Understanding the evidence base for COVID-19 mitigation and containment strategies in Canada

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INTRODUCTION

The ongoing pandemic of 2019 coronavirus disease (COVID-19, caused by the virus SARS-CoV-2) poses a significant threat to public health and economic wellbeing globally and within individual countries. The first COVID-19 case in Canada was documented on January 23, 2020 in Toronto.[1] As of 13 April, 2020, 25.663 cases including 780 deaths have been reported across all Canadian provinces and territories.[2] The apparent exponential rise in COVID-19 cases across Canada suggests that, in the absence of stringent mitigation measures, the epidemic trajectory may resemble experience in other countries where surges in cases exceeded the capacity of hospitals and intensive care units.

Given no vaccines or specific chemotherapies, social distancing measures are the principle strategy by which public health authorities have aimed to lessen the burden of COVID-19. Social distancing aims to reduce the frequency of interaction among members of a population in an effort to slow transmission of infection. In practice, strategies have included closure of businesses (e.g. restaurants, bars), schools, workplaces, as well as public gathering spaces, and issuing of stay-at-home orders. The considerable societal and economic impact of these interventions underscores the need to understand their potential impacts on transmission.[3] In parts of Canada, large-scale aggressive mitigation strategies came into force in the second half of March, 2020, after similar measures were implemented in severely affected regions of the United States and western Europe.

Limited information is available about technical considerations informing the implementation and ultimate relaxation of social distancing measures at both federal and provincial levels in Canada, although the decisions are reported to be informed by mathematical modeling.[4,5] Here we outline key theoretical principles of epidemic dynamics alongside practical considerations about COVID-19 in Canada. We aim to identify points where clarity is needed to understand the assumptions of models informing Canadian policymaking, and the specific interventions for the Canadian population should expect to prepare.

UNDERSTANDING THE EVIDENCE BASE FOR CANADIAN DECISION-MAKING

Cumulative infection prevalence

A recent technical briefing on internal modeling conducted by the Public Health Agency of Canada (PHAC) revealed three scenarios guiding response:[6]

1. No control effort, leading to a cumulative prevalence of infection in the range of 70-80%;

2. "Stronger" epidemic control with high degrees of physical distancing and high proportions of cases and their contacts traced and isolated or quarantined, leading to a cumulative prevalence of infection in the range of 1-10%;

3. "Weaker" controls (aiming to delay and reduce the peak) with low degrees of physical distancing, low proportions of cases and their contacts traced and isolated or quarantined, leading to a cumulative prevalence of infection in the range of 25-50%.

However, PHAC's technical basis for arriving at these findings was not disclosed. Traditionally, epidemics are not expected to self-extinguish until the number of immune individuals is sufficiently high that those who are infectious transmit, on average, to fewer than one susceptible contact. We address the relationship between the basic reproductive number (R_0)—indicating the number of new infections each infectious individual is expected to cause in a fully-susceptible population—and the effective reproductive number (R_E), indicating the number of infections expected under prevalent levels of immunity—in **Figure 1**. Alongside this, we plot estimates of the prevalence of immunity needed to achieve reductions in the incidence of new cases—as may be expected to occur when depletion of the susceptible population leads to R_E=1.

It should be noted that the prevalence of immunity at which R_E=1 indicates only the circumstances under which new incident infections would be expected to reach their peak and decline, rather than the cumulative proportion of the population infected. Definitionally, the cumulative prevalence of infection would be higher than what we plot in **Figure 1B**. For R_0=2.19, as reported by PHAC, the proportion of the population infected at the time the epidemic is expected to begin its decline would be around 54%. Notably, this estimate of infection prevalence at the timing of an epidemic peak is greater than expected cumulative prevalence of infection reported under PHAC modeling scenarios of either "stronger" and "weaker" epidemic control.

