

Topic 2 research plan

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1 Introduction

The objective of this work is to try to determine the effect of specific NPIs on SARS-CoV-2 viral diversity in Ontario and Quebec. Initially, the focus will be on the Gamma and Alpha variants of concern (VOC) as they differed significantly in prevalence between Ontario and Quebec during the 3rd wave of the pandemic in Canada (February 2021 to June 2021). The key differences between Alpha and Gamma are in immune escape and transmissibility [9]. Alpha has less immune escape (for neutralising sera from vaccinated or convalescent individuals), but binds ACE2 more readily and therefore relatively higher transmission. We will not need to consider the S:E484k mutation, which affects immune escape, since it was in a negligible proportion of Canadian Alpha infections during this time period. On the other hand, the Gamma lineage likely has greater immune escape but is probably relatively less transmissible. In contrast to Ontario, during this time the government of Quebec was actively prioritizing the distribution of mRNA vaccines to groups more vulnerable to hospitalization and communities with VOC outbreaks. Therefore, both the mRNA (Pfizer, Moderna) and AstraZeneca vaccine will be included in our model.

Compartmental differential equation models have been used extensively to model competing viral strains in the past (e.g. [2, 16, 19, 25]), and have been invaluable to informing policy throughout the pandemic [4, 12, 18]. One approach to address this research question is to develop a parsimonious model that accurately reproduces observed data. Such a model would generate generalizable insights into the effect of NPIs more broadly. To this end, here we suggest a compartmental model to act as a jumping-off point (Section 2, Figure 1), and request data fields to parameterize it (Section 4). Most disease parameters can be obtained from literature. We will estimate underreporting and underascertainment multipliers by comparing observed case data with serological studies [12].

2 Model

- The structure of the model is Susceptible-Exposed-Infected-Asymptomatic-Recovered, outlined in Figure 1.

- The mRNA vaccine lowers transmission rates and increases the proportion of asymptomatic infections compared to the AstraZeneca vaccine
- Focus on infections in two lineages
- Each lineage has different infection rates, recovery times, and latent periods
- Co-infection negligible
- Time scale short enough that recovery from either infection grants immunity
- Strains interact in the model only in that they compete for hosts
- Vaccination immunity does not wane over model timescale (i.e., single pandemic wave)
- Vaccination reduces infection rate by a proportion
- Some constant fraction of cases are asymptomatic
- Vaccination rate is constant (not necessary since we have data on exact vaccination rates)
- Transmission rate is affected by current level of state policy (determined by the stringency index) and the current level of infection (corresponding to social distancing)

Further extensions

- Compartments will be added to test the effect of population and policy heterogeneity on viral prevalence
- Postal code data for genomes would enable us to track mutations in space, and compare to small variations PHU-level closure data in a network model such as [8]
- There is a lot of genomic information not captured in high-level lineage assignments that could be used in a more detailed model of viral strain competition
- Another technique that is popular for estimating epidemiological parameters, particularly in the comparison of VoC is a semi-mechanistic approach (e.g. [3, 6, 10, 18, 20, 26])

Symbol	Description
S	Susceptible, unvaccinated
$A^{(i)}$	Asymptomatically infected with i th variant
$I^{(i)}$	Infected with i th variant
$E^{(i)}$	Exposed to i th variant
$R^{(i)}$	Recovered from i th variant
S_{V_i}	Susceptible, unvaccinated
$A_{V_i}^{(i)}$	Asymptomatically infected with i th variant, vaccinated by i th vaccine
$I_{V_i}^{(i)}$	Infected with i th variant, vaccinated by i th vaccine
$E_{V_i}^{(i)}$	Exposed to i th variant, vaccinated by i th vaccine
$R_{V_i}^{(i)}$	Recovered from i th variant, vaccinated by i th vaccine
$C(t, \Sigma_i I^{(i)})$	Function reducing transmission rate due to NPIs
β_i	Transmission rate of i th variant
$\eta_i(t)$	Vaccination rate for i vaccine
s	Fraction of asymptomatic
$\sigma^{(i)}$	Inverse of latent period for i th variant
$\gamma^{(i)}$	Recovery rate for i th variant
ν_{V_i}	Infectiousness reduction for vaccination by i th vaccine

