



MODELING THE IMPACT OF SOCIAL DISTANCING MEASURES ON THE SPREAD OF SARS-CoV-2 IN MINNESOTA

TECHNICAL DOCUMENTATION (UPDATED APRIL 8, 2020)

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Executive Summary

This document details the methods and data sources for the COVID-19 transmission model developed as part of a collaborative effort between the University of Minnesota (UMN) and the Minnesota Department of Health (MDH). It reflects updates through April 8, 2020 as part of developing version 2 of the model and associated output. The model structure, methods of calibration, and parameter values are informed by an exhaustive review of published data and other COVID-19 models in the literature.

At this early stage of the COVID-19 pandemic, there is still substantial uncertainty in many key model parameters. Results of this model, not included in this methods documentation, must be interpreted in light of the uncertainty and limitations detailed at the end of this document. As such, updates to the model and revisions to the accompanying documentation should be expected in the coming weeks as more research is published on COVID-19 cases in the United States.

Background

Eight days after the first case of SARS-CoV-2 infection was reported in Minnesota, MDH confirmed “community spread” of the novel virus on March 15, 2020. Since then progressively expansive social distancing orders have been issued by Governor Walz, required Minnesotans to avoid social contact outside the home where at all possible. In the absence of effective therapies or a vaccine, non-pharmaceutical interventions including case isolation and social distancing measures has been demonstrated to mitigate the impact of the COVID-19 pandemic. In response to the statewide epidemic, Minnesota also instituted school closures on March 13, 2020¹ followed by a statewide stay-at-home order on March 26, 2020.² To inform these and future decisions by the administration, businesses, and individuals, MDH partnered with UMN to conduct a modeling study. In this document, we provide an overview of the model, including model structure, assumptions, parameters and validation.

Methods

Model structure

We used an extended version of the susceptible-exposed-infected-recovered (SEIR) model that accounts for the age and comorbidity distribution of the population of Minnesota to assess the potential impact of specific non-pharmaceutical interventions (Figure 1). The model tracks the number of susceptible, exposed, infectious, and recovered persons in the state of Minnesota each day. Infection is assumed to result from contact between individuals in the susceptible (“S”) and infectious (“I”) states. Infected individuals initially enter an exposed (“E”) state prior to becoming infectious. A proportion of infectious individuals are assumed to progress clinically to the point of requiring either hospitalization (the “H” state) or an ICU bed (the “ICU” state); at this point, the model does not provide for hospitalized individuals to transition to the ICU. All infected individuals are able to recover regardless of their clinical state by progressing to the recovered “R” state, though they are assumed to do so at different rates depending on their clinical severity, their age, and comorbidity status (dichotomized as either having no comorbidities or having at least one). We assume that only those who reach the ICU state may die as a result of COVID-19 (by progressing to the dead “D” state) at rates conditional on their

