

Appendix 1 (as supplied by the authors): Mathematical modeling of COVID-19 transmission and mitigation strategies in the population of Ontario, Canada: Technical Appendix

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Model overview

We developed an age-structured compartmental model that describes COVID-19 transmission in the province of Ontario, Canada. We used a modified ‘Susceptible-Exposed-Infectious-Recovered’ framework that incorporated additional compartments to account for public health interventions, different severities of clinical symptoms, and hospitalization risk. An overview of the model compartments and movements between them is provided in **Figure 1** of the main text. The model was run for a period of two years and we assumed that recovered individuals remain immune from re-infection for the duration of the epidemic. Individuals remained infectious until they recovered or were hospitalized; we did not model transmission within healthcare settings. For simplicity, we assumed that all deaths occurred in cases requiring intensive care.

Model equations

For individuals of a given age group (i) and health status (j), the model is described by the following system of differential equations. Model states are provided in **Table S1** and parameter definitions are provided in **Table S2**. Parameter values used in the model are provided in the main text. Details on parameter value derivations are provided below.

$$\frac{dS_{i,j}}{dt} = -\lambda_{i,j}S_{i,j} - \mu S_{i,j} + \mu S_{i-1,j}$$

$$\frac{dE_{i,j}}{dt} = (1 - \delta_e)\lambda_{i,j}S_{i,j} - \epsilon E_{i,j} - \mu E_{i,j} + \mu E_{i-1,j}$$

$$\frac{dQ_{i,j}}{dt} = \delta_e\lambda_{i,j}S_{i,j} - \epsilon Q_{i,j} - \mu Q_{i,j} + \mu Q_{i-1,j}$$

$$\frac{dA_{i,j}}{dt} = \epsilon E_{i,j} - \gamma_p A_{i,j} - \mu A_{i,j} + \mu A_{i-1,j}$$

$$\frac{dW_{i,j}}{dt} = \epsilon Q_{i,j} - \gamma_p W_{i,j} - \mu W_{i,j} + \mu W_{i-1,j}$$

$$\frac{dB_{i,j}}{dt} = (1 - \sigma_{s_{i,j}})\gamma_p A_{i,j} - \gamma_m B_{i,j} - \gamma_d B_{i,j} - \mu B_{i,j} + \mu B_{i-1,j}$$

$$\frac{dC_{i,j}}{dt} = \sigma_{s_{i,j}}\gamma_p A_{i,j} - \gamma_s C_{i,j} - \mu C_{i,j} + \mu C_{i-1,j}$$

$$\frac{dY_{i,j}}{dt} = (1 - \sigma_{s_{i,j}})\gamma_p W_{i,j} - \gamma_m Y_{i,j} - \mu Y_{i,j} + \mu Y_{i-1,j}$$

$$\frac{dZ_{i,j}}{dt} = \sigma_{s_{i,j}}\gamma_p W_{i,j} - \gamma_s Z_{i,j} - \mu Z_{i,j} + \mu Z_{i-1,j}$$

$$\frac{dG_{i,j}}{dt} = \gamma_d B_{i,j} - \gamma_i G_{i,j} - \mu G_{i,j} + \mu G_{i-1,j}$$

$$\frac{dH_{i,j}}{dt} = (1 - \sigma_{c_{i,j}})\gamma_s(C_{i,j} + Z_{i,j}) - \psi H_{i,j} - \mu H_{i,j} + \mu H_{i-1,j}$$

$$\frac{dH1_{i,j}}{dt} = \sigma_{c_{i,j}}\gamma_s(C_{i,j} + Z_{i,j}) - \pi_a H1_{i,j} - \mu H1_{i,j} + \mu H1_{i-1,j}$$

$$\frac{dI_{i,j}}{dt} = \pi_a H1_{i,j} - \pi_b I_{i,j} - \mu I_{i,j} + \mu I_{i-1,j}$$

$$\frac{dH2_{i,j}}{dt} = (1 - \kappa_{i,j})\pi_b I_{i,j} - \pi_c H2_{i,j} - \mu H2_{i,j} + \mu H2_{i-1,j}$$

$$\frac{dR_{i,j}}{dt} = \gamma_i G_{i,j} + \gamma_m(B_{i,j} + Y_{i,j}) + \psi H_{i,j} + \kappa_{i,j}\pi_b I_{i,j} + \pi_c H2_{i,j} - \mu R_{i,j} + \mu R_{i-1,j}$$