Table 1: Table of symbols for Model 1

3 Model 2: Characterizing evolution pressures in Sars-CoV-2 on a broader scale

The evolution of Sars-CoV-2 throughout the pandemic is marked by antigenic drift [28], giving rise to new variants that exhibit significant immune escape. The model of Gog and Grenfell [11] constrains strain space to a one or two dimensional lattice, thereby making the analysis of strain evolution tractable. In two dimensional strain space, cross-immunity of a pathogen is given specified by a coefficient σ_{ijkl} , and mutation is implemented as discrete diffusion with some fixed speed. These ideas were generalized to n-dimensional strain space, and applied to modeling drift in influenza A by Kryazhimskiy et al [13]. This application of these models to influenza was partially motivated by the work of Lapedes and Farber [14], and Smith et al. [22], which suggests that the antigenic evolution of Influenza A primarily occurs within two dimensions. The idea for this line of Sars-CoV-2 research is to handle strain space similar to the aforementioned work, but include further compartments and dynamics specific to Sars-CoV-2 to test hypotheses of evolution.

$$S'_{ij}(t) = - \sum_{kl} \beta_{kl} \sigma_{ijkl} S_{ij} I_{kl} + \gamma R_{ij} \quad (1)$$

$$I'_{ij}(t) = \beta_{ij} S_{ij} I_{ij} - \xi I_{ij} + M(-4I_{ij} + I_{i-1,j} + I_{i+1,j} + I_{i,j-1} + I_{i,j+1}) \quad (2)$$

$$R'_{ij}(t) = \xi I_{ij} - \gamma R_{ij} \quad (3)$$

Symbol	Description
S_{ij}	Susceptible to strain (i, j)
I_{ij}	Infected by strain (i, j)
R_{ij}	Recovered/Immune to strain (i, j)
σ_{ijkl}	Probability that exposure to strain (i, j) causes immunity to strain (k, l)
β_{ij}	Transmission rate of strain (i, j)
ξ	Recovery rate of all strains
γ	Rate of immunity loss of all strains

Table 2: Table of symbols for Model 2

Equations 4-5 represent the model of [11] with a two-dimensional strain space, with a few changes to better reflect mechanisms of Sars-CoV-2. I have added an immunity period, changing the model to an SIRS mechanism, and removed the vital dynamics, as I do not think natural population birth rates are significant in the time scale of the pandemic. A key assumption made by this model is that exposure grants complete immunity to some fraction of individuals, rather than partial immunity (interpreted as reduced transmission rates) to all exposed individuals. Many other methods of dealing with cross-immunity are possible, but this method gives a simpler state space [1].

To incorporate vaccination, consider each vaccine affecting a different region of strain space. That is, for a vaccine v we can associate a matrix $v_{ij} \in [0, 1]$ which determines the relative effect of that vaccine on the immunity of hosts to strain i, j . The function $\eta(t)$ represents some base rate of vaccination. This results in the following equations for $S'_{ij}(t)$ and $R'_{ij}(t)$ (the infected equation 2 is unchanged).

$$S'_{ij}(t) = - \sum_{kl} \beta_{kl} \sigma_{ijkl} S_{ij} I_{kl} + \gamma R_{ij} - \eta(t) v_{ij} S_{ij} \quad (4)$$

$$R'_{ij}(t) = \xi I_{ij} - \gamma R_{ij} + \eta(t) v_{ij} S_{ij} \quad (5)$$

This model could be used to test the effect of NPIs on Sars-CoV-2 evolution. Mechanisms for NPIs and additional compartments for heterogeneity are straightforward to add to the model equations. If a given NPI mechanism is more able to fit data with a mechanism that does not act on all strains equally, then this could be evidence that NPIs are affecting Sars-CoV-2 evolution.