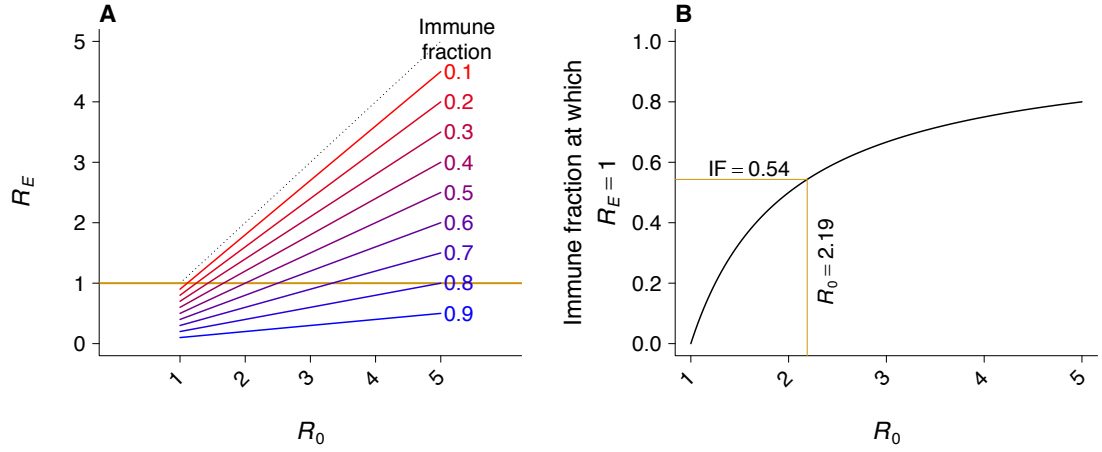

Figure 1: Theoretical considerations. We illustrate the relation between the basic reproductive number (R_0) and the effective reproductive number (R_E) under varying levels of population immunity (**A**). If depletion of the susceptible population is considered to be the primary mechanism reducing R_E, the prevalence of immunity at which reductions in incidence of new infections can be expected follows the curve we plot in (**B**). For R_0=2.19, as estimated by PHAC for transmission dynamics in Canada, incidence is expected to peak when 54% of the population is infected.

Epidemic dynamics in Canada

If herd immunity resulting from natural transmission is not expected to resolve Canada's epidemic, it is important to understand what other assumptions are contributing to scenarios where 1-10% or 25-50% of the population is ultimately infected in PHAC modeling. We note that quantities such as reproductive numbers and transmission rates are not fixed properties of pathogens, and instead reflect transmission dynamics under prevailing real-world conditions including non-pharmaceutical interventions as now enacted to alter transmission. We therefore assessed R_E and how it has changed amid increases in public awareness and public health response efforts in response to COVID-19 in Canada.

To understand the state of transmission and population susceptibility in Canada, we reconstructed the cumulative prevalence of infection using daily hospitalizations reported through 7 April, 2020.[7] We used data on hospitalizations to maximize uniformity in clinical severity and reporting; changes over time in the proportion and clinical characteristics of patients receiving tests for confirmation of COVID-19 (as PHAC apparently used) make unadjusted case data an unreliable basis for inferring dynamics.[8] We used the observed probability of hospitalization among all reported cases with hospitalization data available for stochastic imputation of hospitalization status, within 10-year age groups, among cases with missing hospitalization status. We used time-to-event distributions and hospitalization probabilities listed in **Table S1** to sample from the distribution of infection dates for hospitalized cases, and to project total infections from observed hospitalized cases, accounting for censoring of infections not yet hospitalized.[9,10] We applied the method of Wallinga and Teunis[11] to reconstructed time series of daily infections to estimate R_E for infections acquired each day, also accounting for right-censoring of infection pairs (**Figure 2**).