Cumulative number of infections (Inc), detected cases (Detect), hospitalized cases (Hosp), and deaths (D) are

calculated as follows:

$$\frac{dInc_{i,j}}{dt} = \lambda_{i,j} S_{i,j}$$

$$\frac{dDetect_{i,j}}{dt} = \gamma_d B_{i,j}$$

$$\frac{dHosp_{i,j}}{dt} = \gamma_s (C_{i,j} + Z_{i,j})$$

$$\frac{dD_{i,j}}{dt} = \kappa_{i,j} \pi_{b_{i,j}} I_{i,j}$$

Force of infection

To capture variability in transmission, specifically the observation that the basic reproduction number (R_0) is over-dispersed, with some cases transmitting to many others (superspreader events), while many other cases transmit much less, we added a volatility term (ω) such that the average R_0 value was 2.3 but was allowed to vary over time in an autocorrelated manner (Camacho et al. 2015). The model was initiated with 750 prevalent cases (based on 150 number of cases on March 19, 2020 and an assumed reporting rate of 20%), which were randomly distributed across the infectious compartments.

The rate at which susceptible individuals are infected ($\lambda_{i,j}(t)$) depends on the number of daily contacts (c_{ijkl}), the transmission probability (β), volatility in the transmission parameter ($\omega(t)$), the reduction in transmission associated with isolation and quarantine (rr_i), and the reduction in contacts associated with social distancing (rr_{c_i}), where i and k represent the age groups, and j and l the health status groups of the susceptible and infectious populations, respectively:

$$\lambda_{i,j}(t) = \beta \omega(t) \sum_{k=1}^{16} \frac{c_{ik} rr_{c_i} (A_{k,l} + B_{k,l} + C_{k,l} + rr_i (G_{k,l} + W_{k,l} + Y_{k,l} + Z_{k,l}))}{N_{k,l}}$$

Population structure, aging, and births

The population was divided into 5-year age groups using 2019 population estimates for Ontario (Statistics Canada 2019). The last age group ($i = 16$) included the population aged 75 and older. We assumed a life expectancy of 80 years. The rate of exit from each age group (μ) and into the next age group was calculated as:

$$\frac{1}{da}$$

where da is the width of the age group. We assumed a constant population size. For the youngest age group, the rate of entry into the susceptible group was calculated as:

$$\mu_{16} N_{16}$$

and rate of entry into all other compartments was 0 (i.e., all new individuals were assumed to be susceptible to infection).

We used age-specific estimates of underlying medical conditions associated with enhanced vulnerability to severe outcomes to further stratify the model. We obtained comorbidity estimates by age from the Canadian Community Health Survey for Ontario (Statistics Canada 2016). We included the following conditions: hypertension, heart disease, asthma, stroke, diabetes, and cancer. For younger age groups (<12 years) we used estimates from Moran et al. (Moran et al. 2009). We excluded chronic obstructive pulmonary disease (COPD) from the list of conditions for this analysis, because data on this condition are only collected for certain age groups and we were unable to extract joint probabilities of multiple underlying medical conditions by age using the public use files when COPD was included. For a given age group, the number of daily contacts was proportionately divided among those with and without underlying conditions. We assumed

no difference in susceptibility to infection by health status, but those with underlying conditions were more likely to present with severe disease. Estimates