3.1 Parameterization

Parameterizing this model is challenging and would require a lot of assumptions about the antigenic space of Sars-CoV-2 that there is unlikely to be much data to support. The aforementioned research with these models do not use data to estimate parameters, focusing on broad characterization of dynamics with

numerical or analytical approaches. However, genomic data does include a huge amount of admittedly very noisy information. There is some recent work on parameter estimation by comparing simulated phylogeny with observed phylogeny using a suite of summary statistics for tree structures [7,15,21], but these models do not explicitly include genomic structure, which might provide additional inferential power.

Placing individual samples into the collapsed strain space could be done by using neutralizing antibody studies. The neutralizing response has been characterized for most variants of concern with respect to monoclonal antibodies, convalescent plasma, and plasma from vaccinated persons [24]. To an even higher level of detail. Starr et al. characterized polyclonal antibody binding over all mutations of the Receptor Binding Domain (RBD) [23]. If the neutralizing response is known, we assign strains positions such that the distance between any two strains is equal to that neutralizing response. If the response is not known, we just assume that the position is close to the most recent ancestor for which the response is known (likely a VoC). This approach is especially appropriate for recurrent mutations, since it is unlikely that a mutation that has occurred many times in the viral history but has not evolved further confers a significant advantage. The immune-space position of vaccinate-induced immunity can also be computed this way, although we will still need to make significant assumptions on their geometry. It might be best to assume a simple symmetric shape with a centre given by neutralization results.

Mirroring the work on mapping the strain space for influenza [5, 14, 22] computing this embedding is a metric multidimensional scaling problem. This method has been applied to the antigenic space of the Sars-CoV-2 as well [17,27].