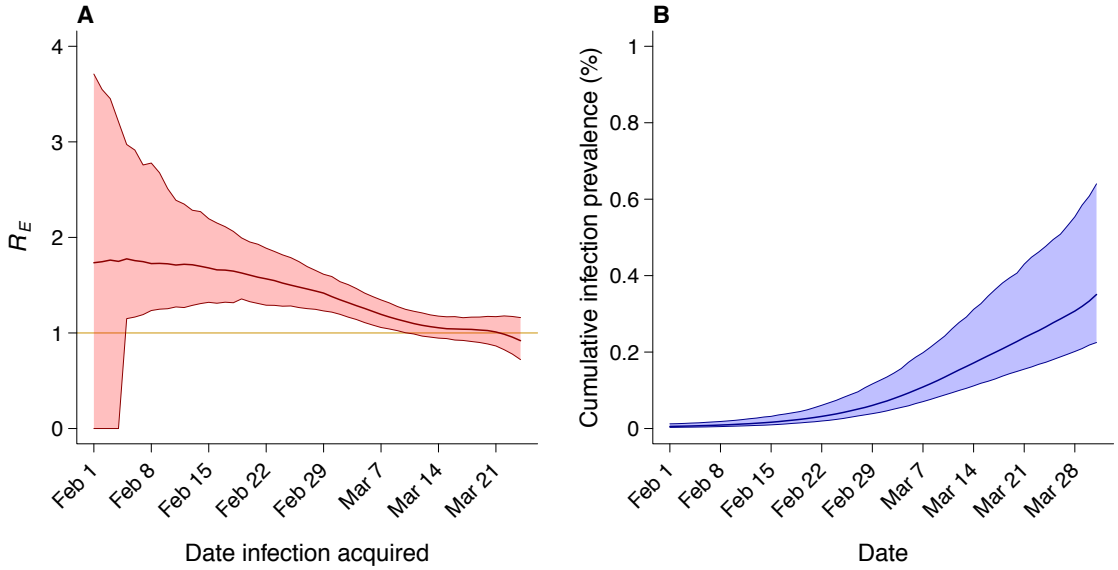

Figure 2: Effective reproductive number (R_E) and cumulative prevalence of infection based on Canadian daily hospitalization data as through April 7, 2020. We present estimates of R_E for infections acquired each date from February 1 through March 24, 2020 (**A**); extreme right-censoring of hospitalization data prevent reliable estimation beyond this date. We present estimates of cumulative infection prevalence through March 31, 2020 (**B**). Shaded regions delineate 95% confidence intervals around median estimates (lines).

Our estimates suggest a point estimate of R_E equal to 1.73 for infections acquired February 1, declining to 0.92 for infections acquired March 24, 2020. We estimated that 0.35% (0.23-0.64%) of the Canadian population experienced SARS-CoV-2 infection by March 31, 2020, implying that nearly all the population remains susceptible. While these estimates summarize transmission across all Canadian communities, masking heterogeneity in local epidemic dynamics, the lack of reporting of cases by onset date, severity, and age group for most provinces prevents analysis at smaller geographic scales. Collectively, our estimates suggest the average number of secondary cases caused by each infectious individual in Canada declined by 47% between February 1 and March 24, reflecting the effects of behavior changes and public health interventions.

Anticipated long-term impacts of social distancing interventions

We used our estimates of the population occupying susceptible, exposed, and infectious classes from the analyses described above to assess the trajectory of transmission under alternative intervention scenarios with R_0 equal to either 1.73 or 2.19, consistent with our estimates (**Figure 2**) and those of PHAC. As a base-case scenario, we assumed non-pharmaceutical interventions would sustain 42% lower rates of transmission, as estimated from time-varying values of R_E. We also considered scenarios where transmission would be lowered by 70% (for instance, due to expansion in case ascertainment and isolation) or by 30% (for instance, due to lower population compliance with social distancing interventions than what was witnessed by March 24, or exhaustion of public health resources). We considered scenarios where interventions would be lifted after 60-240 days. We assumed continuation of SARS-CoV-2 importation from outside Canada at a rate of one infection per day within each age group. We modeled the number of hospitalizations occurring among all infections within each age group as a binomial random variable, given total infections and the per-infection probability of hospitalization, by age,[10] and accounted for the distribution of time from infection to hospitalization (**Table S1**).

