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 include the impact of variants and vaccination on the risk of hospitalization. Specifically, we have now included functionality for vaccination to decrease the risk of symptomatic disease, hospitalization, and death among vaccinated individuals who are not protected from infection. We have additionally added in structure to simulate the impact of increasing prevalence of variants of concern (VoC) in Colorado, including B.1.1.7 and B.1.427/B.1.429.

Variants of Concern

Variants are assumed to affect the transmission rate, as well as the risk of hospitalization and death. Variants are allowed to affect transmission rate by including a multiplier to beta:

$$(pvar_1 * \theta_1) + (pvar_2 * \theta_2) + (1 - (\theta_1 + \theta_2))$$

Where $pvar_i$ is the proportionate increase in transmission due to a given variant, and θ_i is the proportion of infections in the population estimated to be attributable to that variant. Currently the model is set up to include B.1.1.7 and B.1.427/B.1.429 but could be expanded to account for other variants. Similar weighting is used to alter the risk of hospitalization and death in the model, accounting for the variant-specific increase in hospitalization or death and the proportion of infections attributed to the variant in the population.

We use data from CDPHE on the estimated prevalence of VoC to fit the model under the assumption of VoC-related increase in transmission, hospitalizations and deaths. By fitting to known prevalence of VoC, we can estimate the level of transmission control attributable to policy and behavior, accounting for VoC, or $TC_{PB.}$ We can use TC_{PB} to estimate overall levels of transmission control (TC) as well as to estimate the difference between observed TC and what TC would have been without the presence of the VoC.

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 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 the hospitalized compartment 8 days after the onset of symptoms [5]. We assume that the average length of hospital stay is dependent on age and is calculated from hospital LOS data. These values, shown in Table 2, are based on hospital data for COVID-19 patients in Colorado through the end of January. 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 – July, and mean length of stay August – 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.

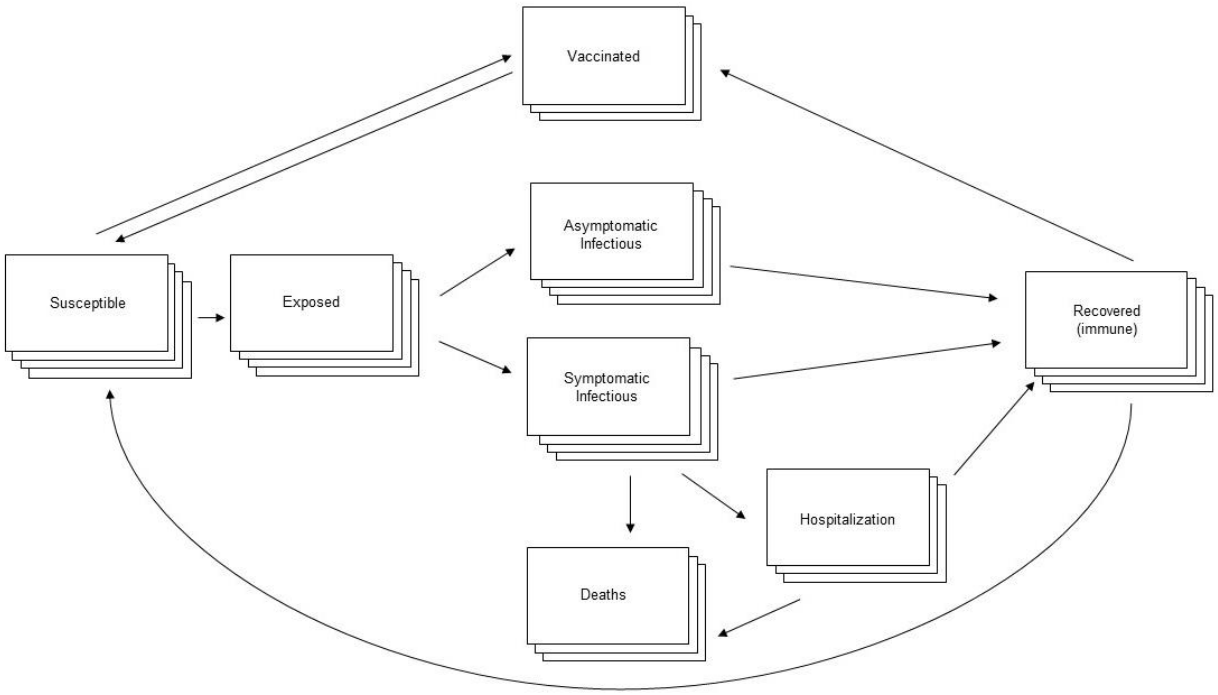

Figure 1. The structure of the SEIR model. The model is age-stratified, with separate compartments for each of four age groups 0-19, 20-39, 40-64, and 65+. The symptomatic infected compartment includes a 1-day period where individuals are infectious but not yet symptomatic.