Interventions

Physical distancing measures were implemented as age-specific reductions in contact rates (rr_{c_i}). Enhanced testing was implemented as an increased probability of detection of mild cases and increased quarantine of exposed cases. Assumptions for the model scenarios are provided in the main text (**Table 2**). We explored different fixed durations of interventions. We also explored scenarios where interventions were implemented in a dynamic manner. Interventions were turned on for an initial 4-week period when a pre-determined threshold was passed (200 cases in ICU) and was maintained until cases fell below that threshold. The intervention was allowed to cycle on or off, whenever the number of cases exceeded or fell below the threshold, respectively. For these scenarios, we calculated the intervention intensity as the proportion of 2-year model time period during which the intervention was implemented.

Model states and parameters

Table S1: Model states and definitions.

State	Definition
S	Susceptible
E	Exposed
Q	Exposed, quarantined
A	Infectious, pre-symptomatic
W	Infectious, pre-symptomatic, in isolation
B	Infectious - mild
C	Infectious - severe
Y	Infectious - mild, in isolation
Z	Infectious - severe, in isolation
G	Isolated - mild, not previously in quarantine
H	Hospitalized, never in ICU
$H1$	Hospitalized, pre-ICU admission
I	Hospitalized, in ICU
$H2$	Hospitalized, post-ICU
R	Recovered
D	Dead
Inc	Cumulative incidence
$Detect$	Cumulative incidence of mild cases detected and isolated
$Hosp$	Cumulative incidence of hospitalizations

Table S2: Parameter symbols and definitions.

Symbol	Definition
i	Age group
j	Health status
μ	Rate of entry/exit from age group
λ	Force of infection
ρ	Rate of entry into quarantine
ϵ	1/Average duration of exposed state
γ_p	1/Average duration of pre-symptomatic infectious period
γ_s	1/Average duration of symptomatic infectious period (severe infection)
γ_m	1/Average duration of symptomatic infectious period (mild/moderate infection)
γ_d	1/Average time to case detection

Symbol	Definition
γ_i	1/Average time in isolation
β	Transmission probability
rr_i	Relative risk of transmission with isolation
rr_s	Relative number of contacts with physical distancing
δ_e	Probability exposed case is quarantined
σ_s	Probability case is severe
σ_i	Probability severe case enters intensive care unit
ψ	1/Average time in hospital (non-ICU case)
π_a	1/Average time in hospital, pre-ICU admission (ICU case)
π_b	1/Average time in ICU (ICU case)
π_c	1/Average time in hospital, post-ICU admission (ICU case)
κ	Probability of death among ICU cases
θ	Number of contacts
$\omega(t)$	Volatility term for reproduction number

Model parameterization

Model parameters were guided by the available data.

Basic reproduction number and serial interval

The basic reproduction number was estimated as 2.3 based on the estimates by Li and colleagues (Q. Li et al. 2020). The incubation period was estimated as 5 days according to the estimates of Lauer et al. (Lauer et al. 2020). However, it increasingly appears that the R_0 for COVID-19 is overdispersed (Lloyd-Smith et al. 2005), with remarkably little transmission in some contexts (Wu et al. 2020; Burke et al. 2020), and superspreading events in others (Mahbubani 2020). We attempted to simulate such overdispersion by incorporating volatility into our R_0 estimates (Camacho et al. 2015). From Woelfel et al. (Woelfel et al. 2020), we can see that mean duration of shedding of culturable virus is 7 days (gamma distribution with $k, \theta = (13.7, 0.5)$). This corresponds to an approximate serial interval of 8-9 days. However, other investigators have suggested far shorter serial intervals (4.5) based on contact follow-up data (Tindale et al. 2020). Perhaps the best estimate to date comes from Bi et al. (Bi et al. 2020), who followed the Shenzhen contacts of known cases from Wuhan, at a time when Shenzhen had little disease transmission. In this setting, serial intervals were estimated at 6 days, representing a midpoint in the plausible range of estimates. As such, we used a 6-day serial interval in our basecase analysis.