Continuation of transmission patterns we inferred as of 24 March, 2020 would be expected to result in a gradual decline in new incident hospitalizations over the intervention period (**Figure 3**). However, immediate and precipitous rises in incidence would be expected if such an intervention were relaxed, with point estimates of peak hospitalization volumes in the range of 17,083-17,508 new admissions daily across Canada under a scenario with R_0=1.73 and a cumulative infection prevalence of roughly 70%. Notably, this expectation may not represent reality in the sense that outbreaks may follow distinct trajectories across Canadian provinces; however, lack of appropriate data for province-level analysis prevents detailed examination. Similar expectations of the magnitude of the peak and cumulative prevalence of infection arose with 70% reductions in transmission achieved under social distancing, although the time from relaxation of interventions to reaching peak incidence would be delayed under such scenarios. With higher baseline transmission intensity (R_0=2.19), we expected shorter times to peak incidence and higher peak hospitalization volumes (23,817-31,290 new admissions/day) following relaxation of interventions.

Steady increases in incidence would be expected under a scenario where interventions achieved only 30% reductions in R_E (such that R_E would remain above 1 during the intervention period), with cumulative infection prevalence at the time interventions are lifted ranging from 1.4-14.2% (with R_0=1.73) or from 2.8-57.1% (with R_0=2.19). Peak hospitalization volumes ranged form 9,917 new admissions/day (with a 240-day social distancing intervention) to 17,182 (with only 60 days of social distancing) for scenarios with R_0=1.73, with cumulative infection prevalence reaching 64.5-70.2%. For these scenarios with low intervention efficacy, peak incidence was expected to occur prior to relaxation of social distancing interventions with R_0=2.19.

