COVID-19 in Canada: epidemiology, severity and control

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List of Acronyms and Abbreviations

AIDS – Acquired immune deficiency syndrome

AB – Alberta

BC – British Columbia

CCM – Case and Contact Management System

CD – Census division

CDC – Centers for Disease Control and Prevention

CEPI – The Coalition for Epidemic Preparedness Innovations

CI – Confidence interval

CIHI – Canadian Institute for Health Information

CMA – Census megapolitan area

COVAX – COVID-19 Vaccines Global Access

COVID-19 – Coronavirus disease 2019

CT – Census tract

DA – Dissemination area

EC50 – Half maximal effective concentration

EUA – Emergency use authorization

FDA – Food and Drug Administration

HCoV – Human Coronavirus

HIV – Human immunodeficiency virus

IBM – Individual-based model

ICUs – Intensive Care Units

iPHIS – Integrated Public Health Information System

LOS – Length of stay

LTCH – Long-term care homes

MB – Manitoba

MED-ÉCHO – The Maintenance et exploitation des données pour l'étude de la clientèle hospitalière database

MERS-CoV – Middle East respiratory syndrome coronavirus

mRNA – Messenger ribonucleic acid

NB – New Brunswick

NL – Newfoundland and Labrador

NPIs – Non-pharmaceutical interventions

NS – Nova Scotia

ODE – Ordinary differential equations

ON – Ontario

PCCF – Postal Code Conversion File

PCCF+ – Postal Code Conversion File Plus

PEI – Prince Edward Island

PHAC – Public Health Agency of Canada

PHAC EMN-ID – External Modelling Network for Infectious Diseases

PHEIC – Public health emergency of international concern

PHRDW – Public Health Reporting Data Warehouse

PPE – Personal protective equipment

QC – Québec

R_0 – Basic reproduction number

R_t – Effective reproduction number

RNA – Ribonucleic acid

SAGE – Scientific Advisory Group for Emergencies

SARS-CoV – Severe acute respiratory syndrome coronavirus

SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SD – Standards deviation

SDOH – Social determinants of health

SIR – Susceptible-Infected-Recovered

SK – Saskatchewan

SPI-M-O – Scientific Pandemic Influenza Group on Modelling-Operational

STI – Sexually transmitted infections

TCL – Target cell-limited model

TCLE – Target cell-limited model with an eclipse phase

TSP – Trajectoire de santé publique

VOC – Variants of concern

WHO – World Health Organization

Abstract

The COVID-19 pandemic emphasized the importance of strong surveillance systems and epidemiological data to inform local and global responses. Successful responses needed to be comprehensive and consider health inequities, morbidity and mortality patterns, pharmaceutical and non-pharmaceutical interventions, and SARS-CoV-2's transmission dynamics. My thesis aims to understand and document Canada's management of local COVID-19 epidemics by investigating these different facets of the pandemic to improve future preparedness.

To inform their response, provincial authorities relied on mathematical models. In my first manuscript, I reviewed these efforts by conducting a scoping review of 20 models. I found that provincial modelling efforts were tailored to local contexts and influenced by the local expertise available. Surveillance datasets for cases, hospitalizations, and deaths were some of the main data sources used by models. Despite varying structures in knowledge translation across provinces, common challenges included timely access to high-quality data and the integration of data across surveillance databases.

My review evidenced that provincial models did not consider social determinants of health. To improve our understanding of how they shaped transmission, I quantified the geographic concentration of SARS-CoV-2 by social determinants of health in 16 Canadian cities in my second manuscript. Leveraging surveillance data on confirmed cases and census data for area-level social determinants of health, I observed a geographic concentration of cases, with 50% of the cumulative cases reported within areas containing 21-35% of their population in each city. Additionally, I estimated the Gini covariance coefficients (co-Gini), which indicated a disproportionate concentration of cases in vulnerable communities, especially those with a higher proportion of visible minorities.

Mathematical models used in Canada focused heavily on projecting the SARS-CoV-2 healthcare burden. My third manuscript described the temporal trends in in-hospital COVID-19 mortality risk, the drivers, and length of hospital stay through the first three epidemic waves. Using surveillance databases from Ontario and Québec, totaling nearly 50,000 hospitalizations, I estimated that the in-hospital mortality risk peaked at 31% during first wave and declined to 6-7%

by the third wave. I also found that patient load negatively affected survival and that hospital lengths of stays decreased over time.

With the scale-up of SARS-CoV-2 vaccination, both morbidity and mortality drastically decreased, highlighting its fundamental role in mitigating pandemic risks. Robust tools for evaluating vaccine candidates and rollout strategies are essential. My fourth manuscript explores the vaccine features required to contain the transmission of a future Disease X, focusing on three key features under development: 1) EC50 (the concentration of antibodies required to achieve 50% of the vaccine's maximum effect), 2) the half-life of plasma secreting cells (which produce antibodies), and 3) the vaccine's impact on the virus's infection rate of target cells. Using an agent-based model of transmission of this potential (re)emerging respiratory virus, I found that, in general, an EC50 ≤ 3 or half-life of plasma secreting cells ≥ 1 year is needed to contain an epidemic with a basic reproductive number ≤ 3. Vaccines lowering the infection rate of target cells has minimal impact.

My thesis synthesizes knowledge on some of the important features of Canada's COVID-19 epidemic and its responses, and proposes tools to enhance pandemic preparedness. First, it underscores the need to enhance Canadian modelling capacity, and ensure access to timely, high-quality surveillance data. Second, it examines the heterogeneities in transmission and in-hospital mortality risks, which informed vaccination strategies and provided estimates of key indicators for models projecting healthcare demands. Moreover, it demonstrates the value of descriptive epidemiology and explanatory studies. Finally, it proposes a flexible model that can be used to evaluate the impact of vaccine candidates for future Disease X pandemics.

Resumé

La pandémie de COVID-19 a souligné l'importance d'une surveillance rigoureuse et de données épidémiologiques pour éclairer les réponses locales et mondiales. Les réponses efficaces doivent être globales et tenir compte des inégalités en matière de santé, des schémas de morbidité et de mortalité, des interventions pharmaceutiques et non pharmaceutiques et de la dynamique de transmission du SRAS-CoV-2. Ma thèse vise à comprendre et à documenter les réponses du Canada aux épidémies locales de COVID-19 en étudiant ces différentes facettes des réponses à la pandémie afin d'améliorer la préparation future.

Pour éclairer leur réponse, les autorités provinciales se sont fiées à des modèles mathématiques. Dans mon premier manuscrit, j'ai passé en revue ces efforts en effectuant un examen de la portée de 20 modèles. J'ai constaté que les efforts provinciaux de modélisation étaient adaptés aux contextes locaux et influencés par l'expertise locale disponible. Les ensembles de données de surveillance des cas, des hospitalisations et des décès faisaient partie des principales sources de données utilisées par les modèles. Malgré les différentes structures d'application des connaissances d'une province à l'autre, les défis communs comprenaient l'accès en temps opportun à des données de haute qualité et l'intégration des données dans les bases de données de surveillance.

Mon examen a révélé que les modèles provinciaux ne tenaient pas compte des déterminants sociaux de la santé. Pour améliorer notre compréhension de la façon dont ils ont façonné la transmission, j'ai quantifié la concentration géographique du SRAS-CoV-2 par les déterminants sociaux de la santé dans 16 villes Canadiennes dans mon deuxième manuscrit. En tirant parti des données de surveillance sur les cas confirmés et des données de recensement sur les déterminants sociaux de la santé au niveau des aires de dissémination, j'ai observé une concentration géographique des cas, avec 50 % des cas cumulés signalés dans des zones contenant 21 à 35 % de leur population dans chaque ville. De plus, j'ai estimé les coefficients de covariance de Gini (co-Gini), qui indiquaient une concentration disproportionnée de cas dans les communautés vulnérables, en particulier celles comptant une proportion plus élevée de minorités visibles.

Les modèles mathématiques utilisés au Canada se sont fortement concentrés sur la projection du fardeau des soins de santé liés au SRAS-CoV-2. Mon troisième manuscrit décrivait

les tendances temporelles du risque de mortalité hospitalière due au COVID-19, les facteurs déterminants et la durée des séjours à l'hôpital au cours des trois premières vagues épidémiques. À l'aide de bases de données de surveillance de l'Ontario et du Québec, totalisant près de 50 000 hospitalisations, j'ai estimé que le risque de mortalité à l'hôpital atteignait un sommet à 31 % lors de la première vague et diminuait à 6 à 7 % lors de la troisième vague. J'ai aussi constaté que le nombre de patients affectait négativement la survie et que la durée des séjours à l'hôpital diminuait avec le temps.

Avec l'intensification de la vaccination contre le SRAS-CoV-2, la morbidité et la mortalité ont considérablement diminué, ce qui met en évidence leur rôle fondamental dans l'atténuation des risques de pandémie. Des outils robustes pour évaluer les vaccines candidats et les stratégies de déploiement sont essentiels. Mon quatrième manuscrit explore les caractéristiques du vaccin nécessaires pour contenir la transmission d'une future maladie X, en se concentrant sur trois caractéristiques clés du développement de vaccins : i) la CE50 (la concentration d'anticorps requise pour atteindre 50 % de l'effet maximum du vaccin), ii) la demi-vie du plasma, et iii) l'impact du vaccin sur le taux d'infection des cellules cibles. En utilisant un modèle de transmission basé sur des agents de ce prochain virus respiratoire, j'ai découvert qu'en général, une CE50 $\leqslant$ 3 ou une demi-vie des cellules sécrétant du plasma $\geqslant$ 1 an est nécessaire pour contenir une épidémie avec un nombre reproducteur de base $\leqslant$ 3. Les vaccins qui réduisent le taux d'infection des cellules cibles ont un impact minime.

Ma thèse synthétise les connaissances en épidémiologie de l'épidémie de COVID-19 et des réponses au Canada et propose des outils pour améliorer la préparation à une pandémie. Premièrement, cela souligne la nécessité d'améliorer la capacité canadienne en modélisation mathématique et d'assurer un accès plus rapide à des données de surveillance opportunes et de haute qualité. Deuxièmement, elle a examiné les hétérogénéités de la transmission des cas et les risques de mortalité à l'hôpital, qui ont éclairé la stratégie de vaccination et fourni des estimations d'indicateurs clés pour les modèles projetant les demandes de soins de santé. De plus, elle démontre la valeur des études descriptives et explicatives. Finalement, ma thèse propose un modèle flexible qui peut être utilisé pour évaluer l'impact des candidats vaccins sur les futures pandémies de la maladie X.

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This thesis is the result of an incredible journey, made possible by the support, guidance, and encouragement from many remarkable individuals. I am deeply grateful to the mentors, colleagues, friends, and family who stood by me throughout this process. Your encouragement and belief in me have meant everything. I would like to take this opportunity to express my heartfelt thanks to everyone who played a role in this milestone. Thank you all for accompanying me on this journey and making my PhD experience a relatively enjoyable one.

First and foremost, I would like to thank my dear supervisor, Prof. Mathieu Maheu-Giroux, whose guidance, wisdom, support, and mentorship have been invaluable. It has been almost six years since our first encounter in your mathematical modelling course during the last semester of my master's. I was about to graduate but had no idea what I truly wanted to do. Then, the course you offered became like a stream of light cutting through the swamp–I finally discovered my passion: mathematical modelling. Thank you so much for offering this course and for your email inviting me to join the lab after that. It gave me the opportunity to deepen my knowledge of modelling and, most importantly, offered me with the perfect supervisor to work with and pursue my PhD (a little secret–before your email, I just told my friend that I wanted to be your student but was too shy to ask at that time!). At the beginning of my PhD, you asked me what type of person I want to be in the future. You interpreted my answer "I want to become a person like you" as having quantitative skills in infectious disease, but I meant it in the literal sense. You are such a sweet and smart person (I rarely use this word to describe a person!) who's willing to devote himself to students. Your availability, support, and constant backing have been invaluable to me. Moreover, you have a remarkable ability to understand what we want and respect our choices, and you are always generous with the opportunities you offer. With your guidance and encouragement, I fell in love with epidemiology and research, and have truly become a better version of myself. I often doubt about the decision I made, but I've never questioned the choice to have you as my supervisor. Thank you for everything you've done to help me grow both professionally and personally.

Next, I would like to thank Dr. Sharmistha Mishra, my committee member and former supervisor, for your support and valuable contributions to both my thesis and my life. It is no

exaggeration to say that the multi-province collaborations in my thesis would not have progressed so smoothly without you being the linchpin. Though you often called yourself the "bottleneck," I truly value the experiences of working with you. I'm grateful for your enthusiasm, warmheartedness, wisdom, and many other qualities that have taught me to communicate more effectively, think critically, be patient, and become a better researcher. Moreover, thank you for being so flexible and agreeing to take me on your team in Ontario. Even though it was just one year, it profoundly bonded me with the members of Mishra lab and better equipped me with the skills needed to accomplish my PhD. Finally, I find it interesting that, although we've known each other for four years and collaborated on tons of papers, we've never actually met in person. Well, I'm adding it to my list of goals for the new year–to finally meet you in the flesh!

I would also like to thank Dr. David Buckeridge, my committee member, and Dr. Mélanie Prague, for your invaluable guidance, thoughtful feedback, and support. Your expertise and insights have greatly enriched my works, and I am deeply grateful for the time and effort you have dedicated to my thesis works. Your contributions have been instrumental.

My thesis heavily relies on the multi-province collaboration among modellers and researchers who worked tirelessly during the COVID-19 pandemic. I am particularly grateful to my collaborators from provinces across Canada, whose insights and contributions have been invaluable in shaping the findings of my work. Thank you all for your dedication and support.

The support and encouragement from my friends have been just as vital to me. First, a special thank you to Carla, James, and Huiting, whose support, kindness, and warmth made this experience so much more enjoyable. You've been incredibly sweet and always made time to not only help me with all sorts of questions of mine, but also comfort me when I was stressed and take me in to have fun together. Your friendship has truly been a highlight of my PhD experience. Then, a huge thank you to Siyi and Linda, who have been a constant source of support. Your encouragement, understanding during the "blue" moments, and unwavering belief in me have been a lifeline, and I can't thank you enough for being there for me. Finally, to Rachael, Jorge, Max, Yi, Wenlu, and all others from the MMG lab, my cohort, and the department, for your camaraderie, support, and the shared experiences that made this journey so much richer and more meaningful.

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Contribution to Original Knowledge

The work presented in this thesis is original and provides distinct contributions to the advancement of knowledge during the COVID-19 pandemic in Canada, including the transmission patterns and severity of those epidemics, Canada's response towards it, and the preparedness for future epidemics. Specifically, Manuscript 1 is the first comprehensive overview of Canada's diverse provincial modelling efforts against COVID-19 epidemic over the first 2 years. Additionally, this paper draws lessons for future responses to public health challenges. My second and third manuscripts contributed to the understanding of the two essential parameters for those models that guided provincial responses. Specifically, manuscript 2 provided quantified evidence of geographical concentration of SARS-CoV-2 cases in cities across provinces of Canada and identified drivers associated with the observed heterogeneities. Manuscript 3 provided estimates of the time-varying in-hospital COVID-19 mortality risk and patient length of stay throughout the first three epidemic waves. Moreover, it identified the drivers that led to those changes. Finally, my fourth manuscript contributes knowledge on pandemic preparedness using a mathematical model. Manuscript 4 pinpoints the desired vaccine features that are preferred to contain future epidemics caused by a SARS-CoV-2 type of virus.

The following four manuscripts are presented in my thesis:

[1]. **Xia Y**, Flores Anato JL, Colijn C, Janjua N, Irvine M, Williamson T, Varughese MB, Li M, Osgood N, Earn DJ, Sander B, Cipriano LE, Murty K, Xiu F, Godin A, Buckeridge D, Hurford A, Mishra S, Maheu-Giroux M. Canada's provincial COVID-19 pandemic modelling efforts: A review of mathematical models and their impacts on the responses. *Canadian Journal of Public Health.* 2024 Aug; 115(4):541-557.

[2]. **Xia Y**, Ma H, Moloney G, García HA, Sirski M, Janjua NZ, Vickers D, Williamson T, Katz A, Yiu K, Kustra R, Buckeridge D, Brisson M, Baral S, Mishra S, Maheu-Giroux M. Geographic concentration of SARS-CoV-2 cases by social determinants of health in metropolitan areas in Canada: a cross-sectional study. *Canadian Medical Association Journal*. 2022 Feb 14; 194(6):E195-204.

[3]. **Xia Y**, Ma H, Buckeridge DL, Brisson M, Sander B, Chan A, Verma A, Ganser I, Kronfli N, Mishra S, Maheu-Giroux M. Mortality trends and length of stays among hospitalized patients with COVID-19 in Ontario and Québec (Canada): a population-based cohort study of the first three epidemic waves. *The International Journal of Infectious Diseases*. 2022 Aug 1; 121:1-10.

[4]. **Xia Y**, Alexandre M, Thiebaut R, Maheu-Giroux M, Prague M. Examining the desired vaccine features against future pandemics: an individual-based within- and between-host model (Under Review).

In addition to these papers, I first-authored 2 articles and co-authored 8 publications during my doctorate on a wide range of topics (i.e., prophylaxis, diagnostics, transmission dynamics, vaccination) related to mathematical modelling and infectious diseases (i.e., HIV, mpox, syphilis). These are included for reference:

Published:

[1]. **Xia Y**, Caya C, Morin V, Singh AE, Serhir B, Libman M, Goldfarb DM, Wong T, Xiu F, Bélanger R, Touchette JS, Yansouni CP, Maheu-Giroux M. The population-level impact of introducing rapid diagnostic tests on syphilis transmission in Canadian arctic communities–a mathematical modeling study. The Lancet Regional Health–Americas. 2024 Sep 1; 37:100845.

[2]. Doyle CM, Milwid RM, Cox J, **Xia Y**, Lambert G, Tremblay C, Otis J, Boily MC, Baril JG, Thomas R, Blais AD. Population-level effectiveness of pre-exposure prophylaxis for HIV prevention among men who have sex with men in Montréal (Canada): a modelling study of surveillance and survey data. Journal of the International AIDS Society. 2023 Dec; 26(12):e26194.

[3]. Milwid RM, Li M, Fazil A, Maheu-Giroux M, Doyle CM, **Xia Y**, Cox J, Grace D, Dvorakova M, Walker SC, Mishra S, Ogden NH. Exploring the dynamics of the 2022 mpox outbreak in Canada. Journal of Medical Virology. 2023 Dec; 95(12):e29256.

[4]. Anato JL, Ma H, Hamilton MA, **Xia Y**, Harper S, Buckeridge D, Brisson M, Hillmer MP, Malikov K, Kerem A, Beall R, Wagner CE, Racine É, Baral S, Dubé É, Mishra S, Maheu-Giroux M. Impact of a vaccine passport on first-dose SARS-CoV-2 vaccine coverage by age and area-level social determinants of health in the Canadian provinces of Quebec and Ontario: an interrupted time series analysis. Canadian Medical Association Open Access Journal. 2023 Sep 1; 11(5):E995-1005.

[5]. Stansfield SE, Heitner J, Mitchell KM, Doyle CM, Milwid RM, Moore M, Donnell DJ, Hanscom B, **Xia Y**, Maheu-Giroux M, Vijver DV, Wang H, Barnabas R, Boily MC, Dimitrov DT. Population-level impact of expanding PrEP coverage by offering long-acting injectable PrEP to MSM in three high-resource settings: a model comparison analysis. Journal of the International AIDS Society. 2023 Jul; 26:e26109.

[6]. Caya C, Singh AE, Serhir B, Morin V, Libman MD, Corsini R, Goldfarb DM, Wong T, **Xia Y**, Maheu-Giroux M, Yansouni CP. Rapid diagnostic testing for syphilis in Arctic communities (the STAR study): a multisite prospective field diagnostic accuracy study in an intended-use setting. Clinical Microbiology and Infection. 2023 Oct 1; 29(10): 1335.e1-1335.e7.

[7]. Caya C, Maheu-Giroux M, **Xia Y**, Serhir B, Morin V, Libman M, Corsini R, Goldfarb DM, Wong T, Singh AE, Yansouni CP. Stopping syphilis transmission in Arctic communities through rapid diagnostic testing: The STAR study protocol. Plos one. 2022 Sep 12; 17(9):e0273713.

[8]. Milwid RM, **Xia Y**, Doyle CM, Cox J, Lambert G, Thomas R, Mishra S, Grace D, Lachowsky NJ, Hart TA, Boily MC, Maheu-Giroux M. Past dynamics of HIV transmission among men who have sex with men in Montréal, Canada: a mathematical modeling study. BMC infectious diseases. 2022 Mar 7; 22(1):233.

Submitted:

[1]. **Xia Y**, Ma H, Malikov K, Straus E S, Fahim C, Moloney G, Huang Q, Asgari S, Boyd M J, Ferro I, Johns J, Mistry J, Wang L, Chan A, Baral D S, Maheu-Giroux M,

Mishra S. Association between staff movement and COVID-19 outbreaks in long-term care homes. (Under Review)

[2]. Allorant A, Kuchukhidze S, Stannah J, **Xia Y**, Masuku SS, Ekanmian GK, Eaton JW, Maheu-Giroux M. Socio-Demographic and Geographic Disparities in HIV Prevalence, HIV testing, and Treatment Coverage: An Analysis of 108 National Household Surveys in 33 African Countries. (Under Review)

Contribution of Authors

Manuscript 1: **Yiqing Xia**, Jorge Luis Flores Anato, Caroline Colijn, Naveed Janjua, Mike Irvine, Tyler Williamson, Marie B. Varughese, Michael Li, Nathaniel Osgood, David J. D. Earn, Beate Sander, Lauren E. Cipriano, Kumar Murty, Fanyu Xiu, Arnaud Godin, David Buckeridge, Amy Hurford, Sharmistha Mishra, Mathieu Maheu-Giroux.

I conceptualized this study with my supervisor, Prof. Mathieu Maheu-Giroux, and Jorge Luis Flores Anato. With assistance from Prof. Mathieu Maheu-Giroux and my committee member, Dr. Sharmistha Mishra, we identified and invited provincial teams engaged in the COVID-19 pandemic response in Canada to participate in this study. I developed the data collection tools that were used to collect and standardize the information reported by each provincial modelling team. Then, I summarized the information, performed the analyses, interpreted the results, and drafted the manuscript. All authors supported data curation, interpreted results, critically reviewed and edited the manuscript. All authors read and approved the final manuscript.

Manuscript 2: **Yiqing Xia**, Huiting Ma, Gary Moloney, Héctor A. Velásquez García, Monica Sirski, Naveed Z. Janjua, David Vickers, Tyler Williamson, Alan Katz, Kristy Yiu, Rafal Kustra, David L Buckeridge, Marc Brisson, Stefan D Baral, Sharmistha Mishra, Mathieu Maheu-Giroux.

I conceived and designed the study with Huiting Ma, Gary Moloney, Dr. Stefan Baral, my thesis committee member Dr. Sharmishtha Mishra and my supervisor Prof. Mathieu Maheu-Giroux. I developed the data analysis plan, with contribution from Huiting Ma. I wrote the code for analysis and adapted it for use by the different provincial teams. I coordinated code sharing across provincial teams and met with each team to explain and troubleshoot statistical issues. Data analyses were conducted by each provincial team separately due to the confidential nature of provincial surveillance data (i.e., surveillance data cannot be shared across jurisdictional boundaries). I performed the analyses for Québec. I aggregated the outputs from each province, summarized the results, and drafted the manuscript. Dr. Naveed Janjua, Dr. David Vickers, Dr. Tyler Williamson, Dr. Alan Katz, Kristy Yiu, Dr. Rafal Kustra, Dr. David Buckeridge (my thesis committee member), Dr. Marc Brisson, Dr. Sharmistha Mishra and Prof. Mathieu Maheu-Giroux interpreted data. All of the authors assisted in data acquisition, revised the manuscript critically for

important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Manuscript 3: **Yiqing Xia**, Huiting Ma, David Buckeridge, Marc Brisson, Beate Sander, Adrienne Chan, Aman Verma, Iris Ganser, Nadine Kronfli, Sharmistha Mishra, Mathieu Maheu-Giroux.

I conceptualized and designed the study with my supervisor Prof. Mathieu Maheu-Giroux and my committee members Dr. Sharmistha Mishra and Dr. David Buckeridge. I cleaned the data, conducted the statistical analysis, performed the literature search, and drafted the manuscript. Huiting Ma supported data curation and cleaning for the province of Ontario. Huiting Ma, Dr. David Buckeridge, Dr. Marc Brisson, Dr. Beate Sander, Dr. Adrienne Chan, Aman Verma, Iris Ganser, Dr. Nadine Kronfli, Dr. Sharmistha Mishra, and Prof. Mathieu Maheu-Giroux edited the manuscript and critically reviewed it for intellectual content. All authors approved the final version of the manuscript.

Manuscript 4: Yiqing Xia, Marie Alexandre, Rodolphe Thiebaut, Mathieu Maheu-Giroux, Mélanie Prague.

I conceived and designed the study with Dr. Mélanie Prague and my supervisor Prof. Mathieu Maheu-Giroux. Dr. Mélanie Prague is a permanent researcher at Inria (University of Bordeaux, France) in the SISTM team (Statistics in Immunology and translational medicine), who hosted me during my two-month visit to University of Bordeaux, funded by the CIHR *Michael Smith Foreign Study Supplements* award. I developed, parametrized, and simulated the individual-based model and the within-host compartmental models, conducted the literature review, and drafted the manuscript. Dr. Mélanie Prague and my supervisor Prof. Mathieu Maheu-Giroux provided advice on the model. Dr. Marie Alexandre estimated the parameters used to link antibody level and susceptibility. Dr. Rodolphe Thiebaut, Dr. Marie Alexandre, Prof. Mathieu Maheu-Giroux, and Dr. Mélanie Prague edited the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Chapter 1. Introduction

1.1. Background

The first SARS-CoV-2 case was reported in December 2019 in Wuhan (China). This newly identified coronavirus then spread rapidly worldwide, leading to the Coronavirus 2019 (COVID-19) pandemic–one of the most significant public health crises of the 21st century. It has impacted the world on an unprecedented scale, leading to a drastic loss of human life, increased health inequalities, and triggered a global economic crisis (1, 2).

To mitigate its spread, extensive non-pharmaceutical interventions (NPIs) were implemented (e.g., travel restrictions, closure of non-essential services) (3). The implementation and lifting of these measures depended mostly on the local situations of COVID-19 epidemics. Canada's decentralized healthcare infrastructure led to a unique adoption of various mathematical modelling approaches across provinces and territories to support these decisions (4). A common thread, however, was that vulnerable individuals (e.g. essential workers, low-income population) were disproportionately affected by the burden of SARS-CoV-2 infections and COVID-19 mortality (5, 6). Moreover, the prolonged surges in COVID-19 hospitalizations placed unprecedented pressure on the healthcare system, leading to significant overload (7, 8).

Nowadays, drawing lessons learned from the COVID-19 pandemic and preparing for future pandemics are priority research areas. To bolster global preparedness, one strategic approach is to develop vaccine candidates targeting prototype pathogens from families identified in the *World Health Organization* (WHO)'s blueprint for priority diseases (9, 10). In addition to advances in vaccine development, understanding the population-level effectiveness of these candidates may inform research directions for refining these vaccines.

My thesis aligns with the multifaceted aspects and interdisciplinary nature of pandemic response and preparedness, from understanding inequalities, the burden on hospital resources and mortality, and the evidence-to-decision pipeline, to vaccine developments for pandemic preparedness.

1.2. Organization of this thesis

This manuscript-based thesis is structured around the following four objectives:

1. Review and document Canada's diverse provincial mathematical modelling efforts in response to COVID-19 epidemics, understand how these efforts evolved along with the changes in local epidemics and increased knowledge on SARS-CoV-2, and draw lessons from Canada's experiences.

2. Quantify the degree of geographical concentration of SARS-CoV-2 transmission in Canada's largest cities and epicentres of the country's COVID-19 epidemics, and understand how area-level social determinants of health are associated with these heterogeneities across metropolitan areas.

3. Describe the temporal trends in in-hospital COVID-19 mortality risk and its drivers, and estimate the changes in the length of hospital and intensive care unit (ICU) stays using data from the two largest provinces in Canada.

4. Contribute to pandemic preparedness by examining the desired vaccine features to contain the transmission and maintain healthcare capacity for a future pandemic.

My thesis is organized into eight chapters. Chapter 1 presents the background and objectives of the thesis. Chapter 2 provides a contemporary overview of past and recent pandemics, including COVID-19, and contextualizes my doctoral work. Chapter 3 summarizes the data sources and methodologies used in my different manuscripts. Chapters 4 to 7 comprise the four manuscripts that each address one of the abovementioned objectives, in sequence. Finally, Chapter 8 synthesizes the findings of my research and interprets the results in the context of pandemic responses and pandemic preparedness.

Chapter 2. Literature review

2.1. Important pandemics in human history

Previous pandemics and their impacts

The word "pandemic" first appeared in print in England in 1666 to refer to a disease occurring in a region or country (11), even if pandemics occurred well before that time. The meaning of the term evolved, and the vocabulary became more specialized with terms such as outbreak, endemic, and epidemic, to better characterize the spread of communicable diseases. A pandemic, from the Greek *pandēmos* (*"*common to all people*"*), is an epidemic that occurs over a very wide area, crossing international boundaries, and usually affecting a large number of people (12). An epidemic is the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season (13, 14). An epidemic that is limited to a localized increase in the incidence of disease is an outbreak (12). When an outbreak is consistently present but limited to a particular region, it becomes endemic (15).

Pandemics of the past have been caused by diseases with various mode of transmission, such as vector-borne, waterborne, airborne, bloodborne, and sexually transmitted. In addition to having significant health consequences for populations, these pandemics have profoundly shaped human societies throughout history. Their impacts are not limited to the realms of health, but also include changes in public infrastructure, social behaviors, and economy, among others (16, 17). Important historical pandemics include those caused by plague, cholera, and flu.

Plague has caused at least three of the deadliest pandemics in human history that have resulted in over 200 million deaths (18). It is a high-fatality flea-borne disease caused by *Yersinia pestis*, a gram-negative bacteria whose animal host and reservoir are rodents. The first plague pandemic began with the Plague of Justinian in the 6th century that affected the entire Mediterranean Basin, Europe, and the Middle East (19, 20), with at least 18 waves spanning over 200 years that killed 33-60% of the Mediterranean population (18, 21, 22). The most prominent plague pandemic is the second one, which started with the famous Black death (often referred as "the Plague"; 1347-1351 AD). It is estimated that up to 60% of the European population perished during the Black Death alone (23, 24). After the Black Death, plague travelled from Europe to

Asia, and gave rise to the third plague pandemic in late 20th century (25-27). Notably, the first known quarantine measures, a type of NPIs, were enacted in response to the Black Death (17). Even nowadays, quarantine remains an effective public health measure against the spread of infectious diseases (28).

More recently, over the 19th and 20th centuries, cholera caused several major pandemics. Cholera, caused by *Vibrio cholerae*, is an acute and often fatal waterborne disease. Cholera originates from the Ganges Delta and has caused several major epidemics outside of this area with the expansion of global travel in the 19th century. The 1854 Broad Street cholera outbreak in Soho, London, is well-known among epidemiologists. It was during this epidemic that John Snow conducted the landmark investigation that laid the foundation for modern epidemiology. By using data-driven approaches such as data mapping, spatial analysis, and descriptive statistics, John Snow refuted the long-held Miasma theory (a misconception that diseases were caused by bad air) with the germ theory of disease (pathogens cause disease), and contributed to the improvement of outbreak control measures for waterborne diseases (29). However, Cholera outbreaks are still a concerning public health issue worldwide, often related to poverty and inequality, as exemplified by the 2010 epidemic in Haiti (30, 31).

Unlike the other infectious diseases described above that tend to spread rapidly, the contagion process for sexually transmitted infections (STI) is often slower and limited to people who are having multiple sexual partners. For instance, HIV is thought to have originated in Central Africa in the first half of the 20th century, but AIDS was only recognized in 1981. Since 1981, over 42 million people have died of HIV and, in 2023, there were approximately 40 million people living with HIV (32). Similarly, the WHO declared in 2022 that the multi-country epidemics of mpox (clade IIb) was a "*public health emergency of international concern*" (PHEIC). Transmission during this outbreak was principally attributed to sexual contacts among men who have sex with men and saturation of high sexual-activity groups limited the spread of this pathogen (33, 34).

Nowadays, respiratory pathogens are among the most significant public health threats and of greatest concern for their potential to lead to pandemics. The 1918 Spanish flu, caused by the H1N1 strain of influenza virus, was another deadly pandemic that wiped out 1-5.4% the world's

population (50-100 million deaths) (17, 35-37). Though the pandemic ended after two years, the impact of the Spanish flu persisted for decades. Evidence shows that viral reassortment among influenza viruses may have caused subsequent pandemics, including the 1957 Asian flu (H2N2), the 1968 Hong Kong flu (H3N2), and the 2009 Swine flu (H1N1) (25, 38). Recently, the H5N1 avian influenza has gathered increasing concerns due to its zoonotic spillover potential to other species, including humans (39, 40).

Coronaviruses make up an important family of respiratory viruses. This family includes four genera groups: alpha-, beta-, gamma-, and delta-coronaviruses (41). Up to now, several human coronaviruses (HCoV) have been identified: HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, the severe acute respiratory syndrome coronavirus (SARS-CoV), the Middle East respiratory syndrome coronavirus (MERS-CoV), and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (42). The later three coronaviruses all belong to the most pathogenic genus (the beta-coronavirus) and have caused three pandemics and epidemics in the 21st century, in 2003, 2012, and 2020, respectively (25, 43). However, the health burden of the SARS-CoV and MERS-CoV pandemics never reached the one caused by SARS-CoV-2.

Several pathogen characteristics can influence the course of an outbreak. First, a high basic reproduction number (R_0) indicates that the transmission potential is substantial. The R_0 represents the average number of secondary cases resulting from the infection of a primary case in a completely susceptible population (47). For example, the R_0 of SARS-CoV-2 (the original strain) ranges between 2-2.5 according to the WHO estimates, which is higher than that for SARS-CoV (1.7–1.9) and MERS-CoV (<1) (44). Coupled with a short generation interval (i.e., average time between the infection of a primary case and subsequent transmission events), pathogens with high R_0 result in more explosive epidemic growth. The second characteristic is the timing of the onset of symptoms relative to peak infectivity (45). The peak infectivity of SARS is between 5 to 10 days after symptom onset, which contributed to its containment (46). As asymptomatic infections are difficult to detect, pathogens with a higher fraction of asymptomatic (or sub-clinical) infections are more difficult to control. Thirdly, variability in transmission (e.g. overdispersion) can affect the likelihood of an outbreak and its subsequent control. When transmission events are overdispersed, case importation is less likely to result in outbreaks. However, when outbreaks do occur, high overdispersion may lead to more explosive growth of the outbreak and difficulty

controlling it (47). Finally, the existence of a natural reservoir makes it less likely for an outbreak to be eliminated. For instance, zoonotic diseases can transmit naturally between vertebrate animal and humans, either directly, or indirectly through the environment, challenging outbreak control (48).

The mode of transmission of a pathogen will influence its pandemic potential. Compared to other infectious diseases, respiratory viral pandemics pose several unique challenges. First, respiratory viruses can transmit through droplets and/or aerosols released from an infected individual during social interactions (49). Further, the generation interval is often quite short and measured in days for most respiratory viruses (i.e., as compared to years for HIV). Furthermore, the high mutation rates of respiratory viruses, especially RNA viruses, allow them to potentially evade immune responses, develop resistance to treatment and vaccines, reassort themselves to continuously circulate in the population (e.g., seasonal influenza), or allow viral recombination and reassortment at the human-animal interfaces that could give rise to future pandemics (e.g., the coronavirus pandemics) (38, 50-54).

Key parameters to estimate for an emerging pathogen and the role of mathematical modelling

At the onset of an outbreak, several key parameters need to be estimated to assess the pandemic potential of an emerging pathogen. These parameters will help identify the type of interventions required to control it. These include R_0, overdispersion, the generation (or serial) interval, the incubation period, the infectious period, the proportion of asymptomatic transmission events, and case severity (by the infection-hospitalization ratio and/or infection-fatality rate). Such parameters are often informed by case investigation, contact tracing studies, and surveillance data, although the latter is affected by completeness of case ascertainment. The WHO has proposed a series of templates and protocols to collect such information on the "*First Few X cases and contacts*" (FFX). These activities require a case definition that should be clear and adaptable, with inclusion of confirmed, suspected, and probable cases.

Once these parameters have been estimated, the next steps can involve nowcasting (situational awareness), forecasting, assessing the impact of NPIs and pharmaceutical (if available) interventions, resource planning, and informing policy decisions. These activities often involve the use of mathematical models of disease transmission. The main advantage of such models is

that they enable the simplification of abstract systems into more manageable problems. Mathematical modelling offers a structured approach to simplify the complex processes into representation of reality and project epidemic indicators under various "*what if*" scenarios (e.g., policy options) (55). In addition, it can help interpreting situations where data may be incomplete or missing, providing insights into historical trends and the effectiveness of public health measures, even when the details are unclear (56, 57). These strengths of mathematical modelling make it a well-suited tool in both planning and evaluating responses to public health crises, such as pandemics.

The use of mathematical modelling in infectious disease epidemiology can be traced back to the 18th century when Daniel Bernoulli applied the first mathematical models to study smallpox inoculation and its effect on mortality rates (58). The fundamental framework (the susceptible-infected-removed "SIR" model) was later introduced by William Kermack and Anderson Mckendrick in 1927 (59), after which mathematical models have been increasingly used to simulate disease transmission and inform responses, from influenza, to SARS, and HIV (60).

2.2. The COVID-19 pandemic

Global COVID-19 pandemic timeline, epidemiology and responses

In December 2019, several patients with pneumonia of unknown origin, presenting symptoms such as fever, cough, and respiratory distress, were reported in the city of Wuhan, Hubei Province, China (61). Shortly after the detection of these cases, the Chinese government notified the WHO about the situation on the last day of 2019. Epidemiological investigations suggested a connection between the cases and the *Huanan Seafood Wholesale Market*. On January 7th, 2020, the mysterious pneumonia was confirmed to be caused by a novel coronavirus, which was later named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Even now, the origin of SARS-CoV-2 is still controversial (62). However, the leading hypothesis in the scientific community is that it originated from a zoonosis spillover to humans in a wet market of Wuhan, China (63). One month into the new year, this new coronavirus had already swept across continents (64). With outbreaks being detected all over the world, the WHO first declared the COVID-19 outbreak a "*public health emergency of international concern*" on January 31st, 2020. Later on

March 11th, 2020, it was declared a pandemic. At that time, SARS-CoV-2 cases had been confirmed in over 100 countries, passing 100,000 confirmed cases globally (64).

Following the WHO's declaration of a pandemic, countries announced COVID-19 national emergencies and implemented public health measures. A small number of countries and regions such as Australia, China, New Zealand, North Korea, and some Canadian regions adopted an elimination strategy, which is referred to as the "Zero-COVID" approach. The underlying goal was to achieve local elimination by containing new outbreaks before they spread and lead to community transmission (65). The other strategy used was mitigation (i.e., flattening the epidemic curve) which attempted to reduce levels of community transmission such that it would not overburden the healthcare system. No matter which strategy was chosen, they relied on NPIs. Common interventions included lockdowns, physical distancing, mandatory masking, travel restrictions, quarantine for travellers (and regular testing), contact tracing, and case isolation (66). The major difference between the two strategies was that regions with an elimination goal acted faster and often implemented the measures more strictly (65, 67). Eventually, with the availability of vaccines and therapeutics, all regions that initially aimed to eliminate SARS-CoV-2 switched to a mitigation strategy.

During the COVID-19 pandemic, the necessity, effectiveness, and societal impacts of some public health measures were debated due to their collateral impacts on economy, mental health, and social inequalities. Contentious measures included face masks, closure of school and non-essential businesses, lockdowns, and curfews. For instance, in Canada, school closure aroused heated discussions over its broader societal and economic impacts. Proponents argued that school closure could efficiently mitigate community transmission, especially during the early stages when the community transmission was low (68-73). On the other hand, opponents disputed that this measure resulted in severe educational disruptions, and negative effects on children's mental health and social development (74-76). Critics also pointed that most infections among children do not result in high morbidity, whereas an unacceptably high proportion of COVID-19 deaths occurred among residents of long-term care homes. However, balancing public health priorities and individual wellness is ethically challenging, especially during emergencies (77).

By December 2020, nearly one year after the detection of the first case, effective COVID-19 vaccines from Pfizer-BioNTech, Moderna, and AstraZeneca had already been approved under emergency use authorization (EUA). Vaccine rollout began in the following months for countries that were able to secure doses, with much of low and middle-income countries left without access. Due to the limited supply and very high demand, national authorities often prioritized healthcare workers, elderly people, and other high-risk groups, before gradually expanding eligibility (61). In the meantime, three new variants of concern (VOC) of SARS-CoV-2 emerged: Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P1). While many countries began to ease their restrictions (i.e., lockdowns) alongside declining case numbers in the summer of 2021, the Delta (B.1.617.2) variant caused a resurgence of SARS-CoV-2 cases. Delta had higher transmissibility, higher viral load and longer duration of shedding, and higher likelihood of immune escape, resulting in a notably lower vaccine effectiveness for this variant (78-81). The rise of the Delta variant led to the reintroduction of restrictions in several jurisdictions.

The global vaccine coverage reached 50% by January 2022 (82). Meanwhile, the Omicron variant (B.1.1.529), a SARS-CoV-2 VOC with high transmissibility, but slightly reduced severity (as compared to Delta), became the predominant variant circulating worldwide (83). These factors, combined with economic pressures, pandemic fatigue, and other negative population health impacts, led many countries to shift towards a "living with COVID" strategy starting in late 2021. As of November 2nd, 2024, a total of 777 million SARS-CoV-2 cases and 7.1 million COVID-19 deaths were reported to the WHO (84). Although affected by underreporting, there were still over 50,000 new cases and approximately 1,000 reported deaths to the WHO every week in October of 2024.

Global mathematical modelling efforts

Never have mathematical models played such a prominent role in informing public health actions than during the COVID-19 pandemic. For example, mathematical modelling studies from Imperial College London's *COVID-19 Response Team* were among the very first to estimate the scale of the emerging epidemic in January 2020, the transmission potential, the severity of the virus, and the impact of NPIs (85). The *U.S. Centers for Disease Control and Prevention* (CDC) undertook mathematical modelling efforts to forecast disease burden. They provided an "ensemble"

forecast that combined outputs from multiple, independently developed models to increase the validity of their estimates (86). Furthermore, the *COVID-19 Vaccines Global Access* (COVAX) initiative, led by the WHO, used mathematical modelling to ensure the equitable distribution of COVID-19 vaccines (87). These models helped guide policy decisions by projecting the epidemic indicators (e.g., cases, hospitalizations, deaths), evaluating the potential impact of interventions, and providing insights on healthcare resource allocation and vaccine prioritization strategies.

2.3. Canada's response to the COVID-19 pandemic

The first SARS-CoV-2 case in Canada was reported on January 25th, 2020. By the time WHO declared the end of the PHEIC on May 5th, 2023, over 4.6 million SARS-CoV-2 cases and 52,231 COVID-19 deaths had been reported in Canada (88). However, these numbers hide important regional variations in transmission dynamics, disease burdens, and responses because of Canada's decentralized healthcare infrastructure, that puts the administration and delivery of healthcare services under the jurisdiction of provincial and territorial governments. (89).

During the Canadian COVID-19 epidemics, the federal government was responsible for border and travel restrictions, quarantining of incoming travelers, and procurement of personal protective equipment (PPE), testing kits, and vaccines (90). Through the *Public Health Agency of Canada* (PHAC), the federal government supported and coordinated the responses at the provincial/territorial levels. However, the core elements of COVID-19 responses were planned and organized by the provincial and territorial governments (91, 92). Provinces adopted different strategies based on their local epidemiological, political, and social contexts (93, 94). For example, in provinces heavily impacted during the early stages of the COVID-19 pandemic, such as Ontario and Québec, public health measures were primarily focused on mitigating transmission due to already high levels of sustained community spread, despite quite stringent NPIs. At the other end of the spectrum, in the four Atlantic provinces (New Brunswick, Newfoundland and Labrador, Nova Scotia, and Prince Edward Island) there were less outbreaks, and outbreaks were more rapidly detected and controlled. As such, early interventions in those provinces were aimed at avoiding case importation. Together, they created the "Atlantic Bubble", which allowed unrestricted travel among residents of the four provinces, but restricted travel for travelling from elsewhere (e.g., those from neighboring Québec). However, this policy was suspended in late

November 2020 and gradually abandoned as sustained community transmission occurred, despite the “Bubble”. requiring a shift in public health strategies.

Both the federal and provincial/territorial governments of Canada undertook substantial mathematical modelling efforts. At the federal level, PHAC established an *External Expert Modelling Group*. They produced models to guide the country’s response and provided support and coordination across provinces and territories. They also facilitated collaboration across provinces through regular meetings that involved provincial/territorial modellers (95, 96). At the provincial level, most provinces either officially established modelling teams involving academic researchers or conducted in-house modelling within government units (97-101). The three territories of Canada, with their limited modelling capacity, primarily relied on federal modelling efforts or collaborated with modellers from other provinces to support their responses. The provincial models were used to monitor epidemic indicators, project healthcare demands and resources planning, evaluate impacts of interventions, and optimize vaccine rollout strategies. These modelling efforts complemented those of the academic community that published several influential models in Canada (95, 100, 102-105).

2.4. Determinants and heterogeneities in SARS-CoV-2 transmission

The transmission of SARS-CoV-2 is determined by multiple factors including biological, virological, social, and environmental ones. Variations in host characteristics including age, comorbidity, viral load, and immune responses also contribute to differential transmissibility and susceptibility. Studies have found lower proportions of asymptomatic infections among older age groups compared to children (106, 107), while asymptomatic cases, though less infectious, can go undetected (i.e., not isolated) and contribute to onward SARS-CoV-2 transmission (108). Individuals’ viral load and antibody levels (immunity acquired from natural infection or vaccine-induced) are directly linked to their infectiousness and susceptibility (109, 110). Additionally, variations in individual-level viral loads can lead to overdispersion in transmission (i.e., “superspreading events”), which can result in many secondary infections being caused by a small proportion of cases (111, 112). Considering this, a NPI that limits large gatherings may be more effective for SARS-CoV-2 than for a pathogen whose transmission is not overdispersed.

NPIs such as lockdown, masking, closure of non-essential business and schools, and work-from-home order were able to reduce transmission (72, 113, 114). However, disparities in risk of SARS-CoV-2 infection by social determinants of health (SDOH), the nonmedical factors influencing health outcomes, were observed (115). Essential workers were disproportionately exposed to SARS-CoV-2 infections due to occupational hazard and lack (or improper use) of personal protective equipment (116, 117), resulting in intervention-generated inequalities in transmission. A study found 3.3-fold higher burden of SARS-CoV-2 cases among essential workers (118) while another study suggested 11.6-fold higher hazard of infection among healthcare workers compared to the general population (119). These occupational hazards were compounded by SDOH that contributed to onward transmission of the virus. Poor household conditions (e.g., lack of appropriate ventilation), high household density, and living in a multi-generational household were correlated with SARS-CoV-2 infections (120-123). Other SDOH such as being in disadvantaged ethnic groups (e.g., visible minorities), low income (124), and immigrants could have negative impacts on SARS-CoV-2's burden (125-128). These factors resulted in geographically and temporally clustered transmission dynamics of SARS-CoV-2.

2.5. Morbidity and mortality of SARS-CoV-2 infection

The COVID-19 pandemic placed immense pressure on healthcare systems. Many hospitals, and particularly their ICUs, were strained and over-occupied, often for long periods (7, 129-131). Healthcare workers infected with SARS-CoV-2 had to isolate, which further reduced the capacity of hospitals to care for patients. The prolonged surges of hospital admissions also severely disrupted treatment and care for other conditions (132, 133). A survey conducted by WHO in May 2020 found wide disruptions of health services for non-communicable diseases. Among the 155 participating countries, 31% experienced partial or complete interruptions for cardiovascular emergency services and 63% for rehabilitation services (134).