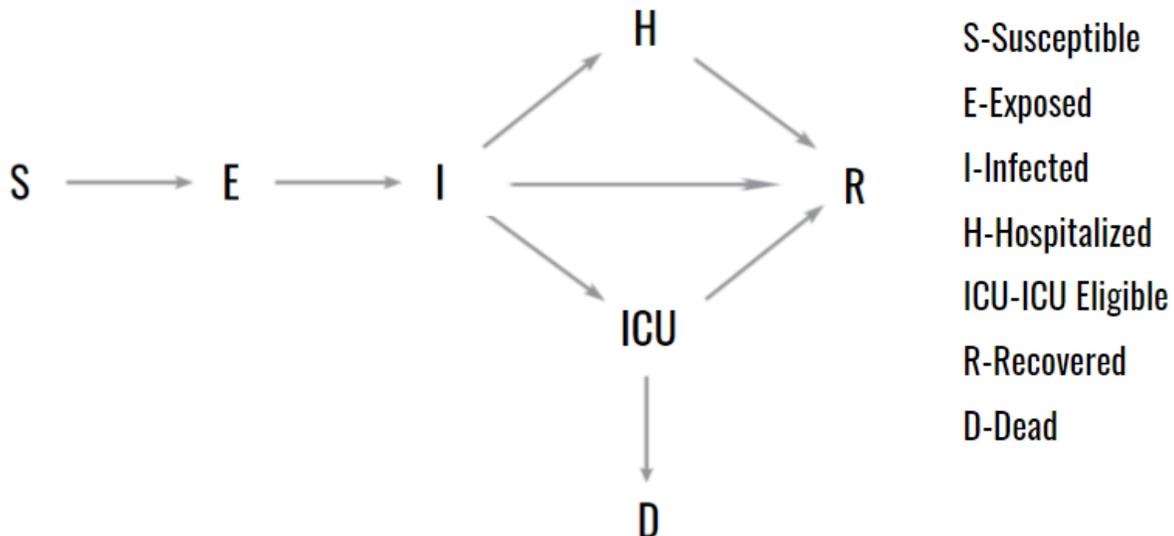
age, comorbidity status, and whether the state’s ICU capacity has been exceeded. Lastly, our model structure currently assumes complete immunity among those who recover for the duration of the modeled time period. The difference equations describing the flow of individuals through each compartment are presented in the Appendix.

Analysis

The difference equations presented in the Appendix (Equations 1-9) are discrete approximations of ordinary differential equations. Each difference equation contains parameters on the natural history of COVID-19 disease and other parameters. Because of the uncertainty in many model parameters, we conducted simple and probabilistic sensitivity analyses. For simple sensitivity analyses, we specified alternative plausible values for model parameters and re-ran the model. For probabilistic bias analysis, we repeatedly sampled model parameters from distributions representing our uncertainty in those parameters and re-ran the difference models with the sampled parameter values.

We describe model parameters in detail below, giving the value most supported by the literature as well as a range of values used in sensitivity analyses. We used the model to predict epidemiological outcomes from March 23, 2020 through March 22, 2021 to capture both the short and long term effects of different mitigation strategies. Epidemiologic outcomes include the cumulative number of SARS-CoV-2 infections, the cumulative number of COVID-19 deaths, the number of ICU beds needed at peak demand and time to reach intensive care unit (ICU) capacity. All analyses were run in R v3.5.3, a programming language and software environment used widely for statistical computation and development of data visualization.

Figure 1. Extended SEIR model for the COVID-19 epidemic in Minnesota, 2020



Key Model Parameters

Model parameters are summarized in Appendix Table S1.

Population Initial conditions

The age distribution of the population of Minnesota was based on data from the United States Census Bureau³ and the distribution of comorbidities was estimated from the Minnesota All Payer Claims Database (Table S2).⁴ The initial number of infections in the model were estimated from the number of confirmed cases, by age, reported by MDH as of March 22, 2020. We multiplied the number of confirmed cases by a factor to reflect the probability that an infected individual would be detected at that time given testing policies and availability. This generated an estimate of the total number of infected individuals in Minnesota on March 22, 2020. This parameter was calibrated to match the trend in number of deaths (see Model Calibration).

Natural History

We assumed a mean incubation period (time in the “E” state) of 5 days (range from 2 to 12.5 days^{6–10}), and that individuals remain infectious (time in the “I” state) for a mean of 8 days before requiring hospitalization, ICU care or recovering (range, 1 to 24 days).^{6,11–14} Both “E” and “I” states were modeled using gamma distributions, rather than standard exponential ones, for greater fidelity to observed data. This was accomplished by having 4 “E” states and 7 “I” states (see details below).

