course of COVID-19 transmission to date

Estimating proportion of infections detected. We estimate the proportion of SARS-COV2 infections (including both asymptomatic and symptomatic infections) that are being captured by Colorado state surveillance systems over time using the SEIR model outputs of the daily number of new infections (symptomatic + asymptomatic). We compared this output to the number of cases captured by state surveillance systems. We used the number of cases reported by CDPHE, using the onset date of symptoms or, if this is not available, the onset date as imputed by CDPHE. The ratio of reported cases to model output gives us the estimated proportion of infections detected.

Estimation of the effective reproductive number. To compute the effective reproductive number (Re) for the age-structured model, we followed two separate processes. The first follows the process outlined in [19]. The Colorado model includes 4 age categories as well as subcompartments for exposed, asymptomatic, and symptomatic individuals. We consider all 12 compartments which contain infected individuals and collect them in a vector. Roughly speaking, the matrix that updates the population numbers in the vector is called the Next Generation Matrix. The dominant eigenvalue for this matrix is Re, which we thus compute at each timepoint. We additionally estimated Re from the model output alone (as opposed to using parameter values, as with the former method), giving a partially smoothed estimate akin to the methods of [20]. To estimate Re from model output we calculated an approximate estimate of individuals from all four age categories (i) newly exposed (E_t) on a given day and divided by the number of infectious individuals three-days prior ($(I+A)_{t-\alpha-1}$), divided by the length of the infectious period (equation below).

$$R_e = \frac{\sum_i^4 \frac{E_t}{\alpha}}{\sum_i^4 \frac{(I+A)_{t-\alpha-1}}{\gamma}}$$

Current parameter estimates and estimates of the reproductive number are described separately: see Parameter estimates and model fit.

Because we base our parameter estimates on COVID-19 hospitalization data, our estimates of the current state of COVID-19 in Colorado reflect the state of infections occurring approximately 2 weeks prior. The lag in estimation is the result of an approximately 13-day lag, on average, between infection and hospitalization. Hospitalization data is a robust indicator of transmission trends, as reported COVID-19 case data are sensitive to testing capacity and consequently may represent a variable proportion of actual infections over time when testing capacity is changing, however it is important to recognize that hospitalizations today reflect infections generally occurring two weeks ago.

The model is updated weekly to re-estimate time-varying parameters including transmission control and the proportion of infections detected.

Projecting the future course of COVID-19 in Colorado

The SEIR model and the most recent parameter estimates can be used to generate projections of the estimated number of cases, hospital needs and deaths in the future. Model projections are generated based on scenarios – or "what ifs." For example, projections can be generated to estimate the number of hospitalizations if transmission control remains at the current estimated level or increases or decreases. These estimates are generated by using the scenario-defined transmission control value, as well as the other most recent parameter estimates, to drive the model and generate projections. Recent projections have included holiday scenarios, examining the impact of a decrease in transmission control over the holidays due to increased social gatherings.

Uncertainty in estimation of current parameters including TC and Re. Given that the estimates of TC and current Re are subject to substantial uncertainty, we are visualizing uncertainty now using 95% Confidence Intervals (95% CI) in estimating TC and other measures at present using established methods [21, 22]. We calculate the 95% CIs using Markov Chain Monte Carlo methods and sample from the distribution of possible parameter estimates we fit each week [23]. Restating in less technical terms, we run thousands of repeats of the model, introducing some statistical variation into the model's variables. This gives us a range of possible parameter estimates for the last three TC parameters. When we run the model, carrying out the range of TC estimates, we produce a 95% CI for TR, R_e, and current prevalence.