Besides putting pressure on health systems, the burden of SARS-CoV-2 infections was severe. Among the roughly 60-70% of infections that would be symptomatic (135-137), cough, fever, fatigue, headache, myalgias, anosmia, and diarrhea were the most common initial symptoms of the original strain (wild-type) of SARS-CoV-2 (138). For approximately 20% of laboratory-confirmed SARS-CoV-2 cases, the severity of the diseases required hospitalization (139-142).

Patients with severe COVID-19 may develop acute respiratory distress syndrome, lymphopenia, thromboembolic complications, disorders of the central or peripheral nervous system, and acute cardiac, kidney, and liver injury that ultimately led to multi-organ failure (143-147). It was estimated that one-fifth to one-third of hospitalized COVID-19 patients experienced critical illness, among whom approximately 70% require invasive mechanical ventilation (148). The mortality rate among hospitalized patients was estimated to be 12% for general admissions and increased to 41% for those who were critically ill (149).

Variations in the severity and mortality of SARS-CoV-2 were observed for age, sex, and other factors. It was estimated that the risk of hospitalization and case mortality for the original SARS-CoV-2 strain increased by 3.4% and 7.4% per age year (150). Male patients had 86% higher risk of mortality compared to female patients and those with comorbidities had a risk up to 4.9 times higher than that of patients without comorbidities (151). Though associations between race and ethnicity and COVID-19 severe outcomes have been inconclusive, evidence has shown that socioeconomic determinants were strongly associated with outcomes of COVID-19 among ethnic and racial minority groups (152, 153). Disparities in healthcare resources and access (e.g., hospital capacity, vaccine coverage), and differences in population structure and health conditions also underlined the varied outcomes of patients across regions and different settings (154-157). Residents of long-term care homes in Canada accounted for 69% of the total COVID-19 related deaths during the first two waves (from March 1st, 2020, to February 15th, 2021), far exceeding the international average of 41% (158).

Besides these acute symptoms, COVID-19 symptoms can persist for more than 12 weeks after the infection, which is known as “long COVID” (159). It can occur among any individual infected with SARS-CoV-2 and has an estimated incidence of 10-30% among non-hospitalized cases, 50-70% among hospitalized patients, and 10-12% among vaccinated cases (160-162). Symptoms of long COVID encompass multiple organ systems with the most common symptoms including fatigue, post-exertional malaise, cognitive dysfunction, cardiovascular, thrombotic, and cerebrovascular diseases (163, 164). The symptoms can last for years and can relapse (165). Long COVID can negatively impact individuals’ quality of life, as many affected experience difficulties returning to work and daily activities. It also puts a strain on the healthcare system due to the need for long-term, multidisciplinary care (166).

2.6. SARS-CoV-2 vaccines

One of the few success stories of the COVID-19 pandemic is certainly the rapid development, trials, and production of SARS-CoV-2 vaccines, including the first messenger RNA (mRNA) vaccines (60, 167). A variety of candidates for COVID-19 vaccines are available – the latest update of WHO's COVID-19 vaccine tracker and landscape recorded 183 vaccines in clinical development and 199 in pre-clinical development as of March 30, 2023 (168). These vaccines were developed using various technology platforms with different efficacies. The major vaccines that are granted EUA by WHO and have been instrumental in global COVID-19 immunization efforts are summarized in Table 2.6.1.

Table 2.6.1. Characteristics of the major vaccines approved for emergency use authorisation (169). Vaccine efficacy and risk ratios with 95% confidence intervals from randomized clinical trials are presented.

Vaccine	Platform	Number of doses	Vaccine efficacy against		Risk ratio of all-cause mortality (Intervention vs placebo group)
			Symptomatic infection	Severe or critical infection	
Pfizer/BioNTech (BNT162b2)	mRNA	2	97.9% [44.3-99.9%]	95.7% [73.9-99.9%]	1.07 [0.52-2.22]
Moderna (mRNA-1273)	mRNA	2	93.2% [91.1-94.8%]	98.2% [92.8-99.6%]	1.06 [0.54, 2.10]
AstraZeneca (AZD1222)	Adenovirus (CHAdOx1) vector	2	70.2% [62.1-76.6%]	Unavailable	0.48 [0.20, 1,14]
Johnson & Johnson (Ad26.Cov2.S)	Adenovirus (CHAdOx1) vector	1	66.9% [59.1-73.4%]	76.3% [57.9-87.5%]	0.25 [0.09-0.67]
SinoPharm (BBIBP-CorV)	Whole inactivated Coronavirus	2	87.1% [64.8-86.3%]	Unavailable	Unavailable
Sinovac (CoronaVac)	Whole inactivated Coronavirus	2	69.81% [12.27-89.61%]	Unavailable	0.5 [0.05, 5.52]
Bharat Biotech (BBV152)	Whole inactivated Coronavirus	2	77.8% [65.2-86.4%]	93.4% [57.1-99.8%]	0.5 [0.17-1.46]
Novavax (NVX-CoV2373)	Protein subunit	2	82.9% [50.5-94.1%]	100% [87.0-100%]	0.9 [0.3-2.68]

One year since the FDA approval of first COVID-19 vaccines under EUA, over 50% of the world's population received at least one dose of vaccine by the end of 2021 (82). It was estimated that vaccinations have prevented approximately 14 million COVID-19 related deaths in

185 countries and territories during the first year of vaccination (87). However, significant inequities in vaccine access and distribution were evident – high income countries administrated 69 times more doses per inhabitant than low-income countries within the first few months of vaccination (170).

2.7. Preparing for the next Disease X pandemic

On May 5th, 2023, WHO declared an end to COVID-19's status as a PHEIC (171). However, concerns over potential future pandemics have not faded as human activities that favor new or re-emerging infectious diseases persist (172). Associated factors include increased risk of zoonotic disease spillover due to more frequent interactions between human and domestic or wild animal reservoirs, climate change and urbanization, and increased speed of transmission because of the rapid global mobility (16, 173, 174). In just the first quarter of the 21st century, there have already been at least eight major (re)emerging pathogens (e.g., West Nile, SARS-CoV, H1N1, MERS-CoV, Zika, Ebola, SARS-CoV-2, and mpox), of which two resulted in pandemics (H1N1 and SARS-CoV-2) (175). Pandemic preparedness remains a strategic priority for the 21st century, as it is more cost-effective in minimizing the health, social, and economic impacts of emerging infectious diseases, than not taking proactive actions (176). Pandemics are mainly the result of human activity that influence the interactions between humans, animals, and the environment. As such, preventing future pandemics requires a One Health approach that involves all relevant sectors. One Health is an integrated approach guided by systems thinking and transdisciplinary action, that seeks to address urgent, ongoing, or potential health threats at the human-animal-environment interface at subnational, national, global, and regional levels (177). It ensures a sustainable balance and optimizes the health of all people, animals, and ecosystems (178).

Disease X, a placeholder concept first introduced by WHO in 2018, represents a disease that is currently unknown but may cause future pandemics (179). While the range of potential pathogens for Disease X is large, WHO has identified a list of priority diseases for research and development, as the resources are limited. They include COVID-19, SARS-CoV and MERS-CoV, Crimean-Congo hemorrhagic fever, Ebola virus disease and Marburg virus disease, Zika, and several other pathogens that are considered to pose the greatest public health risk (180). Recognizing the role of vaccines in previous pandemics and the unprecedented speed of vaccine

development during COVID-19, the *Coalition for Epidemic Preparedness Innovations* (CEPI) proposed the "*100 Day Mission*" initiative. Embraced by the G7 and G20, this initiative aims to prepare the world to respond to the next Disease X by facilitating the development of safe, effective, and accessible vaccines within 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognized (9). In order to achieve this ambitious goal, CEPI outlined 5 areas of innovation that are necessary (181):

1) Creating a library of prototype vaccines for representative pathogens from virus families with the greatest pandemic potential.
2) Pre-establishing networks to facilitate clinical trials.
3) Using advanced technology to speed up the identification of immune markers.
4) Enhancing global manufacturing capacity for vaccines.
5) Optimizing global disease surveillance and early warning systems.

2.8. Knowledge and evidence gaps

My doctoral work was completed from 2021 to 2024. The knowledge and evidence gaps addressed by my four articles inevitably evolved with the pandemic and its unprecedented scientific efforts. For instance, a search using the term "COVID-19" on PubMed resulted in close to 450,000 publications as of the end of November 2024. The work presented in this dissertation reflects the interdisciplinary nature of pandemic responses that require health scientists to draw from different fields. The specific knowledge and evidence gaps addressed by each of the next chapters are described in the following paragraphs.

As the COVID-19 pandemic swept across the world, decision-makers were faced with numerous uncertainties about SARS-CoV-2. In Canada, each provincial government deployed various mathematical modelling efforts to guide decision-making. Documenting Canada's diverse provincial mathematical modelling efforts can help understanding how local contexts influenced the modelling responses in each province and help draw valuable lessons for future public health challenges. However, these efforts have not yet been comprehensively documented, reviewed, and analyzed. My first thesis manuscript addresses these gaps.

One of the most striking features of the COVID-19 pandemic was that the risk of transmission, morbidity, and mortality was highly heterogenous: some people were at much higher risk of adverse health outcomes than others. Yet, little attention was devoted in our pandemic response to alleviating those health inequities. With increasing evidence on heterogeneities in transmission risks associated with SDOH, there was a need to understand these patterns and their associated factors to better understand SARS-CoV-2's transmission dynamics in Canada. To address this, I conducted the first Canadian multi-provincial study that compared whether the magnitude of inequities varied across Canadian cities.

Models developed and used during the pandemic were not static: they were continuously updated and adapted to enhance their precision and validity. Given COVID-19's impacts on morbidity and mortality, quantifying the time-varying hospital burden –in terms of length of stay and ICU admissions– was therefore important to accurately parameterize those mathematical models. At that time, the only evidence available in Canada came from a single city or hospital. To address that, I used the administrative data of the country's two largest province and epicenters of the epidemics.

Finally, as the world moves onward from the COVID-19 emergency response, pandemic preparedness should remain at the crux of the global health agenda. Anticipating the next Disease X through potential vaccine candidates of prototype pathogens is warranted. Mathematical models that can evaluate the potential population-level impact of those vaccines and their immunological characteristics are needed. However, existing disease transmission dynamic models do not consider host-level variations in their time-varying viral load and immune responses. My last thesis manuscript addressed these knowledge gaps.

In summary, my thesis constitutes a research program that weaves together mathematical modelling and evidence-to-decision pathways, heterogeneity in infections and their social determinants of health, patterns of healthcare consequences, and future pandemic preparedness and immunological characteristics of vaccines.

Chapter 3. Methods

This chapter summarizes the main data sources utilized and methodological approaches applied across the four manuscripts.

3.1. Data sources

My thesis leveraged data from multiple sources including new surveys, administrative databases, census data, and the published scientific literature. The main data sources my thesis were provincial surveillance and administrative databases including laboratory data on confirmed SARS-CoV-2 infections and COVID-19 hospitalizations. These datasets generally contain basic demographic characteristics but limited sociodemographic information. As such, I leveraged census data to complement this gap and used the Postal Code Conversion File (PCCF) to link each case to their corresponding census area. Another key data source of my thesis was the Québec Connect study, which was used to inform the contact behavior of the mathematical model I developed in my fourth manuscript. The following sections give a more detailed description of these data sources.

3.1.1. Provincial COVID-19 surveillance databases

COVID-19 is a notifiable disease in each province. Healthcare is a provincial jurisdiction in Canada and each province manages their own COVID-19 surveillance databases. These databases record all identified diagnoses of SARS-CoV-2 infections by the provincial public health laboratories, COVID-19 hospitalizations within each province, and COVID-19 deaths. At the time I conducted the analyses of my second and third manuscripts, only data from some provinces were available for analysis without breaching any data confidentiality agreements, as summarized below.

British Columbia

In British Columbia, confirmed SARS-CoV-2 cases were recorded in the *Public Health Reporting Data Warehouse* (PHRDW) (182). First developed in 2011, this data warehouse continuously integrates new data on notifiable diseases per their provincial surveillance forms,

laboratory tests, and deaths (i.e., enteric diseases, vaccine preventable diseases, chronic diseases, respiratory diseases, environmental health conditions, sexually transmitted and blood borne infections). By linking data from different sources using a custom person-matching algorithm (validated match rate close to 100%), PHRDW creates de-identified profiles of individuals to support real-time public health surveillance, identifying trends in disease activity through linked and cleaned datasets prepared for analysis.

Manitoba

In Manitoba, the COVID-19 surveillance data and contact tracing information were requested through the *Manitoba Population Research Data Repository* (183). This database integrates administrative (e.g., hospital, pharmaceutical prescriptions), survey (e.g., health survey, census), and registry (e.g., health insurance, vital statistics) data from agencies such as *Manitoba Health*. It supports interdisciplinary research across healthcare, education, social services, and justice, aiming to analyze health patterns and outcomes. Data access is managed by the *Manitoba Centre for Health Policy*. This data warehouse includes three datasets on COVID-19: *COVID-19 Lab Testing and Results Data*, *COVID-19 Surveillance Data – Case and Contacts*, and *COVID-19 Vaccinations, Appointments, and Screening Data*. The latter two are collected in the *Public Health Information Management System*. Briefly, these databases contain information on the laboratory tests (e.g. result, date of collection), demographic information (e.g., age, postal code), acquisition classifications, case outcome, risk factors, and vaccination status.

Ontario

In Ontario, data on laboratory-confirmed SARS-CoV-2 cases and COVID-19 hospitalizations were recorded in the *Case and Contact Management System* (CCM) (184, 185). The CCM system was a dynamic reporting platform designed to manage the extensive COVID-19 data flow. It facilitated tracking cases, contacts, outbreaks, and adverse events following immunizations while linking lab results with data from local health authorities. On June 1, 2024, data entry into CCM ceased, with all COVID-19 related information transitioned to the *Integrated Public Health Information System* (iPHIS) for continued management.

Québec

In Québec, lab-confirmed SARS-CoV-2 cases and those detected through epidemiological links were recorded in the *Trajectoire de santé publique* (TSP) database (186). The TSP database is a comprehensive public health database to track and analyze the health trajectories of individuals across the province. It integrates various sources of health information, including administrative health data, medical service utilization records, hospitalizations, and other relevant healthcare interactions. During the COVID-19 epidemic, it was used to collect data on SARS-CoV-2 cases including epidemiological and sociodemographic information until July 13th, 2022.

The individual-level COVID-19 hospital data were obtained from the *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* database (MED-ÉCHO live) (187). This database, administrated by the *Ministère de la Santé et des Services Sociaux* (MSSS, Ministry of Health and Social Services), contains clinico-administrative information on care and services provided to individuals admitted to, or registered with, a Québec hospital, including day surgeries. It is used for evaluating service needs and consumption and supports the planning, organization, and assessment of delivered healthcare services. Daily hospital-level capacity data were extracted from the *Relevé quotidien du centre hospitalier* report which provides a daily overview of active hospitalizations for COVID-19 patients (188).

3.1.2. Canadian Census (2016)

In my second manuscript, data from the 2016 *Canadian Census of Population* was used to inform the dissemination area (DA) level population size and social determinants of health. The use of census data was chosen because it is the most complete, comparable, and representative source of area-level characteristics of the population in each city (189). At the time manuscript 2 was conducted, the 2016 data was the most recent available version. The sex and age structures of the modelled population in manuscript 4 were extracted from the 2021 Census of Population.

The census is conducted by *Statistics Canada* every 5 years to provide a detailed statistical portrait of Canada, its residents, and citizens outside of Canada. It provides information on the population, age and sex, type of dwelling, families, households and marital status, language, income, immigration and ethnocultural diversity, housing, Aboriginal peoples, education, labour,

journey to work, language of work and mobility and migration (190). At each census, two cross-sectional survey formats are conducted: the short-form and the long-form. In 2016, the short-form questionnaire was distributed to 100% of the population without any sampling. On the other hand, the long-form census was collected from a random sample of 1 in 4 private dwellings in Canada.

Responding to the short-form census survey was mandatory (191). Quality of the responses were screened, and follow-ups were performed to complete missing information. Omissions and inconsistencies were corrected using deterministic imputation and donor imputation. Deterministic imputation is an approach often used to handle systematic errors or missing data by applying a predefined solution based on subject-matter knowledge. The donor imputation, also referred to as the nearest neighbour, is a technique commonly used to deal with non-responses by using values taken from similar respondents (192). The final responses to the long-form survey are weighted to represent the Canadian population living in private dwellings.

3.1.3. Postal Code Conversion File (PCCF) and Postal Code Conversion File Plus (PCCF+)

The Postal Code Conversion File (PCCF) is a tool created by Statistics Canada that links the six-character Canadian postal codes to standard geographic areas, such as dissemination areas (DAs), census tracts (CTs), census divisions (CDs), census metropolitan areas (CMAs), as well as other administrative geographies like health regions and federal electoral districts (193). It provides geographic coordinates (latitude and longitude) for each postal code's representative point, enabling spatial analysis and mapping. The PCCF is updated every five years after each census to align with new census geographic areas. It is often used by researchers to conduct health services planning, demographic analysis, and policy development by associating postal codes with population-based data (194).

In my second manuscript, each SARS-CoV-2 case was linked to their corresponding DA and CMA using the PCCF that was released in 2017. DA is the smallest geographic unit for which census data is distributed in Canada. It is a small, relatively stable geographic unit consisting of one or more adjacent dissemination blocks based on data from the preceding Census of Population Program. The average population for each DA is between 400 to 700 persons (195). A CMA is composed of one or more adjacent municipalities. To be classified as a CMA, that area must have

50,000 or more residents in its core area and a total population of at least 100,000, based on adjusted data from the previous Census of Population Program. Other adjacent municipalities are included in a CMA if they have a high degree of integration with the core. Once an area is designated as a CMA, it remains a CMA even if its total population declines below the thresholds (196).

The Postal Code Conversion File Plus (PCCF+) is a SAS control program that builds on the PCCF by incorporating additional features, including population-weighted random allocation for postal codes that cover multiple DAs (197). It is served as a link between the Canada Post six-character postal codes, census geographic areas (e.g., DA, CMA), and supplementary administrative regions and neighborhood income quintiles. This file was used in my second manuscript to obtain the income status of each DA. Data access was request through the *Data Liberation Initiative*.

3.1.4. The Québec Connect study

In my fourth manuscript, I developed a mathematical model to simulate the transmission of a novel pathogen. To efficiently capture epidemiological patterns, the social behaviors of the modelled population need to be reproduced. This was informed by data extracted from the Québec CONNECT study (*CONtact and Network Estimation to Control Transmission*). It is a population-based survey aimed to understand the contact patterns and social networks of all non-institutionalized Quebecers (e.g., residents of long-term care homes were not eligible). The survey was conducted through 4 phases which covered the period before, during, and after the pandemic: February 2018 to March 2020 (phase 1); April 21st to May 25th, 2020 (phase 2); and July 3rd, 2020, to February 26th, 2021 (phase 3 to 5). The recruitment procedure involved two stages of sampling. First, a digit dialing sampling of households was used to recruit participants. This sampling method is often used to provide a sample of households, families, or persons through a random selection of their telephone numbers (198). Then, stratified sampling based on the age and sex structures of the household was used to select one person in each household to complete the questionnaire. For each participant, their sociodemographic characteristics as well as their contacts, relationship information, locations of contacts, durations, and frequency of contacts were collected. Data used

in my manuscript were extracted from published figures. Detailed description and methodology of the study are summarized in *Drolet et al.* (199).

3.2. Methodologies used

I employed a variety of epidemiological methods in my thesis, from descriptive, analytic, to modelling and simulation approaches. This section follows the order of my manuscript to briefly describe the study designs and the methods I utilized. Some justifications and explanations of the designs and methods that were not included in the manuscripts are presented here.

3.2.1. Manuscript 1: Narrative review and customized data collection tool

My first manuscript is a review of the provincial modelling efforts that informed responses to the COVID-19 epidemics in Canada. As published information in the peer-reviewed literature to document these experiences was scarce, a systematic review would have provided an incomplete picture of the situation. Instead, I chose to conduct a narrative review. This type of review is useful to obtain perspectives on complex topics thanks to its ability to synthesize varied information and provide a comprehensive summary (200, 201). Although this method could be more prone to bias than a systematic review, it allows the authors to integrate findings from diverse sources, highlight knowledge gaps, and provide interpretation, which can help contextualize findings and propose meaningful new insights (202).

Provincial teams were identified using a *Criterion-I purposeful sampling strategy*, a technique widely used in qualitative research to identify and select all cases that meet some predetermined criterion of importance (203). To collect the necessary information from each provincial team, I created a customized data collection tool to gather detailed information from identified provincial modelling teams. The tool was designed to capture 1) model type, characteristics, and evolution, 2) surveillance data used to inform the models, 3) knowledge translation structure, and 4) main challenges encountered in a structured format. Key points were listed to ensure the collection of the most essential information. The tool was administered through a digital survey to facilitate efficient data collection while minimizing the burden on the teams.

3.2.2. Manuscript 2: Measurements of inequality and social determinants of health

For this manuscript, I used a multi-provincial lens to quantify and compare the city-specific geographical concentration of SARS-CoV-2 by social determinants of health. However, harmonizing, validating, and pooling administrative and surveillance data from multiple provinces in Canada is extremely challenging (204-206). Provincial legislation mandates that "*administrative data cannot cross provincial jurisdictional boundaries, requiring that linkage and analyses take place province-by-province*" (205), creating "legal interoperability" barriers to data sharing. In addition, socio-demographic variables related to important social determinants of health were often not collected in surveillance databases. To overcome these barriers, and to have a broader picture of the inequalities of SARS-CoV-2 transmission across Canada, I used an ecological study design by examining at the DA-level. To do so, I developed and deployed a decentralized data processing approach that ensured the confidentiality of provincial surveillance data and enabled interpretation across provinces. Briefly, I cleaned, coded, and analyzed all Québec data as a part of the provincial modelling team in Québec. After that, I generalized the code to ensure that the other provincial teams could easily use my codebase for their purposes. Then, a detailed analysis plan, the code, and examples of outputs were distributed to each provincial team, along with province-specific meetings for further explanation and troubleshooting. This approach allowed consistency in the analytical approach across provinces.

Provinces with DA-level SARS-CoV-2 data available were included in the study. The choice of the CMAs followed the criteria that ensured a sufficiently large numerator (the cases) and denominator (population size) with which local transmission patterns could be examined. The selection of social determinants of health (SDOH) were based on the characteristics of SARS-CoV-2 transmission (i.e., those related to contact rates and types of potential exposures) and the existing literature. The final list of SDOH examined was limited by the availability of DA-level data. A detailed list of the SDOH and their definitions are provided in Table 5.4.1.

The area-level concentration of SARS-CoV-2 cases were quantified using Gini coefficients, calculated as twice the area under the Lorenz curve (207). The Gini coefficient is a statistical measure of inequality that ranges from 0 to 1, where 0 represents perfect equality and 1 means perfect inequality (208). The inequalities by SDOH were measured using Gini covariance

(co-Gini) coefficients and concentration curves (209). Compared to other assessments of inequalities, such as the concentration index, weighted correlation, and regression, the Gini coefficient is widely recognized and interpretable across disciplines, which can facilitate greater understanding of results for a broader audience. Moreover, the Gini coefficient is a non-parametric measure (209).

3.2.3. Manuscript 3: Risk of in-hospital mortality using logistic regression

For my third manuscript, I conducted a retrospective population-based cohort study using provincial databases on COVID-19 hospitalizations from Ontario and Québec. The risk of in-hospital mortality was estimated using a logistic regression with cubic splines for calendar time, adjusted for patient-level characteristics and hospital-level determinants. The choice of logistic regression over survival analysis for a time-to-event outcome with censoring was based on my research question that aimed to examine variations in the in-hospital mortality risk over time, instead of hazard ratios or the time-to-death. This is in line with previous analyses that used logistic regression to examine in-hospital mortality risk due to COVID-19 (210-212). The time-varying adjusted mortality risks and 95% confidence interval (CI) were obtained using marginal standardization with 1,000 bootstrap replicates of the individual hospitalizations. Marginal standardization is a method that sums predicted probabilities to create a weighted average that reflects the distribution of characteristics in the target population. This allows for inferences to be made about the total population (marginal instead of conditional) from which the data was drawn (213).

When measuring the length of stay, approximately 17% of the hospitalizations in Ontario were missing the date of discharge and were therefore excluded from the analyses, assuming data were missing completely at random. The rationale for this assumption stemmed from a combination of expert insights and data. Surveillance data specialists from Ontario suggested that the missing dates were due to clerical errors made by the medical archivists who entered the information and were thus likely independent from the characteristics of the hospitalizations. Supporting this claim, I conducted an empirical examination of potential differences in the age and gender distribution of the hospitalizations with observed and missing dates. I found that these were almost identical.

3.2.4. Manuscript 4: Mathematical model of disease transmission

The 2024 update of WHO's disease research and development (R&D) *Blueprint for Epidemics Priority Pathogens* listed several respiratory virus families including Coronaviridae (e.g., family of SARS-CoV-2 virus) and Orthomyxoviridae (e.g., family of influenza virus) as high PHEIC risk. For respiratory viruses, the host's viral load level is highly associated with infectiousness and the duration of infection (10). To examine the desired vaccine features for a potential Disease X caused by such a respiratory virus, I adopted a mathematical modelling approach that combines the between-host population transmission of infection and the within-host individual-level dynamic of viral load and immune responses. Mathematical models can simulate the transmission of a hypothetical pathogen and the impact of potential vaccine scenarios that capture both the direct and indirect (herd-immunity) benefits of vaccination. Broadly, mathematical models of infectious diseases can be classified into two categories: compartmental models and individual-based models (IBM) (214). Compartmental models are a common approach that divide the study population into different compartments according to their infection status and other characteristics (e.g., age, sex, intervention) (215). These models are often programmed using a set of ordinary differential equations (ODE) and are generally more computational efficient than IBMs (216), if the number of compartments is reasonably small. IBMs, on the other hand, simulate each individual within the population, which allows a high level of population heterogeneity, more complex behaviors, and memory-dependent interventions or processes (e.g., contact tracing) (217, 218). As such, I developed a hybrid approach that combines an IBM of inter-host transmission with within-host compartmental models of virus and antibody dynamics. The IBM of this hybrid model was used to simulate: 1) the time-varying between-host contact network, stratified by household or non-household contacts, 2) virus transmission (based on the within-host viral load and antibody level of each individual), 3) natural progression of the disease (i.e., infection, hospitalization, and death), and 4) vaccine characteristics and rollout strategies.

My hybrid modelling approach also used compartmental models. Specifically, target cell-limited (TCL) models are mathematical models that describe the dynamics of viral infections within a host, that are often used in studies of HIV and influenza (219, 220). The dynamics of viral infections describe how a virus interacts with the host's cells and immune system over time (221). A TCL assumes that viral replication is primarily constrained by the availability of uninfected

target cells. In studies of the SARS-CoV-2 virus, extension of the TCL model with an eclipse phase (TCLE model) was found to provide the best fits to empirical data (222). The eclipse phase of the infected cell is defined as the time elapsed between successful cell infection and the start of virus production (223). As such, in manuscript 4, a TCLE model proposed by *Marc et al.* (110) was utilized to project the individuals' time-varying viral load. To model the antibody kinetics (i.e., the temporal changes in the concentration of antibodies), the mechanistic model proposed by *Clairon et al.* (224) was adopted. This simplified model is more computationally efficient, and it can analyze the joint kinetics of anti-spike IgG antibodies (i.e., an antibody that targets the spike protein of SARS-CoV-2) and neutralization capacity (i.e., the antibody's ability to block the virus from infecting host cells).

3.3. Ethics

This thesis used existing studies, publicly available information, and individual participant data to conduct secondary data analyses. All individual-level data were de-identified. Ethics approvals were not required for my first and fourth manuscripts, as confirmed by McGill's Institutional Review Board. For my second manuscript, ethics approvals were obtained from the Research Ethics Board of the University of British Columbia (H20-02097), the Health Research Ethics Board of the University of Manitoba (HS24140 (H2020:352)) and the Health Information Privacy Committee of the Government of Manitoba (No. 2020/2021-32) in Manitoba, the Health Sciences Research Ethics Board of the University of Toronto (no. 39253) in Ontario, and the Institutional Review Board of McGill University in Québec (A06-M52-20B). Ethics approvals for my third manuscript were acquired from the Health Sciences Research Ethics Board of the University of Toronto (no. 39253) in Ontario, and the Institutional Review Board of the Faculty of Medicine and Health Sciences of McGill University in Québec (A06-M52-20B).

Chapter 4. Canada's Provincial COVID-19 Pandemic Modelling Efforts

4.1. Preface to Manuscript 1

Mathematical modelling efforts during the COVID-19 pandemic were not developed in isolation–they were built upon the experiences and frameworks developed during previous epidemics and pandemics. At the beginning of the COVID-19 pandemic, models from the United Kingdom highlighted the potentially high morbidity and mortality burden of unmitigated SARS-CoV-2 transmission. In that country, the COVID-19 response was relatively centralized, and modelling efforts were primarily performed by members of the *Scientific Pandemic Influenza Group on Modelling-Operational* (SPI-M-O) that reported directly to the *Scientific Advisory Group for Emergencies* (SAGE) (225, 226). In contrast, the response was decentralized in Canada. Most provinces developed their own modelling approaches to inform their local public health responses.

Provincial modelling efforts, in contrast to those of the academic community (95, 100, 102-105), have not undergone formal review yet. This is, in part, because the research agenda prioritized immediate public health needs over publication-oriented activities. My first thesis manuscript addresses this gap, documenting and analyzing Canada's provincial COVID-19 mathematical modelling approaches. By contextualizing provincial responses and challenges within the Canadian landscape, this chapter sets the foundation for understanding how mathematical frameworks guided decisions for managing the pandemic. It forms an important starting point for improving Canadian pandemic preparedness. Importantly, the review of the models in this manuscript also provides foundational insights into why my second and third manuscripts are vital for understanding and improving pandemic responses in Canada.

The resulting article was published in *Canadian Journal of Public Health (CJPH)* in May 2024.

4.2. Manuscript 1: Canada's provincial COVID-19 pandemic modelling efforts: a review of mathematical models and their impacts on the responses

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Declarations

Conflict of interest: MM-G reports contractual arrangements from the *Institut national de santé publique du Québec* (INSPQ), the *Institut d'excellence en santé et services sociaux* (INESSS), the *Public Health Agency of Canada*, the *World Health Organization*, and the *Joint United Nations Programme on HIV/AIDS* (UNAIDS).

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Consent for publication: Not applicable.

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Code availability: Not applicable.

Author contributions: YX, JFL and MMG conceived of and designed the study. YX, JFL and MMG collected the information. YX conducted the literature search, conducted the summarizing analyses and drafted the manuscript. JFL, CC, NJ, MI, TW, MBV, ML, NO, DJDE, BS, LEC, KM, FX, AG, DB, AH, SM, and MMG interpreted results, supported data curation, critically reviewed and edited the article.

Abstract

Setting: Mathematical modelling played an important role in the public health response to COVID-19 in Canada. Variability in epidemic trajectories, modelling approaches, and data infrastructure across provinces provide a unique opportunity to understand the factors that shaped modelling strategies.

Intervention: Provinces implemented stringent pandemic interventions to mitigate SARS-CoV-2 transmission, considering evidence from epidemic models. This study aimed to summarize provincial COVID-19 modelling efforts. We identified modelling teams working with provincial decision-makers, through referrals and membership in Canadian modelling networks. Information on models, data sources, and knowledge translation were abstracted using standardized instruments.

Outcomes: We obtained information from 6 provinces. For provinces with sustained community transmission, initial modelling efforts focused on projecting epidemic trajectories, healthcare demands, and evaluating impacts of proposed interventions. In provinces with low community transmission, models emphasized quantifying importation risks. Most of the models were compartmental and deterministic, with projection horizons of a few weeks. Models were updated regularly or replaced by new ones, adapting to changing local epidemic dynamics, pathogen characteristics, vaccines, and requests from public health. Surveillance datasets for cases, hospitalizations and deaths, and serological studies were the main data sources for model calibration. Access to data for modelling and the structure for knowledge translation differed markedly between provinces.

Implication: Provincial modelling efforts during the COVID-19 pandemic were tailored to local contexts and modulated by available resources. Strengthening of Canadian modelling capacity, developing and sustaining collaborations between modellers and governments, and earlier access to linked and timely surveillance data could help improve pandemic preparedness.

Résumé

Contexte : La modélisation mathématique a joué un rôle de premier plan dans les ripostes sanitaires à la COVID-19 au Canada. Les différentes trajectoires épidémiques provinciales, leurs approches de modélisation et infrastructures de données représente une occasion unique de comprendre les facteurs qui ont influencé les stratégies de modélisation provinciales.

Intervention : Les provinces ont mis en place des mesures de santé publique strictes afin d'atténuer la transmission du SRAS-CoV-2 en tenant compte des données probantes provenant des modèles épidémiques. Notre étude vise à décrire et résumer les efforts provinciaux de modélisation de la COVID-19. Nous avons identifié les équipes de modélisation travaillant avec les décideurs provinciaux parmi les réseaux Canadiens de modélisation et par référence. Les informations sur les modèles, leurs sources de données et la mobilisation des connaissances ont été obtenues à l'aide d'instruments standardisés.

Résultats : Nous avons colligé les informations provenant de 6 provinces. Pour les provinces qui ont eu de la transmission communautaire soutenue, les efforts de modélisation initiaux se sont concentrés sur la projection des trajectoires épidémiques, des demandes de soins de santé et sur l'évaluation des impacts des interventions proposées. Dans les provinces où la transmission communautaire a été faible, les modèles visaient à quantifier les risques d'importation. La plupart des équipes ont développé des modèles à compartiments déterministes avec des horizons de projection de quelques semaines. Les modèles ont été régulièrement mis à jour ou remplacés par de nouveaux, s'adaptant aux dynamiques locales, à l'arrivée de nouveaux variants, vaccins et des demandes des autorités de santé publique. Les données de surveillance des cas, des hospitalisations et des décès, ainsi que les études sérologiques, ont constitué les principales sources de données pour calibrer les modèles. L'accès aux données pour la modélisation et la structure de mobilisation des connaissances différaient considérablement d'une province à l'autre.

Implication : Les efforts de modélisation provinciaux pendant la pandémie de la COVID-19 ont été adaptés aux contextes locaux et modulés par les ressources disponibles. Le renforcement de la capacité canadienne de modélisation, le développement et le maintien de collaborations entre les modélisateurs et les gouvernements, ainsi qu'un accès rapide et opportun aux données de

surveillance individuelles et liées pourraient contribuer à améliorer la préparation aux futures pandémies.

Keywords: COVID-19; Mathematical modelling; Policy making; Knowledge translation; Pandemic; SARS-CoV-2.

Mots-clés : COVID-19; Modélisation mathématique; Élaboration de politiques; Application des connaissances; Pandémie; SRAS-CoV-2.

1. Introduction

Governments worldwide have relied on epidemic modelling, along with other epidemiological studies, to guide responses to the coronavirus disease (COVID-19) pandemic (James et al., 2021; McBryde et al., 2020; Rhodes & Lancaster, 2020). Mathematical models of infectious diseases can integrate knowledge about the pathogen, human behaviors, and interventions to generate projections under various "*what if*" scenarios that considers uncertainty (Brooks-Pollock et al., 2021; MacIntyre & Heslop, 2022). These tools have been previously used to inform public health responses to such as Ebola, Zika, and HIV (Johnson & White, 2011; Lewnard et al., 2014; Morrison & Cunha, 2020) —but their unprecedent adoption during the COVID-19 pandemic created tensions in the production and use of modelling. In Canada, these efforts were partly inspired by earlier works against SARS in 2003 (Gumel et al., 2004) and the 2009 H1N1 influenza (Biggerstaff et al., 2022; York University. (n.d.)).

The federal *Public Health Agency of Canada* (PHAC) developed models (Gabriele-Rivet et al., 2021; Ludwig et al., 2020; Ogden et al., 2020) to advise national-level public health matters (e.g., border closures, vaccine distribution (National Collaborating Centre for Infectious Diseases, n.d.; Government of Canada, n.d.)). PHAC served an important convening role through its "*External Modelling Experts Group*" that established a network of provincial and territorial modelling experts, providing support, coordination, and facilitating collaborations (Allin et al., 2022b). The Canadian federal government was responsible for procurement of personal protective equipment, testing kits, vaccines and testing kits, and provision of financial support. However, some of the core elements of the COVID-19 responses were planned and organized by Canadian provincial and territorial governments (Allin et al., 2022a; Canadian Public Health Association, 2021). Complementary to PHAC's convening role, provinces and territories relied on their own modelling teams to monitor and project epidemic trends, plan for healthcare resources, and assess the potential impact of various pharmaceutical/non-pharmaceutical interventions (e.g., physical distancing, school closures, curfews, vaccine passport, immunization strategies) (BC COVID-19 Modelling Group, n.d.; Government of Alberta, 2020; Government of Saskatchewan, n.d.; Hurford et al., 2021; Government of Manitoba, n.d.; INSPQ, n.d.; INESSS, n.d.; Ontario COVID-19 Science Advisory Table, n.d.). Despite having similar health systems, provincial/territorial teams employed a wide range of models that answered different questions. This diversity provides a

unique opportunity to understand how the different provincial/territorial contexts influenced what modelling strategies were chosen and how collaborations, knowledge translation and exchange between modellers and decision-makers were structured.

This study aims to describe, summarize, and analyze provincial COVID-19 modelling efforts in Canada. There has been no comprehensive overview of those efforts, and this will complement the province-specific literature on the subject (Hillmer et al., 2021). Specifically, we document the main model types, their evolution, the availability of surveillance data and other resources, the strategies used to mobilize modelling expertise and sustain collaborations, and how these models shaped the pandemic responses. Documenting and understanding Canada's diverse provincial modelling efforts will help us draw appropriate lessons for future public health challenges (Eker, 2020; Padmanabhan et al., 2021; Soman Pillai et al., 2020; Tan, 2006).

2. Methods

We reviewed Canada's provincial modelling efforts by identifying the main modelling teams with government mandates to model SARS-CoV-2 in British Columbia (BC), Alberta (AB), Saskatchewan (SK), Manitoba (MB), Ontario (ON), Québec (QC), New Brunswick (NB), Nova Scotia (NS), Prince Edward Island (PE), and Newfoundland and Labrador (NL) between March 2020 and December 2021. We included dynamic transmission models and excluded those used solely to estimate the effective reproduction number or other epidemiological quantities (e.g., phenomenological models).

Teams were identified through memberships in modelling networks and referrals. Once identified, data collection instruments were provided to abstract information on four domains: a) model type, characteristics, and evolution, b) surveillance data used to inform the models, c) knowledge translation structure, and d) main challenges encountered. A total of 20 models were included in this review, and results are summarized as a narrative review.

3. Results

3.1 Overview of epidemic settings and initial modelling efforts

Shortly after declaration of public health emergencies in March 2020 (Mishra et al., 2022; Vickers et al., 2022; Xia, Ma, Buckeridge, et al., 2022; Xia, Ma, Moloney, et al., 2022), several provinces mandated modelling groups to support responses: SK's *University of Saskatchewan* Computational epidemiology & Public Health Informatics Laboratory (*CEPHIL)*, ON's *COVID-19 Modelling Consensus Table (MCT)* (Hillmer et al., 2021), QC's two COVID-19 modelling teams at *McGill University* and *Université Laval* , and NL's *Predictive Analytics Team* (CanLII, n.d.). In total, half of the provinces established modelling teams composed of academic researchers working in collaboration with provincial governments. Throughout the pandemic, most provinces had one or two main modelling teams while ON and BC mobilized several teams simultaneously. Some provinces (MB, NS) relied primarily on internal teams within health authorities. In other cases, academic modellers provided assistance and expertise (AB, NB, PE). Public availability of information on these models' methods was limited in most cases. In all provinces, modelling projections from PHAC were often referenced and informed policymaking in provinces with limited modelling capacity. Atlantic provinces faced specific circumstances (i.e., timing of travel and spread), which allowed for a suppression strategy and maintained very low prevalence of community cases before June 2021. In NL, modelling efforts quantified the risk of SARS-CoV-2 importation on community transmission (Hurford et al., 2021, 2023). For other provinces, a mitigation strategy was adopted due to sustained community transmission. Policies were aimed at "*flattening*" the epidemiological curve and maintaining hospitalizations below hospital capacity (Government of British Columbia, 2020; Government of Alberta, n.d.; University of Saskatchewan, n.d.; Tuite et al., 2020). Modelling efforts were mainly focused on: 1) projecting epidemic indicators (e.g., cases, hospitalizations, deaths) and demands on healthcare resources; and 2) evaluating the potential impact of proposed interventions (Table 4.2.1).

Table 4.2.1 Features of mathematical models and type of evidence provided to policy makers during the epidemic in each province.

a. Provinces with initial sustained community transmission that aimed to control transmission (mitigation strategy)

Use of the evidence	Model type	Developer	Overarching Goal	Projection horizon	Update frequency	Direct reporting institution	Public availability
British Columbia							
Impact evaluation and forecasting epidemic indicators	Covidseir (compartmental)	SFU/DFO/ UBC/BCCDC	Estimating the impact of distancing measures, the leeway to relax measures, and forecast cases under different scenarios	3-8 weeks	Weekly	Governmental institutes (BC center of disease control)	Code is available on GitHub
Forecasting epidemic indicators and modelling contact tracing	Branching process (stochastics)	MOH/SFU/UBC/BCCDC	Estimate impact of contact tracing in lower-incidence circumstances	2-6 weeks	Weekly	Governmental institutes (BC center of disease control)	Findings disseminated in COVID-19 communications
Modelling time-varying contact rates	Age- and contact-structured model (compartmental)	BCCDC/UBC	Vaccination rollout, modelling with BC Mix survey data.	Not used for routine projections	Ad hoc	Governmental institutes (BC Centre for Disease Control)	Methodological details available as a journal article (Iyaniwura et al., 2022; Ringa et al., 2022).
Forecasting epidemic indicators and impact evaluation (in long-term care)	Combined compartmental with Bayesian hierarchical model	BCCDC/SFU	Estimate transmission potential and impact of interventions in long-term care settings in BC.	Not used for routine projections	Ad hoc as work took place	Governmental institutes (BC Centre for Disease Control)	Code is available on github. Methodological details and results published as journal article (Stockdale et al., 2022).
Planning for vaccine allocation	Essential workers model & modified covidseir (both compartmental)	SFU MAGPIE group (Colijn) & BCCDC	Compare vaccination rollout	1-6 months	Ad hoc	Governmental institutes (BC Centre for Disease Control)	Code is available on GitHub
Alberta							
Policy development, impact evaluation, and planning for healthcare resources	Compartmental SIR Model	Alberta Health/ University of Alberta	Estimate transmission, underreporting, impacts of public health interventions and project case counts and hospitalizations	4-6 weeks	Ad hoc	Alberta Health	Results shared by CMOH at various times during the pandemic.

Use of the evidence	Model type	Developer	Overarching Goal	Projection horizon	Update frequency	Direct reporting institution	Public availability
Saskatchewan							
Impact evaluation and planning for healthcare resources (Feb 2020-Mar 2020)	Compartmental model	University of Saskatchewan Computational Epidemiology & Public Health Informatics Laboratory	Estimating transmission and projecting case count and hospitalizations	12 months	Not updated -- Replaced by below modelling types of 4/2020	Governmental institutes (Saskatchewan Health Authority and Saskatchewan Ministry of Health; J Basran co-lead)	Findings disseminated via initial MoH press briefings
Forecasting epidemic indicators and planning for healthcare resources (Jun 2020-Jul 2020)	Hybrid Age & Regional Stratified compartmental -ABM-DES with detailed acute care DES		Acute-care capacity planning	12 months	Not updated -- Replaced by below modelling types of summer 2020		Findings disseminated via physician town halls & semi-weekly MoH press briefings
Impact evaluation and planning for medium-term healthcare resources (Apr 2020-Present)	Hybrid geographically explicit agent-based & discrete event simulation model		Evaluating candidate regional & province-wide public health orders Long-term scenario projection Assessing LTC rules	3-12 months	Biweekly		Findings via physician town halls & semi-weekly MoH press briefings
Forecasting epidemic indicators and planning for short-term healthcare resources (Jun 2020-Present)	Machine Learning (Bayesian Particle Filtered/SMC) compartmental model		Providing accurate daily reporting on diverse epidemiological quantities from health system & wastewater data Projecting posterior state estimate forward	Multi-week	Daily	Governmental institutes (Saskatchewan Health Authority & Saskatchewan Ministry of Health)	Findings disseminated daily via dashboard & email & physician town halls & semi-weekly MoH press briefings
Manitoba							
Details on the modelling works were not publicly available							

Use of the evidence	Model type	Developer	Overarching Goal	Projection horizon	Update frequency	Direct reporting institution	Public availability
Ontario							
Impact evaluation, planning for healthcare resources, and vaccine allocation	CORE Model (agent-based)	COVID-19 Modelling Collaborative (University Health Network, Sunnybrook Hospital, University of Toronto, others)	Estimating acute care resource use (hospital and ICU admissions and occupancy, mechanical ventilations) under different scenarios and interventions. Also use to estimate acute care PPE demand and ICU medication demand.	Multi-week	Variable (weekly to bi-weekly in 1st year, approx. monthly in 2nd year)	Modelling consensus table, Governmental institutes, Science advisory tables (e.g., critical care table)	Model description published as journal article (Barrett et al., 2020). Findings were routinely published in Science Table updates.
	CORE+ Model (agent-based)	COVID-19 Modelling Collaborative (University Health Network, Sunnybrook Hospital, University of Toronto, others)	Estimating transmission and projecting case count under different scenarios and interventions (non-pharmaceutical interventions, vaccines, school closures)	Multi-week	Variable (approx. monthly)	Modelling consensus table, Governmental institutes	Model description and results (assessment of the effect of school closures) published as journal article (Naimark et al., 2021). Findings were described in some Science Table updates.
	McMaster Pandemic ("macpan") (compartmental)	McMaster macpan working group	Estimate effects of non-pharmaceutical interventions (NPI) and vaccines on epidemic dynamics and health care system burden under different scenarios	A few weeks to a few months	Every 3 weeks	Modelling consensus table	Code is available on GitHub; results are described in blog posts on GitHub and in Science Table updates .
	Western-LHSC Covid Model (compartmental)	Lauren Cipriano & Wael Haddara	Estimate effects of NPIs, vaccines, testing strategies, and arrival of new variants on epidemic dynamics and health care system burden under different scenarios	A few weeks to a few months	Every 3 weeks	Modelling consensus table, governmental institutes (London health science center) and community health system partners.	Two public reports outline methods, assumptions, and data sources in detail.
Planning for vaccine allocation	COVID Hotspot Model (compartmental)	Unity Health Toronto	Compare vaccination prioritization and roll-out strategies	Up to 3 months	Variable, and ad-hoc	Modelling consensus table, Governmental institutes	Mixing code publicly available, remainder of code is not yet publicly available, public reports outline methods

Use of the evidence	Model type	Developer	Overarching Goal	Projection horizon	Update frequency	Direct reporting institution	Public availability
Québec							
Planning for healthcare resources	INESSS-McGill model (compartmental)	McGill University COVID-19 modelling team	Monitoring the evolution of SARS-CoV-2 transmission to evaluate hospital demands for COVID-19 regular and ICU beds under different scenarios	3 weeks	Weekly	Institut national d'excellence en santé et services sociaux (INESSS)	Description of the early model is published as journal article (Godin et al., 2021); first version of code is available on GitHub; equations and results available on INESSS website.
Impact evaluation	INSPQ-ULaval model (compartmental, stochastic)	Université Laval COVID-19 modelling team	Examine the potential impact of NPIs and vaccination strategies on the dynamics of infection, detected cases, hospitalizations, and deaths by age	Up to 6 months	Variable	Institut National de Santé Publique du Québec (INSPQ)	Results and methods are available on INSPQ website.

b. Provinces that aimed to eliminate transmission and avoid case importation (suppression strategy)

Newfoundland and Labrador							
Assessing effectiveness of an existing policy	Memorial U Travel Restrictions Model (compartmental, stochastic)	Memorial University/ Predictive Analytics team	Quantify the impact of travel restrictions on COVID-19	9-weeks	Not applicable	Department of Health and Community Services, NL	Code and data are publicly available on figshare and results are published at RSOC (Hurford et al., 2021).
	U of Toronto Travel Restrictions Model (Agent-based)	University of Toronto/ Predictive Analytics Team	Quantifying the impact of travel restrictions on COVID-19	Not applicable	Not applicable	Department of Health and Community Services, NL	Preprint available here
Impact evaluation and assessing effectiveness of an existing polity	Memorial U community outbreak risk model (importations, stochastic)	Memorial University	Quantify the risk of a community outbreak given alternative border restrictions, and explore future scenarios for community outbreaks	2-weeks	Daily	Department of Health and Community and Community Services, NL	Model description and results are available as a journal article (Hurford et al., 2023). Code and data are publicly available.
New Brunswick, Nova Scotia, and Prince Edward Island							
Details on the modelling works were not publicly available							

Abbreviation: SFU: Simon Fraser University; DFO: Fisheries and Oceans Canada; UBC: University of British Columbia; BCCDC: BC Centre for Disease Control; SIR: Susceptible-Infectious-Recovered; MOH: Ministry of Health; ABM: Agent-Based Model; DES: Discrete Event Simulation.