Contact and Transmission

In light of evidence of substantial heterogeneity in COVID-19 mortality by age and underlying comorbidities, we stratified our model population by nine 10-year age groups (0-9, ..., 70-79, 80+; indexed by α) and by comorbidity status (no comorbidities vs. ≥ 1 comorbidity; indexed by κ). An age-based contact matrix, $CM[i,j]$, was constructed to indicate the relative frequency of effective daily contact between age groups i and j , and which was informed by data from the 2008 POLYMOD study in Europe.⁵ We assumed the same contact patterns for those with and without underlying comorbidities and uniform contact behaviors across comorbidity status within members of the same age group. As newer data on US- and MN-specific social contact patterns become available, updating these inputs will provide insights more relevant to our local context.

The number of new infections per time step was calculated as the product of β , the probability of transmission per effective contact, λ , the number of effective contacts made with each age subgroup, and the prevalence of infection in each age group. λ_i (where i represents the i^{th} age group) is expressed as:

$$\lambda_i = \sum_{\alpha=1}^9 \frac{I_{\alpha}}{n_{\alpha} - D_{\alpha}} * CM[i, \alpha]$$

Where I_{α} is the number of infectious individuals in age group α , and D_{α} is the number of individuals who have died from COVID-19 in that age group. The square matrix $CM[i,\alpha]$ is the

number of contacts that individuals in age group i have with age group α per time step. New infections are driven by the age-specific contact patterns (CM[i,α]) and the age-specific proportions of the living population who are infectious in a given time step.

Values for β were calibrated to yield unmitigated R_0 values that were consistent with the World Health Organization, an analysis from China,⁶ and COVID-19 models of the epidemic for the UK,¹⁵ and for 11 European countries¹⁶ (unmitigated R_0 of 3.87; range, 2.5 – 6.0). Due to the inclusion of population stratification, age-specific mixing patterns, and gamma-distributed incubation and infectious periods, the analytical calculation of R_0 is complex. We therefore used empirical methods to estimate R_0 using doubling times in the first 20 days of our simulation (without mitigation). We varied β to be consistent with a plausible range of R_0 values from 2.5 - 4.7, which resulted in β values ranging from 0.025 to 0.045, with a β of 0.035 yielding an R_0 of 3.87.

Disease Progression and Mortality

We assumed a duration of 13.3 days (range, 7-23 days) from hospitalization to recovery^{12,17} and a duration of 10.3 days (range, 4-17) from ICU admission to recovery.^{12,17} Average lengths of hospital and ICU stay used in the model do not currently depend on age or comorbidity status. Age-specific proportions of infectious individuals requiring hospitalization or ICU care, as well as age-specific COVID-19 mortality rates, were informed by the Report of the WHO-China Joint Mission on Coronavirus Disease⁸ and have been utilized by other models.^{15,18} Hospitalization risks were reported per confirmed case in China. However, the proportion of infections that were detected in China is uncertain. In our initial model runs, we assumed that all infections were detected by the stringent symptom-based screening criteria in place in China at the time of these estimates. However, a recent estimate cited by the US CDC director Dr. Robert R. Redfield that 25% of all infections are asymptomatic.²¹ Therefore, in the base case we multiply hospitalization risks by 75% to reflect the 25% of infections that would not have been detected. We vary this parameter between 50-90% based on data from China and a recent model of the COVID-19 epidemic in Europe.^{16,18}

Age-specific COVID-19 mortality rates were obtained from a study of over 74,000 patients in China,¹⁹ which has informed other peer models.^{15,18} Although data on age-specific COVID-19 mortality is available from the US, we believe these may overestimate true mortality due to official advice from the US CDC that people with milder symptoms undergo home-based self-care²⁰ (which could deflate the denominator). For model simplicity, we estimated mortality risk among those with at least one comorbidity as a factor by which mortality risk is amplified, and which was informed by pooled estimates of comorbidity associated mortality. This factor was estimated by pooling data from three studies from China to calculate the relative risk of death (7.5) in those with at least one comorbidity versus those without pooled across three studies.^{8,19,20} In the absence of any data to inform the relative risk of excess mortality for those in the “ICU” state who would be denied life support in to critical cases who would not be provided life support in the event that hospitals reach ICU bed capacity, we multiplied the age-specific ICU mortality rate by 100, which results in an increase in mortality of between 1.5x and 16.5x, depending on age and comorbidity status.