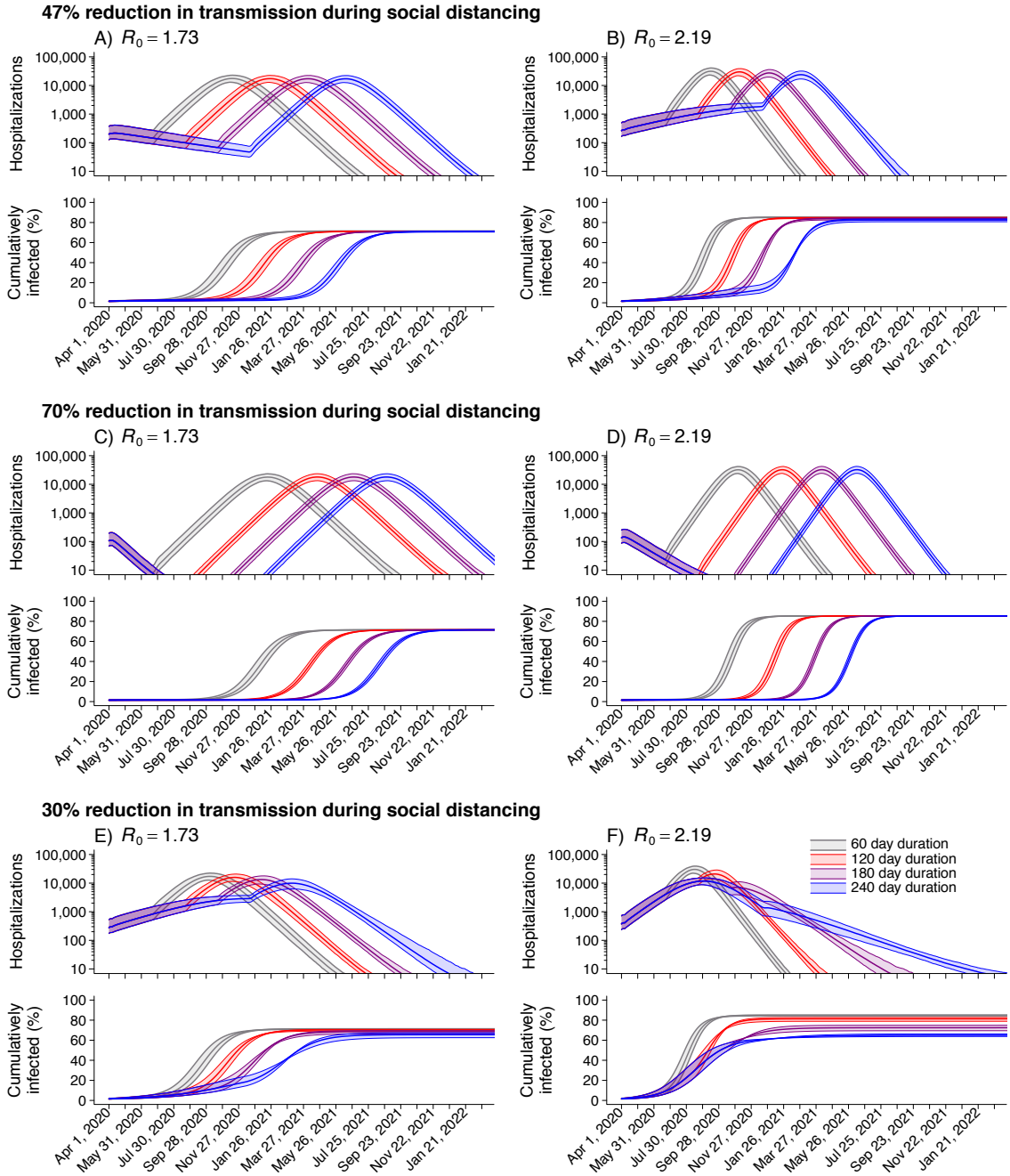

Figure 3: Impact of non-pharmaceutical interventions on hospitalizations and cumulative infection prevalence. We illustrate modeled stochastic epidemic dynamics under differing values of R_0 and with differing assumed effectiveness of non-pharmaceutical interventions in reducing transmission. (**A**-**B**): 47% reductions (consistent with estimates in **Figure 2**); (**C**-**D**) 70% reductions, and (**E**-**F**): 30% reductions. Each modeled scenario identifies epidemic cessation only with high (>64%) cumulative infection prevalence. Shaded areas delineate 95% confidence intervals around median estimates (lines).

Understanding PHAC planning scenario expectations

While the scenarios we consider here do not aim to cover an exhaustive set of possible intervention strategies and considerations around the potential effectiveness of each approach, our findings provide a visualization of the intuitive reasoning that populations remain at risk for allowing increases in transmission provided R_E remains above 1. While the scenarios considered here allowed epidemic exhaustion with cumulative infection prevalence ranging from 56.7-84.5%, this range falls outside the

cumulative infection prevalence that PHAC models reportedly predict at time of epidemic exhaustion with either “stronger” or “weaker” control.

Factors that we do not consider here, but which may contribute to further variation in cumulative infection prevalence, may include assumptions about seasonality and rates of importation of new infections. However, previous models incorporating seasonal forcing (with R_0 varying from 1.4-2.0 over the calendar year) have projected cumulative infection prevalence exceeding 60%, with no impact of this variable on the herd immunity threshold.[12] Availability of a large susceptible population has elsewhere been predicted to limit any role of seasonal forcing, as seen with many respiratory viral pathogens in temperate settings, in the near-term transmission dynamics of SARS-CoV-2.[13] While stochastic extinction of transmission is possible for pathogens with $R_E<1$, as may occur with effective non-pharmaceutical interventions, the likelihood of extinguishing all transmission chains in a population of over 37 million individuals is vanishingly unlikely,[14,15] particularly given our estimate of 31,155 (20,213-55,841) individuals shedding SARS-CoV-2 in Canada as of March 31, 2020. While reductions in travel volume have likely helped to reduce rates of importation of new infections presently, complete prevention of new introductions into the largely susceptible Canadian population will be unlikely as SARS-CoV-2 continues to spread across other countries, including those with limited public health capacity.[16,17]

RECOMMENDATIONS AND CONCLUSIONS

We have sought to reconcile reported results of PHAC’s modeling of COVID-19 dynamics and control in Canada with first-principles concepts in mathematical epidemiology. While the basis for expectations of 70-80% cumulative infection prevalence in the absence of control measures is consistent with conventional results, the technical considerations leading to PHAC’s predictions of 1-10% and 20-50% cumulative infection prevalence under scenarios of “stronger” and “weaker” intervention are unexplained and doubtful.