3.2 Model characteristics, calibration, and validation

Developing mathematical models for pandemic response involves trade-offs between data availability, model complexity, and computing efficiency (Padmanabhan et al., 2021). In all provinces, models built at early stages of the pandemic were usually simple in structure and dealt with substantial uncertainty in key epidemiological parameters (e.g., fraction asymptomatic, pre-symptomatic transmission, severity) (Jewell et al., 2020). Two-thirds of those models were compartmental (13/20) and only two of those (2/13) were stochastic (Table 4.2.1). The remaining one-third were agent-based or hybrid (e.g., agent-based and discrete event simulation) models. Definitions of different models can be found in Box 4.2.1. The projection's time horizon was usually short (a few weeks) and did not exceed 12 months.

To capture heterogeneities in the population and refine estimates, models were often stratified. Common model stratification included age, geographic areas, and those that allowed for heterogenous contact structures (e.g., occupation, long-term care homes; LTCH). None of the teams developed ensemble projections that statistically combined the outputs from multiple models (Ray et al., 2020), although "*consensus projections*" were used in Ontario (Table 4.4.1).

Box 4.2.1: Definitions of the main general types of mathematical models used by Canadian provincial teams during the COVID-19 pandemic.

- **Compartmental model.** This type of model divides the population into distinct categories (i.e., compartments/states) and tracks the number of individuals within each of them. These models can be deterministic or stochastic.
- **Stochastic model**. A stochastic model accounts for the random variations in the probability of transitions between states. In contrast, deterministic model will describe the average population without uncertainties, where the outcomes are completely determined by the initial conditions.
- **Agent-based model**. A model that simulates the behavior and outcome of each individual in the modelled population. They are also referred to as individual-based models. It enables the incorporation of a high degree of heterogeneity in the population and can track the trajectory of each modelled individual.
- **Discrete Event Simulation** (DES). DES models the system as a series of 'events' that occur over time and assumes no change in the system between events. In DES, patients are modelled as independent entities each of which can be given associated attribute information (Allen et al., 2015).

Most models were calibrated to surveillance data (Table 4.4.1) using Bayesian methods. Other calibration algorithms include manual fitting (e.g., manually tuning parameters to reproduce outcomes) and optimization (e.g., minimizing the root mean square error). Among the models with information available, the most common calibration outcome was the daily number of new COVID-19 hospitalizations (7/11) and confirmed cases (6/11). The latter was especially common for models estimating importation risks. Serological studies, new admissions to intensive care units (ICU), hospital and ICU censuses of COVID-19 patients, and COVID-19 deaths were also used. Using surveillance data posed several challenges due to inherent under-ascertainment of cases (Ibrahim, 2020), nosocomial infections for hospitalizations (Xia et al., 2022), and the distinct transmission dynamics in specific settings (e.g., LTCH) (Wang et al., 2020) which may affect accuracy of projections. However, only three of the models were able to adjust for underreporting and/or exclude nosocomial infections and cases from LTCH (Table 4.4.1). To alleviate some of these issues, provincial seroprevalence studies were used (Héma-Québec, n.d.; Jentsch et al., 2021; COVID-19 Immunity Task Force, n.d.). This was also complemented by screening and/or sequencing data for new variants (e.g., B.1.1.7, B.1.351, P.1, B.1.617, B.1.1.529). Calibration to daily reported cases became more challenging during the Omicron wave in December 2021 when mass PCR testing was saturated and restricted over time in most jurisdictions while the use of at-home rapid antigen tests was encouraged. During this period, hospitalizations were commonly used as calibration targets.

The great majority of models (9/11) with information available involved some form of validation. Models that were not validated evaluated the potential impact of intervention(s) or estimated importation risks. For models projecting key epidemic indicators, validation usually involved comparing past projections with the observed surveillance data and identifying discrepancies (if any) and the reasons behind them (Table 4.4.1). Teams reported varied validation metrics such as the median absolute errors or compared previous projections' uncertainty intervals with observed data. For models estimating the impacts of public health measures (e.g., proportional reduction in incidence), results were often compared with other published estimates.

3.3 Model evolution

As the pandemic progressed, models were updated and new ones were developed, reflecting the changing epidemiology and types of interventions available (e.g., reopening, vaccines) (Figure 4.2.1). The key reasons for changes in model structure were a better understanding of the natural history of COVID-19, changes in transmission dynamics (e.g., time-varying transmission rate among different age groups, geographical areas), the demands for more granular model outputs, changes in surveillance data, and the need for increased computing efficiency. To refine results, stratification was the most common change to model structure (86% of models; Table 4.4.1). Geographical areas (75%), age (67%), and occupation (17%) –key determinants of heterogeneities in transmission and health outcomes – were the most common stratification factors (Davies et al., 2020; Mishra et al., 2022; Xia, et al., 2022). None of the models stratified by sex/gender or ethnicity. Additionally, some models were adapted to simulate transmission of co-circulating variants, allowing for immune escape when warranted.

During the course of the pandemic, new questions were asked to modelling teams, leading to the development of new models that provided information on optimization of vaccine allocation strategies. These models include the *Essential Workers Model* in BC (Mulberry et al., 2021), the *Vaccine prioritization model* in NL (Martignoni et al., 2022), and the *Hotspot Model* in ON (Mishra et al., 2021) that focused on geographic heterogeneity in transmission.

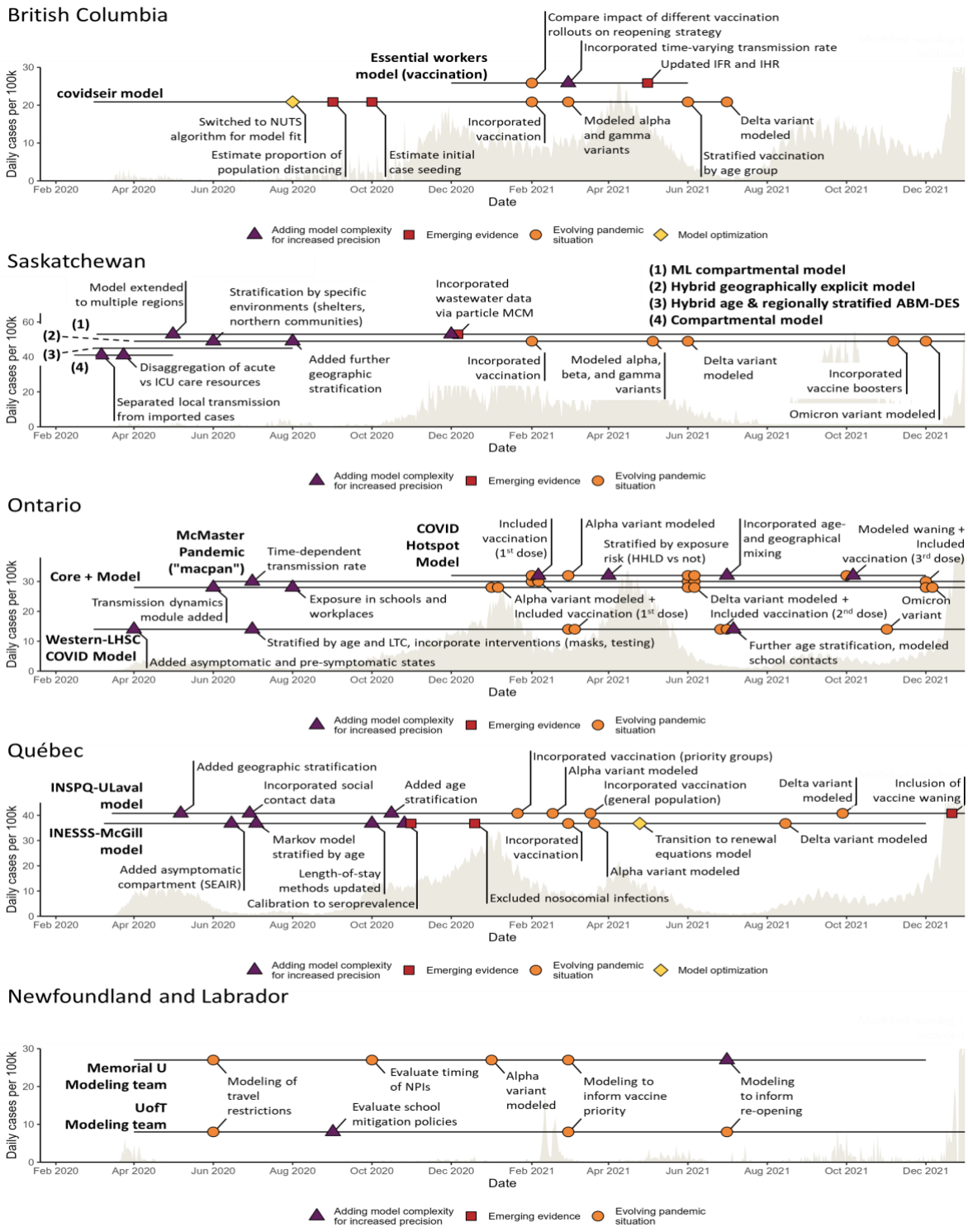

Figure 4.2.1. Evolution of models over time and the main reasons for change in selected provinces.

Note: Only models with detailed information on evolution are shown. ABM=Agent-based model; INESSS=*Institut national d'excellence en santé et services sociaux*; INSPQ=*Institut national de santé publique du Québec*; SEAIR=Susceptible-Exposed-Asymptomatic-Infected-Recovered; UofT=University of Toronto; LHSC=London Health Science Center.

3.4. Data availability and access

Access to surveillance data was an important feature of provincial modelling efforts. Most of the model inputs, model parameters, and calibration outcomes were informed by such provincial surveillance datasets (Table 4.4.2). We can categorize data access into three broad groups (Table 4.2.2).

Table 4.2.2 Three broad types of surveillance data access by Canadian provincial and territorial modelling teams during the COVID-19 pandemic (2020-2021).

	Data access type		Provinces
1	Teams that relied almost exclusively on publicly available information.		Some teams in BC
2	Teams that were provided access to raw or aggregated epidemiological, clinical, and laboratory data directly by the province through:	Data-sharing agreements.	BC, SK, QC, NL
		Already-established partnerships.	AB
3	Teams in provinces that established formal data sharing mechanisms mediated by a third party.		ON's *MCT*

Working with surveillance data presented various challenges. First, reporting delays could be important and were often longer during rapidly increasing waves. This was a particular challenge for projection models, which required minimal reporting delays and consistency across multiple datasets. Non-stationary reporting delays made it hard for modellers to censor time-series or to appropriately model those delays. Moreover, surveillance databases were often not linked together or standardized, especially in the first waves, with discrepancies being detected between some datasets. Many contact-tracing systems were managed by local public health units and often unharmonized across authorities, hindering data aggregation. Additionally, clinical databases were not linked to epidemiologic and public health databases, meaning that key information such as the patient's travel history, socio-demographical characteristics, and comorbidity status were not systematically available. A related issue noted in some provinces was inconsistencies in geographic attribution for patients in public health and clinical databases. Finally, epidemics were marked by wide heterogeneity in transmission risk across social determinants of health (Mishra et al., 2020; Mishra et al., 2022; Wang et al., 2020; Xia, et al., 2022), but rarely did provinces collect information on these individual-level determinants.

Overall, engagement with public health institutes and provincial ministries of health was required to understand the nuances related to data collection, surveillance systems (e.g., communication of reporting delays) and data interpretation.

3.5. Team-government collaboration structure, knowledge translation, and communication cycles

The organization of the modelling teams and the pathways from data to decisions varied greatly among provinces (Figure 4.2.2, Table 4.4.3), but can be broadly grouped in three categories (Table 4.2.3).

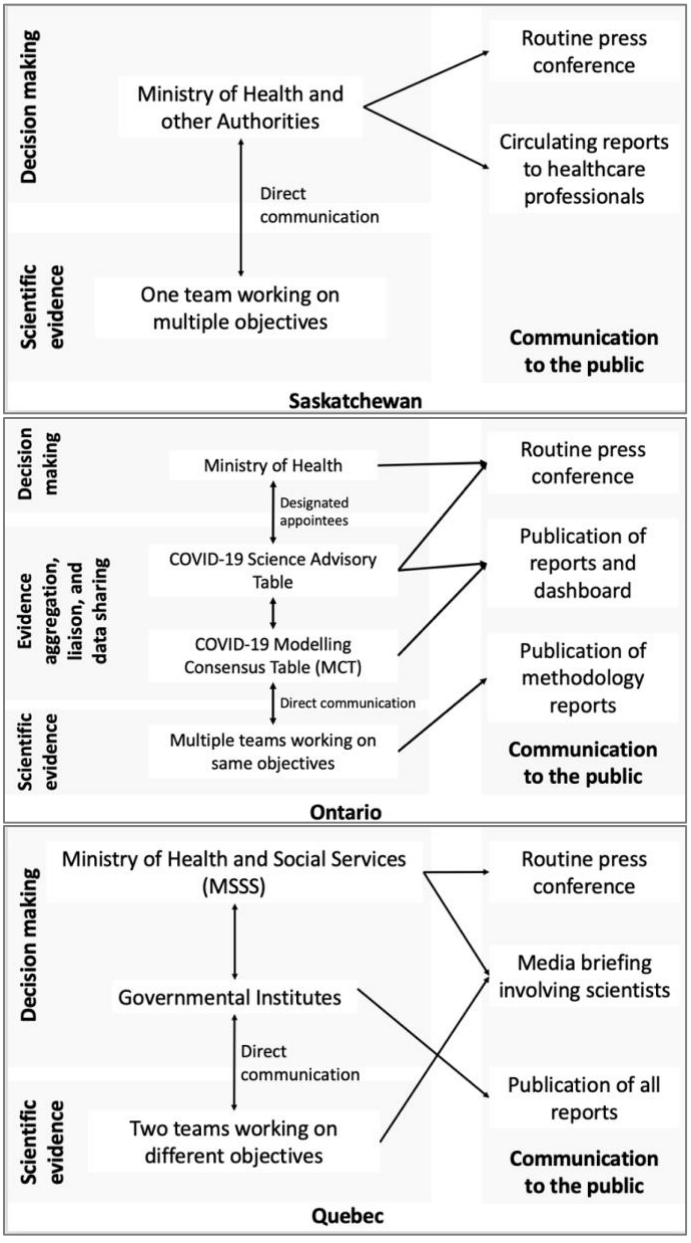

Figure 4.2.2. Structure of provincial modelling teams and the communication of evidence to decision-makers and the public in Saskatchewan, Ontario, and Québec during the COVID-19 pandemic.

Table 4.2.3. Types of organization of the Canadian provincial modelling teams during the COVID-19 pandemic (2020-2021).

	Organization of provincial modelling teams	Provinces
1	Small number of academic teams with direct and frequent contact with decision-makers	BC, SK, QC, NL
2	Larger number of academic teams with communication to decision-makers liaised by designated appointees	ON
3	Government researchers producing projections in-house and/or in collaboration with external/academic consultants	AB, BC, MB, NB, NS, PE

Provinces with less teams had complementary models that answered different questions. For instance, Québec had a team responsible for weekly projections of short-term hospital demand and another one for medium-term forecasts and scenarios. Through routine meetings, model results and uncertainties were presented to decision-makers, followed by a discussion on interpretation of findings. Given the decision-makers' short communication cycles, model calibration, interpretation, and results were usually communicated less than 24-36 hours after analyses were initiated (Figure 4.2.2). For provinces without sustained transmission (NL), collaborations and communications between the government and the modellers often occurred through case-by-case requests.

Ontario was the only province with the capacity to mobilize multiple modelling teams working on related questions. Instead of direct team-government contact, a *Modelling Consensus Table* was established to mobilize expertise and coordinate teams, provide data, interpret findings, and communicate consensus results to decision-makers through appointees and routine meetings (Hillmer et al., 2021). The gap between receiving data and presenting results was slightly longer than with the smaller team structure (~2 days) but provided additional opportunity to validate findings.

Despite different collaboration structures, all teams made efforts to communicate modelling results to the public. Reports were published on government websites (BC COVID-19 Modelling Group, n.d.; Government of Alberta, 2020; Government of Saskatchewan, n.d.; INSPQ, n.d.; INESS, n.d.; Ontario COVID-19 Science Advisory Table, n.d.), and/or in scientific journals

(Barrett et al., 2020; Hurford et al., 2023; Hurford et al., 2021; Iyaniwura et al., 2022; Naimark et al., 2021; Stockdale et al., 2022). Routine press briefings were one of the most common approaches for direct communication to the public, and scientists were invited to answer questions concerning the models at the early stages of the pandemic. Additional communication efforts were also made at varying degrees. For example, two thirds of the models had code and/or detailed methodology/equations available (Table 4.2.1), while other teams focused on explaining the model outputs directly to the public, for example through pre-prints and dissemination of videos. Best practices for modelling often include providing detailed information on methods, code, and underlying assumptions. However, during the pandemic, the public sharing of methods was in some case limited due to competing needs and prioritization of urgent activities.

Finally, only half of the academic teams with mandates received financial support directly from the government or through governmental operating research grants. The rest obtained other funding sources or worked on a volunteer basis (Table 4.4.1).

4. Discussion

Mathematical models of SARS-CoV-2 transmission have been extensively used at the provincial level in Canada to assist public health responses, with most provinces establishing formal collaborations with academic teams. Models were continuously updated throughout the pandemic to account for changes in transmission dynamics and epidemiology, as well as various interventions considered. We observed considerable variety in modelling approaches and organization of teams, reflecting diverse public health demands and modelling capacity across provinces. Summarizing these diverse modelling efforts offers insights into the challenges faced by modelling teams and valuable lessons for future public health emergencies.

There was no "*one size fits all*" modelling approach or team structure, highlighting the distinct provincial needs for pandemic decision-making. With widespread community transmission and a mitigation strategy, decision-makers required various types of projections to tailor responses to the specific local contexts. The models were used to answer a range of questions: from the impact of implementing/lifting of specific measures (sometimes in distinct community settings), anticipation of healthcare burden, to resource planning and allocation. As such, models used in those provinces were often complex and relied heavily on local surveillance

data. The level of model complexity was a function of the research questions, while balance between complexity, data availability, and computational efficiency had to be achieved. For the Atlantic provinces, where community outbreaks were initially suppressed, different modelling approaches were needed (Hurford et al., 2023).

The number and organization of the provincial modelling teams was influenced by the available expertise and existing relationships. With large teams, multiple models provided additional opportunities for cross-validation at the expense of longer lags between evidence generation and decision-making: aggregating evidence, resolving discrepancies (if any), and reaching consensus could require additional time (Chen et al., 2020; Wang, 2020). In Ontario, communication of aggregated evidence by specific appointees facilitated knowledge translation. Additionally, this structure enabled frequent dissemination of modelling evidence to the public and supported the scientific independence of modelling teams. Mobilizing several teams is not possible in settings where expertise is limited. With smaller teams, it could be easier to coordinate analyses and data access, as well as to establish close collaborations with decision-makers and other important stakeholders.

The provincial modelling efforts in Canada shared some common features with other countries: from the choices of models and the data challenges (Brooks-Pollock et al., 2021; Meehan et al., 2020; Pagel & Yates, 2022; Panovska-Griffiths et al., 2021) to the structure used to mobilize evidence and knowledge translation (e.g., ON's MCT was similar to the *Scientific Pandemic Influenza Group for Modelling, Operational sub-group* in the UK, SPI-M-O) (Medley, 2022). One difference, however, is that provinces did not rely on ensemble modelling, an approach adopted by some (e.g., *U.S. Center of Disease Control and Prevention* (Ray et al., 2020)) to statistically combine multiple model outputs and produce more robust estimates (Brooks-Pollock et al., 2021). Similar efforts were made by PHAC using two models (Public Health Agency of Canada, 2021).

As provinces transitioned away from a public health emergency response, the collaboration between modelling teams and decision-makers evolved. In Québec, the responsibility for weekly projections of COVID-19 hospitalizations was transferred to a government institute (INESSS) through knowledge translation activities. In Ontario, the organization (MCT) that integrated

modelling efforts from independent teams (Ontario COVID-19 Science Advisory Table, n.d.), was disbanded as part of the dissolution of *Ontario Science Advisory Table*, and a new structure was formed (i.e., the *Ontario Public Health Emergencies Science Advisory Committee*) under the jurisdiction of *Public Health Ontario* (Public Health Ontario, 2022). As relationships between governments and modelling teams continue to evolve, a key priority remains increasing transparency in public reporting systems and in the frameworks for synthesizing and processing knowledge (Shea et al., 2020).

Supporting and strengthening collaborations between academic modelling teams and governments should be considered a priority for ongoing pandemic preparedness. This would help mitigate challenges that emerged during the COVID-19 pandemic (e.g., delayed data sharing, lacking data accessibility) and facilitate knowledge translation. Irrespective of the type of collaborations, academic and government partners should ameliorate the granularity of surveillance data, increase accessibility to public reporting systems while protecting privacy, and ensure rapid public dissemination of evidence used for decision-making (Shea et al., 2020). Improving our understanding of barriers to data sharing and results dissemination is needed, both between provincial governments and academic teams, and between provinces/territories and the federal government. Mechanisms to encourage collaboration and prompt sharing of privacy-preserving linked data are required.

In the aftermath of the 2003 SARS outbreak, PHAC was established in order to improve Canada's public health systems to anticipate and respond to public health threats (Gumel et al., 2004). Analogously, the COVID-19 pandemic has highlighted a need to reinforce provincial-level mathematical modelling capacity. The *ad hoc* and non-systematic, process through which many modelling teams were set up shows the need to maintain close collaborations between a diverse set of modelling teams and provincial knowledge users. Future modelling initiatives need to consider idiosyncrasies of each province's public health system: differences in decision-making culture, surveillance systems, and public health contexts; unevenly distributed modelling capacity; and limited public health capacity in Atlantic Canada (Public Health Agency of Canada, 2024) and other jurisdictions.

Overall, this review highlighted the following takeaways. First, surveillance systems would benefit from improved infrastructure to help facilitate linkage across harmonized databases. For academic modellers, collaboration structures and funding resources that can minimize perceptions of conflict of interest and prioritize independence should be considered. Second, there is a need for policies and resources that facilitate the appropriate use of public health data, appraisal of modelling assumptions by multidisciplinary teams of surveillance experts, epidemiologists, and public health practitioners, and modellers, and the communication and dissemination of model results and methodology. Third, it is important to have established protocols to facilitate data access and sharing during emergencies such as pandemics, and to communicate data limitations of surveillance systems. Cultivating ongoing collaborations and engagement between academic and government partners would also minimize such barriers. Finally, investments should be made to train and retain highly qualified personnel with modelling expertise, both in academia and in government. Capacity to develop multiple independent models, and to compare their results, could further increase the validity and reliability of modelling results. While the government of Canada has already made some first steps (Government of Canada, 2021), complementary efforts are needed at provincial levels, and operational linkages should be established between modelling groups. All these recommendations will help avoid the inequities and negative health outcomes caused by the poorly coordinated Canadian COVID-19 pandemic responses (Clark et al., 2023).

Our review acknowledges some limitations. First, provincial modelling teams were identified through referral which may have missed models and teams. However, our approach should have included all main provincial models used. Second, we did not consider modelling efforts in the territories or those for specific groups/communities despite their local importance. Third, we did not attempt to evaluate which models had the most accurate projections, despite its importance, as the latter was often contingent upon data availability and quality. In terms of strengths, we included detailed information on 20 models from 6 provinces to provide a comprehensive review of pandemic modelling efforts.

7. Conclusion

Provincial modelling efforts to inform COVID-19 pandemic policy responses were tailored to local epidemiological situations, strategies, and available resources (e.g., trained personnel,

access to surveillance data, and research funding). Access to ‘near real time’ quality surveillance data (Colijn et al., 2022) is crucial to pandemic modelling. Continued efforts need to be made to overcome data limitations, whilst balancing data privacy and governance. Furthermore, capacity and expertise for modelling in both governments and academic settings should be strengthened and resourced.

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Newfoundland and Labrador: Maria Martignoni, J. C. Loredo-Osti, Proton Rahman, Dionne Aleman, Randy Giffen, and Sanjeev Seahra.

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4.4. Manuscript 1: Supplementary Materials

4.4.1. Supplementary tables

Table 4.4.1. Model stratification, model validation, and detailed funding source of each model.

Model Name	Model Stratification	Model calibration and validation	Calibration algorithm	Detailed funding source
British Columbia				
covidseir	By geographic area: BC vs. health authorities within BC (in the internal use)]	/	/	Michael Smith Foundation for Health Research, volunteer
Age- and contact-structured model	By age and contact structure	/	/	
Essential workers model	By age and essential workers	Validation: age-based incidence in Fall 2020.		Genome BC
Alberta				
Compartmental SIR Model	Aggregate level, vaccinations, and emerging variant dynamic	Model calibrated to: - Historical case - Hospitalization - Immunization data Validation: - The performance to overall fit of data (post-simulation) - Comparisons to serology data (when available).	Bayesian	N/A
Saskatchewan				
Compartmental model	Not stratified	/	/	/
Hybrid Age & Regional Stratified compartmental -ABM-DES with detailed acute care DES	By population type and geographic areas: (1) general population members (2) health workers in (separately) acute-care and associated with long-term care and community cohort facilities (3) teachers (4) those living on religious (e.g., in Saskatchewan Hutterite and Mennonite) colonies (5) workers in homeless shelters and associated with screening and contact tracing	/	/	/

Model Name	Model Stratification	Model calibration and validation	Calibration algorithm	Detailed funding source
Hybrid geographically explicit agent-based & discrete event simulation model	/	/	/	/
Machine Learning (Bayesian Particle Filtered/SMC) compartmental model	/	/	/	/
Manitoba				
Information not available				
Ontario				
CORE Model (agent-based)	By age-groups (10-year bands), household size, and exposure types (school, work, household, other)	Model calibrated to: - Hospitalizations and ICU admissions by age-group	/	Funded by Ontario COVID-19 Rapid Research Fund
CORE+ Model (agent-based)	By age-groups (10-year bands), household size, and exposure types (school, work, household, other)	Model calibrated to: - Cases by age-group - Hospitalizations by age-group	/	Funded by Ontario COVID-19 Rapid Research Fund
McMasterPandemic ("macpan") (compartmental)	Generic structure that facilitates compartmental models with heterogeneities in age/social/spatial structure and testing, vaccination in multiple doses, etc. However, mostly homogeneously mixed versions have been used for forecasting to date.	Models used for MCT forecasts were calibrated to: - Case reports and/or - Hospitalization reports The software allows calibration to any number of observed time series simultaneously. Code is typically validated by applying it to stochastic epidemic simulations for which the correct underlying parameter values are known.	Bayesian	M. G. DeGroote Institute for Infectious Disease Research (IIDR), Public Health Agency of Canada (PHAC), Canadian Network for Modelling Infectious Diseases (CANMOD).
Western-LHSC Covid Model (compartmental)	By age groups (0-4, 5-11, 12-17, 18-24, 25-49, 50-59, 60-69, 70+) and two separate groups based on very different contact structures LTC residents and College/University students	Model is calibrated to: - ICU occupancy and hospital occupancy - Estimated infections (case counts adjusted for estimated underdiagnosis) - Earlier versions were also calibrated to deaths. Earlier versions impacts of NPIs were validated to other model's estimates presented in published analyses from NYC and Lombardi.	Manual fitting	Initially some internal funding from Western University (Catalyst Grant). No current funding.

Model Name	Model Stratification	Model calibration and validation	Calibration algorithm	Detailed funding source
COVID Hotspot Model (compartmental)	By geographic area (hotspots; 10 strata) and age-group (10 strata)	Model is calibrated to: - Hospitalizations per-capita by hotspots (10 strata) and age-group (10 strata) - Deaths per-capita by hotspots (10 strata) and age-group (10 strata) Model projections were cross-checked against diagnosed cases and positivity rates; and validated against age-stratified serology at two time-points	/	Funded by CIHR Rapid Response grant and funds from the St. Michael's Hospital COVID-19 Research Innovation Council.
Québec				
McGill-INESSS model	By geographic area: (1) Overall Québec (2) Groups of health regions (RSS) with similar epidemiological trends	Model calibrated to: - Observed daily number of hospitalizations (excluding nosocomial infections and LTCH residences) - Seroprevalence of SARS-CoV-2 infection Model projections are validated using observed daily number of hospitalizations time series. The observed numbers were within the 95% CrI of the projections for most of the times.	Bayesian	Initially funded by the McGill Interdisciplinary Initiative in Infection and Immunity (Mi4,), then by INESSS
INSPQ-Laval model	By Region, Age, Vaccine status (up to 4 doses), variant (up to 4 variants), 13 Mixing Matrices	Model fit to: - Daily new hospitalisations for 8 age groups since February 2020 - Daily new deaths for 8 age groups since February 2020 - Seroprevalence for two time windows and 4 age groups - % increase Alpha, Delta, Omicron Validation: - Daily new cases by 8 age groups since February 2020 - Daily new hospitalisations for 8 age groups by vaccine status - Daily new deaths for 8 age groups by vaccine status - Seroprevalence for two time windows and 4 age groups - % increase Alpha, Delta, Omicron	/	Funded by INSPQ

Model Name	Model Stratification	Model calibration and validation	Calibration algorithm	Detailed funding source
Newfoundland and Labrador				
Memorial U Travel Model (compartmental, stochastic)	Not stratified	Model calibrated to: - published daily number of cases.	Manual fitting	Department of Health and Community Services
U of Toronto Travel Model (Agent-based)	/	/	/	/
Memorial U community outbreak model (importations, stochastic)	Vaccination status, variant, travel-related and community cases	Model fit to: - Travel-related cases - Occurrence of community outbreaks - Reported cases during the Alpha variant outbreak in February 2021	Manual fitting	Department of Health and Community Services, NSERC Emerging Infectious Disease Modelling Consortium Initiative
New Brunswick				
Information not available				
Nova Scotia				
Information not available				
Prince Edward Island				
Information not available				

Table 4.4.2. Data availability, challenge, and funding status.

Data Source and Data Sharing	Evolution of Available Data	Available Data at Present	Data Challenges	Other Challenges (resources, personnel)
British Columbia				
Information not available				
Alberta				
Data for modelling was processed and analyzed within the Ministry of Health.	1. Due to limited geographic-specific information prior to May 2020, jurisdictional based (including summaries from the Public Health Agency of Canada) and provincial (where possible) data was used to inform modelling projections 2. Overall various surveillance data systems within the Ministry of Health related to cases, hospitalizations, and immunizations were used to inform modelling projections	Surveillance data systems within the Ministry of Health related to cases, hospitalizations, and immunizations are used. In addition, methods related to modelling accounted for data impacted by changes in definitions and policies.	Surveillance data used for modelling was obtained from the integration between large multi-system data warehouses. These surveillance systems have its own limitations (independent from the pandemic) including reporting delays. Modelling methods adjusted for these delays in the data.	Data analytics, communicable disease, and immunization teams within the Ministry of Health played an important role in preparing, understanding, and interpreting data used to support modelling efforts.
Saskatchewan				
Information not available				
Manitoba				
Information not available				

Data Source and Data Sharing	Evolution of Available Data	Available Data at Present	Data Challenges	Other Challenges (resources, personnel)
Ontario				
Modelling consensus table (MCT) included a partnership with Ontario Ministry of Health which provided data for the modelling to all MCT members.	1. Full, anonymized, person-level surveillance data (cases, hospitalizations, ICU admissions, deaths) via CCM+. 2. Full, anonymized, person-level data on vaccination (COVAXON). 3. Full, anonymized, person-level and event-level testing data from Ontario Laboratory Information System (OLIS). 4. Aggregated cellphone-based mobility data from BlueDot (purchased by Ontario Ministry of Health and shared with MCT); 5. Separate surveillance data tracker for long-term care homes (LTC tracker).	The MCT disbanded in September 2022, and access to available data include public repositories and separate data-sharing agreements with the Ministry of Health; McMaster macpan working group is seconded to Public Health Ontario for ongoing projections and has internal access via Public Health Ontario.	1. Rapid and timely sharing of data meant that data required processing and cleaning, a process that was subsequently conducted by Public Health Ontario prior to uploading to MCT on a daily basis. 2. Discrepancies between LTC data from surveillance (CCM+) and LTC tracker. 3. Socio-demographic data limited to age and gender; but dissemination area included in future iterations allowing for area-level socio-demographic information from census data linkage. 4. Limited data on exposure risks. 5. Changes to case-definition for classifying re-infection limited use of surveillance data to examine and incorporate re-infections into models. 6. Data on variants of concern were limited based on the proportion screened and type of screening as sequencing was not universal in Ontario.	A key strength was the responsiveness of the Ministry of Health Data Analytics Team with respect to understanding and preparing the data for the MCT, the PHO team for supporting interpretation of the data; and the Ministry of Health Data Analytics Branch for provision of additional data sources as needs evolved for the modelling questions.

Data Source and Data Sharing	Evolution of Available Data	Available Data at Present	Data Challenges	Other Challenges (resources, personnel)
Québec				
The MED-ÉCHO datasets came from Québec Health Insurance databases: the *Régie de l'assurance maladie du Québec* (RAMQ), and databases from the *Ministère de la Santé et des Services sociaux* (MSSS) du Québec. The access to these databases is made possible through a tripartite agreement between the MSSS, the RAMQ and the *Institut national d'excellence en santé et en services sociaux* (INESSS). Data were transmitted from INESSS on a weekly basis.	1. Seroprevalence data was not available until October 2020 2. Hospital data was not linked to testing database and administrative surveillance database until late 2020	The MED-Écho datasets came from Québec Health Insurance databases (Régie de l'assurance maladie du Québec (RAMQ)) and databases from the Québec Ministry of Health and Social Services (Ministère de la Santé et des Services sociaux (MSSS)). The access to these databases is made possible through a tripartite agreement between the MSSS, the RAMQ and the Institut national d'excellence en santé et en services sociaux (INESSS). Data were transmitted from INESSS on a weekly basis.	1. Non-stationary reporting delay of admission and discharge 2. Date of admission for patients infected in hospital is the original date of admission and no indicator of nosocomial infection 3. Hard to identify patients transferred from long-term care facilities 4. Missing key socieo-demographic informationn	
Newfoundland and Labrador				
Two data sharing agreements are in place. One agreement since April 2020 allows for sharing of data to respond to requests from the Department of Health and Community Services. Data to be used in publications is covered by a separate Health Research Ethics Board approval completed in March 2021.	Data that could be used for analysis to appear in publications was provided by NLCHI in June 2021 and June 2022.	All necessary and requested data was provided to June 3, 2022.	Provincial data was provided when requested. For responding to rapid requests, frequently multiple data types were needed, and lack of real-time access to government data was a barrier, such that public data was often used in its place due to better availability of the latter.	
New Brunswick, Nova Scotia, and Prince Edward Island				
Information not available				

Table 4.4.3. Description of organization provincial modelling teams and communication of evidences with the government and the public.

Description
British Columbia
Information not available
Alberta
Leveraged a pre-existing collaborative relationship with academic mathematical modellers and shared results within the Ministry of Health.
Saskatchewan
Daily reports were sent to the Saskatchewan Authority and the Saskatchewan Ministry of Health. The Saskatchewan stakeholders then use the reports to inform day to day decision making regarding public health orders and interventions, and for shorter-term health service delivery decisions (e.g., planning surge capacity, suspending elective surgery, etc.), circulating reports to hundreds of medical officers of health, epidemiologists, physicians, higher-level public health decision makers. Model results were presented for feedback to the top public health officials and high-level heath service delivery parties through weekly meeting.
Manitoba
Information not available
Ontario
A group of volunteers, independent, and academic mathematical modellers, along with epidemiologists and other experts in surveillance data, were brought together via invitation by a leadership team comprised of Dalla Lana School of Public Health, Public Health Ontario, and Ministry of Health. The group formed the Ontario Modelling Consensus Table (MCT), and was later embedded under the overarching umbrella of the Ontario Science Advisory Table (of which, the MCT was a specific working group). MCT co-chairs represented the MCT at the Ontario Science Advisory Table, and responded to the requests of the Ontario Chief Medical Officer of Health, the Ministry of Health, and other stakeholders at various public health levels (e.g. local public health jurisdictions, Ministry of Education). For the Ontario Science Advisory Table and Ontario Chief Medical Officer of Health, the MCT provided consensus modelling projections based on policy scenarios, by combining results across independent mathematical models. All MCT consensus modelling presented to the stakeholders were publicly shared via reports and slide-decks. MCT co-chairs also presented consensus modelling to the ministerial cabinet meetings. The frequency of the modelling ranged from every 1-3 weeks, and usually every 2 weeks, with a focus on near-casting (3-week projections) to medium-term (up to 3-month projections). The MCT also included public health agency modellers at Public Health Ontario and Ontario Ministry of Health Data Analytics Branch, which each developed independent mathematical models of SARS-CoV-2 transmission, and whose outputs were also included in the consensus modelling. The consensus modelling presented to stakeholders varied based on availability and feasibility of each volunteer modelling group being able to update and provide results.

Description
Québec
There are 2 teams contributing to the modelling efforts in Québec: the McGill University COVID-19 modelling team (McGill team) and the University of Laval COVID-19 modelling team (UofL team). At the beginning of the pandemic, the McGill team updated the model for hospitalization projection twice a week and directly reported to the responsible government institute (*Institut national d'excellence en santé et services sociaux*; INESSS) through scheduled meetings. After the first wave, the frequency of update and meeting changed to once a week. Model results were made publicly available via INESSS official website. It took approximately 4-5 days from receiving the data to results being published. The UofL team updated their model upon request and reported the results directly to the responsible government institue (*Institut national de santé publique du Québec*; INSPQ) through meetings. The model results were made publicly available via INSPQ official website. Approximately, it took X days from receiving the data to results being published. After the meeting with INESSS (McGill team) and INSPQ (UofL team), the results were then presented to the final decision maker (*Ministry of Health and Social Services*; MSSS) through a weekly meeting by INESSS and INSPQ. Overall, it took 1-2 days (McGill team) and *X* days (UofL team) from receiving the data to the results being presented to the decision maker.
Newfoundland and Labrador
At the request of the Premier, a provincial modelling team was formed with accountability to NLCHI. The membership of the provincial modelling team changed over time, but most consistently included modellers from IBM, Memorial University, and the University of Toronto. The Department of Health and Community services would communicate requests for modelling, which would then be handled by members of the provincial modelling team. When results were complete presentations would be given to the Department of Health and Community Services (6-8 presentations from April 2020-December 2021). Modelling results were communicated via public presentations as part of the NL government's COVID-19 communications. Complete publications, for example, which detailed methodology were produced by research teams independently.
New Brunswick
Information not available
Nova Scotia
Information not available
Prince Edward Island
Information not available

4.4.2. Supplementary text: Links to publicly available information in Table 4.2.1

British Columbia

- SFU/DFO/UBC/BCCDC model code: https://github.com/seananderson/covidseir
- BCCDC/SFU model code: https://github.com/sempwn/cr0eso
- SFU MAGPIE group (Colijn) & BCCDC model code:

  https://github.com/nmulberry/essential-workers-vaccine

Alberta

- Alberta Health/University of Alberta model results:

  https://www.alberta.ca/respiratory-illness#jumplinks-3

Ontario

- Science Table updates: https://covid19-sciencetable.ca/science-briefs/
- McMaster macpan model
  - Code: https://github.com/mac-theobio/McMasterPandemic
  - Results: https://mac-theobio.github.io/covid-19/

Québec

1. McGill University COVID-19 model
   a. Code: https://github.com/pop-health-mod/covid19-release
   b. Equations and results:

      https://www.inesss.qc.ca/covid-19/risques-dhospitalisation-et-projections-des-besoins-hospitaliers.html
2. Université Laval COVID-19 model results:

   https://www.inspq.qc.ca/covid-19/donnees/projections

Newfoundland and Labrador

3. Memorial University/ Predictive Analytics team model data and code:

   https://doi.org/10.6084/m9.figshare.12906710.v2.

4. Memorial University model code and data:

   https://github.com/ahurford/pandemic-COVID-zero

Chapter 5. Geographical Concentration of SARS-Cov-2 Cases by Social Determinants of Health in Canada

5.1. Preface to Manuscript 2

In my first manuscript, I reviewed the provincial modelling efforts during the COVID-19 pandemic in Canada. Among the models that were reviewed, none of the those developed at the early stage of the epidemic considered heterogeneities in SARS-CoV-2 transmission, beyond age and sex differences. Yet, important within-city geographic disparities in the COVID-19 burden became apparent during the first wave (227). Despite the importance of social determinants of health in shaping COVID-19's burden, attempts to address these disparities were few.

Social determinants of health, such as socioeconomic status, housing conditions, and occupational exposure, emerged as critical factors shaping SARS-CoV-2 transmission risks (118, 227-229), highlighting the urgent need to understand the patterns and drivers of SARS-CoV-2 transmission in Canada. To address this knowledge gap, I conducted the first multi-provincial Canadian study to quantify and compare these inequalities across 16 metropolitan areas in four provinces: British Columbia, Manitoba, Ontario, and Québec. I employed descriptive analyses for this purpose, as these methods are essential for identifying patterns, generating hypotheses, and guiding targeted interventions, despite often being undervalued in contemporary epidemiology (230). By quantifying heterogeneity, this chapter links population-level patterns to potential interventions, enhancing the insights gained from provincial models.

The resulting article was published in the *Canadian Medical Association Journal (CMAJ)* in February 2022.

5.2. Manuscript 2: Geographical concentration of SARS-CoV-2 cases by social determinants of health in 16 large metropolitan areas in Canada – a cross-sectional study

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Conflict of interest

MM-G report contractual agreements with the *Institut national de santé publique du Québec (INSPQ)* and the *Institut d'excellence en santé et en services sociaux* (INESSS).

Funding

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Abstract

Background: Understanding inequalities in SARS-CoV-2 transmission along social determinants of health could help develop effective mitigation strategies that are responsive to local transmission dynamics. This study aims to quantify social determinants of geographic concentration of SARS-CoV-2 cases across sixteen census metropolitan areas (CMA) in four Canadian provinces.

Methods: We used surveillance data on confirmed SARS-CoV-2 cases at the level of dissemination area (DA). Gini (co-Gini) coefficients were calculated by CMA based on the proportion of the population in ranks of confirmed cases and each social determinant using census data (income, education, visible minority, recent immigration, housing density, and essential workers) and the corresponding share of cases. Heterogeneity was visualized using Lorenz (concentration) curves.

Results: Geographic concentration was observed (in each CMAs, half of the cumulative cases were concentrated in DAs containing 21-35% of their population): with the greatest geographic heterogeneity in Ontario CMAs (Gini coefficients, 0.32-0.47), followed by British Columbia (0.23-0.36), Manitoba (0.32), and Québec (0.28-0.37). Cases were disproportionately concentrated in areas with lower income, education attainment, and higher proportion of visible minorities, recent immigrants, high-density housing, and essential workers. Although a consistent feature across CMAs was concentration by proportion visible minorities, the magnitude of concentration by social determinants varied across CMAs.

Interpretation: The feature of geographical concentration of SARS-CoV-2 cases was consistent across CMAs, but the pattern by social determinants varied. Geographically prioritized allocation of resources and services should be tailored to the local drivers of inequalities in transmission in response to SARS-CoV-2's resurgence.

Introduction

The COVID-19 epidemics in Canada have varied in size and trajectory across provinces and their large cities (1, 2). At the national-level (3) and within provinces (4, 5), there has been a disproportionate burden of confirmed cases, and thus severe outcomes, among socially and economically marginalized communities (6). Social determinants of health refer to non-medical factors influencing health outcomes while structural determinants encompass cultural norms, policies, and institutions that generate social stratification and determine socio-economic position (7, 8). In Canada and elsewhere, data have consistently highlighted the importance of determinants such as household size and density, work in essential services, and proxies for structural racism in the relative risk of COVID-19 (9-17).

Understanding the factors associated with geographical patterning of transmission within cities can help identify the populations, and specifically the contexts, with the greatest risks; analyses which enable better allocation of resources, tailoring of policies, and implementation of context-specific strategies to more effectively and efficiently curb local transmission (18). Although respiratory virus transmission is often geographically clustered within a city (19), the early public health response to SARS-CoV-2 transmission in Canada did little to take within-city clustering into account (20, 21). Similarly, few studies to date have quantified and compared the geographical concentration of SARS-CoV-2 cases by social determinants across Canada, and the extent to which the magnitude of inequalities might vary between cities and provinces (22, 23). We therefore sought to quantify and compare the magnitude of geographical concentration of cases by area-level social determinants of health across 16 metropolitan areas in four Canadian provinces: British Columbia, Manitoba, Ontario, and Québec. Together these provinces accounted for 79% of cases in Canada by July 8th, 2021.

Methods

Study design and study population

We conducted a cross-sectional study using surveillance data from four provinces, over the January 23, 2020 (report date of the first documented case in Canada) to February 28, 2021 period. Due to the unique context of transmission in long-term care homes, we excluded cases among their

residents to focus on transmission dynamics in the wider community. The unit of analysis was the dissemination area (DA), which is the smallest standard geographic unit with census information, representing between 400-700 residents (24).

Settings

This study includes the four provinces with data available to study teams: DA-level information on SARS-CoV-2 cases to enable linkage with census data. The census metropolitan areas (CMA) included in the analyses are large CMAs that represent more than 80% of diagnosed SARS-CoV-2 cases in each province (summarized in Table 5.2.1). Specifically, we included up to six of the largest CMAs in each province. In British Columbia, Victoria was excluded because it of its low cumulative case count. In Manitoba, only Winnipeg is qualified as a CMA by census definition (25).

Data sources

Individual-level data from provincial surveillance databases were used to calculate the number of SARS-CoV-2 cases per DA. In British Columbia, confirmed cases are recorded in case line list integrated in the *Public Health Reporting Data Warehouse*. In Manitoba, the COVID-19 surveillance data and contact investigation information were requested through the *Manitoba Population Research Data Repository* (26). In Ontario, data on laboratory-confirmed cases were recorded in the *case contact management solutions*. In Québec, confirmed cases were recorded in the *Trajectoire de santé publique* database. For each confirmed case, basic sociodemographic information was collected (i.e., address) by the relevant public health authorities, in addition to epidemiological characteristic such as date of case report and living environment (e.g., long-term care facility). Cases were assigned to a DA according to the residential address using the *Postal Code Conversion File* (27) for all provinces.

Data describing DA-level social determinants of health, with the exception of income, were extracted from the latest available Canadian census data (2016) (28), which represents the most complete, comparable, and representative source of area-level characteristics of the population in each city (29). The after-tax income per person equivalent ranking across DAs was obtained from the *Postal Code Conversion File Plus Version 7A/7D* for each province (30). This variable is

generated by Statistics Canada using administrative data sources and captures household size to generate a per-person equivalent measure (31).