The number of available ICU beds in the state of Minnesota was obtained through communication with MDH (as of April 4, 2020, the number is 2200; the original number was 235). The excess number of individuals in the “ICU” state who would be without a bed in each time step is calculated as the excess of such cases beyond the number of beds:

$$ICU_{overflow} = \frac{\sum_{\alpha=1}^9 ICU_{\alpha} - beds}{\sum_{\alpha=1}^9 ICU_{\alpha}}$$

Non-pharmaceutical intervention strategies

We examined the impact of various interventions that were implemented at different times and for varying durations. The interventions were to do nothing, have social distancing, or shelter in place. The model described above implements the “do nothing” intervention. Other interventions were assumed to have their effect by altering the contact matrix $CM[i,j]$. Social distancing was assumed to reduce contacts by half (50%) while shelter in place was assumed to reduce contacts by 80%.

Additional information about model parameters and model equations, estimates values, and corresponding references are provided in the Appendix.

Model Calibration

The model was calibrated to reproduce the number of daily deaths observed in MN. The parameter that was calibrated in this step was the probability of an infection being detected in MN prior to March 22, 2020. A very low probability of detection (0.01) allowed good fit with observed data. After calibration, the model is able to reproduce the observed number of deaths in MN (through April 5, 2020) and depicts the predicted deaths over the coming weeks. However, these predicted deaths should be interpreted with caution since some of the observed deaths may be due to clustering of infections in nursing homes which the model does not currently capture.

Limitations

- **A large number of parameter values continue to be informed by studies from China.** Given the suboptimal testing for SARS-CoV-2 in many settings, reports from China provide the most complete and detailed data available, as active monitoring systems were implemented throughout the entire country relatively early in the outbreak. However, wherever possible our model parameters are informed directly by data from Minnesota, in particular demographic information including distribution of comorbidities across age groups as well as data on COVID-19 cases and deaths.
- **Published estimates of the basic reproductive number (R_0) are highly variable.** Probability of transmission per effective contact is currently estimated by calibrating the model to published values of the R_0 for SARS-CoV-2. It is important to note that R_0 is a dynamic value that can vary by geography and temporally. We anticipate continual updates to published R_0 values, particularly as more data from the US become available; results of this model will also change accordingly.

- **Death outside of ICU care settings is still poorly understood.** Currently, our model applies mortality only from the ICU. We recognize that this is not the only realistically viable option. As data become available for alternative paths in particular infection or hospitalization, we will expand our model and update the results accordingly.
- **There is still great uncertainty around proportions of infections that remain undetected or are asymptomatic.** Testing availability for SARS-CoV-2 is suboptimal across the US; more challenging for model-based predictions, however, is the heterogeneity in testing policies across states and over time. In addition, new information is continually emerging regarding infections acquired from presumably asymptomatic cases. Updates on these epidemiologic features will also necessarily alter estimates generated by this model.
- **The role of asymptomatic infection in contributing to the spread of SARS-CoV-2 is uncertain.** The role of asymptomatic infections and whether and how they contribute to the spread of SARS-CoV-2 is still being determined. More robust data that supports a role in the spread will necessitate revisions to the model structure, which will also alter the estimates generated by this model.
- **Observed versus predicted reductions in contacts based on different mitigation strategies.** The modeled reductions in contacts and the subsequent impact on ICU capacity and deaths are based on reductions in contact patterns that broadly correspond to closing of schools, universities, places of work etc. The extent to which contacts are reduced in reality and for how long will affect model predictions.

Next Steps

In the service of informing decision-making and public interest into the pandemic and its response, the research partnership between the University of Minnesota School of Public Health and MDH is committed to continuing to refine and expand this disease model.