We recommend the following updates to the technical documentation underlying PHAC projections:

1. Presentations of model structure, including descriptions of state variables and parameters (and their sources, where applicable), similar to the example listing we provide in **Table S1** to clarify the basis of our estimates.

2. Elaboration of quantitative accounting for technical assumptions about the nature of interventions described as “stronger” or “weaker”. For instance, how are variables listed in the model technical documentation[6] such as “degree of physical distancing”, “proportion of cases identified and isolated”, and “proportion of contacts traced and quarantined”, as well as social distancing measures (if applicable), represented quantitatively? What data are available to inform the quantitative values these variables may take on in the setting of “stronger” or “weaker” epidemic control?

3. Clarification of the approach taken to calibrate the model against real-world observations. This can include descriptions of the data used for model fitting (e.g., daily or cumulative cases, deaths, or hospitalizations by age group) and the statistical approach leading to the estimate of $R_0=2.19$.

4. Description of the basis for uncertainty quantification and/or sensitivity analysis, to understand precision of estimates and factors that may alter model predictions.

5. Data and code for replication of analyses and model results. Code for reproducing our analyses using R statistical software is available from https://github.com/joelewnard/canada-covid.

Resolution of these points will transparently clarify the basis and strength of evidence for interventions that PHAC proposes to mitigate the burden of COVID-19 in Canada. This is of increasing importance as policymakers and the public seek to understand the timeframe or circumstances for safe relaxation of social distancing interventions.

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Table S1. Parameters.

Parameters		Distribution	Source
Time from infection to shedding		$\text{Weibull}(k = 5.983, \lambda = 1.455)$	refs.[18–21]
Time from shedding to symptoms		$\text{Weibull}(k = 0.294, \lambda = 0.14)$	refs.[21–24]
Time from symptoms onset to hospitalization		$\text{Gamma}(k = 5.078, \theta = 0.765)$	ref.[25]
Time shedding onset to clearance		$\text{Exp}(1/9)$	ref.[26]
Probability of hospitalization, given infection			
	0-9y[1]	$\text{Beta}(\alpha = 8.65, \beta = 1880.26)$	ref.[10]
	10-19y	$\text{Beta}(\alpha = 8.65, \beta = 1880.26)$	
	20-29y	$\text{Beta}(\alpha = 9.23, \beta = 767.30)$	
	30-39y	$\text{Beta}(\alpha = 8.43, \beta = 208.96)$	
	40-49y	$\text{Beta}(\alpha = 8.07, \beta = 159.93)$	
	50-59y	$\text{Beta}(\alpha = 7.85, \beta = 76.71)$	
	60-69y	$\text{Beta}(\alpha = 7.45, \beta = 48.25)$	
	70-79y	$\text{Beta}(\alpha = 7.01, \beta = 30.02)$	
	80-89y	$\text{Beta}(\alpha = 8.35, \beta = 32.67)$	

We estimate distributions of event times by fitting distributions via maximum likelihood to sampled estimates from cited studies, weighted by the study sample sizes. We fit distributions for time from symptoms onset to hospitalization, and probabilities of hospitalization given infection, by fitting distribution parameters aiming to minimize summed squared errors relative to reported means and 95% confidence intervals.

[1]We assume 0.4% (rather than 0.04%) probability[10] at ages of hospitalization at ages 0-19y to smooth the discontinuity in age-specific estimates; an estimate of 0.04% probability leads to inferences of infection numbers among children exceeding the number of children in the population.