Measures

We defined SARS-CoV-2 cases as polymerase-chain reaction laboratory-confirmed cases (all provinces) (32). For Québec we also included cases confirmed by epidemiological link (individual with COVID-19 symptoms without other apparent cause that had a close contact with a laboratory-confirmed case (33)) due to lack of testing capacity during the first wave in February – April 2020. We considered the following measures of social determinants of SARS-CoV-2 transmission based on previous studies that conceptualized factors as they related to contact rates and types of potential exposures for transmission (23, 34, 35): 1) socio-demographic indices (after-tax income per-person equivalent, proportion population without certificate, diploma or degree, and proxies for systemic racism via the proportion visible minority (self-reported) (36, 37), proportion recent immigration) (17, 18, 35); 2) dwelling-related indicators (proportion not living in high-density housing) (9, 13) and, 3) occupation-related variables (proportion working in essential services conceptualized using national occupation classifications (38) that would least amenable to remote work (39, 40): health, trades and transport and equipment operation, sales and services, manufacturing and utilities, resources, agriculture and production) (16). Determinants were ranked from the highest value to the lowest and grouped into ten deciles within each CMA. *Table S1* details the definitions of each variable.

Analyses

The cumulative numbers of confirmed SARS-CoV-2 cases were aggregated to the DA-level, along with population denominators, and social determinants. First, we quantified the magnitude of overall geographical heterogeneity within each CMA using Gini coefficients and crude Lorenz curves. These non-parametric methods allow for straightforward quantification and visualization of within-CMA inequalities by social determinants (41). Second, we quantified the extent to which cases were concentrated by each social determinant using co-Gini coefficients and concentration curves (42). To generate the curves, we plotted the cumulative share of CMA's population ranked by number of cases or each social determinant on the x-axis and the corresponding cumulative proportion of cases on the y-axis (43). The Lorenz (concentration)

curves depict a diagonal line of equality, and the further the data deviate from the diagonal, the higher the variability (or greater inequality/concentration) in cases across the population. The Gini and co-Gini coefficients were calculated as twice the area between the Lorenz (concentration) curve and the line of equality (44). Values closer to 1 reflect greater inequality while values closer to 0 represents uniform distributions (45). The methods we adopted are appropriate to examine inequalities within each CMA under contexts of varied distributions of social determinants and the health measures of SARS-CoV-2 transmission. Data management and analyses were conducted by each provincial team separately using standardized protocols and a shared code base. Aggregated results were shared across provincial teams as per the data privacy requirements of each province. All analyses were conducted using R statistical software (46).

Ethics approval

Ethics approvals were obtained from the *Research Ethics Board* of University of British Columbia in British Columbia (H20-02097), the *Health Research Ethics Board* of University of Manitoba (HS24140 (H2020:352)) and the *Health Information Privacy Committee* of the Government of Manitoba (No. 2020/2021-32) in Manitoba, the *Health Sciences Research Ethics Board* of University of Toronto (no. 39253) in Ontario, and the *Institutional Review Board* of McGill University in Québec (A06-M52-20B).

Results

During the study period, 63,266 (British Columbia), 15,089 (Manitoba), 239,160 (Ontario), and 224,377 (Québec) cases were recorded in the 16 CMAs included in the study. These 16 CMAs accounted for 81%, 57%, 83% and 80% of all confirmed cases in each province, respectively. Less than 9% of the DAs recorded zero cases during the study period (Table 5.2.1).

Table 5.2.1. Characteristics of census metropolitan areas (CMA) and dissemination areas (DA) included in the study from January 23, 2020 to February 28, 2021 (21).

Census Metropolitan Areas	Population	Cases (N)	Pop with 50% cases[a] (%)	DAs (N)	DA with no reported cases (%)
British Columbia					
Vancouver	2,454,378	54,222	25.8%	3,425	2.7%
Kelowna	184,190	2,865	34.7%	239	3.8%
Abbotsford-Mission	180,230	5,622	27.5%	263	2.3%
Manitoba					
Winnipeg	777,496	15,089	28.5%	1,224	8.3%
Ontario					
Toronto	5,927,779	187,764	29.1%	7,522	0.2%
Ottawa–Gatineau (Ontario part)	991,726	13,975	21.2%	1,456	1.7%
Hamilton	747,545	12,490	26.1%	1,199	0.8%
Kitchener-Cambridge-Waterloo	523,894	9,598	29.6%	736	0.4%
St. Catharines-Niagara	406,074	6,835	23.6%	678	1.6%
Windsor	329,144	8,498	29.7%	548	8.0%
Québec					
Montréal	4,098,927	175,111	29.3%	6,469	6.5%
Québec City	800,296	22,219	30.3%	1,291	5.6%
Ottawa–Gatineau (Québec part)	332,057	5,337	33.1%	491	4.9%
Sherbrooke	212,105	4,572	29.2%	327	6.4%
Saguenay	160,980	5,056	28.2%	295	6.1%
Trois-Rivières	156,042	3,633	33.5%	272	4.8%

[a]Pop with 50% cases = Percentage of population in DAs that accounted for 50% of the total cases.

Magnitude of overall heterogeneity between cities

In each CMA, half of the cumulative SARS-CoV-2 cases were diagnosed in DAs consist of 21-35% of their respective population (Figure 5.2.1, Table 5.2.1). CMAs in Ontario exhibited the greatest heterogeneity (Gini coefficients: 0.32-0.47), followed by British Columbia (Gini coefficients: 0.23-0.36), Manitoba (Gini coefficient: 0.31) and then Québec (Gini coefficients: 0.28-0.37). The magnitude of heterogeneity varied within provinces as well. The largest and smallest Gini coefficients were observed, respectively, in Vancouver and Kelowna in British Columbia; St. Catharines–Niagara and Hamilton in Ontario; and Saguenay and Trois-Rivières in Québec. Lorenz curves and Gini coefficients for each CMA can be found in Figure 5.4.1 and Table 5.2.2.

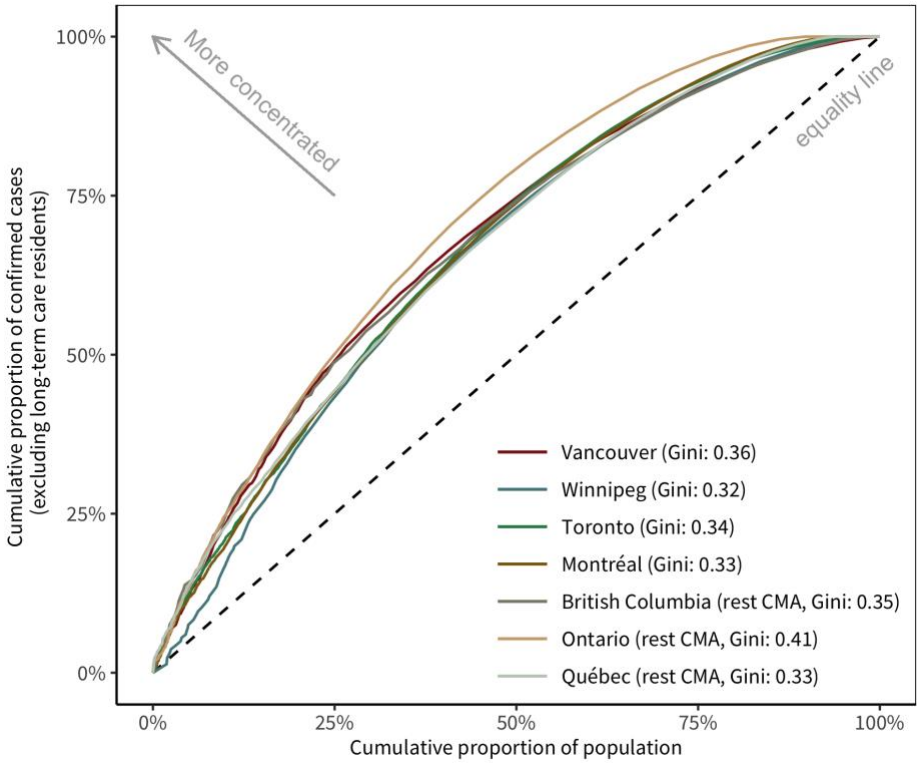

Figure 5.2.1. The Lorenz curves of COVID-19 confirmed cases (excluding long-term care residents) by proportion of the population and corresponding Gini coefficients.
Note: The population was ranked by the number of cases in each DA from the highest to the lowest. To ease interpretation, Abbotsford-Mission and Kelowna are grouped and displayed as "British Columbia (rest CMA)"; Kitchener-Cambridge–Waterloo, Hamilton, Ottawa-Gatineau (Ontario part), St. Catharines–Niagara and Windsor are grouped and displayed as "Ontario (rest CMA)"; Ottawa – Gatineau (Québec part), Québec City, Saguenay, Sherbrooke and Trois Rivières are grouped and displayed as "Québec (rest CMA)". Lorenz curves and the corresponding Gini coefficients for each CMA can be found in *Figure S1*.

Table 5.2.2. Characteristics of social and structural determinants across all dissemination area (DA) of each census metropolitan area (CMA) and the corresponding Gini/co-Gini coefficients of cumulative COVID-19 cases.

Census Metropolitan Area	Population		After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
	IQR[a]	Gini	IQR[a]	Co-Gini	IQR[a]	Co-Gini	IQR[a]	Co-Gini	IQR[a]	Co-Gini	IQR[a]	Co-Gini	IQR[a]	Co-Gini
British Columbia														
Vancouver	588 (478, 767) (0.1%)	0.36	47638 (40026, 56094) (0.0%)	0.13	6.6 (3.4, 11.5) (0.3%)	0.24	45.0 (24.2, 69.2) (0.3%)	0.17	2.0 (5.4, 7.9) (0.3%)	0.11	94.6 (90.0, 97.6) (0.3%)	0.19	46.6 (37.8, 56.5) (0.3%)	0.25
Kelowna	649 (516, 890) (0.4%)	0.23	47923 (40686, 55331) (0.4%)	0.08	8.2 (4.7, 11.6) (0.4%)	0.07	6.6 (3.8, 10.1) (0.4%)	0.11	1.2 (0.0, 2.5) (0.4%)	0.05	97.4 (95.4, 98.8) (0.4%)	0.07	56.1 (49.4, 62.5) (0.4%)	0.08
Abbotsford-Mission	597 (446, 823) (0.0%)	0.35	46023 (39250, 52714) (0.0%)	0.17	14.3 (9.9, 19.2) (0.0%)	0.22	17.2 (8.9, 36.6) (0.0%)	0.27	1.9 (0.0, 4.3) (0.0%)	0.23	95.8 (91.7, 98.1) (0.0%)	0.21	59.6 (52.6, 66.8) (0.0%)	0.21
Manitoba														
Winnipeg	545 (457, 649) (0.1%)	0.32	45914 (37357, 54989) (0.0%)	0.13	8.6 (4.8,10.4) (0.3%)	0.12	17.1 (8.1,34.2) (0.3%)	0.09	6.2 (0.0,9.0) (0.3%)	0.08	95.1 (89.9,98.2) (0.3%)	0.12	50.8 (42.6,58.8) (0.3%)	0.12
Ontario														
Toronto	564 (443, 809) (0.0%)	0.34	50341 (41429, 60411) (0.0%)	0.17	8.1 (4.0, 14.0) (0.4%)	0.20	41.3 (20.7, 68.3) (0.4%)	0.20	3.6 (1.4, 7.1) (0.4%)	0.12	94.1 (88.9, 97.4) (0.4%)	0.18	45.8 (35.7, 56.5) (0.4%)	0.24
Ottawa–Gatineau (Ontario part)	554 (447, 738) (0.0%)	0.47	57664 (46856, 66708) (0.0%)	0.19	5.1 (2.5, 9.1) (0.2%)	0.16	17.8 (9.3, 30.8) (0.2%)	0.21	1.6 (0.0, 3.6) (0.2%)	0.18	97.1 (94.2, 100.0) (0.2%)	0.20	37.5 (30.1, 45.7) (0.2%)	0.16
Hamilton	520 (438, 667) (0.0%)	0.40	50294 (38292, 59801) (0.0%)	0.11	8.5 (4.4, 15.2) (0.3%)	0.09	12.6 (6.2, 21.8) (0.3%)	0.15	0.7 (0.0, 3.0) (0.3%)	0.09	96.8 (93.8, 100.0) (0.3%)	0.09	52.8 (43.5, 62.3 (0.3%))	0.10
Kitchener-Cambridge-Waterloo	544 (440, 749) (0.0%)	0.32	48899 (39710, 57738) (0.0%)	0.13	10.5 (6.4, 16.2) (0.1%)	0.11	12.2 (5.9, 22.3) (0.1%)	0.13	1.3 (0.0, 3.5) (0.1%)	0.11	96.8 (94.1, 98.5) (0.1%)	0.15	54.3 (44.8, 61.8) (0.1%)	0.13
St. Catharines-Niagara	518 (450, 644) (0.0%)	0.44	43266 (35136, 50738) (0.0%)	0.12	9.8 (6.2, 14.7) (0.1%)	0.08	6.7 (2.8, 11.8) (0.1%)	0.11	0.0 (0.0, 2.0) (0.1%)	0.10	97.4 (95.1, 100.0) (0.1%)	0.10	60.0 (52.5, 68.2) (0.1%)	0.07
Windsor	502 (430, 615) (0.0%)	0.35	45227 (32280, 54901) (0.0%)	0.16	8.9 (4.8, 15.2) (0.0%)	0.11	13.8 (5.5, 27.4) (0.0%)	0.15	1.6 (0.0, 3.8) (0.0%)	0.09	96.7 (93.6, 98.4) (0.0%)	0.12	61.1 (52.9, 69.2) (0.0%)	0.09

Census Metropolitan Area	Population		After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
	IQR[a]	Gini	IQR[a]	Gini	IQR[a]	Gini	IQR[a]	Gini	IQR[a]	Gini	IQR[a]	Gini	IQR[a]	Gini
Québec														
Montréal	536 (448, 672) (0.4%)	0.33	40304 (33015, 49411) (0.4%)	0.11	10.3 (5.5, 16.7) (0.6%)	0.09	16.9 (6.8, 32.5) (0.6%)	0.16	2.4 (0.0, 6.2) (0.6%)	0.13	96.2 (92.5, 98.5) (0.6%)	0.14	47.6 (38.1, 56.1) (0.6%)	0.08
Québec City	514 (425, 682) (0.4%)	0.31	45104 (35847, 51917) (0.5%)	0.10	6.8 (3.8, 11.4) (0.6%)	0.08	3.2 (1.1, 6.7) (0.6%)	0.12	0.0 (0.0, 2.4) (0.6%)	0.09	98.4 (96.9, 100.0) (0.6%)	0.07	47.1 (39.6, 54.5) (0.6%)	0.10
Ottawa–Gatineau (Québec part)	543 (425, 805) (0.0%)	0.30	44891 (36112, 53526) (0.0%)	0.10	13.5 (7.3, 21.4) (0.0%)	0.07	8 .0 (2.7,15.6) (0.0%)	0. 13	0.0 (0.0, 2.8) (0.0%)	0.12	97.6 (95.5, 100.0) (0.0%)	0.05	44.7 (35.6, 53.1) (0.0%)	**0.07**
Sherbrooke	543 (455, 734) (0.0%)	0.33	37490 (28906, 44427) (0.0%)	0.17	11.3 (6.7, 19.0) (0.6%)	0.08	3.6 (1.0, 7.7) (0.6%)	0.16	0.0 (0.0, 2.4) (0.6%)	0.15	98.2 (96.7, 100) (0.6%)	0.08	53.7 (46.6, 61.1) (0.6%)	0.09
Saguenay	464 (398, 607) (0.0%)	0.37	41091 (32929, 46566) (0.0%)	**0.14**	10.3 (6.2, 15.9) (0.0%)	**0.09**	0.0 (0.0, 2.2) (0.0%)	0.11	0.0 (0.0, 0.0) (0.0%)	**0.01**	100 (97.6, 100.0) (0.0%)	**0.09**	55.3 (48.3, 61.9) (0.0%)	**0.11**
Trois-Rivières	481 (406, 620) (0.4%)	0.28	36899 (28382, 45459) (0.4%)	**0.08**	12.1 (6.1, 18.5) (0.4%)	**0.07**	1.9 (0.0, 3.8) (0.4%)	0.09	0.0 (0.0, 0.6) (0.4%)	0.09	98.8 (97.5, 100.0) (0.4%)	0.05	55.9 (48.6, 62.9) (0.4%)	**0.08**

[a]IQR = interquartile range of social and structural determinants across all DAs within a CMA.

* The percentages within the brackets after IQR of each variable represents the proportion of DAs with missing variable. (For population, DAs with 0 population are also included).

** Gini coefficients of those Lorenz curves went above and under the equity line were in **bold** font.

*** All the variables are ranked from the highest value to the lowest.

Magnitude of heterogeneity by social determinants between cities

The social determinant across which nearly all CMAs experienced a concentration of cases was the proportion visible minority. Figure 5.2.2 depicts the CMA-specific distribution and the respective co-Gini coefficients by proportion visible minority. Distribution of all the social determinants, co-Gini coefficients, proportion of population and the corresponding percentage of confirmed cases, and concentration curves for each CMA can be found in Table 5.2.2, Table 5.4.2, Figure 5.4.2 and Figure 5.4.3.

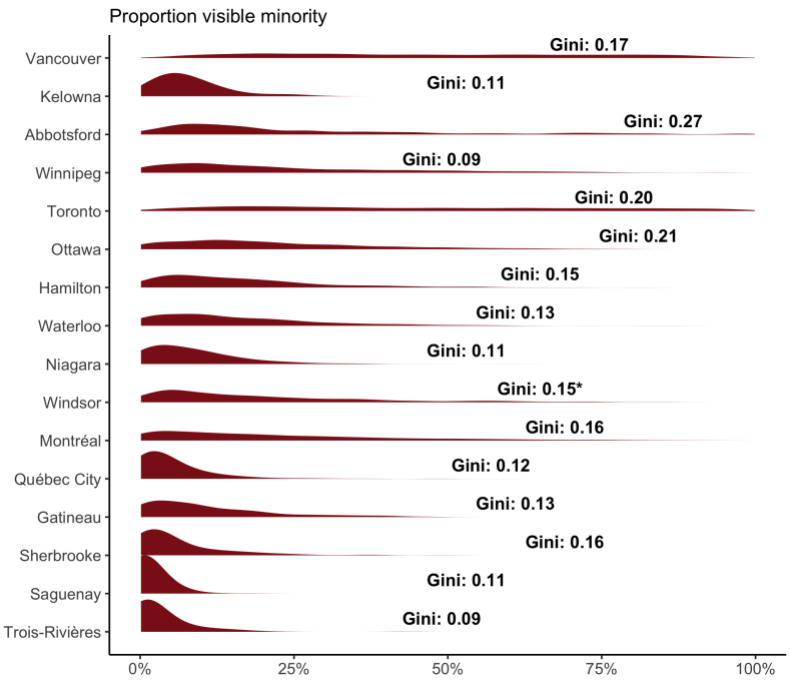

Figure 5.2.2. Density distributions of dissemination area-level proportion visible minority and the corresponding co-Gini coefficients (excluding long-term care residents) of cumulative COVID-19 cases, stratified by census metropolitan areas (CMA).
Note: The x-axis represents the dissemination area-level proportion visible minority and the y axis represents the different CMAs. For each value (X%) on the x-axis, the height of curve represents the proportion of DAs that has X% visible minority.For each CMA, the distribution of proportion minority is shown. Abbotsford-Mission is displayed as "Abbotsford"; Ottawa-Gatineau (Ontario part) is displayed as "Ottawa"; St. Catharines–Niagara is displayed as "Niagara"; Ottawa-Gatineau (Québec part) is displayed as "Gatineau". Co-Gini coefficients followed by a "*" mark represent co-Gini coefficients of those Lorenz curves that went over and under the equality line. Distribution of other social determinants of health and the corresponding Gini (co-Gini) coefficients can be found in Figure 5.4.2.

The distribution of the underlying social determinants was heterogenous across CMAs. Larger CMAs usually had wider distribution of the social determinants (Figure 5.4.2). Cities with less variability in the values of the social determinant tended to have smaller a co-Gini for that determinant: for example, Kelowna had a co-Gini of 0.07 for proportion not living in high-density housing, whose distribution was narrow as compared with Vancouver (co-Gini 0.19, Figure 5.4.2). Across all CMAs, cases were disproportionately concentrated by geographies represented by lower income, higher proportion living in high-density housing, lower education attainment; and a higher proportion visible minority, recent immigration and essential workers (Figure 5.4.3). Concentration by visible minority was the most consistent finding across CMAs, with variability in inequalities across CMAs within provinces. The largest co-Gini coefficient for income was observed in Ottawa (co-Gini 0.17); for lower levels of education in Vancouver (0.24), for visible minority, recent immigration and not living in high-density housing in Abbotsford-Mission (0.27, 0.23 and 0.21), and for essential workers in Vancouver (0.25) (Table 5.2.2). In Winnipeg (Manitoba), after-tax income explained the most heterogeneity (co-Gini 0.13).

When examining the 3 largest CMAs in Canada, the magnitude of geographical concentration by social determinants were similar for Toronto and Vancouver, in particular as they related to essential services (co-Gini 0.24 in Toronto, co-Gini 0.25 in Vancouver). In contrast, although Montréal demonstrated similar overall heterogeneity (Gini 0.33) to Toronto (0.34) and Vancouver (0.36), there was less heterogeneity by the same social determinants. In Montréal, the largest co-Gini was observed for proportion visible minority (co-Gini 0.16).

Interpretation

This study provides comprehensive and robust evidence of high geographical concentration and thus, geographic hotspots of SARS-CoV-2 cases within Canadian cities across four provinces. These hotspots are largely defined along social determinants related to occupation, income, housing, and proxies for structural racism. Specifically, we quantified heterogeneities in cumulative SARS-CoV-2 cases using measures of inequality across sixteen Canadian CMAs from British Columbia, Manitoba, Ontario, and Québec –provinces with the majority of cases in Canada. Although the magnitude of geographical heterogeneity was relatively similar across CMAs, and a

consistent theme across cities was the concentration of cases by proportion visibility minority, the degree of concentration by social determinants differed across cities.

There are two important implications of the city-specific findings for public health. First, given that each city demonstrated geographical concentration –with approximately 21-35% of the population in DAs accounting for 50% of cases– prioritizing and allocating resources to geographical hotspots could lead to a more effective and efficient response, and reduce inequalities (47), especially in the context of limited resources. An example of a hotspot-targeted strategy has been that of vaccination roll-out in some jurisdictions (48), but could also be systematically applied to ensure geographically prioritized resources for timely access to testing, support for isolation and quarantine of contacts. Indeed, data suggest that without a systematic and intentional hotspot and community-tailored strategy, both testing and vaccination coverage were lowest in geographical hotspots (48, 49) and among racialized communities (35) in Canada and other high-income countries (41, 50). Second, even though in each city, cases were concentrated across each social determinants of health, the magnitude of concentration by the same determinant differed between cities. That is, cities may differ with respect to which determinants were most associated with geographical clustering of SARS-CoV-2 cases. Each city would therefore benefit from tailoring its geographically prioritized strategy to its local structural determinants of heterogeneity in cases. For example, the difference in the co-Gini for essential services between Montréal compared to Vancouver and Toronto, despite similar distribution in the proportion essential workers in all three CMAs, suggests that the underlying context for hotspots (e.g., policies for sick leave (51)) may be different and thus signal different unmet needs of populations who shouldered the disproportionate burden of cases. Thus, using the city-specific spatial clustering of cases by social determinants to guide the local response could lead to more equitable allocation of resources and better access to interventions by providing services that actually meet the needs of communities at disproportionate risk. Such an approach may become even more important in the context of appropriately addressing the needs of 'unvaccinated' pockets of contact networks (52), and with increasingly transmissible variants of SARS-CoV-2 (53).

The results are consistent with the socio-geographical clustering patterns observed in other studies from Canada (35, 53), the United States (54-56), and Sweden (57). Higher rates of SARS-CoV-2 cases among racialized communities, or neighbourhoods with greater diversity, have been

a consistent finding across countries, and reflect pathways through systemic racism, including occupational exposure risks and barriers to prevention (58) and access effective isolation (59-61). In a previous study of the first wave in Ontario, the association between area-level proxies for systemic racism (proportion visible minority) and SARS-CoV-2 cases dissolved after adjusting for other relevant explanatory factors, including occupation, household size, and income (35). Clustering of cases in the context of essential services may reflect type and rates of contacts, sometimes without occupational protections, and access to safe working environments (62, 63). Similarly, income, occupation, and educational attainment are often correlated, with the latter further associated with barriers in access to health information and healthcare, including prevention (64, 65). Meanwhile, high-density households represent a barrier to physical distancing and effective isolation or quarantine (66). Importantly, these determinants are often correlated (67) (68), which means that each falls within an explanatory pathway, especially in the relationship between income and cases, and proxies of systemic racism and cases (34). Taken together, concentration in cases by social determinants reflects plausible mechanistic pathways for population-level transmission and, as such, the local contexts that define hotspots under broad stay-at-home policies (69) in each city.

Our descriptive study did not include an explanatory set of analyses to examine sources of heterogeneity in the difference in co-Gini between cities. However, we note that the distribution of each social determinant varied between CMAs, as depicted in Figure 5.4.2. When there is less variability of a given social determinant within a city, it consequently may be less of a determinant of geographical heterogeneity in cases. For example, the distribution of not living in high-density housing was more homogenous in Kelowna than Vancouver, whereas the corresponding co-Gini was higher in Vancouver. As such, the levels of geographical concentration by social determinants of geographical concentration between cities may also vary because of differences in the underlying degree of homogeneity/heterogeneity for the determinant under study.

Limitations of our study include our use of observed cases reported by provincial surveillance systems. We could have underestimated the co-Gini if testing rates were lower among marginalized communities (35). For example, testing capacity constraints were especially salient in the first wave and under-ascertainment of cases was important (70-72). Second, although we excluded residents of long-term care homes, our definition of community-wide cases could still

include other congregate-level settings such as shelters and group homes reflecting other unmeasured social determinants that could lead to geographical concentration within cities. Third, the DA-level social determinants were extracted from the most recent available census data from 2016, which may not accurately represent the characteristics of the population in 2020-2021. Fourth, as individual-level data on social determinants for cases were not available, we conducted our unit of analysis at the smallest area (DA) possible to limit misclassification in the context of an ecological study. Furthermore, in the few surveillance systems (e.g. Ontario) where individual-level data on some social determinants were collected and were available, and despite about 50% missingness, the pattern and magnitude were similar to the DA-level findings (73, 74). We limited the descriptive study to a cross-sectional analysis of each social determinant separately. Future work should examine sources of differences in the magnitude of inequalities/concentration in cases between cities (underlying differences in distribution of social determinants and the application of interventions), over time (to examine longitudinal pattern of heterogeneities over time and in each wave), with mediation or explanatory modelling of pathways to further examine the clustering of cases, and by a composite measure of social determinants or via multivariable analyses (given the potential for differential correlation between social determinants in each city (23)).

In conclusion, geographical hotspots characterized by social determinants have been a consistent feature the COVID-19 pandemic across major urban centers in British Columbia, Manitoba, Ontario, and Québec. The pattern of epidemic concentration and thus, inequalities, by social determinants has varied between cities. Geographically prioritized allocation of resources and services that are tailored to the local drivers of inequalities in acquisition and transmission risk offer a path forward in the public health response to SARS-CoV-2's resurgence as vaccination programs are being scaled-up.

Authors' contributions

YX, HM, GM, SB, SM, and MMG conceived of and designed the study. YX and HM developed the analysis plans, wrote the code, and coordinated code sharing across provincial teams. YX, HM, HVG, and MS conducted the statistical analysis. YX conducted the literature search, conducted the pooled analyses and generated the figures, and drafted the manuscript. GM drafted Table 5.4.1. NJ, DV, TW, AK, KY, RK, DLB, MB, SM, and MMG interpreted results, supported data curation, critically reviewed and edited the article.

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5.4. Manuscript 2: Supplementary Materials

5.4.1. Supplementary figures

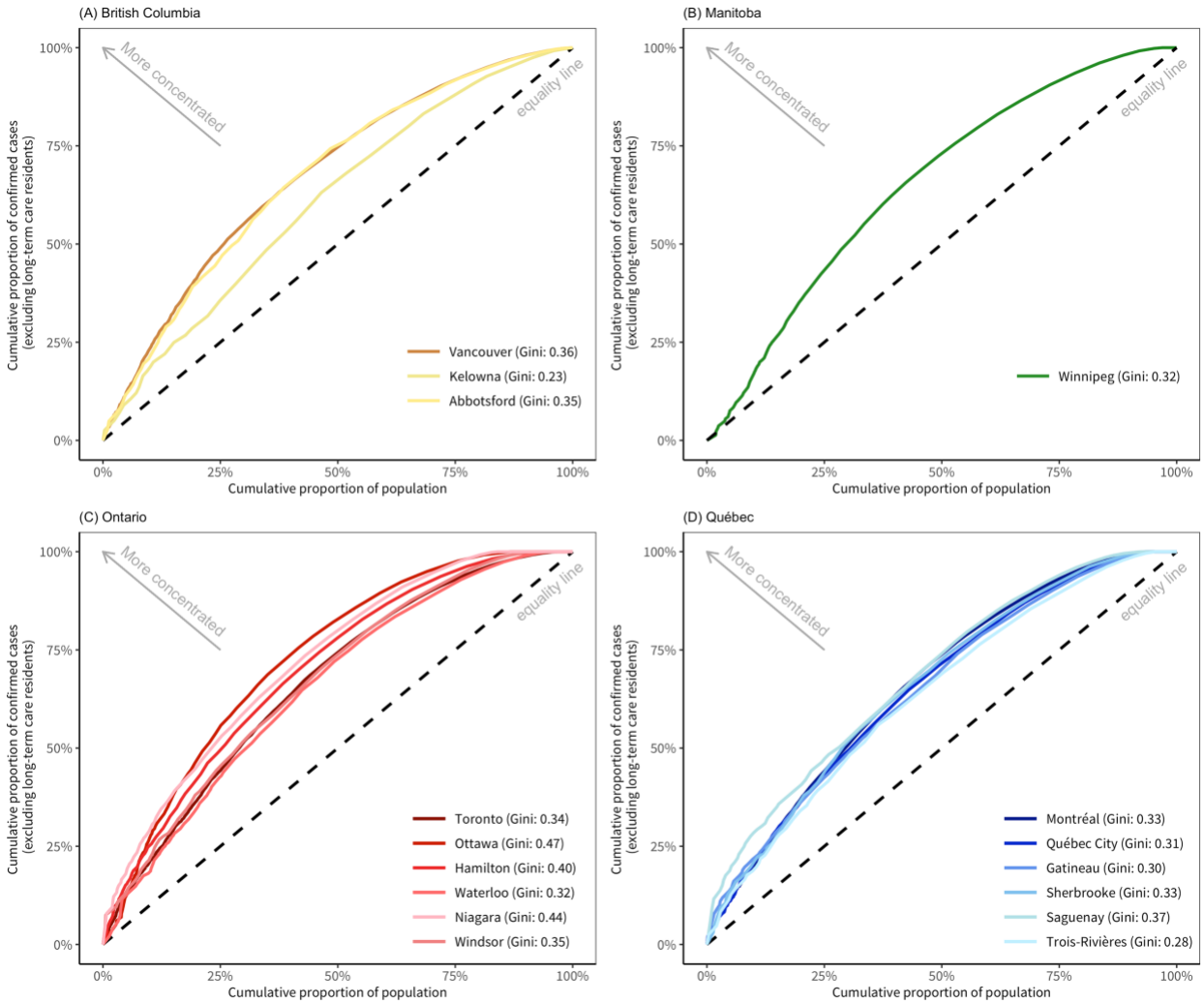

Figure 5.4.1. The Lorenz curves of COVID-19 confirmed cases (excluding long-term care residents) by proportion of population and the corresponding Gini coefficients.
Panel A: Lorenz curves of census metropolitan areas (CMA) in British Columbia (Abbotsford-Mission is displayed as "Abbotsford"). Panel B: Lorenz curves of CMAs in Manitoba. Panel C: Lorenz curves of CMAs in Ontario (Ottawa-Gatineau (Ontario part) is displayed as "Ottawa"; Kitchener - Cambridge – Waterloo is displayed as "Waterloo"); St. Catharines–Niagara is displayed as "Niagara"). Panel D: Lorenz curves of CMAs in Québec (Ottawa-Gatineau (Québec part) is displayed as "Gatineau"). The population was ranked by the number of cases in each dissemination area (DA) from the highest to the lowest.

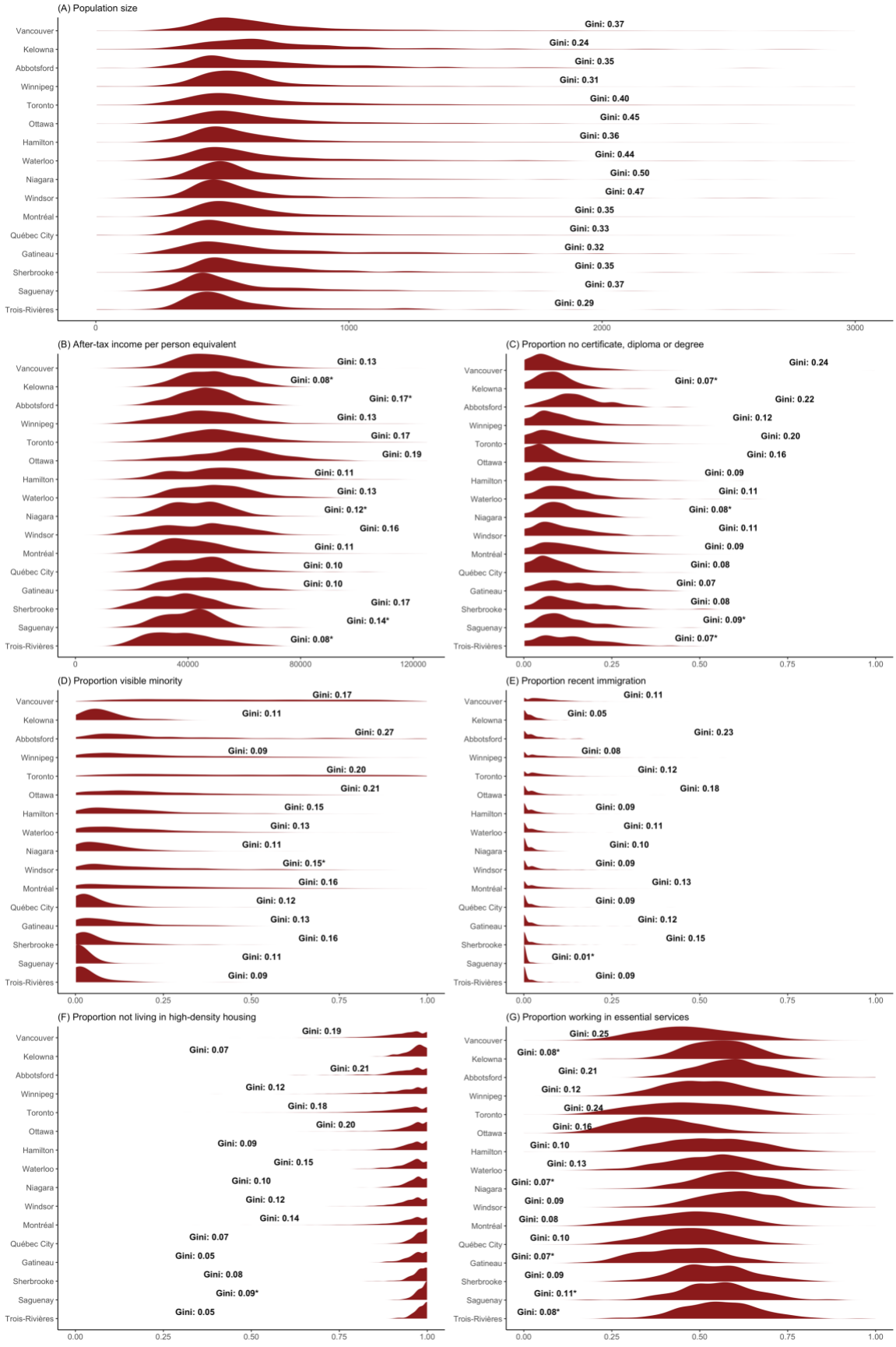
(A) Population size
Vancouver Gini: 0.37
Kelowna Gini: 0.24
Abbotsford Gini: 0.35
Winnipeg Gini: 0.31
Toronto Gini: 0.40
Ottawa Gini: 0.45
Hamilton Gini: 0.36
Waterloo Gini: 0.44
Niagara Gini: 0.50
Windsor Gini: 0.47
Montréal Gini: 0.35
Québec City Gini: 0.33
Gatineau Gini: 0.32
Sherbrooke Gini: 0.35
Saguenay Gini: 0.37
Trois-Rivières Gini: 0.29
0 1000 2000 3000
(B) After-tax income per person equivalent
Vancouver Gini: 0.13
Kelowna Gini: 0.08*
Abbotsford Gini: 0.17*
Winnipeg Gini: 0.13
Toronto Gini: 0.17
Ottawa Gini: 0.19
Hamilton Gini: 0.11
Waterloo Gini: 0.13
Niagara Gini: 0.12*
Windsor Gini: 0.16
Montréal Gini: 0.11
Québec City Gini: 0.10
Gatineau Gini: 0.10
Sherbrooke Gini: 0.17
Saguenay Gini: 0.14*
Trois-Rivières Gini: 0.08*
0 40000 80000 120000
(C) Proportion no certificate, diploma or degree
Vancouver Gini: 0.24
Kelowna Gini: 0.07*
Abbotsford Gini: 0.22
Winnipeg Gini: 0.12
Toronto Gini: 0.20
Ottawa Gini: 0.16
Hamilton Gini: 0.09
Waterloo Gini: 0.11
Niagara Gini: 0.08*
Windsor Gini: 0.11
Montréal Gini: 0.09
Québec City Gini: 0.08
Gatineau Gini: 0.07
Sherbrooke Gini: 0.08
Saguenay Gini: 0.09*
Trois-Rivières Gini: 0.07*
0.00 0.25 0.50 0.75 1.00
(D) Proportion visible minority
Vancouver Gini: 0.17
Kelowna Gini: 0.11
Abbotsford Gini: 0.27
Winnipeg Gini: 0.09
Toronto Gini: 0.20
Ottawa Gini: 0.21
Hamilton Gini: 0.15
Waterloo Gini: 0.13
Niagara Gini: 0.11
Windsor Gini: 0.15*
Montréal Gini: 0.16
Québec City Gini: 0.12
Gatineau Gini: 0.13
Sherbrooke Gini: 0.16
Saguenay Gini: 0.11
Trois-Rivières Gini: 0.09
0.00 0.25 0.50 0.75 1.00
(E) Proportion recent immigration
Vancouver Gini: 0.11
Kelowna Gini: 0.05
Abbotsford Gini: 0.23
Winnipeg Gini: 0.08
Toronto Gini: 0.12
Ottawa Gini: 0.18
Hamilton Gini: 0.09
Waterloo Gini: 0.11
Niagara Gini: 0.10
Windsor Gini: 0.09
Montréal Gini: 0.13
Québec City Gini: 0.09
Gatineau Gini: 0.12
Sherbrooke Gini: 0.15
Saguenay Gini: 0.01*
Trois-Rivières Gini: 0.09
0.00 0.25 0.50 0.75 1.00
(F) Proportion not living in high-density housing
Vancouver Gini: 0.19
Kelowna Gini: 0.07
Abbotsford Gini: 0.21
Winnipeg Gini: 0.12
Toronto Gini: 0.18
Ottawa Gini: 0.20
Hamilton Gini: 0.09
Waterloo Gini: 0.15
Niagara Gini: 0.10
Windsor Gini: 0.12
Montréal Gini: 0.14
Québec City Gini: 0.07
Gatineau Gini: 0.05
Sherbrooke Gini: 0.08
Saguenay Gini: 0.09*
Trois-Rivières Gini: 0.05
0.00 0.25 0.50 0.75 1.00
(G) Proportion working in essential services
Vancouver Gini: 0.25
Kelowna Gini: 0.08*
Abbotsford Gini: 0.21
Winnipeg Gini: 0.12
Toronto Gini: 0.24
Ottawa Gini: 0.16
Hamilton Gini: 0.10
Waterloo Gini: 0.13
Niagara Gini: 0.07*
Windsor Gini: 0.09
Montréal Gini: 0.08
Québec City Gini: 0.10
Gatineau Gini: 0.07*
Sherbrooke Gini: 0.09
Saguenay Gini: 0.11*
Trois-Rivières Gini: 0.08*
0.00 0.25 0.50 0.75 1.00

Figure 5.4.2. Distribution of the social determinants of health and the corresponding Gini (co-Gini) coefficients (excluding long-term care residents) of cumulative COVID-19 cases across census metropolitan areas (CMA).

This "ridgeplot" displays the *dissemination area-level* proportion visible minority on the x-axis and the y-axis represents the different CMAs. For each CMA, the distribution of proportion minority is shown. Panel A: population size. Panel B: After-tax income per person equivalent. Panel C: proportion population without certificate, diploma or degree deciles. Panel D: proportion visible minority. Panel E: proportion recent immigration. Panel F: proportion working in essential services. Panel G: proportion not living in high-density housing. Abbotsford-Mission is displayed as "Abbotsford"; Ottawa-Gatineau (Ontario part) is displayed as "Ottawa"; St. Catharines–Niagara is displayed as "Niagara"; Ottawa-Gatineau (Québec part) is displayed as "Gatineau". Co-Gini coefficients followed by a "*" mark represent co-Gini coefficients of those Lorenz curves that went over and under the equality line.

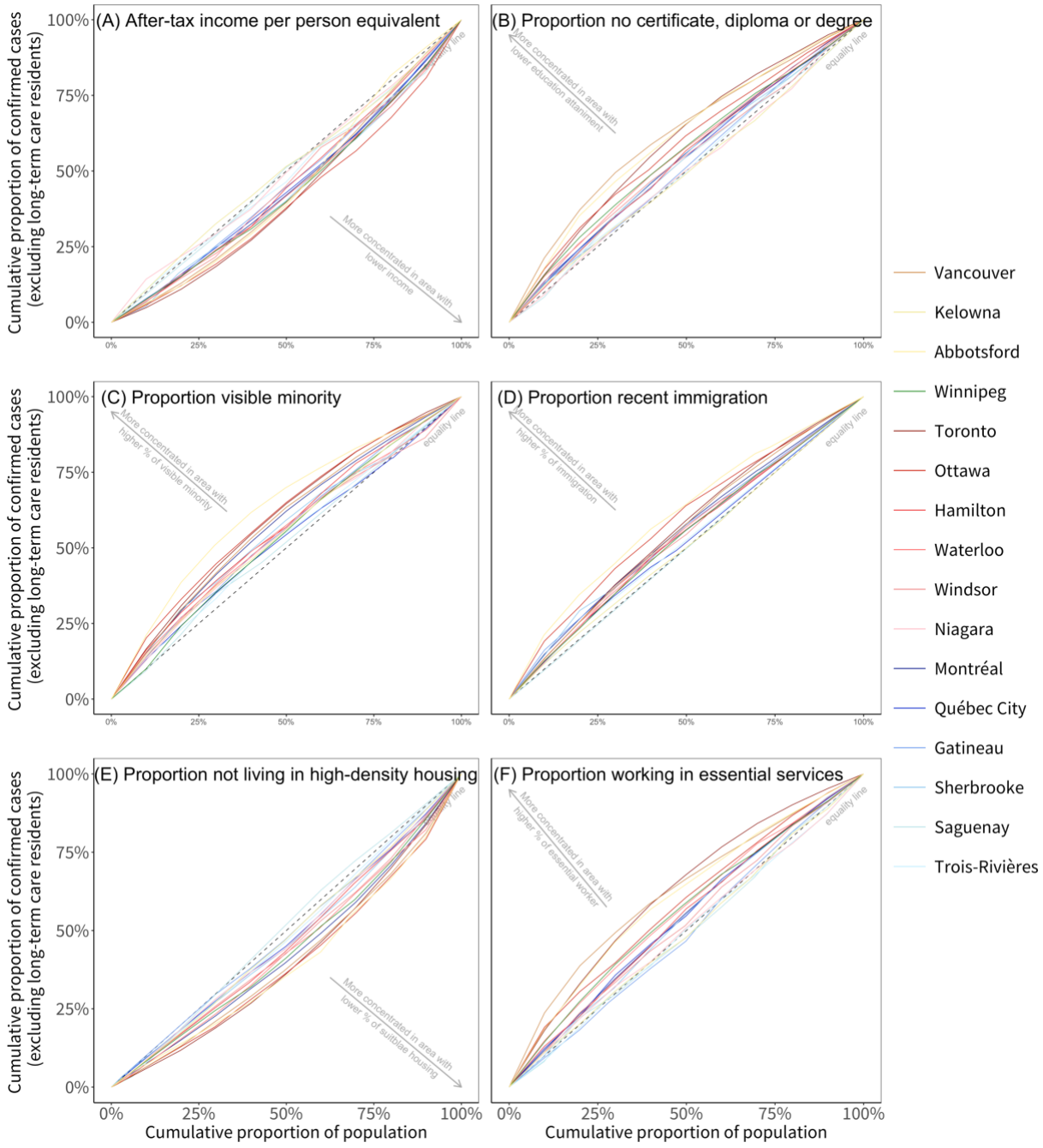

Figure 5.4.3. The concentration curves of COVID-19 confirmed cases (excluding long-term care residents) by social determinants.

Panel A: after-tax income per-person equivalent deciles. Panel B: proportion population without certificate, diploma or degree deciles. Panel C: proportion visible minority deciles. Panel D: proportion recent immigration deciles. Panel E: proportion working in essential services deciles. Panel F: proportion not living in high density housing deciles. Abbotsford-Mission is displayed as "Abbotsford"; Ottawa-Gatineau (Ontario part) is displayed as "Ottawa"; St. Catharines–Niagara is displayed as "Niagara"; Ottawa-Gatineau (Québec part) is displayed as "Gatineau". All the variables were ranked from the highest value to the lowest.

5.4.2. Supplementary tables

Table 5.4.1. Social Determinants of Health–Variables from Statistics Canada 2016 Census of Population.

Measure (Source)[a]	Definition of indicator	Notes[b] [r]
Population size **(100% of census sample)**	Total population count of a Dissemination Area	In this measure and where required, Dissemination Area (DA) population counts are adjusted (reduced) to remove residents of Long-Term Care Homes (LTCH)[c].
Socio-demographic		
Household income **(100% of census sample)[d]**	Decile rank of a Dissemination Area's average total after-tax income, weighted by population	After-tax income is calculated for each household from the income for all household members. Calendar year 2015 is the reference period for all income variables in the 2016 Census. Single-person equivalent is used to account for households of different sizes. To limit variations in the cost of living, the ranking is calculated exclusively from DAs within the same Census Metropolitan Area (CMA).
% recent immigration **(25% of census sample)**	Numerator: Number of persons within each DA who immigrated to Canada in the 5 year period between 2011 and 2016 Denominator: Total population within the Dissemination Area	2016 Census Dictionary states: 'Immigrant' refers to a person who is, or who has ever been, a landed immigrant or permanent resident. Such a person has been granted the right to live in Canada permanently by immigration authorities. 2016 Census Dictionary states: 'Period of immigration' refers to the period in which the immigrant first obtained landed immigrant or permanent resident status. Recent immigrant refers to a person who obtained a landed immigrant or permanent resident status up to five years prior to a given census year. In the 2016 Census, this period is January 1, 2011, to May 10, 2016.
% visible minority **(25% of census sample)**	Numerator: Number of persons who belong to visible minority groups Denominator: Total population within the Dissemination Area	Visible minority groups are defined by the Employment Equity Act: "persons, other than Aboriginal peoples, who are non-Caucasian in race or non-white in colour". 2016 Census Dictionary states: "The visible minority population consists mainly of the following groups: South Asian, Chinese, Black, Filipino, Latin American, Arab, Southeast Asian, West Asian, Korean and Japanese."
% educational attainment **(25% of census sample)**	Numerator: Number of persons aged 15 and over who have not obtained a certificate, diploma or degree from a high school, trades school, college, or university. Denominator: Total of all persons aged 15 and older living in private households in the Dissemination Area.	The certificates, diplomas or degrees included in this measure also capture: high school equivalency certificates; Certificates of Apprenticeship; Journeyperson's designations; trade certificates or diplomas completed at institutes of technology and vocational centres; CEGEP; non-university certificates or diplomas from a private business school or school of nursing; teaching certificates; "non-degree programs of study completed through a university….connected with professional associations in fields such as accounting, banking, insurance or public administration." [2016 Census Dictionary]. Persons included in the numerator have not obtained these types of certificates, diplomas or degrees.