This will consist of reviewing the literature and updating parameter estimates on an ongoing basis, which is particularly important as robust U.S. or MN data (where applicable) become available. In addition, the model structure and underlying assumptions will continue to be subject to revisions as we learn more about the epidemiology of SARS-CoV-2. Finally, the research team is exploring ways to make the model useful to a broader set of application, including by bringing in new information on contact patterns, exploring ways to incorporate geographic differences in disease spread and impact, and considering ways to model mitigation strategies that turn on and off.

Both teams are committed to make new information available as it materializes. We are also working towards posting a user interface and programming code.

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Appendix

Equations E1-9

$$S_{\alpha,\kappa} = -\beta * \lambda_{\alpha} * S_{\alpha,\kappa} \quad (1)$$

$$E1_{\alpha,\kappa} = \beta * \lambda_{\alpha} * S_{\alpha,\kappa} - \text{prob}(t_E) * E1_{\alpha,\kappa} \quad (2)$$

For states E2-En the following equation is used:

$$En_{\alpha,\kappa} = \text{prob}(t_E) * E(n-1)_{\alpha,\kappa} - \text{prob}(t_E) * En_{\alpha,\kappa} \quad (3)$$

$$I1_{\alpha,\kappa} = \text{prob}(t_E) * En_{\alpha,\kappa} - \text{prob}(t_I) * I1_{\alpha,\kappa} \quad (4)$$

For states I2-In the following equation is used:

$$In_{\alpha,\kappa} = \text{prob}(t_I) * I(n-1)_{\alpha,\kappa} - \text{prob}(t_I) * In_{\alpha,\kappa} \quad (5)$$

$$H_{\alpha,\kappa} = \text{prob}(t_I) * \text{frac}_{hosp,\alpha} * \delta * (1 - \text{frac}_{ICU,\alpha}) * In_{\alpha,\kappa} - \text{prob}(rec_H) * H_{\alpha,\kappa} \quad (6)$$

$$\begin{aligned} ICU_{\alpha,\kappa} = & \text{prob}(t_I) * \text{frac}_{hosp,\alpha} * \text{frac}_{ICU,\alpha} * \delta * In_{\alpha,\kappa} \\ & - \text{prob}(t_{ICU,\alpha,b}) * (1 - ICU_{overflow}) * ICU_{\alpha,\kappa} \\ & - \text{prob}(t_{ICU,\alpha,n}) * (ICU_{overflow}) * ICU_{\alpha,\kappa} \end{aligned} \quad (7)$$

$$\begin{aligned} R_{\alpha,\kappa} = & \text{prob}(t_I) * (1 - \text{frac}_{hosp,\alpha}) * \delta * In_{\alpha,\kappa} + \text{prob}(rec_H) * H_{\alpha,\kappa} \\ & + \text{prob}(rec_{ICU,b}) * \text{prob}(t_{ICU,b}) * (1 - ICU_{overflow}) * ICU_{\alpha,\kappa} \\ & + \text{prob}(rec_{ICU,n}) * \text{prob}(t_{ICU,n}) * (ICU_{overflow}) * ICU_{\alpha,\kappa} \end{aligned} \quad (8)$$

$$\begin{aligned} D_{\alpha,\kappa} = & (1 - \text{prob}(rec_{ICU,b})) * \text{prob}(t_{ICU,b}) * (1 - ICU_{overflow}) * ICU_{\alpha,\kappa} \\ & + (1 - \text{prob}(rec_{ICU,n})) * \text{prob}(t_{ICU,n}) * (ICU_{overflow}) * ICU_{\alpha,\kappa} \end{aligned} \quad (9)$$