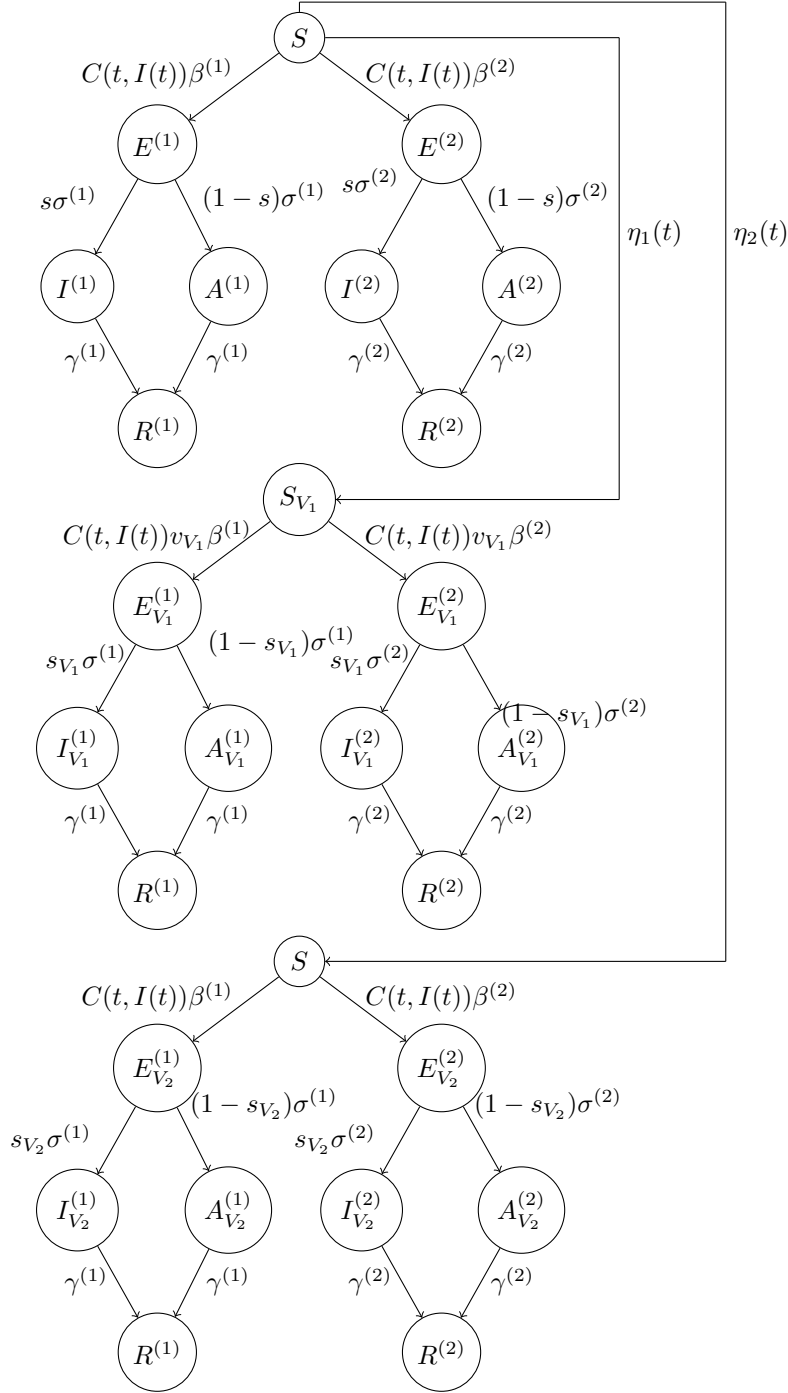


Figure 1: State diagram of model with two different types of vaccination and strong competition. Variables are described in Table 1

4 Requested data fields

The following section contains the fields we plan to request from PHO (and eventually INSP) to inform model parameterization. It is split into two sections: the first containing data which will be important to any epidemiological model and the second containing fields that describe social determinants of health, which we suspect to inform population heterogeneity important to the viral dynamics in Ontario and Quebec. We include long term care workers and residents in the second category because of the significant transmission events in these settings that have occurred throughout the pandemic.

4.1 General

- Client_ID
- Diagnosing_Health_Unit_Area
- Subtype_Name
- RePositive
- Investigation_Lineage
- Investigation_Mutation
- Accurate_Episode_Date
- Case_Reported_Date
- Client_Postal_Code
- Client_Province
- Client_Address_City
- Age_At_Time_of_Illness
- Likely_Acquisition
- Outbreak_Number
- Setting_Combined
- Epidemiologic_Linkage
- Epidemiologic_Link_Status

4.2 Social determinants of health

- Res_AdultDevServices
- Res_AdultYouthAddiction
- Res_ChildrensRes_Site
- Res_CorrectionalF
- Res_HomelessShelter
- Res_LTCH
- LTCH_Resident
- LTCH_HCW
- Ses_Race_East_Asian
- Ses_Race_Southeast_Asian
- Res_RetirementHome
- Res_SupportiveHousing
- Res_OtherCongregateCare
- Res_VAWorAHT_Site
- Ses_Income
- SES_HHSize_Num
- Occ_LTCH
- Ses_Race_Black
- Ses_Race_East_Southeast_Asian
- Ses_Race_South_Asian
- Ses_Race_White
- Ses_Race_Middle_Eastern
- Ses_Race_Latino
- Immunocompromised