Measure (Source)[a]	Definition of indicator	Notes[b] [r]
Dwelling-related		
% not living in high-density housing (% suitable housing) **(25% of census sample)**	Numerator: Number of private households[e] living in dwellings that have "enough bedrooms for the size and composition of the household." [2016 Census Dictionary] Denominator: Total number of private households within the Dissemination Area	The National Occupancy Standard (NOS) is used to classify the suitability of accommodations. A suitable household is defined as "households where the required number of bedrooms based on the National Occupancy Standard (NOS) does not exceed the reported number of bedrooms in the dwelling." The number of required bedrooms is determined using the following criteria: 1. A maximum of two persons per bedroom. 2. Household members, of any age, living as part of a married or common-law couple share a bedroom with their spouse or common-law partner. 3. Lone-parents, of any age, have a separate bedroom. 4. Household members aged 18 or over have a separate bedroom - except those living as part of a married or common-law couple. 5. Household members under 18 years old of the same sex share a bedroom - except lone-parents and those living as part of a married or common-law couple. 6. Household members under 5 years old of the opposite sex share a bedroom if doing so would reduce the number of required bedrooms. This situation would arise only in households with an odd number of males under 18, an odd number of females under 18, and at least one female and one male under the age of 5. https://www23.statcan.gc.ca/imdb/pUtil.pl?Function=getNote&Id=141809&NT=01
Occupation-related		
% essential services not amenable to remote working **(25% of census sample)**	Numerator: Number of persons in the labor force who have occupations in one of the following categories: Manufacturing/utilities, Trades/transport/equipment operators, Sales/services, Health, Resources/agriculture/production Denominator: Total labor force population aged 15 years and over in private households in the Dissemination Area	Occupations are assigned according to the National Occupancy Classification (2016). Occupation was chosen over "Industry" to better represent the type of work performed and skill-level required by a population rather than the industry that provides the employment. Numerators may be defined separately ("or") or added together in different combination sets ("and"). "Labor Force" is all persons in private households aged 15 years and older who were either employed or unemployed during the week of Sunday, May 1 to Saturday, May 7, 2016.

Sources:

Data tables from: Statistics Canada. 2017. 2016 Census of Population. Census Profile - Age, Sex, Type of Dwelling, Families, Households, Marital Status, Language, Income, Immigration and Ethnocultural Diversity, Housing, Aboriginal Peoples, Education, Labour, Journey to Work, Mobility and Migration, and Language of Work for Canada, Provinces and Territories, Census Divisions, Census Subdivisions and Dissemination Areas (File: 98-401-X2016044). Accessed January 2018.

Dictionary definitions from: Statistics Canada. 2017. 2016 Census Dictionary. Statistics Canada Catalogue no. 98-301-X2016001. Ottawa, Ontario. November 29. (https://www12.statcan.gc.ca/census-recensement/2016/ref/dict/index-eng.cfm, accessed November 30, 2020).

Questionnaire used to collect the information: 1) Statistics Canada. Census 2A – 2016. Modified April 23, 2019. (https://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=assembleInstr&a=1&&lang=en&Item_Id=295241) and 2) Census 2A-L - 2016. Modified April 23, 2019. (https://www23.statcan.gc.ca/imdb/p3Instr.pl?Function=assembleInstr&a=1&&lang=en&Item_Id=295122)

a-"Sample" refers to the short-form Census questionnaire (100% sample) or to the long-form questionnaire, received by a random sample of households (25% sample). It is mandatory for recipients to respond to the questionnaires. Statistical inferences for the entire population are drawn from the subset of responses of the long-form questionnaire; these inferences are reported in the tabulated values provided by Statistics Canada. Note that income information was collected solely from administrative data sources (100% sample) and were not part of either questionnaire.

b-Additional details about variable definitions may be included the Census Dictionary; please refer to Statistics Canada's Dictionary for the 2016 Census of Population for complete definitions. Some definitions provided here are taken verbatim from source.

c-Due to reporting methods used by CCM+, case counts among "Long-Term Care Residents" may also include cases that are reported for residents of "nursing home[s] or other chronic care facility[ies]". Adjustments in population counts described here only include adjustments to Dissemination Areas that have one (or more) LTCH facility identified by the Ontario Ministry of Health. The adjustments are made by subtracting the total number of beds in the facility from the population count of the DA.

d-Income deciles for the City of Toronto / Toronto Public Health Unit were tabulated from data contained in PCCF+ (version 7B) and adjusted for population size. Ref: Statistics Canada. 2018. Postal Code Conversion File Plus (PCCF+) Version 7B, Reference Guide. November 2018 Postal codes.

e-Where referenced, "household" refers to a "private household". The 2016 Census Dictionary states: "Private household" refers to a person or group of persons who occupy the same dwelling and do not have a usual place of residence elsewhere in Canada or abroad."

Table 5.4.2. Proportion of population and the corresponding percentage of confirmed cases within each decile group ranked by the social and structural determinants across CMA.

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
British Columbia													
Vancouver	1	10.0%	6.1%	9.9%	21.3%	10.0%	15.5%	10.0%	13.4%	1.8%	1.0%	10.0%	23.7%
	2	20.0%	13.0%	20.0%	37.3%	20.0%	29.6%	20.0%	25.7%	19.7%	13.0%	20.0%	38.8%
	3	30.0%	20.9%	30.0%	49.5%	30.0%	41.8%	29.9%	37.0%	29.9%	21.1%	30.0%	49.3%
	4	40.0%	29.9%	40.0%	58.7%	39.9%	53.1%	40.0%	47.6%	39.9%	29.0%	39.3%	58.3%
	5	50.0%	39.6%	49.9%	66.6%	50.0%	63.4%	50.0%	57.9%	49.3%	37.1%	50.0%	66.5%
	6	60.0%	51.0%	60.0%	73.8%	60.0%	71.6%	60.0%	68.6%	59.8%	47.0%	59.9%	73.6%
	7	70.0%	63.3%	69.6%	80.5%	70.0%	80.0%	70.0%	77.1%	69.9%	57.3%	70.0%	80.4%
	8	80.0%	76.4%	79.7%	87.0%	80.0%	87.3%	79.9%	85.4%	79.9%	68.1%	80.0%	87.2%
	9	90.0%	89.0%	89.9%	94.2%	90.0%	93.8%	88.6%	92.0%	89.9%	81.1%	89.8%	93.8%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Kelowna	1	9.8%	10.5%	9.9%	12.3%	9.9%	14.4%	9.4%	11.0%	2.7%	2.2%	9.6%	10.7%
	2	19.8%	22.0%	19.9%	21.6%	19.1%	25.1%	19.6%	21.8%	19.2%	16.8%	19.9%	20.1%
	3	29.8%	32.5%	29.1%	30.8%	30.0%	37.4%	30.0%	31.7%	29.7%	26.9%	29.8%	30.5%
	4	39.8%	41.5%	40.0%	39.7%	39.7%	45.7%	39.1%	40.5%	39.1%	37.0%	39.9%	39.8%
	5	49.8%	51.4%	49.5%	48.6%	49.5%	55.7%	49.2%	49.4%	49.4%	46.7%	49.8%	47.6%
	6	59.6%	58.6%	59.8%	58.9%	59.8%	65.8%	59.7%	58.9%	59.9%	58.0%	59.7%	58.6%
	7	69.9%	67.7%	69.2%	66.6%	69.5%	74.1%	64.9%	64.7%	69.2%	66.4%	68.0%	66.6%
	8	79.3%	76.3%	79.7%	78.0%	79.0%	83.6%	100.0%	100.0%	79.9%	76.8%	79.7%	80.7%
	9	89.8%	88.6%	89.7%	88.9%	89.9%	92.4%			89.8%	88.5%	89.9%	88.9%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%			100.0%	100.0%	100.0%	100.0%
Abbotsford-Mission	1	10.0%	6.4%	9.6%	17.3%	10.0%	21.1%	9.8%	21.2%	3.1%	2.9%	9.9%	18.4%
	2	19.9%	12.0%	19.7%	35.1%	19.9%	38.6%	19.7%	34.5%	19.3%	13.5%	19.9%	32.5%
	3	30.0%	20.3%	30.0%	46.6%	29.5%	50.9%	29.8%	44.8%	29.5%	20.1%	29.7%	46.2%
	4	39.7%	28.9%	39.8%	56.0%	40.0%	61.7%	40.0%	56.2%	39.6%	26.9%	39.9%	56.8%
	5	49.9%	38.6%	49.6%	65.4%	49.8%	69.9%	49.5%	64.0%	49.1%	34.8%	49.4%	64.4%
	6	59.7%	51.4%	59.7%	74.2%	59.4%	76.3%	59.8%	73.4%	59.9%	43.2%	59.6%	72.5%
	7	69.7%	66.6%	70.0%	80.8%	70.0%	83.0%	69.4%	81.1%	68.4%	54.7%	69.9%	80.9%
	8	79.8%	81.5%	79.9%	88.1%	79.8%	88.1%	73.6%	83.3%	79.7%	66.3%	79.9%	87.4%
	9	89.8%	90.8%	89.3%	94.1%	89.9%	93.8%	100.0%	100.0%	89.9%	79.8%	89.9%	93.8%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%			100.0%	100.0%	100.0%	100.0%

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
Manitoba													
Winnipeg	1	9.9%	7.4%	10.0%	15.6%	9.9%	9.8%	9.9%	12.4%	2.4%	2.1%	10.0%	14.3%
	2	19.8%	14.4%	20.0%	28.1%	19.9%	23.8%	19.9%	23.4%	19.9%	16.2%	19.7%	27.0%
	3	30.0%	22.8%	29.9%	38.6%	29.7%	35.0%	30.0%	35.0%	29.6%	24.0%	30.0%	39.0%
	4	40.0%	29.9%	39.9%	48.5%	39.9%	45.2%	39.9%	45.7%	39.9%	31.6%	40.0%	48.9%
	5	50.0%	39.2%	49.9%	57.9%	50.0%	55.8%	49.9%	56.4%	49.9%	40.9%	49.1%	57.8%
	6	59.9%	49.7%	59.8%	67.0%	59.9%	66.8%	59.6%	65.1%	60.0%	51.1%	60.0%	67.8%
	7	70.0%	60.6%	69.6%	75.7%	69.9%	76.4%	69.9%	75.2%	69.5%	59.8%	70.0%	75.1%
	8	79.7%	72.8%	80.0%	82.7%	80.0%	85.5%	77.9%	80.9%	79.9%	72.0%	80.0%	83.4%
	9	89.8%	84.6%	90.0%	90.9%	90.0%	93.5%	100.0%	100.0%	89.6%	85.2%	89.9%	91.0%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%			100.0%	100.0%	100.0%	100.0%
Ontario													
Toronto	1	10.0%	4.9%	9.8%	15.4%	10.0%	16.6%	9.9%	13.4%	1.6%	1.0%	10.0%	18.1%
	2	20.0%	11.0%	19.9%	30.2%	20.0%	30.9%	20.0%	25.6%	19.7%	11.7%	20.0%	33.1%
	3	30.0%	18.5%	29.9%	43.0%	30.0%	43.6%	29.8%	37.7%	29.9%	19.0%	29.9%	46.7%
	4	40.0%	27.2%	39.7%	54.6%	40.0%	54.5%	40.0%	48.4%	39.9%	26.8%	39.9%	58.4%
	5	50.0%	37.4%	50.0%	65.5%	50.0%	64.6%	49.8%	58.9%	50.0%	36.2%	50.0%	67.9%
	6	60.0%	49.4%	59.9%	74.6%	59.9%	73.2%	60.0%	69.2%	59.9%	46.3%	60.0%	76.7%
	7	70.0%	61.2%	69.9%	82.1%	70.0%	81.8%	69.9%	78.3%	70.0%	57.5%	70.0%	84.2%
	8	80.0%	72.8%	79.8%	88.4%	80.0%	88.6%	80.0%	86.4%	79.9%	69.9%	79.9%	90.1%
	9	90.0%	85.1%	89.9%	95.0%	90.0%	94.8%	85.8%	90.5%	90.0%	83.9%	90.0%	95.4%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Ottawa – Gatineau (Ontario part)	1	9.9%	5.7%	10.0%	17.6%	10.0%	20.2%	9.9%	19.2%	2.9%	1.8%	10.0%	19.1%
	2	19.9%	12.1%	20.0%	31.3%	20.0%	33.0%	20.0%	30.7%	29.6%	19.2%	20.0%	30.5%
	3	30.0%	19.3%	29.9%	42.2%	29.9%	44.7%	29.8%	43.1%	39.6%	27.8%	30.0%	39.7%
	4	40.0%	27.7%	39.4%	50.3%	40.0%	55.0%	40.0%	53.0%	49.6%	36.1%	39.7%	50.3%
	5	50.0%	37.8%	49.8%	61.6%	50.0%	65.0%	49.9%	63.9%	59.9%	45.4%	50.0%	60.6%
	6	59.9%	48.0%	59.9%	70.0%	59.8%	73.5%	60.0%	71.3%	70.0%	55.7%	60.0%	69.4%
	7	70.0%	56.7%	68.7%	76.7%	69.9%	81.8%	66.2%	76.1%	80.0%	67.4%	70.0%	78.1%
	8	79.9%	67.7%	80.0%	85.8%	80.0%	88.5%	100.0%	100.0%	89.9%	79.2%	79.9%	86.8%
	9	90.0%	80.9%	84.1%	89.1%	90.0%	94.0%			100.0%	100.0%	90.0%	94.0%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
Hamilton	1	9.9%	6.9%	10.0%	11.5%	10.0%	16.3%	9.9%	12.5%	2.5%	2.1%	9.9%	13.0%
	2	20.0%	15.1%	19.8%	23.3%	19.9%	28.7%	20.0%	24.3%	29.6%	25.3%	20.0%	22.7%
	3	29.9%	23.9%	30.0%	35.0%	30.0%	39.2%	29.9%	34.9%	39.4%	33.3%	30.0%	34.2%
	4	40.0%	31.7%	39.9%	44.1%	40.0%	48.9%	39.8%	46.7%	49.4%	43.0%	39.9%	45.0%
	5	49.9%	44.4%	49.7%	56.5%	49.9%	56.8%	49.9%	56.1%	59.4%	53.8%	50.0%	57.0%
	6	60.0%	54.4%	59.8%	65.7%	60.0%	68.0%	58.7%	63.2%	69.3%	65.0%	59.9%	65.5%
	7	70.0%	65.3%	69.8%	74.5%	69.9%	78.0%	100.0%	100.0%	79.9%	75.7%	69.9%	75.5%
	8	80.0%	75.8%	79.8%	83.2%	80.0%	85.2%			89.5%	85.3%	80.0%	84.1%
	9	89.9%	87.9%	89.9%	91.2%	90.0%	92.0%			100.0%	100.0%	90.0%	91.4%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%
Kitchener - Cambridge - Waterloo	1	10.0%	7.4%	9.9%	15.2%	10.0%	15.2%	9.9%	12.6%	3.1%	1.8%	9.9%	14.7%
	2	20.0%	15.8%	19.7%	25.7%	19.6%	26.5%	19.9%	23.8%	20.0%	15.4%	19.9%	26.8%
	3	30.0%	22.8%	29.7%	37.4%	30.0%	37.8%	29.8%	36.6%	29.9%	23.5%	29.9%	38.0%
	4	40.0%	31.5%	39.9%	48.6%	40.0%	47.2%	39.8%	46.8%	39.8%	32.4%	40.0%	48.5%
	5	49.2%	41.0%	49.9%	57.8%	50.0%	57.5%	49.8%	56.8%	49.9%	42.8%	49.5%	57.8%
	6	59.9%	51.0%	59.8%	66.3%	59.9%	66.7%	59.8%	65.8%	59.4%	50.6%	59.9%	67.8%
	7	70.0%	61.6%	69.9%	75.4%	70.0%	75.1%	65.0%	69.2%	69.9%	62.1%	70.0%	77.8%
	8	79.9%	71.4%	79.4%	83.7%	80.0%	81.7%	100.0%	100.0%	80.0%	72.4%	79.8%	84.2%
	9	89.9%	83.6%	89.8%	92.7%	90.0%	89.1%			89.8%	82.1%	90.0%	92.5%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%			100.0%	100.0%	100.0%	100.0%
St. Catharines - Niagara	1	10.0%	14.3%	10.0%	9.2%	9.7%	12.5%	9.9%	12.0%	4.2%	3.0%	9.9%	10.9%
	2	19.9%	21.9%	19.8%	20.5%	19.8%	25.6%	19.6%	23.8%	29.9%	28.3%	20.0%	21.9%
	3	29.8%	29.1%	29.5%	30.9%	30.0%	36.9%	30.0%	36.7%	39.3%	36.3%	29.9%	32.2%
	4	39.9%	37.4%	39.9%	41.1%	39.7%	46.6%	39.7%	47.7%	49.5%	43.9%	40.0%	40.1%
	5	50.0%	49.5%	49.9%	50.2%	49.9%	56.4%	42.8%	49.9%	59.8%	55.3%	49.9%	50.9%
	6	59.9%	59.4%	59.8%	57.8%	60.0%	66.7%	100.0%	100.0%	69.7%	66.3%	59.9%	60.6%
	7	70.0%	69.1%	70.0%	68.6%	69.9%	73.2%			79.5%	76.0%	69.9%	69.8%
	8	79.9%	77.9%	79.7%	77.1%	79.7%	81.3%			89.9%	87.0%	79.9%	77.8%
	9	89.9%	88.1%	89.9%	90.8%	88.8%	91.2%			100.0%	100.0%	89.7%	87.3%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
Windsor	1	9.8%	6.8%	10.0%	13.4%	10.0%	13.8%	9.9%	13.4%	2.1%	1.4%	10.0%	11.1%
	2	19.8%	14.5%	19.3%	25.7%	19.9%	26.3%	19.8%	25.3%	29.8%	25.9%	19.9%	23.7%
	3	29.7%	21.6%	29.8%	36.2%	29.9%	38.1%	29.8%	35.6%	38.9%	33.6%	30.0%	33.5%
	4	39.7%	34.0%	39.7%	46.4%	39.9%	48.8%	39.9%	45.9%	49.8%	42.5%	39.4%	43.1%
	5	49.7%	44.9%	50.0%	55.2%	49.6%	57.2%	50.0%	54.4%	59.8%	53.0%	49.7%	51.5%
	6	59.9%	57.8%	59.9%	63.6%	60.0%	66.5%	59.5%	64.8%	69.9%	62.3%	60.0%	63.9%
	7	69.9%	64.9%	69.8%	72.1%	69.6%	73.6%	100.0%	100.0%	79.9%	73.1%	69.9%	72.4%
	8	80.0%	73.8%	79.8%	79.8%	79.8%	80.2%			89.9%	86.6%	79.9%	83.4%
	9	89.9%	84.0%	89.8%	91.8%	89.6%	86.4%			100.0%	100.0%	89.9%	91.0%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%
Québec													
Montreal	1	9.9%	6.8%	10.0%	12.8%	10.0%	15.5%	10.0%	14.9%	2.6%	2.0%	10.0%	11.8%
	2	20.0%	15.3%	20.0%	24.5%	20.0%	29.2%	20.0%	26.6%	20.0%	15.1%	20.0%	23.4%
	3	30.0%	23.9%	29.7%	35.0%	30.0%	41.2%	29.9%	37.7%	29.9%	22.8%	29.8%	34.5%
	4	40.0%	32.5%	40.0%	45.8%	40.0%	52.0%	40.0%	47.9%	39.5%	31.1%	38.5%	43.7%
	5	50.0%	42.0%	49.8%	55.8%	50.0%	62.1%	50.0%	57.9%	49.6%	39.5%	50.0%	55.7%
	6	60.0%	51.8%	60.0%	66.0%	60.0%	70.9%	60.0%	67.0%	60.0%	49.2%	59.9%	65.5%
	7	70.0%	62.4%	70.0%	75.1%	69.9%	78.9%	70.0%	75.6%	69.9%	59.1%	70.0%	75.5%
	8	80.0%	74.4%	79.9%	84.3%	80.0%	86.4%	70.6%	75.9%	80.0%	70.9%	79.9%	83.9%
	9	90.0%	86.7%	90.0%	92.5%	90.0%	93.4%	100.0%	100.0%	89.7%	84.0%	89.9%	92.2%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%			100.0%	100.0%	100.0%	100.0%
Quebec City	1	10.0%	7.6%	10.0%	13.5%	9.9%	13.1%	9.9%	12.2%	6.3%	6.0%	10.0%	12.3%
	2	19.9%	15.8%	19.9%	24.4%	20.0%	24.3%	20.0%	24.3%	39.7%	36.6%	19.9%	22.7%
	3	30.0%	24.7%	29.5%	34.4%	30.0%	35.2%	29.6%	34.0%	49.9%	45.0%	30.0%	35.7%
	4	40.0%	33.7%	39.9%	44.5%	40.0%	45.3%	39.9%	43.6%	59.9%	55.3%	40.0%	45.7%
	5	50.0%	42.9%	49.8%	54.5%	49.8%	54.2%	47.2%	49.1%	70.0%	66.7%	49.9%	54.6%
	6	60.0%	52.3%	59.6%	64.2%	59.9%	63.1%	100.0%	100.0%	80.0%	76.0%	59.9%	66.4%
	7	70.0%	62.1%	70.0%	74.5%	70.0%	70.9%			89.7%	87.1%	69.9%	75.0%
	8	80.0%	73.7%	79.7%	82.8%	79.9%	79.5%			100.0%	100.0%	79.9%	83.8%
	9	90.0%	86.5%	88.3%	89.5%	80.5%	79.8%					90.0%	92.2%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
Ottawa – Gatineau (Quebec part)	1	9.9%	7.9%	10.0%	13.0%	9.9%	13.8%	10.0%	16.2%	2.4%	2.7%	9.9%	9.3%
	2	19.9%	15.3%	19.9%	22.1%	20.0%	27.1%	19.8%	26.5%	29.7%	29.5%	19.9%	18.3%
	3	29.6%	25.1%	29.8%	30.8%	30.0%	35.7%	29.8%	36.7%	39.5%	37.7%	27.9%	26.9%
	4	39.7%	34.5%	40.0%	40.8%	40.0%	47.4%	39.8%	46.1%	49.4%	46.8%	39.9%	37.8%
	5	49.9%	44.7%	49.8%	51.0%	50.0%	56.5%	49.7%	57.3%	59.5%	57.5%	49.8%	46.6%
	6	59.8%	53.7%	59.8%	61.7%	59.9%	67.1%	54.2%	61.0%	69.6%	66.6%	60.0%	60.4%
	7	69.9%	64.8%	69.8%	72.0%	69.9%	75.8%	100.0%	100.0%	79.8%	77.9%	69.7%	70.8%
	8	80.0%	73.7%	79.8%	82.6%	79.9%	85.6%			90.0%	88.7%	79.7%	81.3%
	9	90.0%	87.1%	90.0%	91.9%	89.8%	92.0%			100.0%	100.0%	89.9%	91.2%
	10	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%					100.0%	100.0%
Sherbrooke	1	9.8%	5.1%	9.9%	12.4%	9.7%	14.7%	9.9%	14.4%	3.1%	3.5%	9.3%	9.3%
	2	19.2%	16.3%	19.9%	23.7%	19.7%	29.5%	19.9%	29.3%	39.8%	35.9%	19.8%	22.7%
	3	29.9%	24.9%	29.9%	35.2%	29.6%	38.4%	29.6%	36.5%	50.0%	44.4%	29.6%	31.6%
	4	39.9%	31.5%	39.9%	46.0%	38.9%	48.1%	39.6%	47.1%	59.2%	53.5%	39.6%	43.7%
	5	49.9%	40.0%	49.6%	55.7%	49.8%	59.0%	43.6%	50.2%	69.7%	63.8%	49.8%	55.2%
	6	59.8%	51.2%	59.8%	65.2%	60.0%	68.2%	100.0%	100.0%	79.7%	75.5%	60.0%	65.8%
	7	69.8%	60.6%	69.6%	73.3%	69.7%	74.6%			90.0%	86.3%	69.6%	74.4%
	8	80.0%	71.4%	79.7%	81.4%	78.9%	79.9%			100.0%	100.0%	79.0%	82.9%
	9	90.0%	84.6%	88.9%	89.9%	100.0%	100.0%					89.8%	92.5%
	10	100.0%	100.0%	100.0%	100.0%							100.0%	100.0%
Saguenay	1	9.6%	9.0%	10.0%	8.4%	9.9%	9.4%	9.6%	9.2%	6.1%	3.4%	9.9%	8.1%
	2	19.9%	19.0%	19.8%	21.6%	19.9%	21.4%	14.1%	13.6%	60.0%	63.0%	19.7%	22.1%
	3	29.3%	28.0%	30.0%	35.5%	29.9%	34.9%	100.0%	100.0%	69.6%	72.3%	30.0%	29.5%
	4	40.0%	39.5%	39.1%	43.5%	39.8%	42.7%			79.7%	81.0%	39.9%	38.9%
	5	49.9%	51.2%	49.2%	53.9%	42.9%	45.1%			89.9%	90.4%	49.9%	47.8%
	6	59.8%	58.4%	59.8%	63.2%	100.0%	100.0%			100.0%	100.0%	60.0%	57.6%
	7	69.8%	65.5%	69.8%	72.3%							69.3%	67.1%
	8	79.9%	74.4%	79.5%	81.1%							79.8%	81.3%
	9	89.7%	82.4%	89.8%	90.5%							89.8%	89.6%
	10	100.0%	100.0%	100.0%	100.0%							100.0%	100.0%

Census Metropolitan Area	Decile groups	After-tax household income		% without diploma/certificate		% visible minority		% recent immigration		% not living in high-density housing		% essential worker	
		Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**	Pop*	Case**
Trois-Rivières	1	9.9%	10.7%	9.9%	11.3%	9.3%	13.1%	9.8%	11.5%	6.6%	5.4%	9.8%	8.4%
	2	19.8%	20.4%	19.8%	22.8%	19.7%	22.9%	19.4%	23.3%	48.9%	45.5%	19.7%	18.9%
	3	29.7%	29.0%	30.0%	31.9%	30.0%	33.3%	28.5%	32.4%	59.5%	56.2%	29.9%	30.6%
	4	40.0%	38.1%	39.6%	40.6%	39.6%	45.0%	30.1%	33.6%	70.0%	68.4%	40.0%	38.7%
	5	49.9%	46.4%	49.0%	48.7%	48.6%	54.0%	100.0%	100.0%	79.9%	78.9%	49.4%	50.0%
	6	59.8%	58.9%	59.2%	60.1%	59.9%	63.1%			89.9%	89.6%	59.3%	59.3%
	7	69.8%	67.4%	69.5%	71.4%	61.4%	64.7%			100.0%	100.0%	69.4%	67.7%
	8	79.7%	77.1%	79.7%	79.9%	100.0%	100.0%					79.8%	78.0%
	9	89.8%	87.4%	89.8%	88.9%							89.5%	87.0%
	10	100.0%	100.0%	100.0%	100.0%							100.0%	100.0%

* Pop = cumulative proportion of population

** Case = cumulative proportion of cases

Chapter 6. Mortality Tends and Lengths of Stay Among Hospitalized COVID-19 Patients in Canada

6.1. Preface to Manuscript 3

Expanding from community-level disparities to individual outcomes, my third manuscript examines some of the key parameters used in mathematical models of SARS-CoV-2 transmission to project the healthcare burden: the length of stay in the hospital, the proportion of people hospitalized admitted to the ICU, and in-hospital mortality (231). These parameters were known to potentially vary over epidemic waves, across jurisdictions, and by facility. However, they were still not well understood at that time.

Although the *Canadian Institute for Health Information* (CIHI) compiled hospitalization data from provinces into its *Hospital Morbidity Database*, the available data was limited and lacked the required granularity to inform detailed mathematical models (232). For instance, hospitalizations were only stratified by gender and broad age groups, and there was a lack of stratifications for the durations of hospital stays. Moreover, the trends in hospitalization and in-hospital mortality were aggregated at the national level on a monthly basis. To address these limitations, I utilized administrative health data from Canada's two largest provinces–Ontario and Québec. This approach provided representative and robust estimates of these metrics in Canada.

The resulting article was published in *International Journal of Infectious Diseases (IJID)* in August 2022.

6.2. Manuscript 3: Mortality trends and lengths of stay among hospitalized COVID-19 patients in Ontario and Québec (Canada): a population-based cohort study of the first three epidemic waves

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Abstract

Background: Epidemic of COVID-19 strained hospital resources. We describe temporal trends in mortality risk and lengths of stay in hospital and intensive cares units (ICUs) among COVID-19 patients hospitalized through the first three epidemic waves in Canada.

Methods: We used population-based provincial hospitalization data from the epicenters of Canada (Ontario and Québec). Adjusted estimates were obtained using marginal standardization of logistic regression models, accounting for patient-level and hospital-level determinants.

Results: Using all hospitalizations from Ontario (N=26,541) and Québec (N=23,857), we found that unadjusted in-hospital mortality risks peaked at 31% in the first wave and was lowest at the end of the third wave at 6-7%. This general trend remained after adjustment. The odds of in-hospital mortality in the highest patient load quintile were 1.2 (95%CI: 1.0-1.4; Ontario) and 1.6 (95%CI: 1.3-1.9; Québec) times that of the lowest quintile. Mean hospital and ICU lengths of stay decreased over time but ICU stays were consistently higher in Ontario than Québec.

Conclusion: In-hospital mortality risks and lengths of ICU stay declined over time, despite changing patient demographics. Continuous population-based monitoring of patient outcomes in an evolving epidemic is necessary for health system preparedness and response.

Introduction

The COVID-19 pandemic has put immense pressure on health care systems. Canada's most populous provinces, Ontario and Québec, bore the brunt of the pandemic (Godin et al., 2021). These two provinces accounted for 70% of the country's total number of COVID-19 hospitalizations during the first three epidemic waves (INSPQ, 2021; PHO, 2021). The prolonged surges in hospital admissions led to rapid increases in hospital patient load, especially in intensive care units (ICUs), with associated cancellations of non-urgent care (Derfel, 2021; Favaro et al., 2021a, 2021b; Olivier, 2021).

In-hospital mortality provides a proxy measure of the severity of a pandemic and the quality and effectiveness of hospital care (Finelli et al., 2021). Worldwide, in-hospital mortality was highest in the first months of the pandemic, but progressively declined afterward (Armstrong et al., 2020; Dennis et al., 2021). Reasons for this decline include changes in who became infected (e.g., age and comorbidities) (Cummings et al., 2020; de Rosa et al., 2021), incremental improvements in clinical practice and treatment regimens (Horwitz et al., 2021), and refinement of critical care capacity (Bravata et al., 2021; Harris et al., 2018). However, the evolution of in-hospital mortality across the three epidemic waves has yet to be systematically examined in Canada, and it remains unclear to what extent these different factors might explain changes in the risk of COVID-19 in-hospital mortality.

During the course of the pandemic, projections of future demands for hospital beds have helped decision-makers to manage and allocate limited healthcare resources (CDC, 2021; Maheu-Giroux et al., 2021; ScienceTable, 2021). Predicting those demands requires estimates of the number of incoming patients and their length of stays (Rees et al., 2020). Understanding the drivers of in hospital COVID-19 mortality is important to improve the accuracy of those projections. In addition, the disproportionate needs for care in ICUs warrants a thorough investigation of temporal changes in length of ICU stays (Deschepper et al., 2021; Shryane et al., 2020). The latter is a key metric that provides information on likely healthcare burden (Rees et al., 2020).

In North America, most studies of in-hospital COVID-19 mortality were informed by the experiences of a single city (Mitra et al., 2020; Verma et al., 2021) or hospital (Mah et al., 2021; Yang et al., 2020) and the generalizability of these findings remains unclear. To address these

knowledge gaps, we aim to 1) describe temporal trends in in-hospital COVID-19 mortality risk, 2) understand drivers of changes in mortality risk, and 3) estimate changes in length of hospital and ICU stays using data from the two largest provinces in Canada, where over 60% of the population reside.

Methods

Study design and setting

We conducted a retrospective population-based cohort study using provincial COVID-19 hospitalization databases from Ontario and Québec. Both provinces have a universal health care system, and these databases capture all hospitalizations. Healthcare is under provincial jurisdiction and the magnitude of epidemic waves and clinical protocols for COVID-19 patients differ across provinces.

Cohort eligibility criteria

Cohort entry occurs when individuals are admitted to an Ontario or Québec hospital with a COVID-19 diagnosis or the date of diagnosis if it occurs a week or more after admission (i.e., presumed nosocomial infections) (Elkrief et al., 2020). We included all hospitalizations with a lab-confirmed COVID-19 diagnosis admitted between 2020-03-01 and 2021-05-31 in Ontario and Québec. All observations were censored at discharge, death, or on August 15th, 2021, whichever occurred first. Among the very few individuals that experienced re-infection, only hospitalizations related to the first lab-confirmed episode were included in Québec as reinfections are milder than primary infections (Qureshi et al., 2022). In Ontario, it is not possible differentiate re-infection. Patients admitted or tested after discharge were excluded. Participants with missing date of discharge were excluded from the analyses of length of stays (Figure 6.2.1).

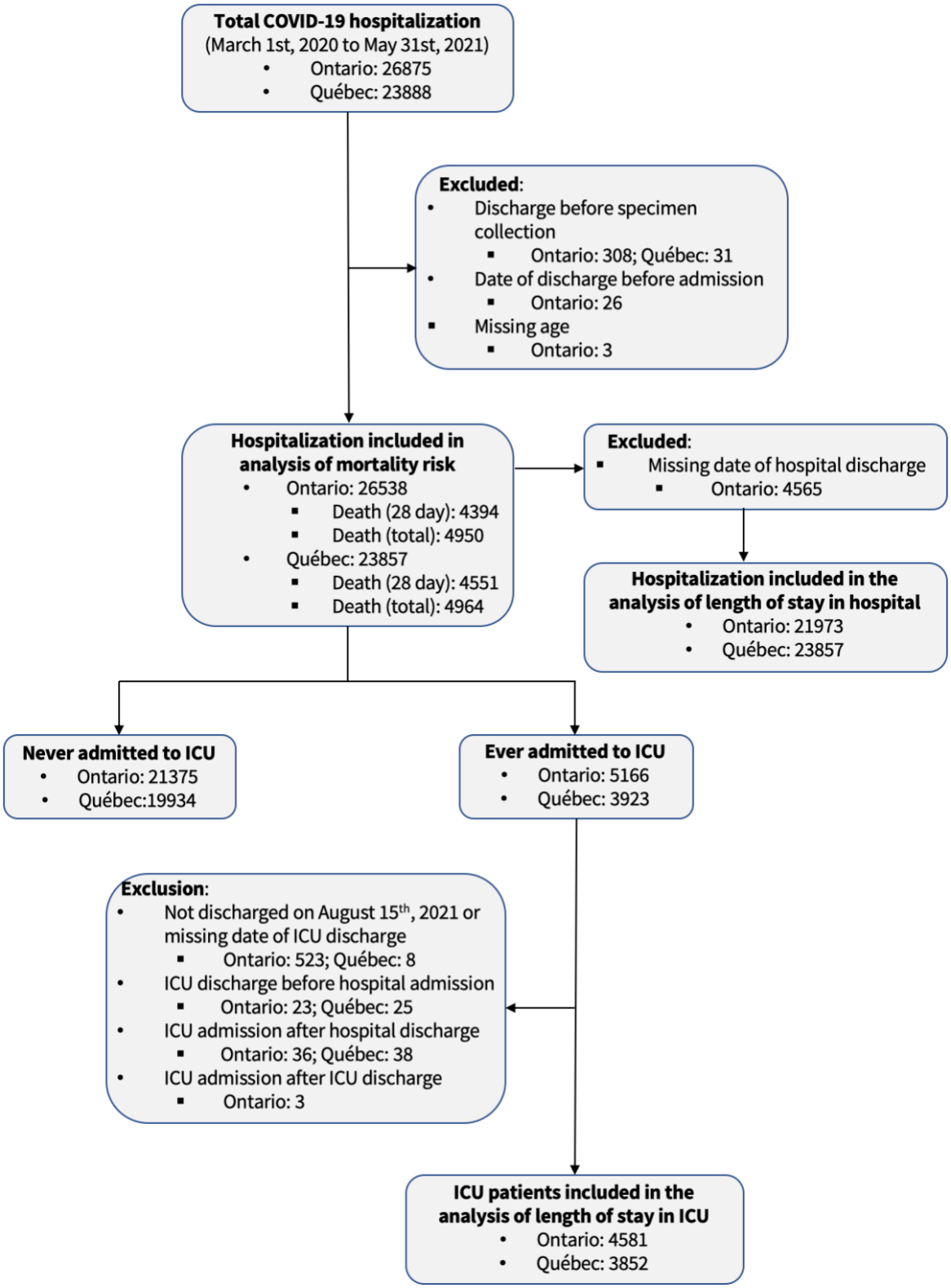

Figure 6.2.1. Flowchart of patients hospitalized with a lab-confirmed SARS-CoV-2 diagnosis included in the different analyses, by province (March 1st 2020 to May 31st 2021).

Data sources

Hospitalization data for Ontario was obtained from the *Ontario's Case and Contact Management* (CCM+), a provincial surveillance database for reporting *Diseases of Public Health Significance*. The approaches dealing with missing observations were summarized in *Text 6.4.1* and *Figure 6.4.1*. Information on daily hospital capacity came from *Bed census summary dataset*. In Québec, data were obtained from the *Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* database (MED-ÉCHO live). Daily hospital capacity data *for each hospital* were abstracted from the *Relevé quotidien du centre hospitalier*.

Outcome and variables

Three primary outcomes were studied. The first was all-cause in-hospital mortality, defined as a death occurring within 28 days of admission, in line with other studies (Churpek et al., 2021; Docherty et al., 2021; Group, 2021; UKHSA, 2022). Patients discharged or dying after 28 days were coded as *alive* at 28 days. The other outcomes were the length of hospital and ICU stay, defined as time from hospital and ICU admission to discharge or death (inclusive of the latter; with no censoring).

We categorized patients based on their admission date and corresponding epidemic wave: *Wave 1* (before 2020-08-01), *Wave 2* (2020-08-01 to 2021-03-20), and *Wave 3* (after 2021-03-20). Hospitalizations with a first positive specimen collected 7 days or more after admission, or whose living environment is the hospital, were classified as *hospital-acquired infection*. In such cases, the date of hospital admission for COVID-19 was replaced with the date of the first positive specimen to better reflect the time of infection. Patients who were admitted to ICU the same day as their hospital admission were defined as *direct ICU admission*. Patients screened positive for a variant of concern (VOC), through mutations N501Y and E484K in Ontario and N501Y, del69/70, and E484K in Québec, were regarded as *VOC positive* (mostly B.1.1.7, with some B.1.351 and P.1). Only those whose specimen collected 14 days after their second dose were treated as *vaccinated* (only available in Québec by linking the provincial vaccine registry and MED-ÉCHO databases). Overall hospital COVID-19 patient load relative to hospital bed capacity (henceforth, *hospital patient load*) was calculated daily using the number of COVID-19 patients currently hospitalized as the numerator and bed capacity (regular + ICU) as the denominator *for each of the*

88 hospitals in Québec and at the level of the 34 public health units in Ontario (due to data limitations). The distribution of all patient loads was categorized into quintiles from the lowest to highest independently for each province. The ICU patient load relative to ICU bed capacity (henceforth, ICU patient load) was calculated based on the same algorithm but using ICU bed capacity as the denominator. The gender of hospitalized patients (as proxy of biological sex) was not available in Québec.

Statistical analyses

Unadjusted weekly mortality risk, stratified by age, wave, and quintiles of patient load were calculated as the proportion of patients admitted with COVID-19 that deceased within 28 days for each time period and group. Uncertainty was quantified using 95% Clopper-Pearson confidence intervals (CI). Generalized linear models were used to fit smoothed curves of the weekly mortality risk (with regression cubic spline for the week of admission) and the mortality risk by age and wave. All analyses were performed for each province separately.

Adjusted estimates of mortality risk were obtained using logistic regression models with cubic splines for calendar time (three knots). In addition, the models adjusted for patient-level characteristics and hospital-level determinants. Patient-level variables included those associated with severe outcome: age (cubic spline with knots at 50, 70, and 80 years; chosen using the Akaike Information Criterion), gender (in Ontario), whether the patient was a resident of long-term care homes (LTCH), hospital-acquired infections status, direct ICU admission, VOC status, and vaccination status (in Québec) (Booth et al., 2021; Challen et al., 2021; Churpek et al., 2021; Lv et al., 2021). Hospital-level determinants comprise the COVID-19 hospital patient load (quintile ranking) at time of admission (Block et al., 2021) and facility-level fixed effects to control for time-invariant measured/unmeasured confounders. Because of lack of data disaggregation in Ontario, both patient load and region fixed-effects were included at the public health unit level. Marginal standardization was used to obtain adjusted mortality risks over time, standardizing over all hospitalized patients. The 95%CI for overall adjusted mortality risks were generated using 1,000 bootstrap replicates.

Finally, we examined change in hospital and ICU lengths of stays. Specifically, we calculated mean and standard deviation and used Kaplan-Meier stratified by age groups (0-49, 50-

59, 60-69, 70-79, 80 years and older), by waves, and by hospital and ICU patient load quintiles. The significance of differences between survival curves was assessed using log-rank tests.

Ethics approval

Ethics approvals were obtained from the *Health Sciences Research Ethics Board* of University of Toronto (no. 39253) in Ontario, and the *Institutional Review Board* of Faculty of Medicine and Health Sciences of McGill University in Québec (A06-M52-20B).

Results

There were 26,541 (Ontario) and 23,857 (Québec) COVID-19 hospitalizations during the study period. Among them, 4,950 (Ontario) and 4,964 (Québec) deceased. Most of the deaths occurred within 28 days of admissions: 4,394 (89%) in Ontario and 4,551 (92%) in Québec. Nearly a fifth of patients were admitted to ICU during their hospital stay: 5,166 (20%) in Ontario; 3,923 (16%) in Québec. Hospital patient load ranged from 0-47% in Ontario and 0-51% in Québec (Table 6.4.1). The ICU patient load varied between 0-83% in Ontario and between 0-123% in Québec.

Hospitalization profiles varied over time: patients admitted during the third wave were younger than those admitted during the first two waves (Table 6.2.1). Patients with presumed hospital-acquired infection, those admitted directly to ICU, those who were not fully vaccinated, and those infected with a VOC were more likely to die in hospital. A decrease in the proportion of hospitalizations transferred from LTCH occurred after the first wave. These patients experienced higher mortality risk throughout the whole study period in Ontario. In Québec, however, LTCH patients were less likely to die in hospitals during the third wave, reflecting partly changes in directives between waves related to these transfers.

Table 6.2.1. Characteristics of patients hospitalized with a laboratory-confirmed SARS-CoV-2 diagnosis and proportion deceased in Ontario and Québec (March 2020 to May 2021).

	Ontario (N = 26,541)			Québec (N = 23,857)		
	Wave 1 (N = 4,751)	**Wave 2** (N = 12,064)	**Wave 3** (N = 9,726)	**Wave 1** (N = 7,437)	**Wave 2** (N = 13,240)	**Wave 3** (N = 3,180)
Number of deaths						
	1,078	2,248	1,068	1,866	2,361	324
Overall mortality risk [95% confidence interval]						
	22.7% [21.5-23.9%]	18.6% [17.9-19.3%]	11.0% [10.4-11.6%]	25.1% [24.1-26.1%]	17.8% [17.2-18.5%]	10.2% [9.2-11.3%]
Age; mean (SD)						
At admission	67.8 (18.1)	68.3 (18.9)	59.9 (18.6)	71.5 (18.5)	69.9 (19.3)	60.8 (18.7)
At death	79.2 (12.5)	79.8 (11.8)	74.0 (13.2)	81.6 (10.7)	82.0 (10.5)	76.7 (11.2)
Gender; proportion (proportion deceased)						
Male	53.4% (23.0%)	54.2% (19.5%)	54.5% (11.8%)	Data not available		
Female	46.6% (22.3%)	45.5% (17.6%)	44.8% (9.9%)			
Other	0.1% (33.3%)	0.3% (20.5%)	0.8% (12.3%)			
Living in long-term care homes; proportion (proportion deceased)						
Yes	18.7% (41.6%)	8.5% (42.7%)	0.4% (30.8%)	11.3% (41.8%)	2.8% (33.2%)	1.3% (2.4%)
No	81.3% (18.3%)	91.5% (16.4%)	99.6% (10.9%)	88.7% (23.0%)	97.2% (17.4%)	98.7% (10.3%)
Presumed hospital-acquired infection; proportion (proportion deceased)						
Yes	10.8% (29.9%)	16.2% (24.4%)	6.4% (23.3%)	16.1% (31.2%)	13.4% (21.0%)	4.6% (20.7%)
No	89.2% (21.8%)	83.8% (17.5%)	93.6% (10.1%)	83.9% (23.9%)	86.6% (17.3%)	95.4% (9.7%)
Ever admitted to ICU; proportion (proportion deceased)						
Yes	21.5% (28.9%)	17.6% (30.3%)	20.7% (22.9%)	20.0% (24.6%)	19.6% (24.7%)	23.6% (18.2%)
No	78.5% (21.0%)	82.4% (16.1%)	79.3% (7.9%)	80.1% (25.2%)	80.4% (16.2%)	76.4% (7.7%)
Direct admission to ICU; proportion (proportion deceased)						
Yes	11.8% (31.6%)	8.2% (31.9%)	9.1% (22.7%)	3.1% (22.8%)	3.1% (24.2%)	4.4% (23.6%)
No	88.2% (21.5%)	91.8% (17.5%)	90.9% (9.8%)	96.9% (25.2%)	96.9% (17.6%)	95.6% (9.6%)
Fully vaccinated before positive test; proportion (proportion deceased)						
Yes	Data not available			Data not available		0.1% (0.0%)
No						99.9% (10.2%)
Infected with variants of concern; proportion (proportion deceased)						
Yes	Not applicable	4.7% (20.4%)	55.3% (14.2%)	Not applicable		39.8% (11.6%)
No		95.3% (18.5%)	44.7% (7.0%)			60.2% (9.3%)

ICU = intensive care unit.

[a]Only deaths occurred within 28 days of admission were included.

[b]Wave1: March 1st, 2020 to July 31st, 2020); Wave 2: August 1st, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021.

Time trends in crude mortality risk among hospitalized COVID-19 patients

The time trends in crude mortality risk were similar between provinces (Figure 6.2.2). In the first two months of the epidemic, the probability of in-hospital death peaked at 31% (95%CI: 27-35%) in Ontario and 31% (95%CI: 28-34%) in Québec; followed by a gradual decrease in mortality that lasted until the beginning of the second wave. Thereafter, the risk of in-hospital death gradually increased, but plateaued at lower levels than in the first wave at 23% (95% CI: 20-27%) in Ontario and 23% (95% CI: 19-27%) in Québec. In both provinces, the risk declined from the middle of the second wave. Overall, the unadjusted mortality risk followed the number of new hospitalizations, except for the third wave when mass vaccination was taking place.

There was a strong gradient in mortality risk with age in both provinces, and generally, the absolute mortality risk decreased over time for all age groups (Figure 6.2.2). However, there may have been less of a difference among the 60-84 group between the second and third wave in Québec. Hospital patient load was also associated with mortality risk in crude analyses in Québec: there was a monotonic increase in crude mortality risk with increasing quintiles of facility-level patient load (Figure 6.4.2). The trend in Ontario, where patient load was measured at the level of PHU, was stable through patient load quintiles.