Identification of cases with mild illness

Most COVID-19 cases appear to be relatively mild (Guan et al. 2020), and truly asymptomatic infection is likely a distinct entity; estimates based on testing on a captive population on the Diamond Princess cruise ship suggest 17-30% of infections are asymptomatic (Mizumoto et al. 2020; Nishiura et al. 2020). In epidemic settings, it has been estimated that only 14% of infections are identified (R. Li et al. 2020). As severity appears to be age-related, it is likely that mild cases are more common in younger ages, and that much of the apparent age-related differential in infection risk (China Centers for Disease Control, n.d.) simply represents under-ascertainment of infection in younger individuals (Verity et al. 2020). In settings which actively tested for pediatric cases, children were found to be infected at the same rates as adults (Bi et al. 2020). Consequently, we assumed no difference in infectivity of virus across age groups.

Length of stay and probability of intensive care among hospitalized individuals

Among 1099 individuals with documented COVID-19 infection, Guan and colleagues found that 173 (15.7%) met ATS/IDSA criteria for “severe pneumonia” (Metlay et al. 2019) and required hospitalization for critical care (Guan et al. 2020). Average time from symptom onset to hospitalization was 7 days, with individuals requiring intensive care admitted to ICU an average of 3 days after admission (Wang et al. 2020). Among individuals who did not require ICU and were discharged home, median length of stay was 10 days; there may be a downward bias in this estimate due to censoring as a result of the relatively short duration of

observation in this study (Wang et al. 2020). Between 20 and 26% of individuals with severe pneumonia required ICU admission (Wang et al. 2020; Yang et al. 2020).

Probability of requirement for hospitalization and intensive care

In our model we consider ICU care as synonymous with requirement for mechanical ventilation. This is a simplifying assumption. We back-estimated the probability of intensive care hospitalization among identified cases by making an additional simplifying assumption: that most deaths occurred in individuals who received intensive care (as a result of acute respiratory distress syndrome). Age-specific numbers of deaths reported in (The 2019-nCoV Outbreak Joint Field Epidemiology Investigation Team and Qun 2020) were inflated by dividing them by death risks by age group reported by Yang et al. (Yang et al. 2020) to create **Table S3** below, with estimates of age-specific, per-case requirements for ICU care. Age-specific risk estimates for ICU care by age were not available; we assumed that among individuals with severe pneumonia the risk of intensive care requirement was 26%, based on ICU-care requirement in 36/138 individuals reported by Wang et al. (Wang et al. 2020). This is similar to the 20.6% estimate reported by Guan et al. (Guan et al. 2020).

As noted above, individuals with comorbid medical conditions were more likely to experience severe pneumonia requiring hospitalization for care than were individuals without comorbidity. However, the proportion of individuals in ICU (40%) (Yang et al. 2020) was the same as the proportion in hospital with severe pneumonia (39%) (Guan et al. 2020), suggesting that, conditional on severe pneumonia, comorbidity did not increase the risk of being admitted to ICU, though it did increase the risk of death once in the ICU (Yang et al. 2020). Among all patients with COVID-19 identified 23.7% had at least one underlying comorbidity (Guan et al. 2020). We estimated hospitalization risk among individuals with and without comorbidity, by age, as follows: we estimated total numbers of cases by comorbidity and age by multiplying case numbers by 0.237 (as age-specific comorbidity estimates for cases were not available). We then estimated hospitalized case numbers by age and comorbidity by multiplying hospitalized case numbers for each age group by 0.4. Hospitalization risk by age and comorbidity was then estimated by dividing hospitalized case estimates by case estimates for each age and comorbidity group. Our estimates appear in **Table S4** below.

Length of stay and risk of mortality in the ICU

We made the simplifying assumption that all deaths in hospitals occurred in individuals receiving ICU care. Currently the best reference on ICU survival and length of stay in COVID-19 is Yang et al. (Yang et al. 2020). Estimates of proportion surviving by age from Yang et al. are presented in the table below. Due to the small numbers of younger individuals in this paper, we modeled probability of death using Poisson regression; these model-based estimates were used to parameterize the transmission model.