Near-term projections. We also use our model to generate near-term forecasts of cases and hospitalization needs over the next two weeks, assuming no change in public health policies or public behavior. Infectious disease forecasting is subject to considerable uncertainty – due to technical challenges and uncertainties regarding behavior and policy changes over the long-term [24, 25]. We focus on generating short-term forecasts over the next two weeks, using established methods that describe uncertainty in cases in the estimation process [21, 22]. With regard to the technical approach, uncertainty in the projections is obtained by fitting all 16 transmission control parameters since March 1st and the date of initial infection using a hybrid optimization approach initially using a particle swarm followed by a weighted nonlinear least squares-based Levenberg-

Marquardt constrained optimization algorithm [18]. An estimated covariance matrix was computed via parametric sensitivity computations [26]. A multivariate normal distribution was created via using the parameters estimates (as means) and the approximate covariance matrix. The predictions were generated via sampling parameters from the multivariate normal distribution and 10% of the resulting solutions are shown in the figures.

Caveats and limitations. While our model of SARS-CoV-2 is based on current scientific literature, the science is evolving rapidly, and our understanding of this virus is incomplete. For example, we do not yet fully understand how long an individual is immune to the virus following infection or how immunity varies among previously infected populations [27]. The model assumes random mixing in the population, a common assumption in transmission models; however, in reality, people do not mix randomly, and non-random mixing may lead to high-risk subpopulations that are not well characterized in this model [28, 29].

Code

Code for our models is posted on Github: https://github.com/agb85/covid-19

Appendix

The length of time a COVID-19 patient spends in the hospital varies by age, as seen in the Colorado hospital data, below. The length of stay for COVID-19 patients that do not require ICU care has remained relatively constant over time. Length of ICU stay and total hospital length of stay appears to have modestly declined for adult age groups. We caution there is considerable variability in the length of stay by patient as evidenced by the high standard deviations. We continue to closely monitor these data and evaluate trends.

Table A1. Mean length of stay of Colorado COVID-19 patients for ICU and non-ICU hospitalizations by age and month based on data provided by Colorado hospitals for patients admitted on or before August 30, 2020 with surveillance through October 30th.

Month of Admission	Ages 0 – 19, mean (SD)	Ages 20 – 39, mean (SD)	Ages 40 – 64, mean (SD)	Ages 65+, mean (SD)
ICU Patients (all days)*				
March	8.0 (5.6)	15.5 (12.1)	20.9 (15.0)	18.6 (14.0)
April	9.1 (9.8)	17.3 (17.1)	21.4 (18.4)	17.2 (15.3)
May	18.6 (7.1)	13.2 (15.2)	19.6 (19.9)	15.8 (15.0)
June	10.0 (18.0)	10.9 (11.7)	15.3 (13.4)	14.7 (12.0)
July	13.3 (5.9)	10.0 (7.4)	15.4 (12.9)	13.0 (10.0)
August	7.8 (21.5)	11.1 (11.4)	18.6 (16.1)	16.3 (12.1)
ICU Patients (ICU days)*				
March	6.3	10.1	13.8	11.6
April	6.8	11.3	15.2	10.9
May	3.7	8.4	12.5	10.0
June	12	6.6	10.5	10.4
July	7.0	5.3	10.7	8.7
August	8.8	6.0	12.5	10.0
Non- ICU Hospitalization				
March	1.4 (0.5)	3.4 (2.1)	4.8 (5.4)	7.4 (8.4)
April	3.2 (3.7)	3.8 (3.1)	4.9 (5.1)	8.0 (7.1)
May	3.9 (4.8)	4.2 (5.8)	4.8 (3.8)	6.3 (6.8)
June	3.5 (4.7)	2.9 (2.0)	5.4 (6.6)	6.5 (5.8)
July	3.6 (4.9)	3.9 (4.2)	4.6 (4.2)	7.0 (7.7)
August	3.6 (5.0)	3.4 (3.1)	5.2 (6.8)	5.5 (3.6)

*Includes days spent in the ICU and days spent in non-ICU care in the hospital.

*Standard deviation was not available for this measure.

Table A2. Current (02/15/2021) age-specific vaccination rates in Colorado

Dates of first Vaccination Dose Administration	0-19 daily vaccination rate*	20-39 daily vaccination rate*	40-64 daily vaccination rate*	65+ daily vaccination rate*
12/15/2020 - 02/01/2020	43	2089	2576	4976
02/01/2020 - 02/15/2020	58	2080	3264	9019

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