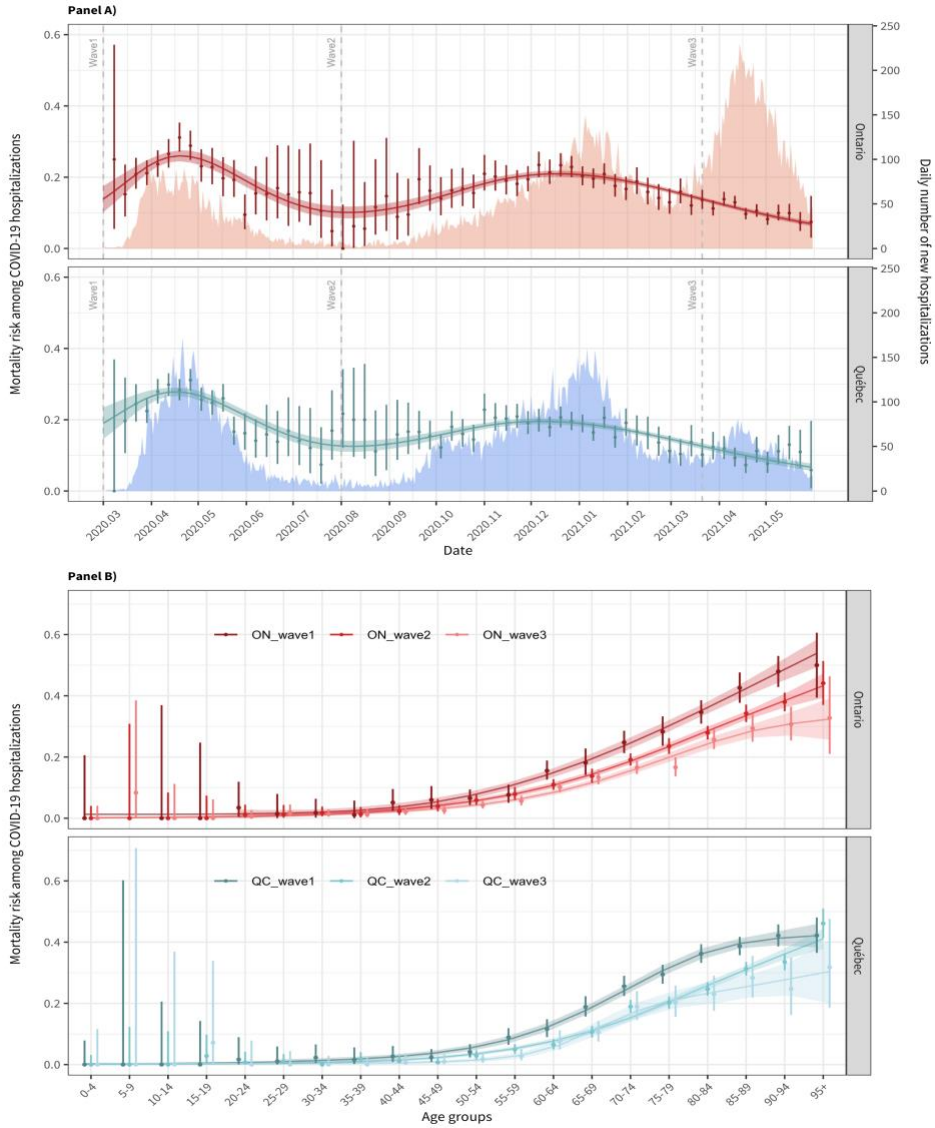

Figure 6.2.2. Panel A: Unadjusted weekly mortality risk among patients hospitalized with COVID-19 in Ontario and Québec. **Panel B: Unadjusted mortality risk among patients hospitalized with COVID-19 by 5-year age groups, stratified by epidemic waves, with 95% Clopper-Pearson confidence intervals in Ontario and Québec.**

Note: **Panel A**: Point estimates are presented with 95% Clopper-Pearson confidence intervals. Mortality for the first week of March 2020 is not presented as only 5 and 1 patients were admitted in Ontario and Québec, respectively. Fitted mortality risk over time using binomial logistic regression models with cubic splines for week of admission are shown (curves) with associated confidence intervals (shaded areas around the curve). Daily numbers of new patients hospitalized with a COVID-19 diagnosis were presented as the shaded background. **Panel B**: For each age group, mortality risks during Wave 1 (before August 1st, 2020), Wave 2 (August 1st, 2020 to March 20th, 2021), and Wave 3 (March 21st, 2021 to May 31st, 2021) are shown separately in that order from left to right. There was no hospitalization aged 5-9 years in Ontario during Wave 1.

Adjusted mortality risk over time

After adjusting for age, living environment, hospital-acquired infection status, direct ICU admission, VOC and vaccination status, and time-varying quintiles of hospital patient load, the estimated temporal trend in mortality risk was similar to the unadjusted ones in both provinces (Figure 6.2.3). Despite this, Québec exhibited a more pronounced decrease in the estimated mortality risk at the beginning of the epidemic: from 37.1% (95%CI: 27.7-45.8%) to 15.2% (95%CI: 13.2-17.4%). In Ontario, the estimated decline for the same period was from 24.7% (95%CI: 18.7-31.6%) to 13.5% (95%CI: 11.3-16.0%). Adjusted highest mortality risks during the second wave were comparable in Ontario (18.9%; 95% CI: 18.0-19.8%) and in Québec (18.2%; 95% CI: 17.3-19.0%) but the decline in the third wave was more pronounced in Ontario.

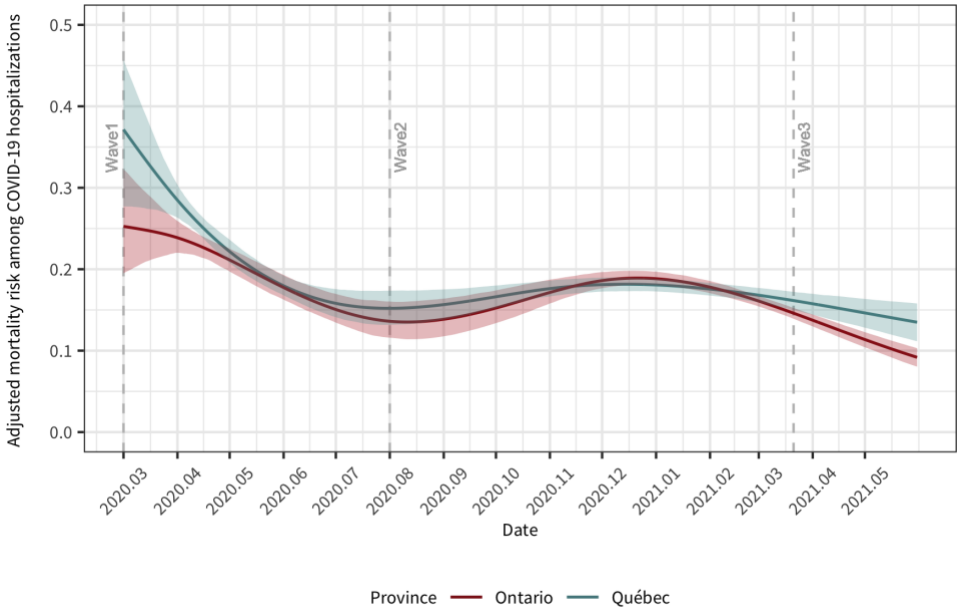

Figure 6.2.3. Adjusted mortality risk among patient hospitalized with COVID-19 and 95% bootstrapped confidence intervals in Ontario (in red) and Québec (in blue) since March 1st, 2020.

The models were adjusted for quintile of hospital patient load at time of admission, age (cubic spline with 3 knots at 50, 70, and 80 years), gender (in Ontario), whether the patient was from long-term care home, had an hospital-acquired infection, direct admission to the intensive care unit, infection with a variant of concern, full vaccination status (in Québec), and either facility-level fixed effects (in Québec) or public health unit-level fixed effects (in Ontario). The absolute adjusted mortality risks were obtained by marginalizing over each province patient's characteristics, which respective distributions differ slightly.

In adjusted analyses, mortality risk was higher at the second and highest patient load quintile in Ontario, while it increased with the patient load in Québec. The adjusted odds of in-hospital mortality in the highest patient load quintile were 1.2 (95%CI: 1.0-1.4) and 1.6 (95%CI: 1.3-1.9) times that of the lowest one in Ontario and Québec respectively (Table 6.4.2). In addition, the odds among patients that were male ($aOR_{Ontario}$: 1.4; 95%CI: 1.3-1.5), LTCH residents ($aOR_{Ontario}$=2.4, 95%CI: 2.1-2.7; $aOR_{Québec}$=1.7 , 95%CI: 1.5-2.0), with presumed hospital-acquired infections ($aOR_{Ontario}$=1.5, 95%CI: 1.4-1.7; $aOR_{Québec}$=1.0, 95%CI: 1.0-1.2), directly admitted to the ICU ($aOR_{Ontario}$=3.7, 95%CI; 3.3-4.1; $aOR_{Québec}$=2.5, 95%CI: 2.1-3.1), or were infected with a VOC ($aOR_{Ontario}$=2.0, 95%CI: 1.7-2.3; $aOR_{Québec}$=1.3, 95%CI: 1.0-1.7), were higher in both provinces. In Québec, none of the fully vaccinated COVID-19 hospitalized patients died.

Hospital and intensive care lengths of stay

Over the whole study period, the average length of ICU stays was longer in Ontario (17.2 days) as compared to Québec (12.9 days; p-value<0.01). This trend was observed for all age groups (all p-values<0.01; Table 6.4.3). Length of stays in ICU decreased steadily over time in Ontario from 19.4 days to 15.6 days (all pairwise p-values<0.01; Figure 6.2.4). In Québec, average length of ICU stays were 13.5 days during the first wave and then stabilized at 12.6 days s. Age was associated with length of stays in both province: hospitalized individuals aged 0 to 49 years and those aged 80 years and older spend less time in ICU than others age groups (all pairwise p-values<0.01). The age-specific pattern was generally consistent across epidemic waves. In addition, there was a trend of shorter length of stays in ICU among hospitalized patients younger than 70 years of age with each wave in Ontario (p-value<0.01; Figure 6.4.3). No conclusive pattern was observed for the length of stays by ICU patient load (Figure 6.4.4). Patients who died and those who never used ventilator spent less time in ICU (p-value<0.01, except for the third wave; Figure 6.4.5, Figure 6.4.6).

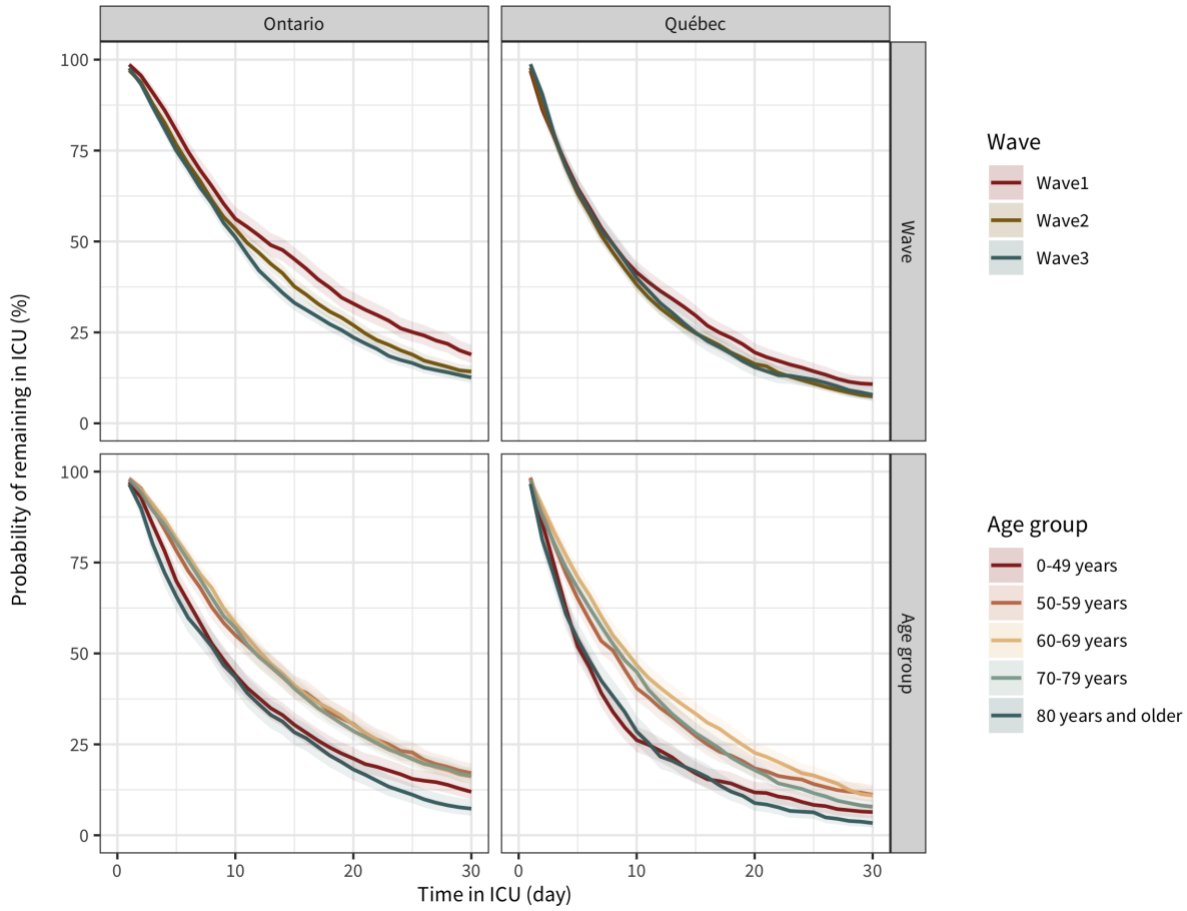

Figure 6.2.4. Kaplan-Meier curves for length of stays in intensive care units (ICU) among patients hospitalized with COVID-19, stratified by age group and by wave, in Ontario (top row) and Québec (bottom row).
Note: Waves are defined as followed: first wave1 (before June 30th, 2020), second wave (August 23rd, 2020 to March 20th, 2021), and third wave (March 21st, 2021 to May 31st, 2021).

Overall length of hospital stays decreased over time from 17-19 days to 12 days (all pairwise p-values<0.01; Table 6.4.4). The inter-province differences were smaller compared to length of ICU stays. Younger patients had shorter stays then those older than 60 years (p-value<0.01, Figure 6.4.7) and this pattern was consistent over time. In Québec, higher patient loads were associated with shorter length of hospital stays across time (p-value<0.01, except for third wave; Figure 6.4.8). The patterns by survival and ventilation status were similar as those for ICU.

Discussion

Using population-based provincial surveillance databases containing records of all hospitalized COVID-19 patients in the two largest Canadian provinces, this study found important variations in mortality risk. Part of the observed decline over the three epidemic waves could be explained by changes in patient characteristics. Specifically, we found that the demographic profile of those acquiring infection (e.g., age, LTCH residents), hospital-acquired infections, VOC, and higher patient loads were associated with higher mortality risk. During periods of highest patient load, the adjusted in-hospital mortality increased in both provinces. The length of ICU stay was consistently longer in Ontario compared to Québec. Patients aged 0-49 years and those 80 years and older were discharged from ICU more rapidly.

The observed substantial decrease in mortality risk during the first wave in both provinces is consistent with results from studies in the United Kingdom and the United States that adopted the same definition of in-hospital death (Anesi et al., 2021; Docherty et al., 2021; Jones et al., 2021). Furthermore, given the discrepant epidemiological curves between Ontario and Québec, the similarity in the adjusted temporal trends in mortality risk also provides evidence that factors beyond patient profiles could have played a role. Reasons behind the persistent reduction in mortality could include adoption of new therapeutics and treatments. For example, dexamethasone and anti-IL-6 receptor monoclonal antibodies, which have been shown to reduce mortality among severely ill patients in the RECOVERY trial (Group, 2021) became part of treatment guidelines in early summer of 2020. Other potential factors include the cumulative experiences of hospital teams and the availability of updated evidence-based COVID-19 protocols (Asch et al., 2021; Coppock et al., 2021; Jones et al., 2021). The availability of first doses of COVID-19 vaccines in the third wave may also contributed to the continuous decreasing mortality risk during that period (Scobie et al., 2021).

Overall, our analyses suggest that part of in-hospital mortality risk reductions could be sustained if hospital capacity is maintained, and hospital-acquired infections are prevented. These findings are aligned with those from studies conducted worldwide (Bravata et al., 2021; Elkrief et al., 2020; French et al., 2021; Gray et al., 2021; Ponsford et al., 2021). Limited critical care resources and rapidly increasing staff-to-patient ratio could have influenced patient outcomes

during periods of high transmission (Docherty et al., 2021; Sprivulis et al., 2006). Additionally, nosocomial infections could exacerbate mortality risk because this population has vulnerable health conditions and comorbidities (Ponsford et al., 2021; Richterman et al., 2020).

Concomitant with reductions in mortality risks, decreases in the length of ICU stays have been observed in multiple settings during the first wave (Roth et al., 2021; Shryane et al., 2020). Our results suggest a continuous decline in ICU stay throughout the study period. Despite the similar temporal patterns between provinces, we observed that the length of ICU stay in Ontario was consistently longer than it in Québec, and the proportion of patients admitted to ICU was higher in Ontario as well. Inter-provincial differences in clinical practices, such as criteria for ICU admission and discharge, could explain part of these differences. Other reasons include the changing demographic profiles of COVID-19 admissions. For example, patients aged 0 to 49 years and those 80 years and older spent less time in ICU than the others. Potentially because younger patients (≤50 years) improve more rapidly (Voinsky et al., 2020) and those in the oldest age group experience higher mortality in ICU (ICNARC, 2020; Oliveira et al., 2021). These findings are consistent with the observed shorter ICU stay among those who died and those who never used ventilator.

Tracking the evolution of patient outcomes can help improve hospital services, supply chain management, human resources planning, and prioritize future research (Bateson and McPeake, 2022). In addition, the average length of ICU stay is a critical metric required to project census ICU bed, which has been a limiting factors of healthcare systems in several settings (Lapidus et al., 2020). Timely availability of high-quality surveillance data should be prioritized. Despite differences in the proportion of patients admitted to ICU and their length of stay, the in-hospital mortality risks were relatively consistent between Ontario and Québec. Improving our understanding of ICU demand may contribute to optimizing patient outcomes and help planning for sufficient hospital capacity to adapt to potential increases in patient flow (Bravata et al., 2021; Rossman et al., 2021).

Our study should be interpreted considering certain limitations. First, we were unable to control for sex (Zha et al., 2021), ethnicity (Price-Haywood et al., 2020; Xia et al., 2022), or comorbidities(Garibaldi et al., 2021) –factors that could be associated with COVID-19 mortality.

Even though we were able to control for some of the main predictors of COVID-19 mortality (e.g., age, hospital-acquired infections, LTCH residents), we cannot rule out residual confounding. In addition, we considered all patients with a laboratory-confirmed SARS-CoV-2 diagnosis although it might not be the principal reason for the hospitalization. Second, the administrative and surveillance databases used do not provide detailed information on treatments received by patients. This limitation hampered our ability to examine how evolving standards of care and specific treatments impacted mortality outcomes. Third, we defined our mortality outcome as patients that died within 28 days after admission which may slightly underestimate mortality risk. However, this definition captures close to 90% of the total in-hospital deaths and our results are robust to expanding the death definition to within 56 days of admission. Additionally, it has the merit of measuring the immediate impact of COVID-19 on deaths more accurately (Heneghan and Oke, 2020). Fourth, the CCM+ data from Ontario did not allow the addition of facility-level variables and vaccine status. We addressed this by using public health unit-level variables to (partially) control for inter-hospital variations. Further, the lack of vaccine status should not affect the results based on the small number of fully vaccinated patients (<0.01%) and the similar timeline of vaccination program implemented during the study period. Finally, missing dates of discharge in Ontario were assumed to be missing completely at random. The potential for bias is low, however, as these errors in data entry and transmission are likely independent of hospitalization -as shown in our examination of the characteristics of hospitalizations with observed and missing dates of discharge.

Strengths of this study includes its representativeness: all hospitalizations in these two provinces are included. This study also adds considerably to the timeline —spanning over three epidemic waves— of COVID-19 inpatient mortality risks and lengths of ICU stay. We controlled for some of the key confounders and results were relatively consistent across provinces operating under different health jurisdiction.

In conclusion, this study demonstrates temporal variability in mortality risk among hospitalized patients that could not be explained by changes in COVID-19 patients' demographic profiles across epidemic waves. Findings highlight the importance of strategies to buffer against surges in hospital capacity and limiting nosocomial outbreaks to reduce in-hospital mortality risk. As the epidemic continues, there remains a potential for future surges from emergence of new

variants, especially if associated with increased virulence, and the potential for waning protection against severity from vaccines; but also, the potential for reduction in hospitalization with the scale-up of outpatient therapeutics. Hence, continued monitoring of the evolution of patient outcomes and re-evaluation of the length of ICU stay will be essential to adapt, and inform hospital capacity planning to improve patient outcomes.

Authors' contribution

YX, SM, DB, and MMG conceived and designed the study. YX conducted the statistical analysis, conducted the literature search drafted the manuscript. HM supported data curation and cleaning for Ontario. HM, DB, MB, BS, AC, AV, IG, NK, SM, and MMG interpreted results, drafted and edited the manuscript, and critically reviewed it for intellectual content. All authors approved the final version of the manuscript.

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Declaration of interest

MM-G reports an investigator-sponsored research grant from Gilead Sciences Inc. MM-G reports an investigator-sponsored research grant from Gilead Sciences Inc., and contractual arrangements from the *Institut national de santé publique du Québec* (INSPQ), the *Institut d'excellence en santé et services sociaux* (INESSS), the *World Health Organization*, and the *Joint United Nations Programme on HIV/AIDS* (UNAIDS), all outside of the submitted work. NK reports research funding from Gilead Sciences, advisory fees from Gilead Sciences, ViiV

Healthcare, Merck and Abbvie, and speaker fees from Gilead Sciences and Merck, all outside of the submitted work.

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6.4. Manuscript 3: Supplementary Materials

6.4.1. Supplementary Text: Missing dates related to hospitalization.

Date imputation was conducted before any inclusion and exclusion process. Therefore, the proportion missing mentioned in this document is based on the raw dataset (the whole IPHIS dataset transferred on August 15th, 2021). According to the nature of administrative dataset, a larger proportion of missing value occurs within more recently entered cases. Individuals marked as "hospitalized" and had at least one date related to hospitalization were regarded as "hospitalizations".

Figure 6.4.1 shows the flow char of the data processing procedure. Of the 28247 records, 62 missing dates of specimen collection were replaced with episode date. Missing dates of hospital admission (523 / 28247, 1.9%) were with date of specimen collection. For missing dates of hospital discharge (6350 / 28247, 22.5%), they were imputed using date of death (if the patient decreased, 885 / 6350, 13.9%), the latest date among date of ICU discharge, and date of the end of ventilation (if case was resolved, 434 / 6350, 6.9%), or the date of data cut-off of the dataset (if case was not resolved, 103 / 6350, 1.6%). After imputation, 17.4% (4929 / 28247) of discharge date were still missing. Missing dates of ICU admission (38 / 5524, <0.1%) were substituted using date of hospital admission if the patient had an indication of ever in ICU. Missing dates of ICU discharge (1025 / 5524, 18.6%) were filled following the same logic as date of hospital discharge (284 / 1025 (27.7%) using date of death, 137 / 1025 (13.4%) using maximum date, and 27 / 1025 (2.6%) using data cut-off date). After processing, there were 10.4% (577 / 5524) missing date of ICU discharge remaining. All missing dates of deaths (21 / 5407, <0.1%) were imputed with the latest date among date of hospital discharge, date of ICU discharge, and date of the end of vitalization.

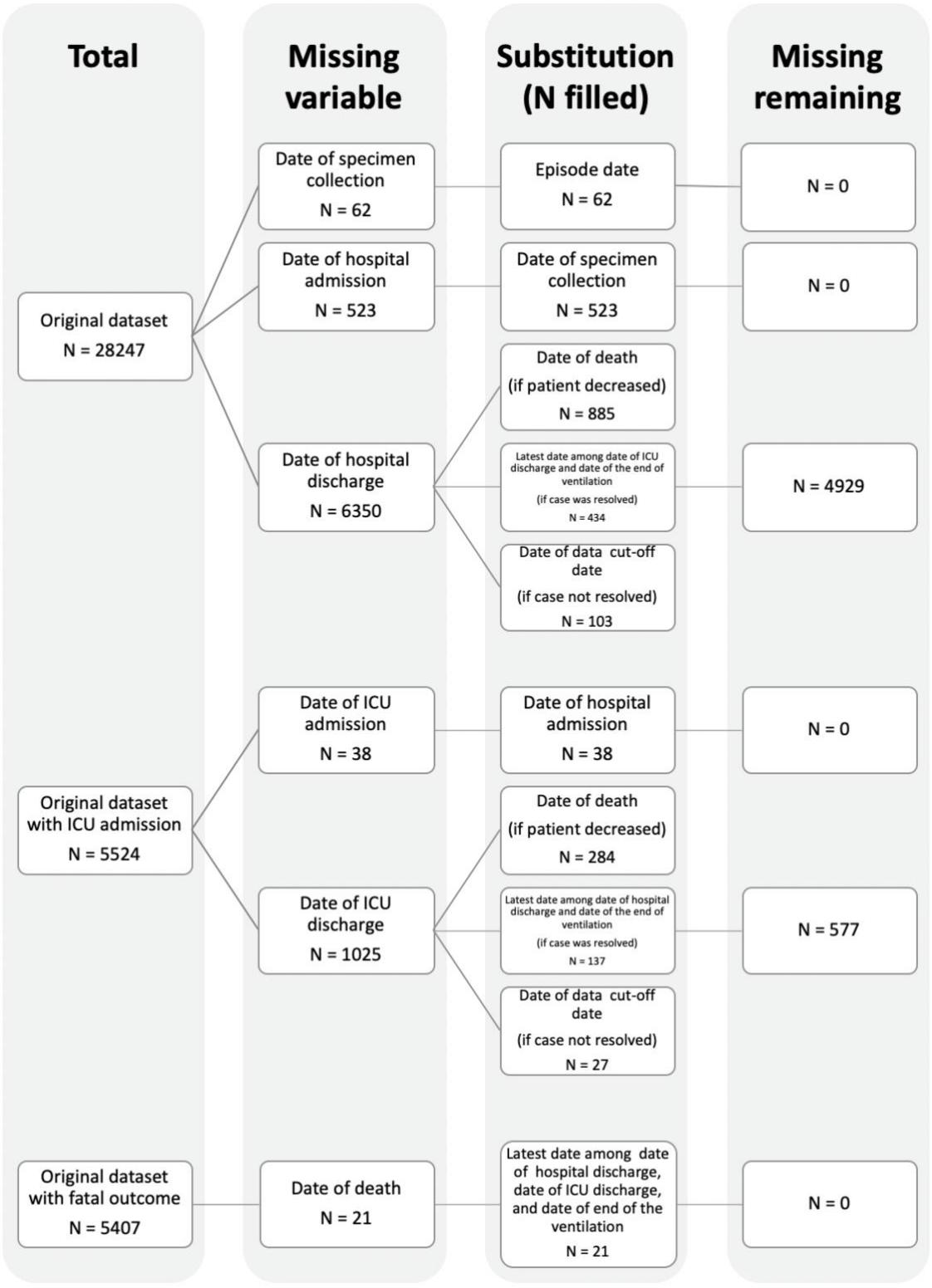

Figure 6.4.1. Flow chart on data processing procedure before analysis in Ontario.

Missing Public Health Units

There were 1.5% (434 / 28247) records missing Public Health Units (PHU) of residence, they were assigned the PHU where the patients were diagnosed.

Missing continuous age

Starting in July 2021, IPHIS reports only reports the 10-year age group to which the individuals belonged to and classifies all cases older than 80 years old into one group. According to a study published using Ontario data (1), survival rate decreased with age (presented in 2-year age group). Therefore, we looked into the latest IPHIS report available with a 2-year age group (this is the most precise age variable in IPHIS reports) to match with the August 15 dataset. The IPHIS report extracted on June 28th, 2021, was used.

Based on the fact that no specific identification variable can be utilized to link the two datasets, we matched on the 10-year age group, the episode date, the date of specimen collection, the PHU of diagnosis, gender, the dissemination area of residence, the date of admission, the date of death, the date of discharge, the date of create of record, the date of report, and the date of information collection. After matching, 270 (<0.1%) of the records in the August 15 dataset failed to find a match. All of the records were in the "80 plus" group. Therefore, those records were imputed with the mean age of people older than 80 years.

Notably, in our study, age is modeled as a continuous variable. Unfortunately, IPHIS reports do not contain the exact age of the patient. As mentioned above, 2-year age group is the finest age information available. As such, we assigned the continuous age of each patient using the mean of the 2-year age group. For example, a patient in the 30-31 age group was given an age of 30.5. Additionally, those who were older than 100 years old were categorized into one group as "100 Plus". To make the model feasible, we imputed the age with 100.5.

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1. Papst I, Li M, Champredon D, Bolker BM, Dushoff J, DJ DE. Age-dependence of healthcare interventions for COVID-19 in Ontario, Canada. BMC Public Health. 2021;21(1):706.

6.4.2. Supplementary figures

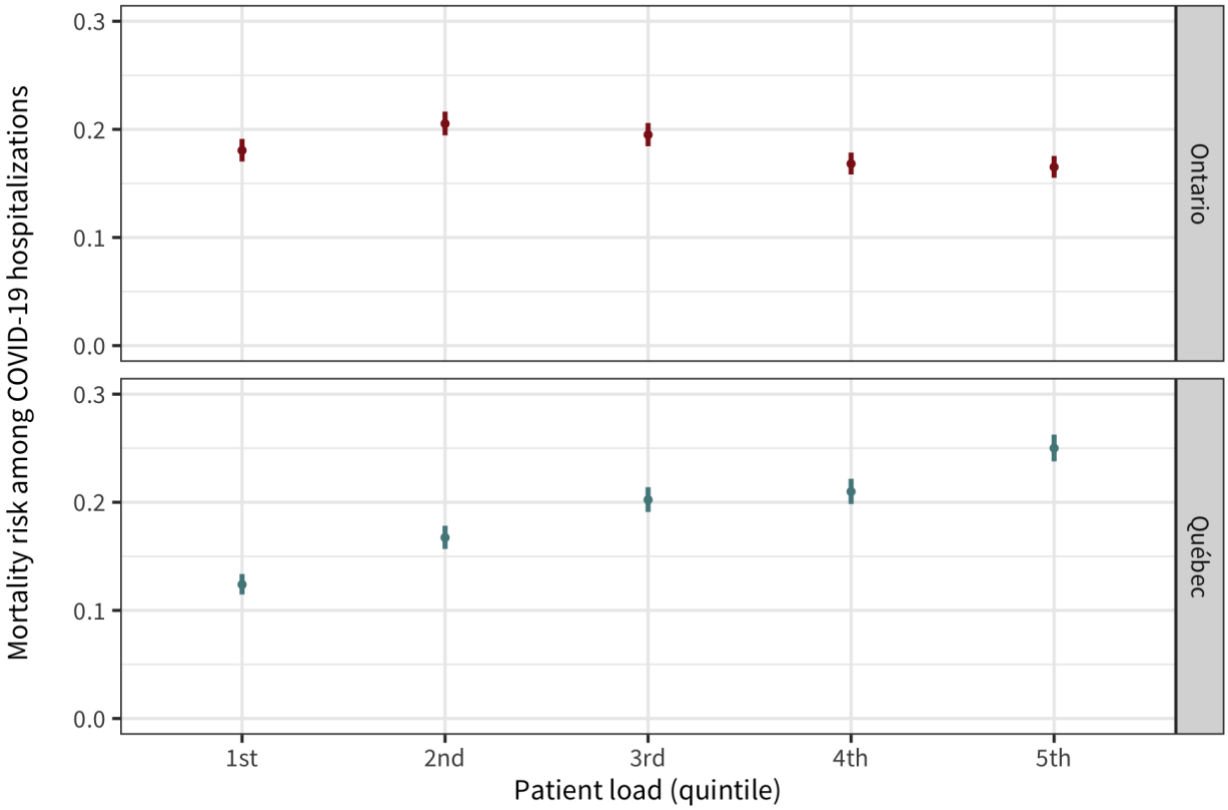

Figure 6.4.2. Unadjusted mortality risk among patients hospitalized with COVID-19 by quintiles of hospital patient load with 95% Clopper-Pearson confidence intervals in Ontario (top panel) and Québec (bottom panel) from March 1st, 2020 to May 31st, 2021.
Note: Patient load is ranked separately from the lowest to the highest quintile by public-health unit in Ontario and by facility in Québec.

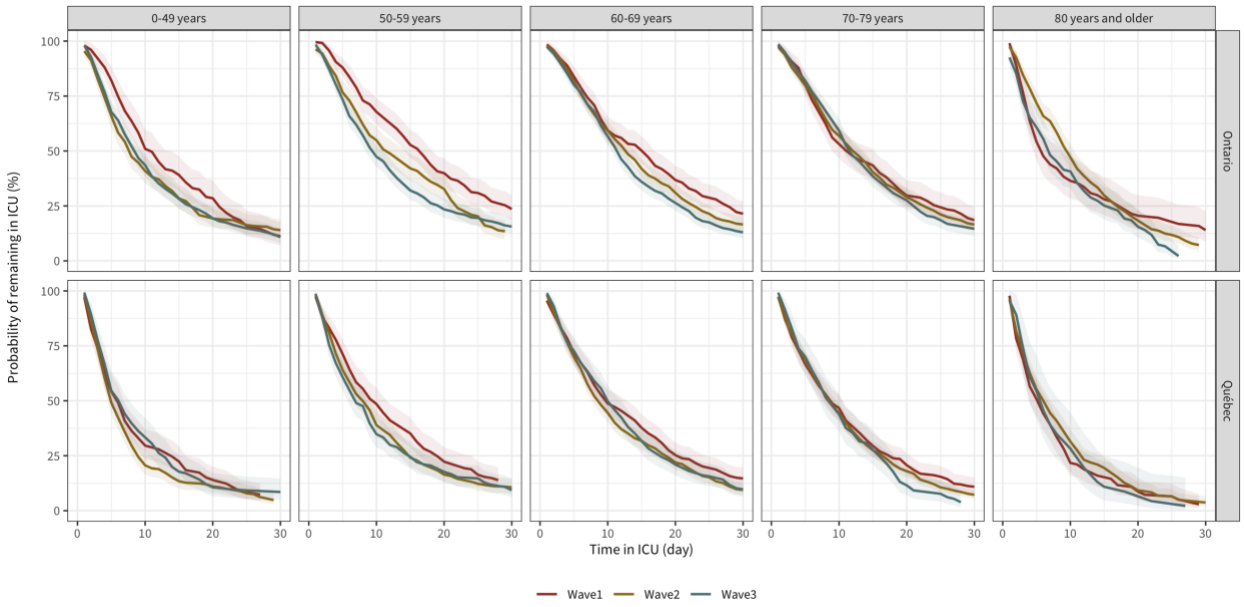

Figure 6.4.3. Kaplan-Meier curves for length of stays in intensive care units (ICU) among COVID-19 ICU inpatients in different age groups, stratified by wave, in Ontario (top panels) and Québec (bottom panels).

Note: Wave1: before June 30th, 2020; Wave 2: Aug 23rd, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021. Summer lull (July 1st, 2020 to Aug 22nd, 2020) is excluded due to small number of hospitalizations.

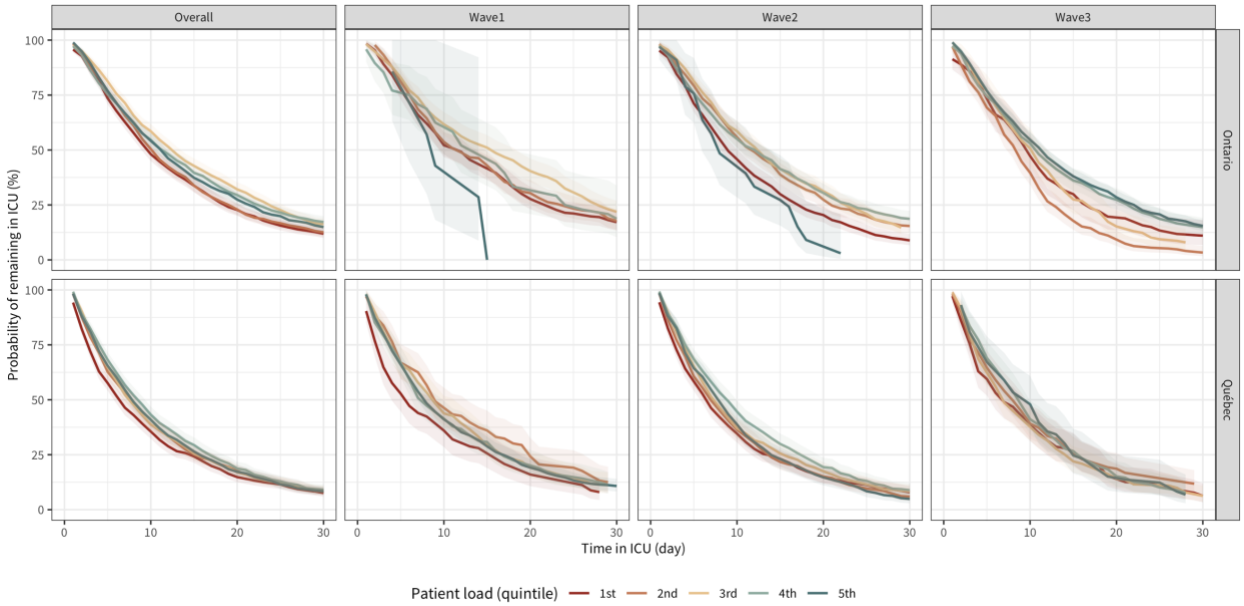

Figure 6.4.4. Kaplan-Meier curves for length of stays in intensive care units (ICU) among COVID-19 ICU inpatients admitted to hospitals in different ranks of ICU patient load, overall and stratified by wave, in Ontario and Québec.
Note: Wave1: before June 30th, 2020; Wave 2: Aug 23rd, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021. Summer lull (July 1st, 2020 to Aug 22nd, 2020) is excluded due to small number of hospitalizations.

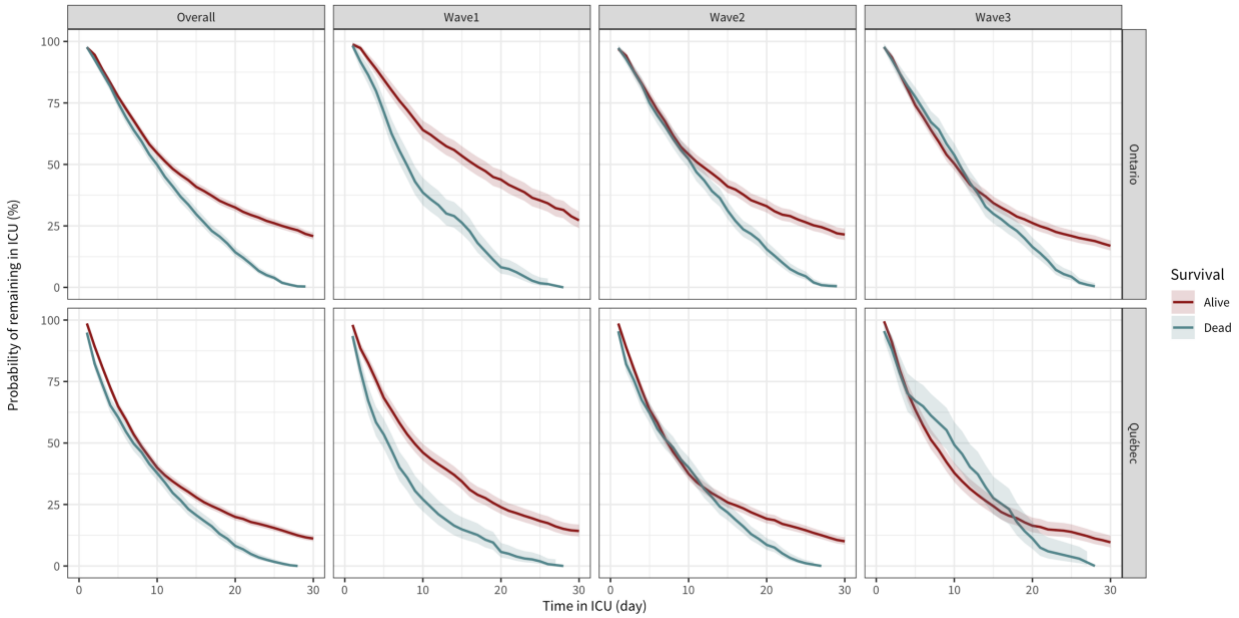

Figure 6.4.5. Kaplan-Meier curves for length of stays in intensive care units (ICU) among COVID-19 ICU inpatients admitted to hospitals stratified by outcome and wave, in Ontario and Québec.

Note: Wave1: before June 30th, 2020; Wave 2: Aug 23rd, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021. Summer lull (July 1st, 2020 to Aug 22nd, 2020) is excluded due to small number of hospitalizations.

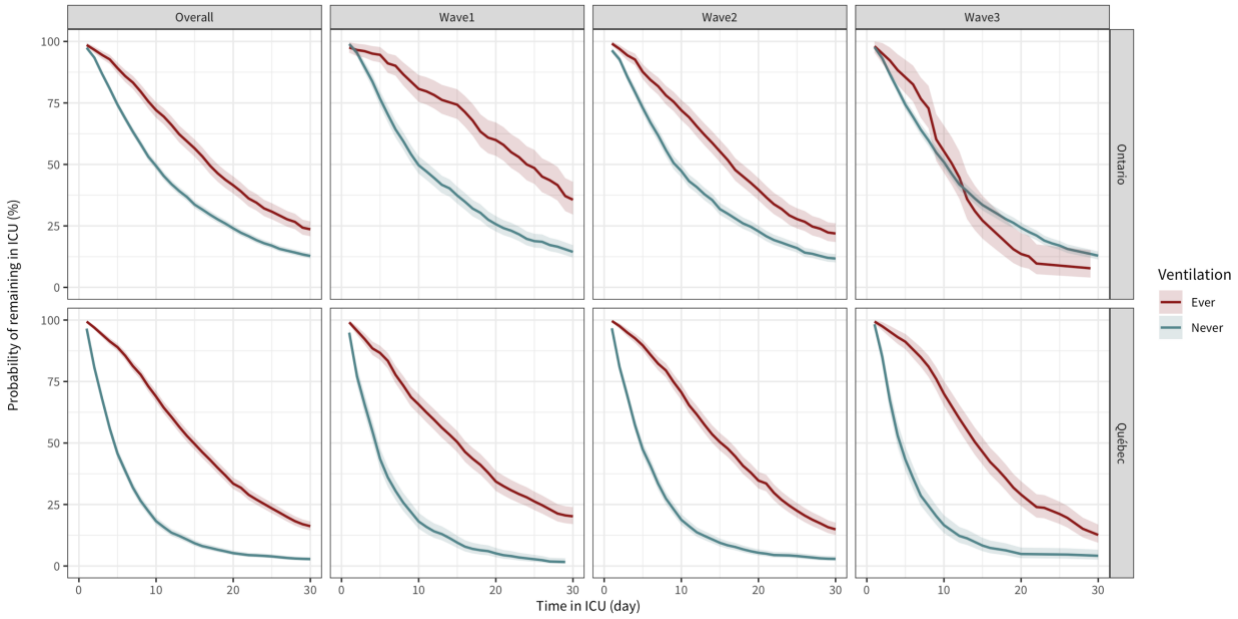

Figure 6.4.6. Kaplan-Meier curves for length of stays in intensive care units (ICU) among COVID-19 ICU inpatients admitted to hospitals stratified by ventilation status and wave, in Ontario and Québec.

Note: Wave1: before June 30th, 2020; Wave 2: Aug 23rd, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021. Summer lull (July 1st, 2020 to Aug 22nd, 2020) is excluded due to small number of hospitalizations.

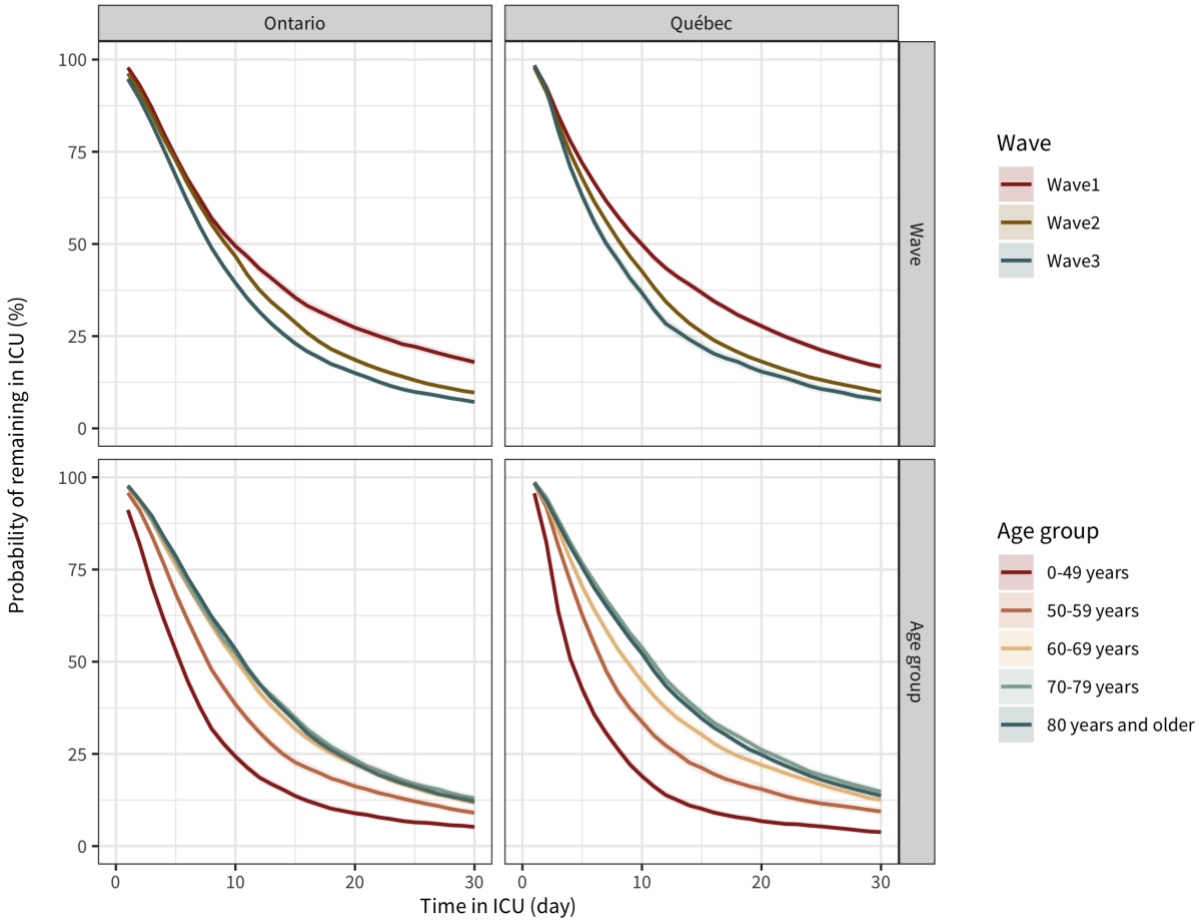

Figure 6.4.7. Kaplan-Meier curves for overall lengths of stay in hospital among patients hospitalized with COVID-19, stratified by age group and by wave, in Ontario (top row) and Québec (bottom row).

Note: Waves are defined as followed: first wave1 (before June 30th, 2020), second wave (August 23rd, 2020 to March 20th, 2021), and third wave (March 21st, 2021 to May 31st, 2021).