Death risks differed according to the presence or absence of comorbidities. Using data provided in by Yang et al. (Yang et al. 2020) it was possible to estimate the relative risk of death among individuals with comorbidities (53% died) compared to those without (20% died); relative risk of death was 2.65. As 21/52 (40%) of individuals in the ICU had chronic health conditions, it was possible to estimate age-specific case fatality (CFR_A) by solving the relation:

$$(1 - p)M + 2.65pM = CFR_A$$

where M is mortality in those without underlying health conditions and p is the proportion with chronic health conditions. We assumed relative risk of death with chronic health conditions was constant across age groups because age-specific comorbidity data were not available. Using the above relation we were able to generate the mortality estimates presented in **Table S5** below.

Length of stay for individuals who died in the ICU was estimated based on death hazards derived from the Kaplan-Meier curve published by Yang et al. (Yang et al. 2020), according to the relation:

$$h_t = \frac{-\ln\left(\frac{(1-p)Die(t)}{(1-p)Die(t-1)}\right)}{t}$$

We estimated the daily hazard of death as 0.039, with average ICU stay among non-survivors estimated as $(1/0.039)$ 26 days (using a declining exponential approximation of life expectancy (DEALE)). Among

Table S3: Estimates of hospitalization and ICU admission in patients with COVID-19 in China

Age Group	Cases	Deaths	Risk of death in ICU	N in ICU	Risk of ICU among cases	Risk of ICU care among hospitalized cases	N in hospital	Risk of severe pneumonia among cases
Under 20	965	1	0.283	4	0.004	0.261	14	0.014
20-29	3619	7	0.283	25	0.007	0.261	945	0.026
30-39	7600	18	0.283	64	0.008	0.261	244	0.032
40-49	8571	38	0.379	100	0.012	0.261	384	0.045
50-59	10008	130	0.509	255	0.026	0.261	979	0.098
60-69	8583	309	0.683	452	0.053	0.261	1734	0.202
70-79	3918	312	0.917	340	0.087	0.261	1304	0.333
80+	1408	208	1.000	208	0.148	0.261	797	0.566

Table S4: Estimates of hospitalization by health status

Age Group	Cases with comorbidity	Cases without comorbidity	Cases admitted	Admitted with comorbidity	Admitted without comorbidity	Risk of severe pneumonia with comorbidity	Risk of severe pneumonia without comorbidity
Under 20	229	736	14	5	8	0.024	0.011
20-29	859	2760	95	38	57	0.044	0.021
30-39	1805	5795	244	98	146	0.054	0.025
40-49	2036	6535	384	154	230	0.075	0.035
50-59	2377	7631	979	392	587	0.165	0.077
60-69	2038	6545	1734	694	1040	0.340	0.159
70-79	930	2988	1304	522	783	0.561	0.262
80+	334	1074	797	319	478	0.954	0.446

individuals who had not died after 28 days of observation, 17 of 20 had been discharged from the ICU, leading to an estimated daily hazard of discharge of 0.068, and an average length of stay of 15 days. Weighted average hazard of discharge or death was:

$$\frac{20 * 0.068 + 32 * 0.039}{52} = 0.047$$

with an average length of stay of 21 days. Following discharge from ICU, 8 of 17 individuals had been discharged from the hospital after an observation time estimated at 13.2 days (based on 28 day observation – 14.8 day average length of stay in ICU among survivors). This led to an estimated hazard of discharge of 0.048, and length of stay after ICU discharge of 21 days.

Table S5: Mortality in the ICU, by age and presence of comorbidity

Age Group	No Comorbidity	Comorbidity
Under 40	0.17	0.45
40-49	0.23	0.60
50-59	0.31	0.81
60-69	0.41	1.00
70-79	0.55	1.00
80+	0.60	1.00

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