Table S1. Parameter definitions, values, and sources

Name	Definition	Estimate (range)	Data source setting
β	Probability that contact with an infectious person results in an infection	Calculated using estimates or R_0 : 3.87 (range 2.5-6.0) ^{6,15,16,22} (details of β calculations in methods section)	China, UK, multiple European countries
λ	Number of contacts per time step that one age group has with infected individuals	See methods section for calculation	8 European countries
prob(case detection)	The percentage of cases which had been detected on March 22, 2020	0.01 (0.005-0.05)	Calibrated to COVID-19 death counts in Minnesota
prob(τ_E)	Probability of transitioning through an exposed state at each time step	Calculated from estimated incubation period: 5 days (range from 2 to 12.5 days) ⁶⁻¹⁰	China, national
prob(τ_I)	Probability of transitioning through an infected state at each time step	Calculated using estimated time from symptom onset to hospital or ICU: 8 days (range, 1 to 24 days). ^{6,11-14}	China (Wuhan)
prob($\tau_{ICU,b}$)	Probability of transitioning out of the ICU at each time step when a bed is accessible	Calculated using estimated time from ICU admission to recovery: 7 days (range, 3-10) ¹⁷	China (Wuhan)
prob($\tau_{ICU,n}$)	Probability of transitioning out of the ICU at each time step when a bed is not accessible	Calculated from estimated time from ICU admission to recovery; 8 days (range, 6-12) ¹⁷	China (Wuhan)
fra _{Chosp}	Fraction of individuals who were hospitalized with a detected infection	Age specific (range from 0.001 to 0.273 per 10 person days) ^{15,18} See table S3	China (national; adjusted for UK/US settings)

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Name	Definition	Estimate (range)	Data source setting
fra_{ICU}	Fraction of hospitalized individuals who need ICU care	Age specific (range from 0.050 to 0.709 per 10 person days) ^{15,18} See table S3	China (national, adjusted for UK/US settings)
$\text{prob}(\text{re}_{\text{CH}})$	Probability of recovery for hospitalized individuals (per time step)	Calculated from estimated duration of hospitalization: 13.3 days (range, 7-23) ^{12,17}	US (Seattle); China (Wuhan)
$\text{prob}(\text{re}_{\text{ICU},b})$	Probability of recovering at each time step when in the ICU when a bed is accessible	Calculated from estimated duration of time in ICU and age-specific mortality rates ^{19,23,24} for those in the ICU state: 10.3 days (range, 4-17) ^{12,17} See table S3	US (Seattle); China (Wuhan); Italy (national)
$\text{prob}(\text{re}_{\text{ICU},n})$	Probability of recovering at each time step when in the ICU when a bed is not accessible	Calculated from estimated duration of time in ICU and age-specific mortality rates ^{19,23,24} for those in the ICU state: 10.3 days (range, 4-17) ^{12,17} See table S3	US (Seattle); China (Wuhan); Italy (national)
δ	Probability of being detected given an infection after March 22, 2020?	0.75 (range, 0.5-0.9) ²¹	US (national)
$\text{ICU}_{\text{overflow}}$	Proportion of individuals who are in the ICU but do not have a bed, when the ICU is not exceeding capacity this will be 0	Calculated, see methods section	

Table S2. Proportion of Minnesotans with one or more underlying conditions by age group estimated from the MN all payer claims data

Age group (years)	>=1 underlying condition
0 to 9	0.023
10 to 19	0.051
20 to 29	0.063
30 to 39	0.118
40 to 49	0.222
50 to 59	0.367
60 to 69	0.500
70 to 79	0.663
80+	0.777

Table S3. Age-specific hospitalization parameter estimates

Age group (years)	Percentage of detected cases needed hospitalization	Percentage of hospitalized cases requiring ICU	ICU mortality rate (per 10 person-days)
0 to 9	0.1%	5.0%	0.000
10 to 19	0.3%	5.0%	0.002
20 to 29	1.2%	5.0%	0.001
30 to 39	3.2%	5.0%	0.002
40 to 49	4.9%	6.3%	0.003
50 to 59	10.2%	12.2%	0.009
60 to 69	16.6%	27.4%	0.024
70 to 79	24.3%	43.2%	0.056
80+	27.3%	70.9%	0.111