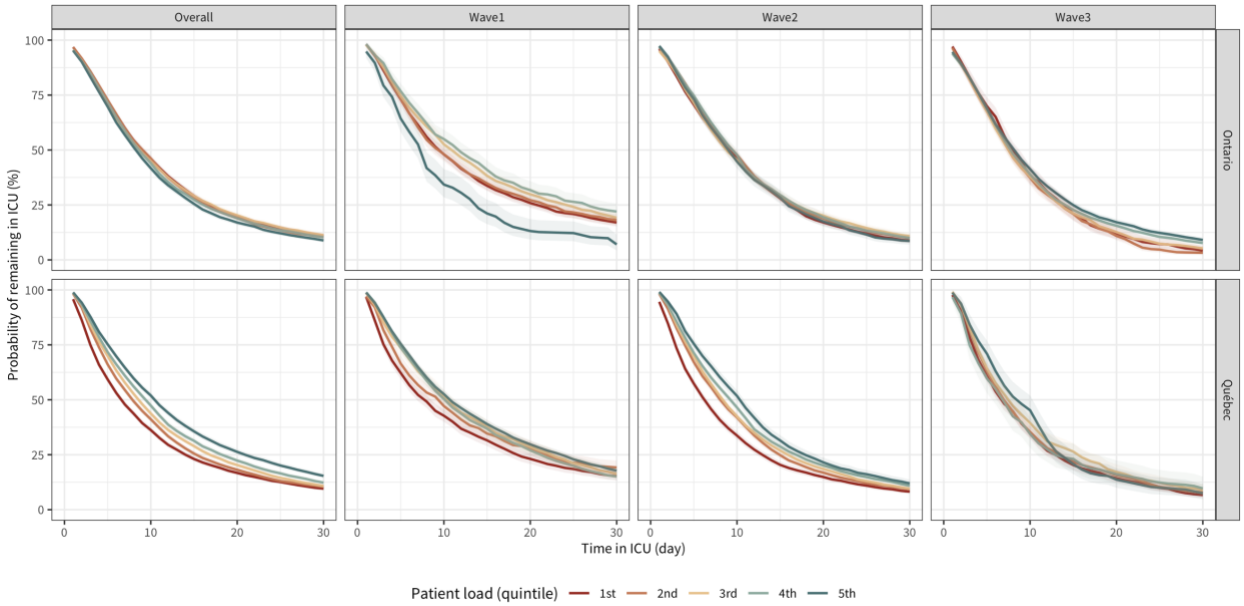

Figure 6.4.8. Kaplan-Meier curves for overall length of stays in hospital among patients hospitalized with COVID-19 in different ranks of hospital patient load, overall and stratified by wave, in Ontario and Québec.

Note: Wave1: before June 30th, 2020; Wave 2: Aug 23rd, 2020 to March 20th, 2021; Wave 3: March 21st, 2021 to May 31st, 2021. Summer lull (July 1st, 2020 to Aug 22nd, 2020) is excluded due to small number of hospitalizations.

6.4.3. Supplementary tables

Table 6.4.1. Ranges of each quintile of COVID-19 patient load and ICU patient load relative to overall bed availability at the level of public health units in Ontario and hospital-level in Québec.

Rank	Ontario		Québec	
	Public Health Units - Hospital	Public Health Units – ICU[1]	Hospital-level	ICU[1]-level
1st quintile	0.0 - 3.5%	0.0 - 2.7%	0.0 - 4.2%	0.0 - 10.9%
2nd quintile	3.5 - 6.0%	2.7 - 6.1%	4.2 - 7.7%	11.1 - 17.9%
3rd quintile	6.0 - 8.6%	6.1 - 8.8%	7.7 - 11.3%	18.2 - 25.8%
4th quintile	8.6 - 12.3%	8.8 - 13.2%	11.3 - 17.3%	25.8 – 37.0%
5th quintile	12.3 - 47.4%	13.2 - 83.3%	17.3 - 50.7%	37.5 - 123.1%

[1] ICU= intensive care unit.

Table 6.4.2. Odds ratios and 95% confidence intervals (CI) for covariates included the logistic regression models[1] of in-hospital mortality in Ontario and Québec.

Covariate	Ontario		Québec	
	Odds ratio	95% CI	Odds ratio	95% CI
Gender[2]				
Female	Ref			
Male	1.4	1.3-1.5	Not applicable	
Other	1.7	0.9-3.0		
Living in long-term care facilities				
	2.4	2.1-2.7	1.7	1.5-2.0
Presumed hospital-acquired infection				
	1.5	1.4-1.7	1.0	1.0-1.2
Direct admission to ICU				
	3.7	3.3-4.1	2.5	2.1-3.1
Infected with variants of concern				
	2.0	1.7-2.3	1.3	1.0-1.7
Patient load				
1st quintile	Ref		Ref	
2nd quintile	1.1	1.0-1.3	1.4	1.2-1.6
3rd quintile	1.0	0.9-1.2	1.5	1.3-1.7
4th quintile	1.0	0.9-1.2	1.5	1.3-1.7
5th quintile	1.2	1.0-1.4	1.6	1.3-1.9
Fully vaccinated before infection[3]				
	Not applicable		0.0	0.0-Inf

[1] The models were adjusted for quintile of patient load at time of admission, age (cubic spline with 3 knots at 50, 70, and 80 years), gender (only for Ontario), whether the patient was from long-term care facility, had an hospital-acquired infection, direct admission to the intensive care unit, infection with a variant of concern, full vaccination status (only for Québec), and either facility-level fixed effects (in Québec) or PHU-level fixed effects (in Ontario).

[2] Due to data limitation, gender is used as an proxy of the biological sex.

[3] Only 0.1% of the hospitalizations were fully vaccinated before infection

Table 6.4.3. Mean and standard deviation (SD) of length of stay in intensive care units (ICU) by wave, age group, and ICU patient load (quintile ranking) in Ontario and Québec.

	Overall (March 1st, 2020 - May 31st, 2021)	**Wave1** (March 1st, 2020 - July 31st, 2020)	**Wave2** (August 1st, 2020 - March 20th, 2021)	**Wave3** (March 21st, 2021 - May 31st, 2021)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Ontario				
Overall	17.2 (18.5)	19.4 (19.0)	17.6 (20.1)	15.6 (15.5)
Occup[a] 1st	15.6 (18.5)	18.1 (20.6)	14.7 (18.4)	13.6 (12.3)
Occup 2nd	16.0 (17.2)	17.9 (16.3)	18.5 (20.9)	10.5 (9.0)
Occup 3rd	19.1 (19.6)	22.5 (22.3)	18.5 (19.0)	13.2 (11.2)
Occup 4th	18.1 (20.0)	17.4 (13.9)	19.2 (22.1)	16.7 (17.0)
Occup 5th	17.1 (16.8)	10.1 (4.5)	10.7 (7.2)	17.4 (17.1)
Age group				
0-49 years	15.1 (18.1)	18.2 (23.2)	15.3 (19.6)	13.8 (14.1)
Occup[a] 1st	14.1 (25.2)	16.0 (29.4)	14.1 (25.6)	9.7 (10.2)
Occup 2nd	12.4 (13.9)	14.9 (13.9)	15.4 (18.5)	8.8 (8.1)
Occup 3rd	19.7 (19.5)	24.3 (21.9)	16.9 (18.4)	18.6 (16.9)
Occup 4th	14.6 (16.2)	5.5 (4.9)	14.5 (17.1)	15.0 (15.5)
Occup 5th	15.1 (14.8)	6.0 (Only 1 observation)	12.7 (12.8)	15.3 (14.9)
50-59 years	18.3 (19.4)	22.3 (20.1)	18.9 (22.9)	15.6 (15.7)
Occup[a] 1st	17.7 (21.6)	20.7 (16.1)	15.9 (28.4)	14.2 (11.8)
Occup 2nd	15.8 (15.4)	17.7 (14.8)	19.5 (20.4)	10.4 (7.9)
Occup 3rd	21.8 (21.8)	28.2 (26.2)	19.4 (18.5)	11.9 (8.4)
Occup 4th	19.7 (20.6)	18.7 (14.8)	21.4 (23)	18.2 (18.8)
Occup 5th	16.9 (16.9)	14.5 (0.7)	13.0 (3.8)	17.0 (17.2)
60-69 years	18.4 (18.0)	20.9 (19.0)	18.6 (18.5)	16.9 (16.7)
Occup[a] 1st	16.9 (15.2)	21.6 (17.7)	15.4 (14.4)	14.3 (11.8)
Occup 2nd	17.4 (18.3)	21.2 (19.2)	18.8 (20.3)	11.3 (11.3)
Occup 3rd	19.7 (19.1)	21.5 (21.1)	20.1 (19.4)	13.9 (10.1)
Occup 4th	19.5 (19.2)	16.1 (11.7)	20.8 (19.9)	18.1 (19.3)
Occup 5th	18.4 (17.7)	9.3 (5.5)	9.9 (6.7)	18.8 (17.9)
70-79 years	18.3 (19.3)	18.1 (18.2)	18.8 (21.4)	17.6 (16.6)
Occup[a] 1st	15.7 (16.4)	16.6 (21.5)	15.2 (13.9)	16.5 (15.1)
Occup 2nd	18.2 (16.8)	19.6 (16.9)	20.4 (19.5)	12.9 (8.4)
Occup 3rd	17.9 (17.8)	17.8 (16.1)	19.6 (19.9)	9.4 (5.7)
Occup 4th	20.2 (24.8)	21.8 (19.1)	21.1 (28.6)	18.1 (16.3)
Occup 5th	19.5 (18.8)	8.0 (Only 1 observation)	10.8 (5.6)	20.0 (19.1)
80 years and older	13.4 (16.2)	14.1 (18.1)	14.6 (17.9)	10.2 (8.3)
Occup[a] 1st	11.7 (13.9)	12.0 (14.9)	11.6 (13.6)	10.2 (11.6)
Occup 2nd	14.7 (20.9)	11.3 (12.3)	17.6 (25.2)	8.8 (7.0)
Occup 3rd	15.3 (19.6)	18.7 (25.4)	15.0 (17.7)	7.3 (5.3)
Occup 4th	13.3 (11.3)	17 .0 (13.3)	14.5 (12.4)	9.7 (7.2)
Occup 5th	11.1 (9.2)	No observation	4.3 (1.5)	11.4 (9.2)
Survival status				
Dead defined as deaths within 28 days of admission				
Alive	19.6 (21.2)	23.5 (22.3)	20.5 (23.7)	16.8 (17.4)
Dead	11.7 (7.5)	10.3 (6.7)	12.0 (7.7)	12.1 (7.5)
Dead defined as deaths within 56 days of admission				
Alive	18.4 (21.6)	22.6 (22.9)	19.2 (24.4)	15.6 (17.4)
Dead	15.1 (11.0)	14.0 (11.2)	15.2 (10.9)	15.6 (10.9)
Ventilation status				
Ever	24.1 (22.9)	29.4 (21.4)	24 (24.6)	14.3 (12.2)
Never	15.8 (17.1)	16.8 (18.5)	15.5 (17.9)	15.7 (15.7)

	Overall (March 1st, 2020 - May 31st, 2021)	**Wave1** (March 1st, 2020 - July 31st, 2020)	**Wave2** (August 1st, 2020 - March 20th, 2021)	**Wave3** (March 21st, 2021 - May 31st, 2021)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Québec				
Overall	12.9 (15.2)	13.5 (15.2)	12.6 (15.5)	12.6 (14.1)
Occup[a] 1st	11.9 (15.9)	12.5 (19.2)	11.8 (15.4)	11.9 (14.1)
Occup 2nd	13.2 (16.4)	15.6 (16.3)	11.9 (15.3)	14.8 (19.1)
Occup 3rd	12.9 (15.4)	14.0 (15.5)	13.3 (17.1)	11.3 (10.6)
Occup 4th	13.8 (15.4)	14.0 (17.3)	14.0 (15.7)	12.7 (12.4)
Occup 5th	12.5 (12.7)	12.8 (12.6)	11.9 (13.1)	12.6 (12.0)
Age group				
0-49 years	10.3 (13.9)	10.9 (15.3)	9.4 (12.1)	11.6 (15.2)
Occup[a] 1st	8.5 (17.2)	11.7 (29.0)	6.8 (12.2)	9.7 (13.8)
Occup 2nd	11.0 (15.7)	9.1 (6.7)	9.5 (13.5)	15.5 (23.0)
Occup 3rd	9.4 (9.2)	9.2 (8.6)	9.3 (9.6)	9.9 (9.4)
Occup 4th	9.8 (11.0)	7.9 (7.6)	11.4 (13)	8.4 (8.9)
Occup 5th	14.0 (13.5)	13.8 (13.3)	12.1 (10.6)	19.6 (19.4)
50-59 years	14.3 (18.8)	15.3 (16.7)	14.9 (22.4)	12.5 (14.2)
Occup[a] 1st	14.9 (21.2)	17.7 (20.1)	15.3 (24.7)	13.0 (15.9)
Occup 2nd	12.8 (20.4)	13.6 (11.2)	11.7 (24.4)	14.3 (17.9)
Occup 3rd	14.9 (19.4)	19.4 (24.1)	16.2 (21.7)	10.5 (10.9)
Occup 4th	14.1 (16.3)	11.8 (12.9)	15.0 (18.1)	13.8 (14.4)
Occup 5th	15.0 (16.9)	14.8 (14.6)	18.2 (24.1)	10.8 (10.3)
60-69 years	14.8 (15.2)	15.8 (15.1)	14.1 (15.0)	15.1 (16.2)
Occup[a] 1st	13.9 (14.2)	18.0 (15.1)	13.2 (13.5)	13.8 (16.2)
Occup 2nd	16.6 (18.0)	23.7 (22.9)	13.6 (11.9)	18.3 (24.1)
Occup 3rd	14.1 (13.7)	17.1 (14.1)	12.6 (14.1)	14.5 (12.2)
Occup 4th	17.0 (18.1)	15.4 (14.3)	18.7 (21.4)	15.2 (13.4)
Occup 5th	12.3 (10.8)	12.7 (11.6)	12.1 (10.2)	10.3 (6.8)
70-79 years	13.2 (14.5)	14.0 (15.8)	13.1 (14.7)	11.5 (9.4)
Occup[a] 1st	12.6 (13.1)	10.1 (12.2)	13.5 (13.9)	12.1 (8.9)
Occup 2nd	12.7 (13.0)	17.2 (15.1)	11.9 (12.9)	12.3 (10.9)
Occup 3rd	14.1 (18.4)	12.3 (13.9)	15.4 (20.8)	10.6 (9.8)
Occup 4th	13.8 (15.3)	17.1 (23.8)	12.8 (11.1)	11.1 (6.4)
Occup 5th	12.7 (11.7)	13.8 (13.1)	11.4 (9.9)	11.3 (9.6)
80 years and older	9.4 (10.6)	8.7 (9.5)	9.9 (11.3)	8.7 (8.5)
Occup[a] 1st	9.4 (11.9)	6.6 (7.1)	10.0 (12.8)	7.6 (8.5)
Occup 2nd	9.8 (11.9)	7.4 (6.6)	10.8 (13.6)	7.5 (5.2)
Occup 3rd	9.4 (7.7)	9.2 (6.4)	9.9 (8.8)	7.9 (4.9)
Occup 4th	11.7 (12.1)	17.2 (18.3)	10.4 (9.1)	10.1 (12.7)
Occup 5th	7.0 (8.2)	6.5 (5.4)	7.4 (10.6)	18.0 (Only 1 observation)
Survival status				
Dead defined as deaths within 28 days of admission				
Alive	14.0 (16.9)	15.3 (16.7)	13.7 (17.5)	13.0 (15.2)
Dead	9.3 (6.9)	8.0 (6.5)	9.5 (6.8)	10.9 (7.3)
Dead defined as deaths within 56 days of admission				
Alive	13.1 (16.7)	14.5 (16.6)	12.7 (17.5)	12.3 (14.9)
Dead	12.3 (10.5)	11.0 (10.6)	12.5 (10.2)	13.8 (10.9)
Ventilation status				
Ever	19.9 (18.0)	19.9 (17.1)	20.5 (19.8)	18.6 (14.9)
Never	7.8 (10.0)	7.4 (9.8)	7.8 (9.5)	8.0 (11.5)

[a] Occup = ICU patient load (quintile ranking from lowest to highest)

Table 6.4.4. Mean and standard deviation (SD) of length of stay in hospital by wave, age group, and ICU patient load (quintile ranking) in Ontario and Québec.

	Overall (March 1st, 2020 - May 31st, 2021)	**Wave1** (March 1st, 2020 - July 31st, 2020)	**Wave2** (August 1st, 2020 - March 20th, 2021)	**Wave3** (March 21st, 2021 - May 31st, 2021)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Ontario				
Overall	14.7 (19.2)	18.8 (25.9)	14.9 (19.3)	12.3 (13.5)
Occup[a] 1st	15.4 (22.5)	18.5 (28.0)	14.3 (20.1)	11.2 (10.2)
Occup 2nd	14.9 (18.4)	17.9 (22.6)	15.2 (18.5)	10.6 (9.5)
Occup 3rd	15.3 (19.6)	20.5 (26.2)	15.0 (19.0)	11.2 (11.4)
Occup 4th	14.6 (18.9)	20.5 (27.3)	15.5 (20.5)	12.5 (14.5)
Occup 5th	13.4 (15.7)	11.4 (12.3)	14.4 (18.7)	13.3 (14.9)
Age group				
0-49 years	9.7 (15.4)	12.9 (23.5)	10.1 (16.5)	8.5 (10.3)
Occup[a] 1st	9.5 (18.7)	11.5 (26.0)	8.6 (15.4)	8.6 (8.4)
Occup 2nd	10.3 (14.8)	12.6 (17.0)	10.9 (16.6)	7.8 (7.6)
Occup 3rd	10.1 (17.1)	14.9 (25.9)	10.5 (17.4)	7.6 (9.8)
Occup 4th	9.7 (13.4)	15.3 (21.7)	10.5 (15.9)	8.7 (10.7)
Occup 5th	9.1 (12.5)	11.3 (11.0)	10.9 (19.5)	8.8 (11.1)
50-59 years	13.7 (20.0)	18.4 (26.0)	13.6 (22.7)	11.9 (13.5)
Occup[a] 1st	14.6 (25.4)	17.8 (25.5)	13.3 (28.3)	10.7 (11)
Occup 2nd	13.4 (19.2)	19.3 (29.3)	12.3 (15.1)	9.1 (8.5)
Occup 3rd	14.2 (17.9)	18.9 (23.5)	14.1 (18.1)	11.8 (13.5)
Occup 4th	14.7 (21)	20.5 (29.2)	16.0 (25.7)	12.9 (16)
Occup 5th	12.0 (15.1)	10.5 (10.9)	13.3 (26.1)	11.9 (12.9)
60-69 years	16.4 (20.8)	20.6 (31.0)	16.3 (19.3)	14.5 (15.3)
Occup[a] 1st	17.2 (26.8)	21.8 (37.9)	15.2 (18.7)	12.1 (11.4)
Occup 2nd	16.0 (17.8)	18.0 (21.3)	16.7 (18.9)	12.3 (8.9)
Occup 3rd	17.4 (22.3)	24.2 (33.1)	16.7 (19.3)	13 (11.8)
Occup 4th	15.7 (18.2)	17.9 (16.6)	17.8 (22.9)	14.2 (15.4)
Occup 5th	15.6 (17.2)	9.6 (7.9)	15.0 (15.6)	16.2 (17.9)
70-79 years	16.9 (20.5)	19.8 (24.6)	17.1 (21.6)	14.9 (15.3)
Occup[a] 1st	17.7 (22.4)	19.4 (23.3)	17.2 (23.1)	14.2 (11.8)
Occup 2nd	17.2 (19.2)	20.9 (20.3)	17.3 (20.2)	13.1 (11.4)
Occup 3rd	16.3 (18.9)	20.3 (20.7)	16.8 (21.5)	12.3 (10.1)
Occup 4th	17.5 (24.5)	22.5 (39.6)	18.7 (25.4)	15.2 (16.9)
Occup 5th	15.6 (16.5)	7.4 (5.4)	14.7 (15.4)	16.6 (17.3)
80 years and older	16.2 (18.3)	20.2 (24.0)	15.6 (17.2)	13.7 (12.1)
Occup[a] 1st	17.1 (18.9)	20.4 (24.5)	15.9 (15.9)	11.8 (7.3)
Occup 2nd	16.1 (19.0)	17.6 (21.9)	16.0 (18.7)	12.2 (10.5)
Occup 3rd	17.0 (19.9)	21.5 (25.5)	15.3 (17.6)	13.0 (9.9)
Occup 4th	15.8 (16.6)	23.0 (24.7)	14.5 (14.0)	13.8 (13.3)
Occup 5th	14.9 (15.9)	15.0 (16.9)	15.4 (19.3)	14.4 (12.8)
Survival status				
Dead defined as deaths within 28 days of admission				
Alive	15.6 (21)	21.8 (29.1)	16.0 (21.6)	12.3 (14.2)
Dead	11.3 (7.6)	9.8 (6.8)	11.4 (7.5)	12.5 (8.2)
Dead defined as deaths within 56 days of admission				
Alive	15.0 (20.9)	21.3 (29.4)	15.4 (21.5)	11.7 (13.8)
Dead	13.8 (10.8)	12.4 (10.8)	13.5 (10.3)	15.5 (11.4)
Ventilation status				
Ever	31.7 (32.1)	38.1 (32.8)	32.7 (34.1)	16.8 (11.5)
Never	14.1 (18.2)	17.8 (25.1)	14.0 (17.8)	12.2 (13.5)

	Overall (March 1st, 2020 - May 31st, 2021)	**Wave1** (March 1st, 2020 - July 31st, 2020)	**Wave2** (August 1st, 2020 - March 20th, 2021)	**Wave3** (March 21st, 2021 - May 31st, 2021)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Québec				
Overall	14.6 (17.5)	17.2 (20.0)	13.6 (16.2)	12.4 (15.3)
Occup[a] 1st	12.7 (16.7)	15.6 (20.0)	11.8 (15.8)	11.7 (14.2)
Occup 2nd	13.7 (17.2)	17.8 (21.6)	13.4 (17.1)	12.1 (13.9)
Occup 3rd	14.3 (16.2)	16.8 (17.0)	13.7 (15.5)	14.0 (18.3)
Occup 4th	15.2 (16.7)	16.5 (16.8)	14.6 (16.6)	12.8 (17.0)
Occup 5th	16.9 (19.9)	18.1 (21.9)	15.2 (15.7)	13.3 (16.8)
Age group				
0-49 years	8.4 (15.4)	10.3 (21.0)	7.7 (13.3)	7.8 (11.7)
Occup[a] 1st	6.8 (10.5)	8.5 (10.7)	5.9 (9.3)	7.4 (12.3)
Occup 2nd	7.9 (14.8)	8.1 (8.9)	8.2 (18.2)	7.4 (10.5)
Occup 3rd	8.9 (14.1)	8.9 (9.6)	8.8 (15.1)	9.2 (14.3)
Occup 4th	9.4 (12.4)	11.6 (15.5)	8.5 (10.7)	6.6 (6.4)
Occup 5th	11.0 (26.2)	12.0 (32.1)	9.2 (12.1)	10.3 (9.5)
50-59 years	12.9 (17.5)	14.4 (17.8)	12.4 (18.0)	12.2 (15.8)
Occup[a] 1st	12.9 (19.0)	12.9 (14.9)	12.8 (22.1)	13.0 (17.2)
Occup 2nd	11.9 (16.7)	14.7 (21.9)	11.3 (17.0)	11.2 (13.3)
Occup 3rd	13.1 (17.1)	15.2 (18.2)	13 (17.5)	11.3 (14.4)
Occup 4th	13.6 (18.4)	13.9 (18.0)	13.1 (17.9)	16.0 (23.5)
Occup 5th	13.7 (16.3)	15.0 (17.3)	11.1 (12.5)	13.1 (18.2)
60-69 years	15.6 (19.6)	18.3 (22.3)	14.6 (18.7)	14.4 (17.4)
Occup[a] 1st	14.6 (19.5)	18.2 (23.8)	13.7 (19.5)	13.0 (14.4)
Occup 2nd	15.5 (21.3)	21.1 (26.0)	15.1 (22.1)	13.9 (16.5)
Occup 3rd	15.2 (17.4)	16.7 (15.4)	14.1 (16.0)	18.6 (23.8)
Occup 4th	14.8 (16.9)	16.1 (18.2)	14.3 (16.4)	13.1 (15.2)
Occup 5th	18.1 (22.5)	19.3 (24.5)	17.0 (19.6)	13.3 (15.3)
70-79 years	17.0 (18.5)	19.7 (20.9)	16.1 (17.5)	14.3 (15.5)
Occup[a] 1st	16.4 (18.4)	19.9 (22.5)	15.5 (17.2)	13.8 (13.6)
Occup 2nd	15.7 (17.2)	20.4 (22.4)	14.8 (16.1)	14.6 (14.8)
Occup 3rd	16.2 (17.1)	20.5 (21.0)	15.4 (15.9)	14.3 (16.3)
Occup 4th	17.4 (18.9)	17.0 (14.8)	18.0 (21.0)	11.8 (10.2)
Occup 5th	19.4 (20.6)	20.8 (22.5)	17.3 (16.0)	17.8 (25.3)
80 years and older	15.9 (15.9)	18.3 (18.3)	14.4 (14.1)	15.3 (14.9)
Occup[a] 1st	14.1 (15.6)	16.6 (21.1)	12.9 (13.1)	14.5 (11.9)
Occup 2nd	15.3 (15.2)	20.2 (21.3)	14.2 (13.9)	15.3 (13.1)
Occup 3rd	15.1 (15.0)	17.6 (15.8)	14.2 (14.3)	16.5 (19.1)
Occup 4th	16.4 (15.6)	18.4 (16.9)	15.0 (14.2)	19.0 (26.4)
Occup 5th	17.6 (17.3)	18.7 (18.3)	15.7 (15.1)	12.7 (11.5)
Survival status				
Dead defined as deaths within 28 days of admission				
Alive	15.7 (19.0)	20.0 (22.1)	14.3 (17.6)	12.5 (16.0)
Dead	9.8 (6.5)	8.8 (6.1)	10.4 (6.6)	11.6 (7.3)
Dead defined as deaths within 56 days of admission				
Alive	15.3 (18.9)	19.6 (22.2)	13.9 (17.4)	12.2 (15.8)
Dead	11.7 (9.6)	10.5 (9.1)	12.4 (9.7)	14.2 (10.8)
Ventilation status				
Ever	29.2 (26.8)	31.5 (30.4)	27.4 (24.8)	29.7 (23.6)
Never	13.1 (15.5)	15.5 (17.7)	12.4 (14.6)	10.5 (12.8)

[a] Occup = ICU patient load (quintile ranking from lowest to highest)

Chapter 7. Defining Optimal Vaccine Features for Pandemic Preparedness

7.1. Preface to Manuscript 4

As the world moves away from its emergency COVID-19 pandemic response, public health priorities have shifted to improving pandemic preparedness (233, 234). Vaccines have played a pivotal role in the COVID-19 response, despite the global inequitable vaccine allocation resulting from the so-called “vaccine hoarding” by high income countries, including Canada.

Nevertheless, pre-established vaccine platforms that can be easily adapted to emerging pathogens hold promise to enhance the agility of our collective response and actions. In line with the WHO's roadmaps to enhance pandemic prevention for the next "Disease X" and the *Coalition for Epidemic Preparedness Innovations'* (CEPI) "*100 Days Mission*" to develop prototype vaccines (9, 235), it is crucial to understand the potential use of these tools to minimize the global impact of future threats. However, the population-level impact of prototype vaccines can be challenging to assess and project given the interplay between vaccine characteristics, host immunity, and disease transmission dynamics. For instance, many existing transmission models do not consider the individual variations in viral loads and immune responses and their time-varying features, which could play a pivotal role in shaping the trajectory of infectious diseases (e.g., the superspreading events that shaped the trajectories of SARS-CoV-2 transmission (236)).

Building on the insights from the preceding manuscripts, I designed a novel modelling framework that incorporates host-level viral load kinetics and immunological dynamics into disease transmission models. Specifically, this manuscript examines the desired vaccine features that are required to respond to a future pandemic caused by a potential SARS-CoV-2-type of virus. The resulting article will be submitted for submission shortly.

7.2. Manuscript 4: Defining optimal vaccine features for pandemic preparedness: An individual-based model bridging within- and between-host dynamics

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Abstract

Background

The next Disease X, a moniker for a yet-to-be identified pathogen that could cause a pandemic, emphasizes the needs for proactive surveillance and preparedness. Developing prototype vaccines for representative pathogens is crucial to achieve this goal. A “100 Day Mission” roadmap was proposed to ensure equitable vaccine access within 100 days. This study aims to identify the desired vaccine features needed to control future SARS-CoV-2-like pathogens effectively.

Methods

To simulate pathogen transmission, an individual-based model was developed, integrating viral load and antibody kinetics models. Various combinations of three vaccine features (the concentration of antibodies required to achieve 50% of the vaccine's maximum effect (EC50), plasma secreting cells (which produce antibodies) half-life, and the vaccine’s impact on the virus's infection rate of target cells) and the basic reproduction number (R_0) were examined and their impact on infections and hospitalizations quantified over an 18-month period with a population of 10,000 individuals. Vaccination began on Day 100, either randomly or age prioritized, with no supply constraints.

Results

Based on the features of the currently available Bnt162b2 vaccine, the overall reduction in cases and hospitalizations could avert 23-47%, and 32-61% of the observed numbers when there’s no vaccine, repsectively, with decreased effectiveness with increased R_0. Lowering EC50 or extending the plasma secreting cells’ half-life increased the reductions observed. However, further improvements beyond an EC50$\leq$ 3 and plasma secreting cells half-life$\geq$ 1 year resulted in minor increases. Changes to the virus-target cell infection rate had minimal impacts on vaccine effectiveness. Vaccine efffectiness did not vary largely by the allocation strategy.

Conclusions

Vaccine development should focus on improving the EC50, followed by extending the half-life of plasma secreting cells.

Keywords: Disease X; 100 Day mission; Vaccine features; mathematical modelling.

Introduction

Since its emergence in late 2019, the SARS-CoV-2 virus has fueled the ongoing Coronavirus Disease (COVID-19) pandemic, with more than 777 million reported cases and over 7 million reported deaths worldwide (as of 2024-10-06) (1). This pandemic has caused considerable morbidity and mortality, disrupted the everyday lives of people, imposed unprecedented pressure on healthcare systems, and generated colossal economic losses globally. A recent systematic review indicated that the indirect cost of COVID-19 was 11% of the global gross domestic product (GDP) while its total cost represented 9% of global GDP and 86% of global healthcare spending (2). Such pandemics, caused by emerging diseases, have been recorded throughout human history, and the interval between them could be accelerating due to factors such as greater population density and travel (3). They include the Spanish Influenza H1N1 (1918-1920), SARS (2002-2003), swine flu (H1N1; 2009), MERS (2012-onwards), among others (4, 5). Pathogens keep (re)emerging and any of these could potentially produce the next Disease X: an as-yet unknown pathogen that could cause a serious international epidemic (6).

Vaccines have proven to be one of the most important interventions to prevent infections, morbidity, and mortality in previous epidemics and pandemics. For example, the seasonal flu vaccine prevents millions of illnesses every year (7) and recently developed vaccines for Ebola are effective against this often-fatal disease (8). During the COVID-19 pandemic, the different vaccines that were rapidly brought to market not only saved millions of lives (9, 10), but helped governments lift their non-pharmaceutical interventions (NPIs) sooner. Although the short timeline for COVID-19 vaccine development was unprecedented (326 days between identification of SARS-CoV-2 and approval of vaccines for emergency use), millions of extra lives could have been saved if vaccines had been available earlier and distributed equitably between countries (11). To overcome these difficulties and better prepare for the next Disease X, the *Coalition for Epidemic Preparedness Innovations* (CEPI), supported by G7 and G20 countries, proposed the "100 Day Mission" initiative to facilitate the development of safe, effective, and globally accessible vaccines within 100 days from the moment that a pathogen is sequenced and/or the need for a vaccine is recognized (12).

Following the current "*100 Day Mission*" roadmap, a key component is to develop several well-characterized candidate prototype vaccines for representative pathogens across multiple virus families (so-called prototype pathogens) (13). Ideally, these vaccines should induce high titers of antibodies that can neutralize the virus or directly block the virus's ability to infect cells, and they should maintain long-lasting immunological memory (14). Although animal models can help understand the within-host characteristics of the vaccine (e.g., efficacy, immune response, dose optimization), the real-world effectiveness of a vaccine within a population is also influenced by the host's characteristics (e.g., population age structure, social contact mixing patterns) and NPIs that attempt to limit population-level contacts (15-17). Further, data from individual randomized clinical trials will continue to support the approval process (phase 3) and these can provide strong evidence on safety and side-effects. However, these trials could be underpowered for some rare disease outcomes and often do not provide estimates of population-level effectiveness that consider both direct (to individual being vaccinated) and indirect (through herd immunity) benefits of vaccines (18).

One potential avenue to comprehensively examine the potential impact of vaccines is to link the within-host vaccine response to population-level transmission dynamics. For instance, studies have found that the majority of subsequent SARS-CoV-2 infections are caused by a small proportion of cases (i.e., overdispersion of transmission), which may be associated with the variance in individual viral loads (19, 20). Bridging the within- and between-host models can help capture these various transmission patterns. Existing mathematical models of SARS-CoV-2 transmission did not consider both the host-level variations of the time-varying viral load and immune responses (21, 22). This study aims to identify the desired vaccine features and allocation strategies against a future SARS-CoV-2-type pathogen (e.g., Disease X) assuming that a vaccine becomes available 100 days after the detection of the pathogen. To achieve this, we developed an individual-based transmission dynamic model incorporating individualized viral load and immune response models.

Methods

Model overview

An individual-based model (IBM) was developed to simulate the epidemic trajectories of a SARS-CoV-2-type virus, integrating NPIs, vaccine characteristics, and vaccine rollout strategies. To simulate the pathogen's transmission dynamics, the IBM considered heterogeneities in contact and social mixing and incorporates within-host compartmental models of viral load trajectories and immune responses after infection (or vaccination). We used a demographic structure and social contacts survey from Canada to parameterize the model (Table 7.4.1, Figure 7.4.1). The model is flexible and can easily be adapted to accommodate various virus features, vaccine characteristics and rollout strategies. A detailed description of the model and parameters can be found in the technical report (Section 7.4.1).

Disease X: SARS-CoV-2-type virus

Disease X is a concept referring to a hypothetical pathogenic threat whose basic reproduction number, generation interval, natural history, and morbidity and mortality profile are unknown. In this study, we assumed that Disease X would be similar to a SARS-CoV-2-type virus, the first Disease X since the term was coined in 2018 and one of the priority pathogens on the WHO's list (23, 24). As we do not expect the next Disease X to have the exact same characteristics as SARS-CoV-2, we investigated the impact of varying the basic reproduction number ($R_0 \in \{2, 2.5, 3, 3.5\}$). With global transmission, imported cases can influence transmission dynamics when local transmission levels are low, even after vaccines are available (e.g., waning immunity, low protection induced by vaccines). For simplicity, the model assumes one initial imported case and allows a weekly importation of one infectious individual, randomly sampled from those aged 20-59 not currently infected with the virus.

Contact networks

The model stratifies each individual's social network into household and non-household contacts, as some NPIs generally attempt to limit non-household contacts (e.g., school closures, remote work, curfews). Both the numbers of household and non-household contacts are age-specific. The contact matrices used in this paper are adapted from Figure 4 of the social contact survey presented by *Drolet et al.* (25) (Figure 7.4.1), which describes the levels and changes in contacts before and during the COVID-19 pandemic in Canada (Québec).

At model initialization, each individual is assigned a household, and members of the same household can come into contact with each other at each time step. For non-household contacts, the number of interactions and the individuals involved are randomly (conditional on the age-mixing matrices) determined at each time step, ensuring both the quantity and composition of contacts vary over time.

Natural history and disease progression

Upon infection with the virus, individuals immediately enter the pre-clinical stage (Figure 7.2.1). This stage ends when an individual's viral load reaches its peak (26, 27), the trajectory of which is projected by the viral load kinetics model. Concomitantly, people will either develop symptoms (mild or severe) or remain asymptomatic. Only individuals with severe symptoms will be hospitalized and are at risk of death from the infection. Individuals recovering from the infection will gain immunity against reinfection, but immunity will wane over time. Parameters governing this process are summarized in Table 7.4.2.

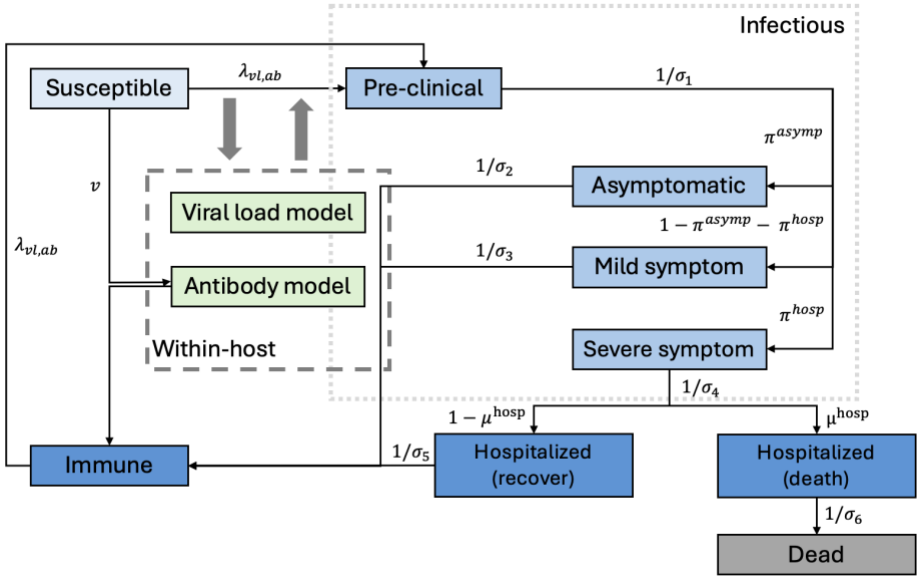

Figure 7.2.1. Schematic diagram of the hybrid individual-based model structure of the natural history, and within-host viral load and antibody trajectory models of the SARS-CoV-2-type virus.
Symbols: $\boldsymbol{\lambda_{vl,ab}}$: probability of infection as a function of the viral load and antibody level of the contact pair at risk of transmission; $\boldsymbol{\sigma_{i(i=1,2,..,6)}}$: duration of each disease stage;$\boldsymbol{\pi^{asymp}}$ and $\boldsymbol{\pi^{hosp}}$: the proportion of infections that are asymptomatic and hospitalized, respectively; $\boldsymbol{\mu^{hosp}}$: proportion of in-hospital mortality; $\boldsymbol{v}$: rate of vaccination.

Within-host viral load and immune response

For each newly infected person, a target cell-limited (TCL) viral load kinetics model and a mechanistic model for antibody kinetics will be run simultaneously, considering the individual-level variance of trajectories. TCL models assume that the rate of viral production is constrained by the availability of susceptible target cells and are widely utilized in studies of HIV and influenza viral dynamics (28, 29). Briefly, once a target cell is infected, it will enter the eclipse phase (i.e., the time elapsed between successful cell infection and the start of virus production (30)) before producing infectious and non-infectious viruses. The parameters governing viral load trajectories are extracted from *Marc et al*. (31) and *Néant et al*. (32) (Table 7.4.3).

To project the individual-level neutralizing antibody concentrations over time, following either infection or vaccination, we adapted the simplified model proposed by *Clairon et al.* (33), which provides the trajectory of waning antibody levels after the second dose of the Bnt162b2 vaccine (Table 7.4.4). The adapted model mainly focused on 3 of the most important vaccine characteristics:

1. The EC50, the concentration of antibodies required to achieve 50% of the vaccine's maximum theoretical efficacy that correlates the immune response and protection from infection (the lower the EC50, the better) (34);

2. The half-life of secreting plasma cells (differentiated B lymphocytes that secrete Igs; hereafter, “S cells”) which partially governs the duration of protection (the longer the better) (35);

3. The rate of virus infecting target cells that influences attachment of the virus to host cells (β) (36).

Between-host virus transmission

Susceptible individuals and those with partial immunity (either from natural infection or vaccination) can (re)acquire the virus. The probability of transmitting the pathogen between each contact pairs is determined by the transmissibility of the index case and the susceptibility of the contact (associated with antibody level) at the time of contact. The infectiousness (i.e., the

probability of transmission) of the index case is modeled as a function of their viral load, using the model proposed by *Marc et al.* (31), which assumes a logit-linear effect of viral load that varies according to the type of the contact (household or non-household) given their different effect on level of infectiousness (Table 7.4.5). Current knowledge on the relationship between antibody level and the protection against infection is limited. Therefore, we assumed an Emax sigmoid model of antibody levels and probability of being protected from infections (i.e., the susceptibility of the contact). More specifically, the EC50 value (4.08 $\log_{10} AU/ml$) was parameterized using simulations of data from non-human primate models (37) (Table 7.4.6).

Non-pharmaceutical interventions

NPIs can affect the number of contacts, as well as mixing by age and household/non-household contacts. Hence, our contact matrices vary over time following the implementation or lifting of NPIs (e.g. lockdowns). Specifically, we divided the non-household contact behaviors into 4 periods: pre-epidemic (time before NPIs are implemented; Day 0-14 of the modeled time), NPI period (Day 15-99, one day before the hypothetical vaccine becomes available), transition period during which the social contact have yet to fully rebound to pre-pandemic levels (Day 100-220, when the mass vaccination campaign ends), and post-epidemic where the contact rates return to their pre-pandemic levels (Day 221 and onwards).

We assumed that before NPIs are implemented (Day 1-14), there is no case isolation. After that period, symptomatic individuals will be isolated 1 day after their symptom onset. That is, before Day 15, all cases who are not hospitalized can transmit the virus; whilst afterwards, only those at pre-clinical and asymptomatic stages will contribute to the transmission.

Simulation strategy

<u>Target vaccine features and rollout scenarios</u>

The effect of a vaccine is determined by multiple features. In this study, we examined the impact of EC50, half-life of S cells, and rate of target cell infection by the virus (β). The values of each were based on the existing Bnt162b2 vaccine (second dose) against SARS-CoV-2 ($EC50 = 4.08 \log_{10} AU/ml$; half-life of S cells $= 70\ days$; $\beta = 3.65 \times 10^{-5}\ ml/virus.day$ (hereafter, "current" scenario). To explore the impact of different vaccine features on transmission, a series

of combinations of different values of the abovementioned three characteristics are examined (Table 7.2.1).

Table 7.2.1. Table of scenarios examined in the model for each basic reproduction number (i.e., $R_0 \in \{2.0, 2.5, 3.0, 3.5\}$).

Scenario descriptions	Scenario names	EC50 ($\log_{10} AU/ml$)	Half-life of the secreting plasma cells	Scale factor of β[1]
Current vaccine features	Current	4.08	70 days	1 time
Improve EC50, keep half-life of S cells and β the current value	EC50 = 1	1	70 days	1 time
	EC50 = 1.5	1.5		
	EC50 = 2	2		
	EC50 = 2.5	2.5		
	EC50 = 3	3		
Change β, keep EC50 and half-life of S cells the current value	0.5 β	4.08	70 days	0.5 time
	1.5 β			1.5 times
Increase half-life of S cells, keep EC50 and β the current value	0.5-year half-life	4.08	Half a year	1 time
	1-year half-life		1 year	
	2-year half-life		2 years	
	20-year half-life		20 years	

[1] The scale factors of β (the current rate of target cells being infected by the virus) correspond to the values of $\beta = 3.65 \times 10^{-5} ml/virus.day$ (1 time), $\beta = 1.83 \times 10^{-5}\ ml/virus.day$ (0.5 time), and $\beta = 5.38 \times 10^{-5}\ ml/virus.day$ (1.5 times).

Two different vaccination strategies were examined. The first corresponds to a random allocation. This strategy ensures equality of vaccine access (18). The second strategy follows an age-based rollout, similar to the approaches widely adopted to minimize severe outcomes during the COVID-19 pandemics (38). Specifically, individuals aged 70 and older will be prioritized with the age threshold lowering by 10 years each week. For both strategies, we assumed a rate that can reach 80% coverage within 4 months (on Day 220), as observed in Israel (one of the fastest vaccine rollouts) during the COVID-19 pandemic (39). Additionally, we assumed a one-dose vaccine, considering the pressure on vaccine supply under high-speed rollout.

Outcomes

For each scenario (Table 7.2.1), we evaluated the impact on several outcomes. First, we calculated the time-varying effective reproduction number (R_t). To overcome computing time limitations, R_t is calculated using the number of new infections divided by the number of actively infectious people on day *t* (using a 7-day moving average), multiplied by the average duration of infectiousness. This method has been suggested to be nearly identical to the definition of the "*instantaneous reproductive number*" (21, 40). Second, we measured the fraction of the cumulative number of infections and hospitalizations averted from Day 100 (start of vaccination) to the end of each month by comparing the vaccine scenarios above to the base case without any vaccination:

$$Averted\ Fraction_{t-t_0} = \frac{\int_{t_0}^{t} I_{No\ vaccine} - \int_{t_0}^{t} I_{vaccine\ scenario}}{\int_{t_0}^{t} I_{No\ vaccine}}$$

Third, we estimated the occupancy rate of hospital beds, defined as the number of patients currently hospitalized per 10,000 population. The length of hospital stay is sampled from a gamma distribution assuming an average stay of 14.6 days (41). Average country-level hospital density per 10,000 population in Europe and Africa (the two continents with the highest and lowest hospital capacity according to WHO data (42)) are used as upper and lower bounds for the hospital capacity levels. We assumed that 80% of the total hospital capacity can be designated to Disease X patients, as observed in the US (43). Finally, we calculated the differences in fractions of cumulative number of infections and hospitalizations to compare the impacts by vaccine rollout strategies.

Time horizon

To evaluate the short-term impact on transmission and hospitalizations of the potential vaccine, the model was simulated over a temporal horizon of 1.5 years with a time step of one day, starting from the introduction of one infectious case into a completely susceptible population of 10,000 individuals. Given the short time span, births, deaths, and migration were not considered. As per the "*100 Day Mission*", mass vaccine campaigns are assumed to start on day 100 with a continuous supply of vaccines (i.e., no stockouts) (44). For all outcomes, the median of 100 stochastic simulations is reported. The model was coded in R version 4.4.1 using a C++ back-end implemented with the *Rcpp* library.

Results

Impact of vaccine characteristics under random vaccine allocation

Shortly after the initiation of vaccinations on day 100, the effective reproduction number (R_t) increases with the lifting of NPIs. For a vaccine with the same features as the currently available second dose of Bnt162b2 vaccine (the "current" vaccine), the R_t remains below 1 for approximately 4-6 months (depending on R_0) before the epidemic resurges (Figure 7.4.3). Within a 1.5-year period, this vaccine could avert 23-47%, and 32-61% of the observed cases and hospitalizations when there's no vaccine, respectively, with smaller averted fractions at higher R_0 (Figure 7.2.2, Figure 7.4.4, Figure 7.4.5). Those reductions peaked at 7 months post-vaccination and decreased over time. In terms of hospital demands, the vaccine was able to bring down the number of patients currently hospitalized; nevertheless, it failed to prevent a resurgence of patient admissions that resulted in exceeding the upper bound of hospital capacity **(**Figure 7.2.3).

Improving EC50 and the half-life of S cells improved vaccine effectiveness, whereas modifying the rate of host cells being infected by the virus (β) had minimal impact on improving the performance of the "current" vaccine. In general, across all values of R_0, decreasing EC50 to 3, or increasing the half-life of S cells to 0.5 years based on the "current" vaccine feature, could keep the $R_t < 1$ and hospitalizations under the upper capacity limit until the end of the 1.5-year period. These vaccine features could prevent >96% of cases and >98% of hospitalizations for viruses with R_0 of 2 to 2.5. Further improvements in EC50 and the half-life of S cells had minimal impact on transmission. For viruses with an R_0 of 3 or 3.5, an EC50 threshold of at least 2.5 or a half-life of S cells of at least 2 years were needed to achieve a maximum effect.