References

- [1] *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: Models, Methods, and Theory*, volume 126 of *The IMA Volumes in Mathematics and its Applications*. Springer New York, 2002.
- [2] Samuel Alizon and Minus van Baalen. Multiple infections, immune dynamics, and the evolution of virulence. *The American Naturalist*, 172(4):E150–E168, Oct 2008.
- [3] Kevin A. Brown, Eugene Joh, Sarah A. Buchan, Nick Daneman, Sharmistha Mishra, Samir Patel, and Troy Day. Inflection in prevalence of sars-cov-2 infections missing the n501y mutation as a marker of rapid delta (b.1.617.2) lineage expansion in ontario, canada. Jun 2021.
- [4] Kate M Bubar, Kyle Reinholt, Stephen M Kissler, Marc Lipsitch, Sarah Cobey, Yonatan H Grad, and Daniel B Larremore. Model-informed covid-19 vaccine prioritization strategies by age and serostatus. *Science*, 371(6532):916–921, 2021.
- [5] Zhipeng Cai, Tong Zhang, and Xiu-Feng Wan. A computational framework for influenza antigenic cartography. *PLoS computational biology*, 6(10):e1000949, 2010.
- [6] Simon Cauchemez, Pierre Nouvellet, Anne Cori, Thibaut Jombart, Tini Garske, Hannah Clapham, Sean Moore, Harriet Linden Mills, Henrik Salje, Caitlin Collins, Isabel Rodriguez-Barraquer, Steven Riley, Shaun Truelove, Homoud Algarni, Rafat Alhakeem, Khalid AlHarbi, Abdulhafiz Turkistani, Ricardo J. Aguas, Derek A. T. Cummings, Maria D. Van Kerkhove, Christl A. Donnelly, Justin Lessler, Christophe Fraser, Ali Al-Barrak, and Neil M. Ferguson. Unraveling the drivers of mers-cov transmission. *Proceedings of the National Academy of Sciences*, 113(32):9081–9086, Aug 2016.
- [7] Gonché Danesh, Victor Virlogeux, Christophe Ramière, Caroline Charre, Laurent Cotte, and Samuel Alizon. Quantifying transmission dynamics of acute hepatitis c virus infections in a heterogeneous population using sequence data. *PLoS pathogens*, 17(9):e1009916, 2021.
- [8] Kathryn R Fair, Vadim A Karatayev, Madhur Anand, and Chris T Bauch. *Population behavioural dynamics can mediate the persistence of emerging infectious diseases*. May 2021.
- [9] Agency for Clinical Innovation. Living evidence - sars-cov-2 variants. <https://aci.health.nsw.gov.au/covid-19/critical-intelligence-unit/sars-cov-2-variants>, Jan 2022.
- [10] Christophe Fraser. Estimating individual and household reproduction numbers in an emerging epidemic. *PLoS ONE*, 2(8):e758, Aug 2007.

- [11] J. R. Gog and B. T. Grenfell. Dynamics and selection of many-strain pathogens. *Proceedings of the National Academy of Sciences*, 99(26):17209–17214, December 2002.
- [12] Peter C Jentsch, Madhur Anand, and Chris T Bauch. Prioritising covid-19 vaccination in changing social and epidemiological landscapes: a mathematical modelling study. *The Lancet Infectious Diseases*, 2021.
- [13] Sergey Kryazhimskiy, Ulf Dieckmann, Simon A. Levin, and Jonathan Dushoff. On State-Space Reduction in Multi-Strain Pathogen Models, with an Application to Antigenic Drift in Influenza A. *PLOS Computational Biology*, 3(8):e159, August 2007.
- [14] Alan Lapedes and Robert Farber. The Geometry of Shape Space: Application to Influenza. *Journal of Theoretical Biology*, 212(1):57–69, September 2001.
- [15] Gabriel E Leventhal, Roger Kouyos, Tanja Stadler, Viktor Von Wyl, Sabine Yerly, Jürg Böni, Cristina Cellera, Thomas Klimkait, Huldrych F Günthard, and Sebastian Bonhoeffer. Inferring epidemic contact structure from phylogenetic trees. *PLoS computational biology*, 8(3):e1002413, 2012.
- [16] Marc Lipsitch, Caroline Colijn, Ted Cohen, William P. Hanage, and Christophe Fraser. No coexistence for free: Neutral null models for multi-strain pathogens. *Epidemics*, 1(1):2–13, Mar 2009.
- [17] Nathaniel L. Miller, Thomas Clark, Rahul Raman, and Ram Sasisekharan. An Antigenic Space Framework for Understanding Antibody Escape of SARS-CoV-2 Variants. *Viruses*, 13(10):2009, October 2021.
- [18] Swapnil Mishra, Tresnia Berah, Thomas A. Mellan, H. Juliette T. Unwin, Michaela A. Vollmer, Kris V. Parag, Axel Gandy, Seth Flaxman, and Samir Bhatt. On the derivation of the renewal equation from an age-dependent branching process: an epidemic modelling perspective. *arXiv:2006.16487 [q-bio, stat]*, Jun 2020. arXiv: 2006.16487.
- [19] Emily J. Nicoli, Diepreye Ayabina, Caroline L. Trotter, Katherine M.E. Turner, and Caroline Colijn. Competition, coinfection and strain replacement in models of bordetella pertussis. *Theoretical Population Biology*, 103:84–92, Aug 2015.
- [20] Pierre Nouvellet, Anne Cori, Tini Garske, Isobel M. Blake, Ilaria Dorigatti, Wes Hinsley, Thibaut Jombart, Harriet L. Mills, Gemma Nedjati-Gilani, Maria D. Van Kerkhove, Christophe Fraser, Christl A. Donnelly, Neil M. Ferguson, and Steven Riley. A simple approach to measure transmissibility and forecast incidence. *Epidemics*, 22:29–35, Mar 2018.
- [21] Emma Saulnier, Olivier Gascuel, and Samuel Alizon. Inferring epidemiological parameters from phylogenies using regression-abc: A comparative study. *PLoS computational biology*, 13(3):e1005416, 2017.