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.

Vaccine

Two vaccines became available in Colorado on December 15th, 2020, with a third (Johnson and Johnson) introduced in March. As of 04/21/21, 2,388,773 individuals have received at least one dose, and 1,513,001 are fully immunized. The Moderna and Pfizer vaccines require two doses per

individual and there is evidence that some individuals are immune after the first dose. We have incorporated the assumption that these vaccines are 52% efficacious 14 days after the first dose and are assumed to become fully effective (90%) 32 days from time of receipt of first vaccine dose [1, 2]. The Johnson and Johnson vaccine requires only one dose and is assumed to become 66% effective 14 days after administration and become fully effective (72%) 28 days after vaccination {Sadoff, 2021 #632}. 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 daily age-distribution of vaccinations in Colorado in the past. 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-specific efficacy (as described above) 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 is also assumed to have an effect on hospitalization and death rates among infectious individuals in the model, proportionate to the number of vaccinated individuals who still become infected, such that vaccination is assumed to decrease risk of symptoms among infectious vaccinated individuals by 50%, decrease risk of hospitalization among symptomatic vaccinated individuals by 50%, and risk of death among infected vaccinated non-hospitalized individuals by 50%. 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 current vaccination rates and estimates of vaccine uptake by age group. Vaccination is assumed to be transmission blocking when effective. 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 who are vaccinated successfully are assumed to remain immune for two years before returning to the Susceptible compartment.

Table 1. Probabilities of symptoms by age group.

Age Category	**Proportion of infected individuals that develop symptoms from [12]**
0-19	0.11
20-39	0.36
40-64	0.56
65+	0.77

Table 2. Probability of hospitalization given symptomatic by age group over time. The probabilities of hospitalization 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 hospitalization before June 18th**	**Probability of hospitalization June 18th - Sep 30th**	**Probability of hospitalization after Sep 30th**
0-19	0.022705	0.022705	0.022705
20-39	0.036565	0.037471	0.023412
40-64	0.050782	0.049972	0.033124

65+	0.078988	0.072478	0.100437

Table 3. Length of hospital stay by age category from Colorado-specific COVID-19 hospitalizations based on Colorado COVID-19 patients with hospitalization onset through December 2020. Source data are described in the Appendix.

Age Category	Estimates for hospitalizations beginning before August 1st	Estimates for hospitalizations beginning August 1st or later
	Mean length of hospitalization (days)*	Mean length of hospitalization (days)*
0-19	5.83	5.57
20-39	6.37	5.23
40-64	10.54	8.49
65+	10.54	8.14

Mortality is based on the probability of death based on age and hospitalization status (Table 3). 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.

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 COVID-19 patients	Probability of death among non-hospitalized reported cases*
0-19	0.00551	0.00001
20-39	0.01472	0.00008
40-64	0.05751	0.00062
65+	0.16057	0.02797

* 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 by age.

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 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. We caution there is considerable variability in the length of stay by patient. 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 December 31, 2020 with surveillance through February 22nd, 2021.

Month of Admission	Ages 0 – 19, mean	Ages 20 – 39, mean	Ages 40 – 64, mean	Ages 65+, mean
ICU Patients (all days)*				
March	77.2	15.5	20.2	18.3
April	11.8	16.1	20.6	16.6
May	5.7	13.2	19.6	14.9
June	14.6	10.8	18.4	14.7
July	10.0	9.9	15.8	13.6
August	15.2	12.6	17.4	15.2
September	14.4	15.1	15.5	12.9
October	23.1	13.4	17.2	13.6
November	4.6	11.3	15.9	14.4
December	5.8	10.1	15.4	13.0
Non- ICU Hospitalization				
March	1.4	3.5	4.6	7.3
April	3.2	3.8	4.9	7.9
May	4.1	5.0	5.5	6.3
June	3.5	3.2	5.3	6.6
July	3.7	3.8	5.5	7.4
August	3.6	5.7	6.3	5.8
September	3.6	3.5	5.1	6.0
October	4.8	3.7	5.1	6.0
November	4.6	4.3	6.9	6.7
December	4.0	3.8	4.9	5.9

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

*Standard deviation was not available for this measure.

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