- [22] Derek J. Smith, Alan S. Lapedes, Jan C. de Jong, Theo M. Bestebroer, Guus F. Rimmelzwaan, Albert D. M. E. Osterhaus, and Ron A. M. Fouchier. Mapping the Antigenic and Genetic Evolution of Influenza Virus. *Science*, 305(5682):371–376, July 2004.
- [23] Tyler N Starr, Allison J Greaney, Sarah K Hilton, Daniel Ellis, Katharine HD Crawford, Adam S Dingens, Mary Jane Navarro, John E Bowen, M Alejandra Tortorici, Alexandra C Walls, et al. Deep mutational scanning of sars-cov-2 receptor binding domain reveals constraints on folding and ace2 binding. *Cell*, 182(5):1295–1310, 2020.
- [24] Philip Tzou, Kaiming Tao, Janin Nouhin, Soo-Yon Rhee, Benjamin Hu, Shruti Pai, Neil Parkin, and Robert Shafer. Coronavirus antiviral research database (cov-rdb): An online database designed to facilitate comparisons between candidate anti-coronavirus compounds. *Viruses*, 12(9):1006, Sep 2020.
- [25] Minus van Baalen and Maurice W. Sabelis. The dynamics of multiple infection and the evolution of virulence. *The American Naturalist*, 146(6):881–910, Dec 1995.
- [26] J Wallinga and M Lipsitch. How generation intervals shape the relationship between growth rates and reproductive numbers. *Proceedings of the Royal Society B: Biological Sciences*, 274(1609):599–604, Feb 2007.
- [27] Samuel H. Wilks, Barbara Mühlemann, Xiaoying Shen, Sina Türel, Eric B. LeGresley, Antonia Netzl, Miguela A. Caniza, Jesus N. Chacaltana-Huarcaya, Xiaoju Daniell, Michael B. Datto, Thomas N. Denny, Christian Drosten, Ron A. M. Fouchier, Patricia J. Garcia, Peter J. Halfmann, Agatha Jassem, Terry C. Jones, Yoshihiro Kawaoka, Florian Krammer, Charlene McDanal, Rolando Pajon, Viviana Simon, Melissa Stockwell, Haili Tang, Harm van Bakel, Richard Webby, David C. Montefiori, and Derek J. Smith. Mapping SARS-CoV-2 antigenic relationships and serological responses. Preprint, Immunology, January 2022.
- [28] Jonathan W. Yewdell. Antigenic drift: Understanding COVID-19. *Immunity*, 54(12):2681–2687, December 2021.