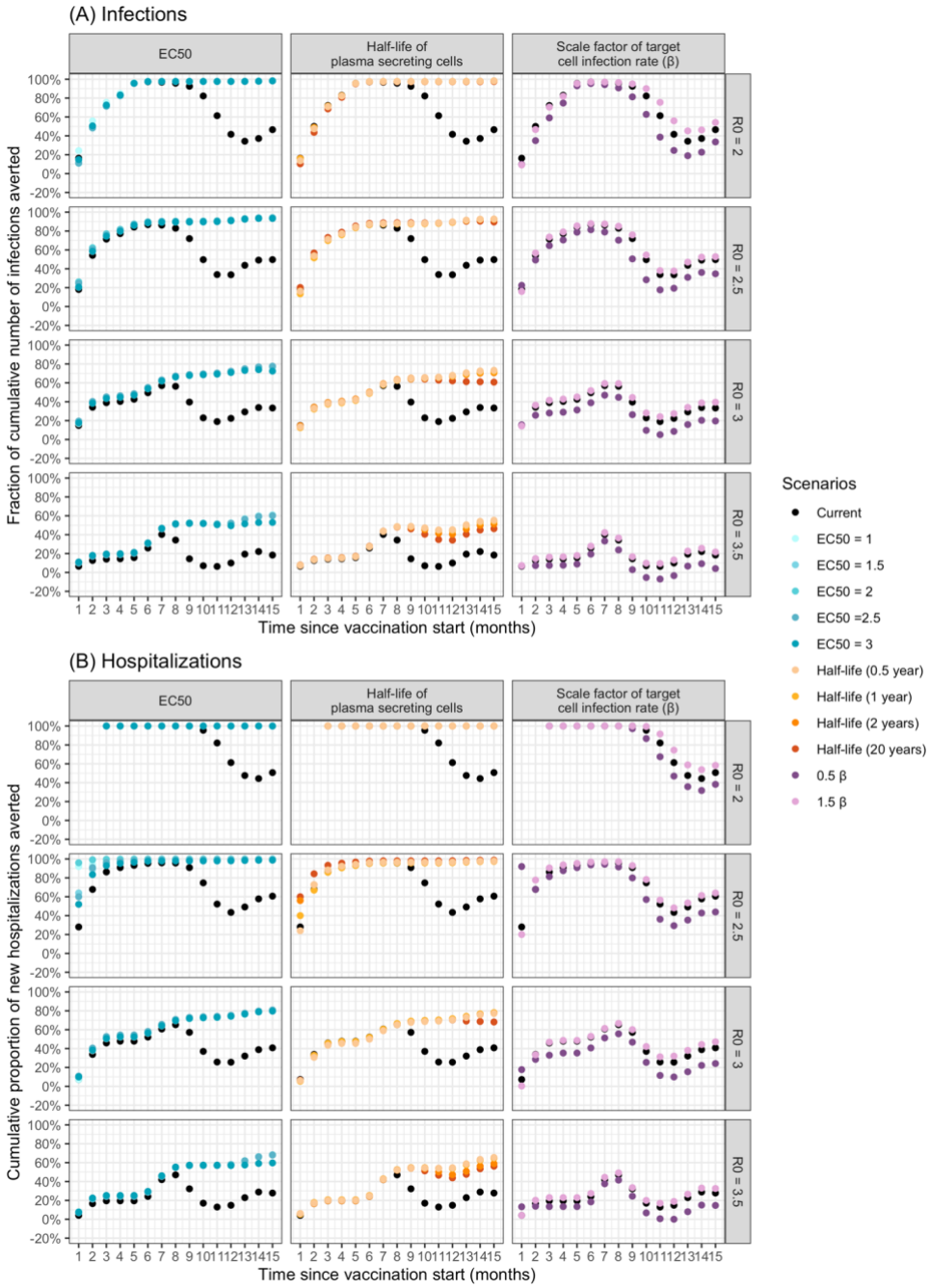

Figure 7.2.2. Cumulative proportion of new infections (Panel A) and hospitalizations (Panel B) averted since vaccination start on Day 100, assuming randomized vaccination.

Note: The "current" scenario assumes the same vaccine charateristics as the current Bnt162b2 vaccine (EC50 = 4.08 $\boldsymbol{log_{10}\, AU/ml}$, half-life of S cells = 70 days, $\boldsymbol{\beta = 3.65 \times 10^{-5}\, ml/virus.day}$). "EC50" scenarios assume the half-life of S cells and $\boldsymbol{\beta}$ remain the same as the current vaccine. "Half-life" scenarios assume the EC50 and $\boldsymbol{\beta}$ remain the same as the current vaccine. "$\boldsymbol{\beta}$" scenarios assume the EC50 and half-life of S cells remain the same as the current vaccine.

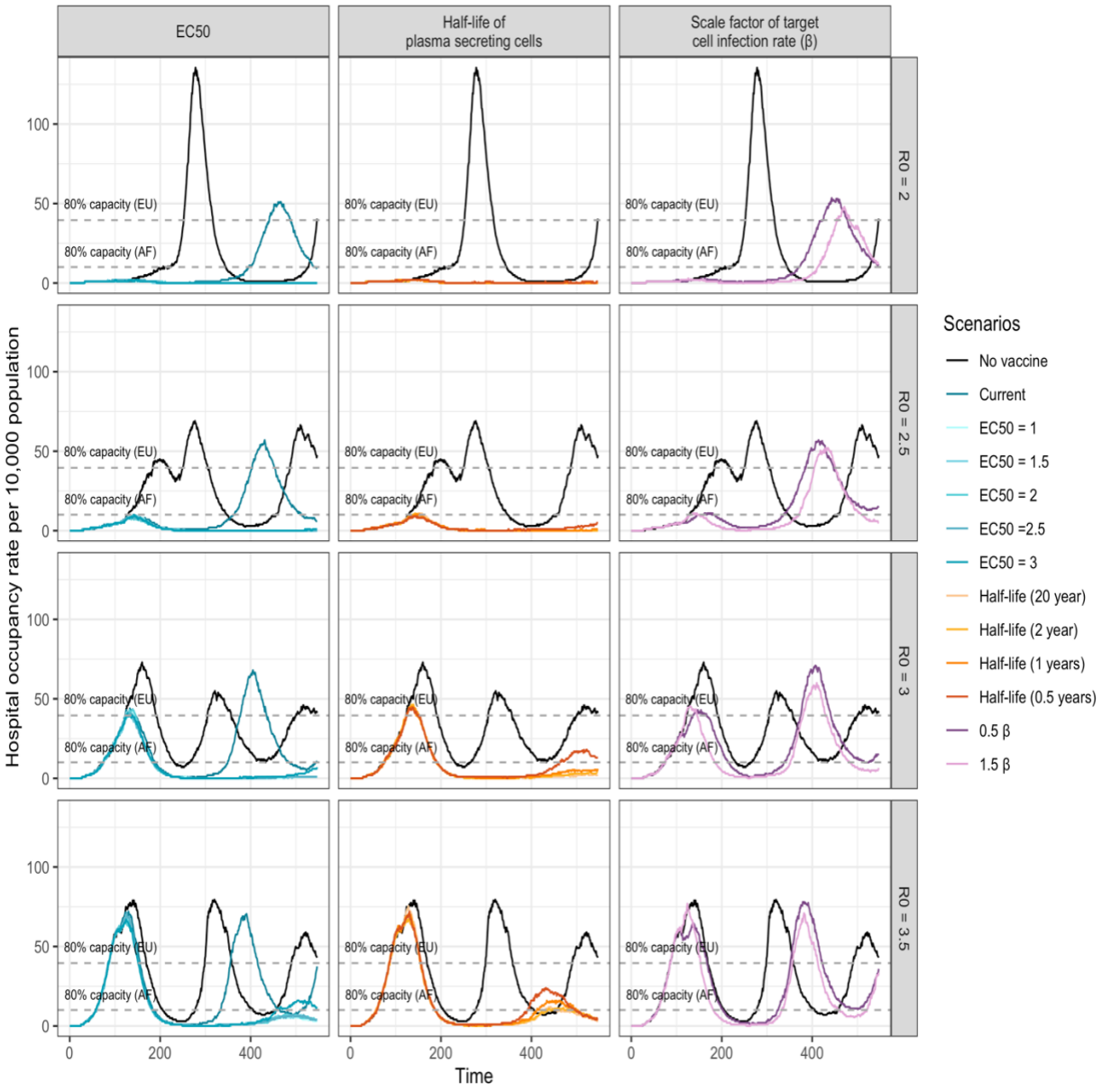

Figure 7.2.3. Hospital occupancy per 10,000 people since the beginning of the epidemics, assuming random allocation of vaccines.

Note: The "no vaccine" scenario represents the status-quo scenario, where there is no vaccine available. The "current" scenario assumes the same vaccine charateristics as the current Bnt162b2 vaccine (EC50 = 4.08 $\boldsymbol{log_{10} AU/ml}$, half-life of S cells = 70 days, $\boldsymbol{\beta = 3.65 \times 10^{-5}\, ml/virus.day}$). "EC50" scenarios assume the half-life of S cells and $\boldsymbol{\beta}$ remain the same as the current vaccine. "Half-life" scenarios assume the EC50 and $\boldsymbol{\beta}$ remain the same as the current vaccine. "$\boldsymbol{\beta}$" scenarios assume the EC50 and half-life of S cells remain the same as the current vaccine.

Comparing the impact of randomized and age-based vaccine rollout strategies

For a virus with an R_0 of 2, compared to a random vaccine allocation strategy, rolling-out vaccinations based on age resulted in a fraction of cumulative infections averted that was 2 to 3%-points lower and a fraction of hospitalizations averted that was 0% to 3%-points lower at the end of 1.5 years across all vaccine scenarios (Figure 7.2.4). However, random vaccine allocation resulted in up to 38%-point (EC50=1) more infections during the first 6 months after vaccination started. For R_0 of 2.5, the fractions of cumulative number of infections and hospitalizations averted with age-based vaccination was 5% to 10%-points and 6% to 7%-points lower than the scenarios with a random allocation strategy. During the first 6 months after vaccination started, the impact was up to 46%-points (EC50=2) and 76%-points (EC50=1) lower for infections and hospitalizations, respectively, if vaccination was rolled-out prioritizing the older age groups. The cumulative fractions of infections averted over the 1.5-year period were 2 to 14%-points (for R_0=3) and 4 to 11%-points (for R_0=3.5) lower with age-based allocation. For hospitalizations, the numbers were 2 to 14%-points and 4 to 11%-points, respectively.

Comparing the effect of EC50 and half-life of S cells

To determine which of the EC50 or the half-life of S cells is more important, cumulative numbers of infections at the end of 1.5 years were compared across different combinations of their values, assuming an R_0 of 2.5 and random rollout strategy. For both infections and hospitalizations, varying the half-life of S cells had minimal impact with an EC50$\leq$3 or EC50$\geq$6 (Figure 7.4.6). With an EC50 of 5, the total number of cumulative infections and hospitalizations decreased with increasing half-life of S cells. When the EC50 is 4, prolonging the half-life of S cells to 0.5 years resulted in reductions in both outcomes. However, further enhancing the half-life showed very small marginal effects compared to the 0.5-year half-life.

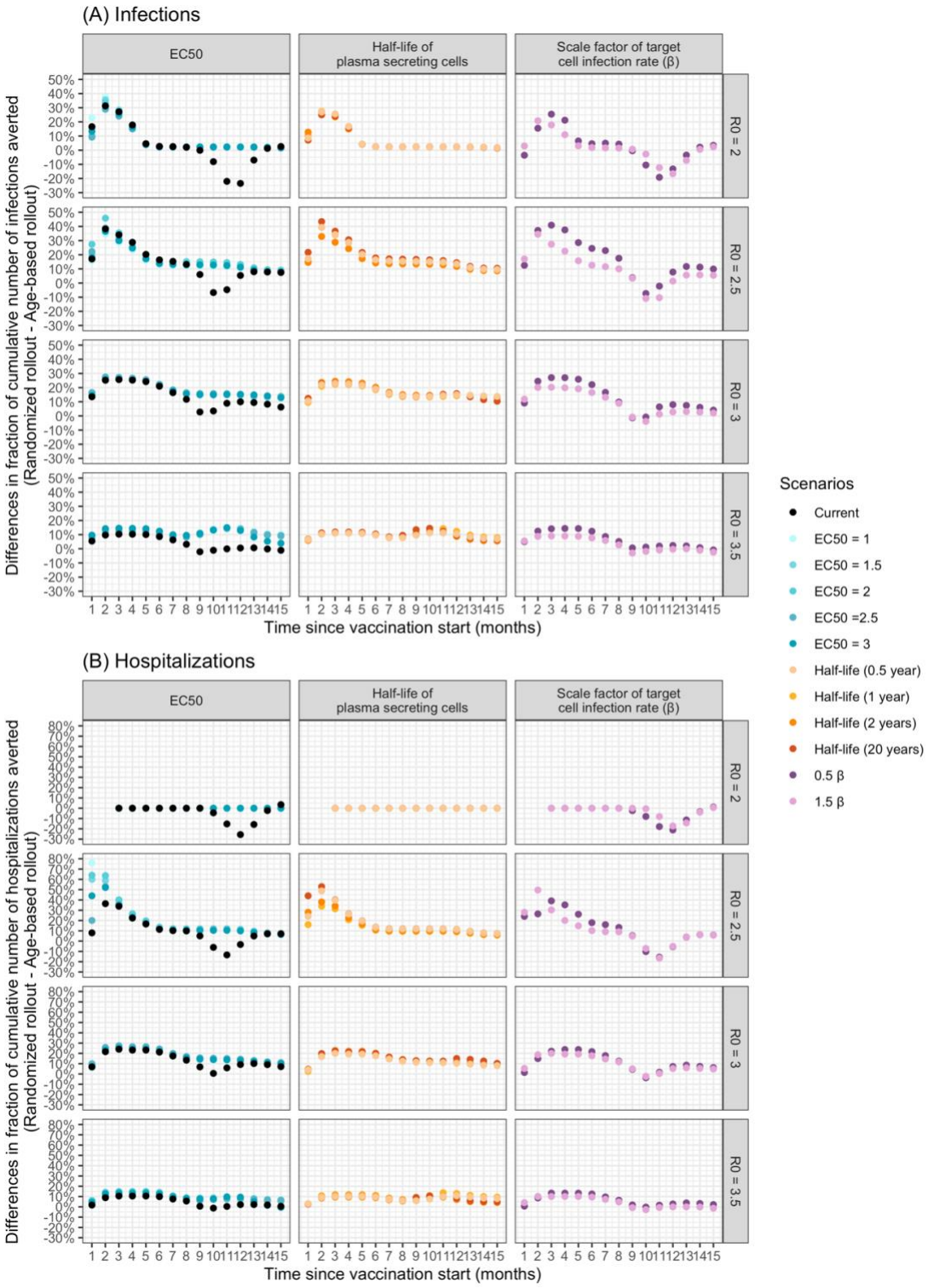

Figure 7.2.4. Differences in the fractions of cumulative numbers of infections and hospitalizations averted comparing randomized and age-based vaccination rollout strategies.

Discussion

To prepare the world for future Disease X, reduce outbreak severity, and save lives, vaccines remain one of our most valuable tools. It is therefore essential to understand the complex interplay between vaccine characteristics, viral load and antibody dynamics, NPIs, and vaccination strategies. Using a detailed IBM that accounts for both individual-level dynamics of viral load and immune responses, as well as population-level transmission of the virus, we found that some specific vaccine and pathogen characteristics determine our ability to control a future SARS-CoV-2-type Disease X. Across modelling scenarios, we found that lower EC50 and a longer half-life of S cells will led to higher fractions of infections and hospitalizations averted, and reduced hospital occupancies. However, there was a threshold (EC50 = 3, half-life of S cell = 1 year) where further optimizing these two characteristics resulted in only minor improvements in effectiveness. Vaccines aiming to modify the rate that a virus infects target cells had minimal impact. In general, a random allocation strategy showed better effectiveness across all scenarios tested.

Our results highlight the significance of the EC50 for vaccine effectiveness, indicating that the neutralization capacity is of primary importance, superseding the durability of immunity. Although the half-life of S cells is a pivotal factor, its effect faded if the EC50 was below or above a certain level. For example, with an EC50 value $\geq$6 or $\leq$3, increasing the half-life to 20 years had a negligible impact on the number of infections and hospitalizations averted (Figure 7.4.6). Our findings are consistent with the conclusions from *Clairon et al.* (33), that indicated a high neutralizing capacity is important against variants of the SARS-CoV-2 virus. Moreover, we observed minimal improvement in vaccine effectiveness when the EC50 reached a certain threshold (e.g., lowering the EC50 value under 3 showed minor advancements across all R_0 scenarios). This suggests that even vaccines with lower serological performance (e.g., lower neutralization capacity or duration of immunity) may provide similar population-level impacts.

During the COVID-19 pandemic, many regions and countries prioritized vaccination among older age groups to avert severe outcomes (45-47). However, we found that a random vaccine rollout strategy could potentially avert more infections and hospitalizations, compared to the age-based rollout, across all scenarios. The differences in impacts between the two vaccine strategies during the first few months after initiating vaccines could be due to the vaccination

rates in our model, as previous research has found diminishing effect of age-based vaccination when the vaccination rate is high (48).

Even with a vaccine effective enough to maintain R_0<1 or keep hospital occupancies below capacity for several months, resurgence of the epidemic was observed in several scenarios. This could be due to the waning protection of antibodies, as is observed with the intraseasonal resurgence of respiratory syncytial virus (RSV) (49), or both waning immunity and case importation. Booster doses could be implemented to counteract waning immunity and avoid resurgence (51).

As with other mathematical models, some limitations need to be considered. Key assumptions include that the first case acquired locally is detected (i.e., no cryptic transmission), public health responses are implemented swiftly 2 weeks after case importation, the population adheres to isolation recommendations, and vaccination rollout is rapid. In practice, these assumptions may be hard to meet, which would lead to higher levels of transmission during the epidemic's exponential growth phase. Additionally, the IBM modeled a population of 10,000 individuals due to computational limitations of running both within- and between-host models at an individual level. Sensitivity analyses modelling 5,000 individuals indicated different effect estimates by population size (Figure 7.4.7). Nevertheless, the qualitative conclusions did not change. Further investigations assuming all contacts are non-household showed similar results across population sizes, indicating the differences observed might be due to household structures (Figure 7.4.8). Finally, we did not link the severity of disease with viral load and antibody level due to inconsistent evidence available (52). To compensate for that, we used an age-specific probability of being symptomatic or hospitalized. Given that Disease X is a concept, it is virtually impossible to examine all potential variations of the next pandemic-causing (re)emerging pathogen. However, the model is designed to be flexible enough to easily incorporate different virus characteristics and intervention timelines.

Nevertheless, our approach has many strengths. our model incorporates both within- and between-host heterogeneities in viral load and immune responses and transmission patterns. This enabled us to model variations in individuals' responses to the virus and the vaccine, and in their contact behaviors. Moreover, the use of mathematical modelling allowed us to consider both direct

and indirect benefits of vaccination (e.g., herd immunity). Finally, we explored several scenarios and conducted sensitivity analyses to support our conclusions. By examining the impact of multiple combinations of key vaccine features across different R_0, our work identified the vaccine characteristics that most affect the population-level vaccine effectiveness and provided suggestions on the minimum required vaccine features needed to contain a future Disease X epidemic under various scenarios.

Conclusions

The population-level effectiveness of vaccines against a future Disease X with characteristics like SARS-CoV-2-type varied across vaccine features, features of the virus, and the vaccine rollout strategy. Improving the EC50 should be prioritized when developing vaccines that target SARS-CoV-2-type viruses, followed by increasing the half-life of S cells. In general, a random vaccine allocation strategy could reduce more infections and hospitalizations compared to an age-based rollout, especially during the first few months after vaccination starts.

Author contributions

YX, MMG, and MP conceived and designed the study. YX conducted the literature review, performed the analysis, and drafted the manuscript. MA estimated the parameters used to link antibody level and susceptibility. MA, RT, MMG, and MP interpreted results, drafted and edited the manuscript, and critically reviewed it for intellectual content. All authors approved the final version of the manuscript.

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Declaration of interests (please add in if you have any COI)

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7.4. Manuscript 4: Supplementary Materials

7.4.1. Technical Appendix

1. Overview

This document describes a combined within- and between-host model that aims to examine the potential impacts of different vaccine features and rollout strategies on epidemic trajectories of Disease X (i.e., a term coined to describe an unknown pathogen of pandemic potential). An individual-based model (IBM) of SARS-CoV-2-type virus transmission and control is developed to incorporate both individual-level dynamics of viral load trajectory and immune responses after infection (or vaccination) and population-level transmission dynamics. The IBM is used to simulate: 1) between-host contact networks within the population, stratified by household or non-household contacts, at different stages of an epidemic, 2) virus transmission (based on the within-host viral load and antibody level of each individual), 3) natural progression of the disease (i.e., infection, hospitalization, and death), and 4) vaccine rollout strategies.

The goal of this study is to explore the desired vaccine features that are needed to contain the transmission of a future Disease X, if vaccines are available on Day 100 since the introduction of an infectious case into a fully susceptible population and without a limit on supply (1). To demonstrate the application of the model, we used Disease X characteristics similar to a SARS-CoV-2-type virus, using a demographic structure and social contacts from Canada. However, the model is flexible and can be adapted easily to accommodate various virus features, vaccine characteristics, and vaccine rollout strategies.

The model was coded in R version 4.4.1 using a C++ back-end implemented with the *Rcpp* package.

2. Model structure and parameterization

2.1 Demography – Population size, age and sex distribution

The model simulates a closed population of 10,000 individuals. This number was chosen to balance model complexity with computing efficiency. The individuals are grouped into 9 age groups (i.e., 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80+) and the model is

stratified by sex (i.e., male, female). The model was parameterized using demographic information from Québec, one of the Canadian provinces at the epicenter of the COVID-19 pandemic (Table 7.4.1) (2). Given the short time-scope of the simulation (1.5 years), no births, aging, deaths (except those caused by the modelled pathogens), or migrations are considered.

Table 7.4.1 Age and sex distribution of the simulated population, based on Canadian data.

Age group (years)	Male proportions	Male population	Female proportion	Female population	Total (both sexes)
0-9	5%	544	5%	517	1,061
10-19	6%	553	5%	528	1,081
20-29	6%	590	6%	572	1,162
30-39	6%	638	6%	640	1,278
40-49	6%	642	6%	639	1,281
50-59	7%	670	7%	669	1,339
60-69	7%	672	7%	701	1,373
70-79	4%	437	5%	488	925
80-	2%	195	3%	304	500
Total	49%	4,942	51%	5,058	10,000

2.2 Contact networks

2.2.1 Overview

Two types of contacts (household and non-household) are considered in the model, given that non-pharmaceutical interventions (NPIs) generally target non-household contacts. At each time step, members within the same household can contact each other, and all individuals can contact members outside of their household. To account for heterogeneities in contact networks by age, the amount of household and non-household contacts varies by age. This information is extracted from the Québec CONNECT study that surveyed social contacts using a representative sample of the population in Québec before and during the COVID-19 pandemic (3).

2.2.2 Household contact networks

At model initiation, each individual is assigned to a household. Members within the same household are assumed to contact each other at each time unit and this contact behavior is not

affected by the restrictions during the epidemic. In other words, the number of household contacts of each individual is constant over time. To assign individuals to a household, people aged 18 years and older are randomly sampled as index persons to look for household members, assuming minors (those who are younger than 18 years old) will stay in a household with at least one adult. For each index person, the number of household contacts (c^h) in each age group (a) is assigned by sampling from Poisson distributions, with an average number of contacts based on the household contact matrix (Figure 7.4.1, Panel A):

$$c_a^h \sim Poisson(\mu_a^h)$$

The household size is assumed to be no larger than 10 people (i.e., if the total number of household members assigned to the index person exceeds 9, a resampling will be performed).

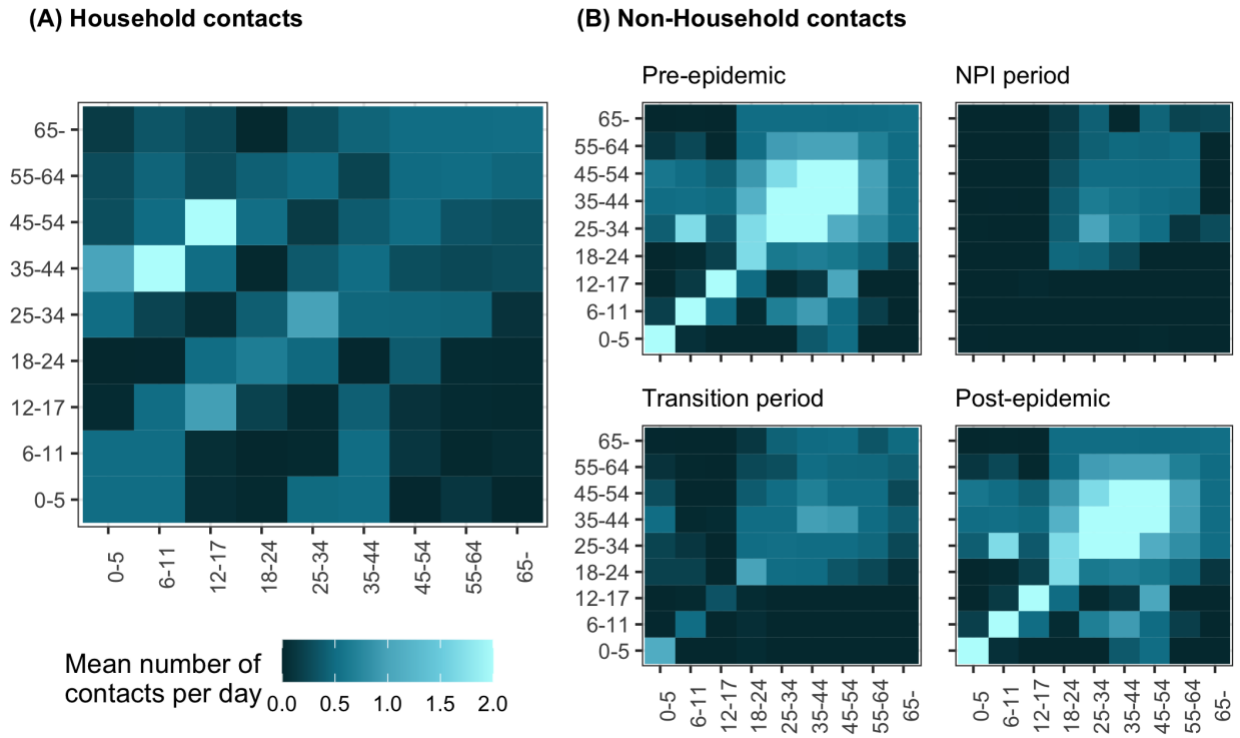

Figure 7.4.1. Mean number of daily household (Panel A) and non-household (Panel B) contact matrices per person. Adapted from Drolet et al. 2022 (3).
Note: Household contact networks are assumed to be fixed over time. Non-household contact networks are assumed to change with the restrictions: pre-epidemic (Day 0 to Day 14), NPI period (Day 15 to Day 99), transition period (Day 100 to Day 220), and post-epidemic (Day 221 to the end, assuming the same as pre-epidemic level).

2.2.3 Non-household contact networks

At each time step, individuals are attributed a number of non-household contacts (c^{nh}) in each age group (a), sampled using Poisson distributions. The number of contacts varies over time (t) following the implementation, or lifting, of NPIs (e.g., lockdowns).

$$c_{a,t}^{nh} \sim Poisson(\mu_{a,t}^{nh})$$

The different contact behaviors over time are divided into 4 periods: pre-epidemic, NPI period, transition period where NPI are lifted, and post-epidemic (Figure 7.4.1, Panel B). The pre-pandemic period is defined as the time before NPI are implemented. In our simulation, we assumed that NPIs are implemented 14 days after the importation of the pathogen into the population. This is informed by the observed timeline in Québec during the COVID-19 pandemic (3). The NPI period begins on day 15 and lasts until the hypothetical vaccine becomes available on day 100. As mass vaccination activities begin, the population enters a 4-month transition period where social contacts have yet to fully rebound to pre-pandemic levels. The duration of the transition period is determined by the assumed vaccination rate, as detailed in Section 2.6. From Day 221 and onwards (post-pandemic period), the contact rates return to the pre-pandemic levels.

2.3 The natural history of the SARS-CoV-2 type virus

The natural history of the SARS-CoV-2 type virus is depicted in Figure 7.4.2. As an emerging disease, all individuals in the model are assumed to be fully susceptible to the pathogen (i.e., no prior immunity). Upon infection with the emerging virus, individuals will enter the pre-clinical stage with a duration (σ_1) based on the time between infection and symptom onset. Symptom onset coincides with the peak of viral load (4, 5), as determined by each individual's viral load trajectory (outlined in Section 2.4.1). After that, people will either continue to be asymptomatic or will develop symptoms.

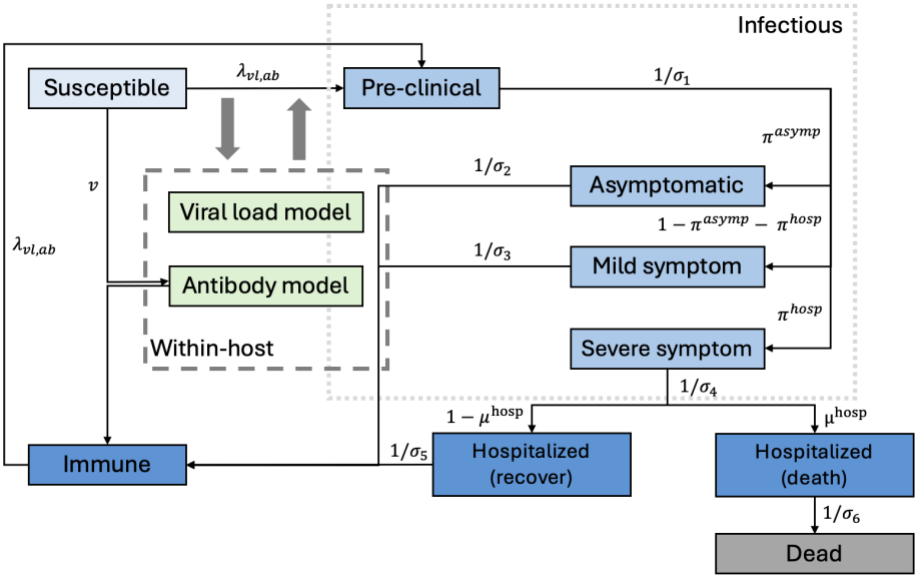

Figure 7.4.2. Schematic diagram of the hybrid individual-based model structure of the natural history, and within-host viral load and antibody trajectory models of the SARS-CoV-2-type virus.
Symbols: $\boldsymbol{\lambda_{vl,ab}}$: probability of infection as a function of the viral load and antibody level of the contact pair at risk of transmission; $\boldsymbol{\sigma_{i(i=1,2,..,6)}}$: duration of each COVID-19 disease stage;$\boldsymbol{\pi^{asymp}}$ and $\boldsymbol{\pi^{hosp}}$: the proportion of infections that are asymptomatic and hospitalized, respectively; $\boldsymbol{\mu^{hosp}}$: proportion of in-hospital mortality; $\boldsymbol{v}$: rate of vaccination.

The severity of symptom is determined using a multinomial distribution that provides age-stratified probabilities of being asymptomatic (p_a^{asymp}), having symptoms that will lead to hospitalization (hereafter "*severe symptoms*"; p_a^{hosp}), or being symptomatic but not requiring hospitalization (hereafter "*mild symptoms*"; $p_a^{symp} = 1 - p_a^{asymp} - p_a^{hosp}$) (Table 7.4.2) (6).

$$Symptom\ status_a \sim Multinomial(p_a^{asymp}, p_a^{symp}, p_a^{hosp})$$

Asymptomatic individuals and those with mild infection will transition to the immune stage (σ_2, σ_3) when their viral load decreases below 10^4 copies/ml, assuming they are no longer infectious (7). For those with severe symptoms, the delay between symptom onset and hospitalization is sampled from a gamma distribution (σ_4). The duration of hospitalization is also sampled from a gamma distribution. After that time, individuals can either be discharged (σ_5) or die of the disease (σ_6) (8). We assumed an in-hospital mortality risk of 16.3%, similar to that observed for COVID-19 (μ^{hosp}).

$$\sigma_4 \sim Gamma(1.9, 0.33)$$

$$\sigma_5 \sim Gamma(0.70, 0.084)$$

$$\sigma_6 \sim Gamma(0.96, 0.097)$$

Table 7.4.2. Probability of asymptomatic infection and probability of hospitalization for each age group.

Probability of asymptomatic infection	**Age 0-9**	**Age 10-19**	**Age 20-29**	**Age 30-39**	**Age 40-49**
	50%	45%	40%	35%	30%
	Age 50-59	**Age 60-69**	**Age 70-79**	**Age 80-89**	**Age 90-**
	25%	20%	15%	10%	10%
Probability of hospitalization	**Age 0-9**	**Age 10-19**	**Age 20-29**	**Age 30-39**	**Age 40-49**
	0.05%	0.2%	0.8%	2.2%	3.6%
	Age 50-59	**Age 60-69**	**Age 70-79**	**Age 80-89**	**Age 90-**
	8.6%	16.9%	29.5%	41.9%	41.9%

2.4 Within-host viral load and immune response

This section describes the within-host module with individual-level projections of viral load and antibody trajectories. This module is run whenever an individual is infected with the emerging pathogen (viral load and antibody models) or an individual is vaccinated (antibody model only) (Figure 7.4.2).

2.4.1 Viral load trajectories

Upon infection with the virus, a target cell-limited viral kinetic model is run for each newly infected case to project the viral load trajectory over time. This model is widely adopted in studies on HIV and influenza viral dynamics (9, 10), which assumes that the rate of viral projection is constrained by the availability of susceptible target cells. It considers the dynamics of the target cells (T), the infected cells in their eclipse phase (I_1; the time elapsed between successful cell infection and the start of virus production (11)), the productively infected cells (I_2), the infectious viruses (V_I), and the non-infectious viruses (V_{NI}). The total concentration of viral load is the sum

of V_I and V_{NI}. Specifically, the model is governed by the following ordinary differential equations (ODEs):

$$\frac{dT}{dt} = -\beta T V_I$$

$$\frac{dI_1}{dt} = \beta T V_I - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta_{I_2} I_2$$

$$\frac{dV_I}{dt} = p\mu I_2 - cV_I$$

$$\frac{dV_{NI}}{dt} = p(1-\mu) I_2 - cV_{NI}$$

Where β, k and p are the rate of T infected by V_I, the rate of I_1 becoming I_2, and the rate of virion release from I_2, respectively; μ is the proportion of produced viruses being infectious; δ_{I_2} and c are the loss rate of I_2 and virions, respectively.

The target cell-limited models are parameterized and individualized based on the works presented by *Marc et al.* (12) and *Néant et al.* (δ_{I_2} by age) (13) (Table 7.4.3). Note that based on the available information, β is calculated using the basic reproduction number (R_0^v), which represents the number of newly infected cells by a single infected cell at the beginning of the infection, i.e. in a fully susceptible population.

$$\beta = \frac{R_0^v c \delta_{I_2}}{p T_0 \mu}$$

To capture the individual-level variance of viral load trajectory, parameters that will vary across individuals are sampled for each individual from log-normal distributions based on the fixed and random effects listed in Table 7.4.3.

Table 7.4.3. Parameters of the target cell-limited SARS-CoV-2 viral load kinetic model (12, 13).

Parameters	Symbol	Fixed effect	Random effect (SD)
Initial numbers of each cell population			
Target cells	T_0	1.33×10^5 cells/ml	/
Infected cells in their eclipse phase	I_{1_0}	0 cells/ml	/
Productively infected cells	I_{2_o}	$\frac{1}{30}$ cells/ml	/
Infectious virus	V_{I_0}	0 cells/ml	/
Non-infectious virus	V_{NI_0}	0 cells/ml	/
Basic reproduction number of virus on target cells	R_0^v	13.60	0.38
Rate of infected cells at an eclipse phase[1] (I_1) becoming productively infected cells (I_2)	k	$4\ d^{-1}$	/
$Age < 65$	$\delta_{I_2}^{age<65}$	1.09 d^{-1}	0.39
$Age \geq 65$	$\delta_{I_2}^{age\geq65}$	$0.84\ d^{-1}$	0.037
Rate of virions released from productively infected cells (I_2)	p	$2.8 \times 10^5 cells^{-1}.d^{-1}$	2.35
Proportion of produced viruses that are infectious (V_I)	μ	10^{-4}	/
Loss rate of infectious and non-infectious cells (V_I)	c	$10\ d^{-1}$	/

[1] Definition of eclipse phase of the infected cell: the time elapsed between successful cell infection and the start of virus production (11).

2.4.2 Antibody responses

Each person can develop immunity against the emerging pathogen through recovering from an infection or vaccination. A mechanistic model for antibody kinetics is used to project the individual antibody concentration (BAU/ml) over time. This simplified model is adapted from the work proposed by *Clairon et al.* (14) and considers the dynamics of the secreting plasma cells (S) and antibodies (Ab). Specifically, it is governed by the following ODEs.

$$\frac{dS}{dt} = fe^{-\delta_V(t-t_0)} - \delta_S S$$

$$\frac{dAb}{dt} = \vartheta S - \delta_{Ab} Ab$$

Where f is the fold-change for the steady-state memory compartment after second injection; δ_V is the declining rate of the induced vaccine antigen; t represents the time since immunization (t_0); δ_S refers to the death rate of secreting plasma cells; ϑ is the initial acceleration for antibody production; and δ_{Ab} stands for the degradation rate of antibodies.

The antibody kinetics models are parameter based on the antibody responses after the second dose of the Bnt162b2 vaccine (14) (Table 7.4.4). Same as for viral load trajectories, parameters that will vary across individuals are sampled for each individual from log-normal distributions to capture the individual-level variance of immune responses. Due to limited information on the dynamics of antibody responses after natural infection, we used the second-dose efficacy of Bnt162b2 vaccine as proxy.

Table 7.4.4. Parameters of the antibody kinetics model (14).

Parameters	Symbol	Fixed effect	Random effect (SD)
Fold change for steady-state memory compartment after second injection	f	7.1	0.9
Induced vaccine antigen declining rate	δ_V	2.7 d^{-1}	/
Death rate of S cells	δ_S	0.01 d^{-1}	/
Initial acceleration for antibody production	ϑ	24.5 d^{-2}	0.5
Antibody degradation rate	δ_{Ab}	0.08 d^{-1}	/

2.5 Between-host virus transmission and case importation

2.5.1 Transmission of the virus

We assume that cases will not isolate until NPIs are put into place. Specifically, during the first two weeks of the epidemic, individuals in the pre-clinical, asymptomatic, and symptomatic (both mild and severe) stages are assumed to transmit the disease. After that period, symptomatic individuals will isolate one day after their symptom onset (which is determined by the viral load of each individual, as described in Section 2.4.1). Upon isolation, these cases will not be able to transmit to non-household members, nor household members. The probability of transmitting the pathogen (p^{trans}) between each contact pair is determined by the transmissibility of the index case (p^{VL}) and the susceptibility of the contact (p^{imm}) at the time of contact (t).

$$p_t^{trans} = p_t^{VL} \times p_t^{imm}$$

2.5.2 Linking viral load to infectiousness

The infectiousness (i.e., the probability of transmission) of the index case is modeled as a function of the viral load (VL). To account for this relationship, we adapted a model proposed by *Marc et al.* (12), which assumes a logit-linear effect of viral load that varies according to the type of the contact (h^c; household or non-household):

$$logit\ (p_t^{VL}) = \begin{cases} \alpha & if\ \log_{10} VL_t \leq 6 \\ \alpha + \left(\gamma_1 h^c + \gamma_2 (1 - h^c)\right) \times \exp\ (b) \times (\log_{10} VL_t - 6) & if\ \log_{10} VL_t > 6 \end{cases}$$

where α is the baseline probability of transmission; γ_1 and γ_2 represent the effect of household and non-household contact on the transmission probability, respectively; h^c serves as an indicator of type of the contact ($h^c = 1$ for household contact and $h^c = 0$ for non-household contact); and b is a Gaussian individual random effect of γ_1 and γ_2 with variance of 0.85^2.

The baseline probability of transmission (α) is simulated to match the R_0 of the virus using the average number of daily household (c^h) and non-household (c^{nh}) contacts, and the abovementioned time-varying probability of transmission model. Brent's method (15) is used to find the best estimate for α given the following equation:

$$R_0 = \beta^h c^h D + \beta^{nh} c^{nh} D$$

$$= \sum_0^D \left(p_t^{VL,h} c^h + p_t^{VL,nh} c^{nh}\right)$$

$$= \sum_0^D \begin{cases} \frac{\exp\ (\alpha)}{1 + \exp\ (\alpha)} \times (c^h + c^{nh}) & if\ \log_{10} VL_t \leq 6 \\ \frac{\exp\ (\alpha + \gamma_1 \times \exp\ (b) \times (\log_{10} VL_t - 6)\ )}{1 + \exp\ (\alpha + \gamma_1 \times \exp\ (b) \times (\log_{10} VL_t - 6)\ )} \times c^h + \frac{\exp\ (\alpha + \gamma_2 \times \exp\ (b) \times (\log_{10} VL_t - 6)\ )}{1 + \exp\ (\alpha + \gamma_2 \times \exp\ (b) \times (\log_{10} VL_t - 6)\ )} \times c^{nh} & if\ \log_{10} VL_t > 6 \end{cases}$$

where β represents the transmission rate; D is the duration of infectiousness.

The rest of the parameters are sampled from log-normal distributions for each individual to incorporate the variances across contact pairs (Table 7.4.5).

Table 7.4.5. Parameters of the viral load to probability of transmission model.

Parameters	Symbol	Fixed effect	Random effect (SD)
Effect of household contact on the transmission probability	γ_1	0.49	0.85
Effect of non-household contact on the transmission probability	γ_2	0.21	0.85

2.5.3 Linking antibody level to susceptibility

Information on the relationship between antibody levels and the protection against infection is very limited. We estimated this relationship by assuming an Emax sigmoid model of antibody levels (Ab) and probability of being protected from infections ($p^{control}$). Then, we obtained the susceptibility (p_t^{imm}) of the contact:

$$p_t^{imm} = 1 - p^{control}$$

$$p^{control} = E_0 + \frac{E_{max} \times (\log_{10} Ab)^{\gamma^{hill}}}{EC_{50}^{\gamma^{hill}} + (\log_{10} Ab)^{\gamma^{hill}}}$$

where E_0 and E_{max} represent the baseline and maximum possible effect of antibody protection against infection, respectively; γ^{hill} is the Hill coefficient that controls the steepness of the curve; EC_{50} is the concentration of antibodies (in log10 scale) required to achieve 50% of the vaccine's maximum effect. To estimate the values of these parameters (Table 7.4.6), we referred to a model based on non-human primate data jointly modelling viral load and antibody dynamics in naïve animals. We defined $p^{control}$ as the probability animals have to maintain an undetectable viral load after infection, and conducted simulations to identify this relationship. Note that, in this preclinical study, antibodies were measured using the MesoScale Discovery (MSD, Rockville, MD) pseudo-neutralization assay and were expressed in Arbitrary unit per milliliter (AU/ml), just as the EC_{50} parameter. As such, the antibody level projected from the immunity model is converted from the WHO International Standard BAU/mL to AU/ml using the conversion formula calibrated by the manufacturer of the MSD assay: BAU/ml = 0.00901×AU/mL (16). The estimated EC_{50} was within the range of the observed estimates of SARS-CoV-2 vaccine EC_{50} (17).

Table 7.4.6. Parameters of the Emax sigmoid mode of antibody levels and susceptibility of the contact.

Parameters	Symbol	Value
Baseline effect of antibody on protection against infection if no antibody generated	E_0	0
The maximum effect of antibody on protection against infection	E_{max}	1
The concentration of antibodies required to achieve 50% of the vaccine's maximum effect	EC_{50}	4.08 $\log_{10} AU/ml$
Hill coefficient	γ	32

2.5.4 Case importation

Imported cases can influence transmission dynamics when local transmission levels are low. For instance, even after transmission is controlled through vaccination, imported cases could trigger new transmission chains under certain conditions (e.g., wanning immunity, low protection induced by vaccine). For simplicity, we allow weekly importation of one individual aged 20-59, who is not currently infected with SARS-CoV-2, to import the virus into the population.

2.6 Vaccine rollout strategies

Though randomized clinical trials (RCT) used to support vaccine approvals can provide strong evidence on their safety and short-term effects, there will be limited information to assess the impact of vaccines on outcomes such as hospitalizations, mortality, and other rare severe outcomes (18). To examine the impact of vaccine rollout strategies on transmission, we assumed vaccines become rapidly available on day 100, and explored two different approaches to vaccination. The first strategy corresponds to a randomized rollout of vaccines. The second strategy follows an age-based rollout, similar to the approaches adopted by many countries during the COVID-19 pandemic to minimize severe outcomes (19). Specifically, individuals aged 70 and older will be prioritized with the age threshold lowering by 10 years each week. For both strategies, we assume a one-dose vaccine and that the vaccination campaign reaches 80% coverage of the population within 4 months, as observed in Israel during the COVID-19 pandemic (20).

3. Model simulation

The model was implemented using a modular coding structure. Each of the 4 modules (① contact and infection, ②case importation, ③disease progression, ④vaccination scenarios) run sequentially at each time step. The model was simulated over 1.5 years, starting from the introduction of one imported case into a completely susceptible population. Results are summarized based on the median of 100 simulation runs.

4. Scenarios and sensitivity analysis

An ideal vaccine is expected to induce high titers of antibodies and maintain long-lasting immunological memory (21). Antibodies induced by vaccines can not only neutralize the virus, but also directly block the virus's ability to infect cells. To evaluate the impact of different vaccine features on transmission, a series of scenarios were examined based on different values of the three important vaccine parameters: 1) EC50, which correlates the immune response and protection from infection (22); 2) half-life of secreting plasma cells, which partially governs the duration of protection (23); and 3) rate of target cell infection by the virus (β), which influences attachment of virus to host cells (24). The choices of scenarios are based on the characteristics of the second dose of the Bnt162b2 vaccine. Detailed combinations of the three parameters are summarized in Table 7.4.7.

Table 7.4.7. Table of scenarios examined in the model for each basic reproduction number $R_0 \in \{2, 2.5, 3, 3.5\}$.

Scenario descriptions	Scenario names	EC50	Half-life of the secreting plasma cells ($\frac{In(2)}{\delta_S}$)[1]	Scale factor of the current rate of target cells being infected by the virus (β)[2]
Current vaccine feature	Current	4.08	70 days	1 time
Improve EC50, keep half-life of S cells and β the current value	EC50 = 1	1	70 days	1 time
	EC50 = 1.5	1.5		
	EC50 = 2	2		
	EC50 = 2.5	2.5		
	EC50 = 3	3		
Change β, keep EC50 and half-life of S cells the current value	0.5 beta	4.08	70 days	0.5 time
	1.5 beta			1.5 times
Increase half-life of S cells, keep EC50 and β the current value	0.5-year half-life	4.08	Half a year	1 time
	1-year half-life		1 year	
	2-year half-life		2 years	
	20-year half-life		20 years	

Note:

[1] The values of half-life of the secreting plasma cells correspond to the values of δ_S = 0.01 (70 days); δ_S = 0.00385 (half a year); δ_S = 0.0019 (1 year); δ_S = 0.00095 (2 years); and δ_S = 0.00009 (20 years).

[2] The scale factors of the current rate of target cell infection correspond to the values of $\beta = 3.65 \times 10^{-5}\ ml/virus.day$ (1 time), $\beta = 1.83 \times 10^{-5}\ ml/virus.day$ (0.5 time), and $\beta = 5.38 \times 10^{-5}\ ml/virus.day$ (1.5 times).

5. Outcome measures

For each vaccine feature examined–EC50, half-life of secreting plasma cells, and infection rate of target cells by virus–we aim to determine the proportion of infections and hospitalizations averted, in the face of pathogens with R_0 ranging from 2 to 3.5. Additionally, we compare the impact of different vaccine features on transmission by presenting the different trajectories of the daily number of new infections, the cumulative rate of hospitalization per 100,000 population, and the number of hospital beds occupied over time. To assess the impact of population size on hospitalization, the model will be run with a population of 5,000, using vaccine features from Scenario 1 ("*Current*" vaccine features) as part of the sensitivity analysis.

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7.4.2. Supplementary figures

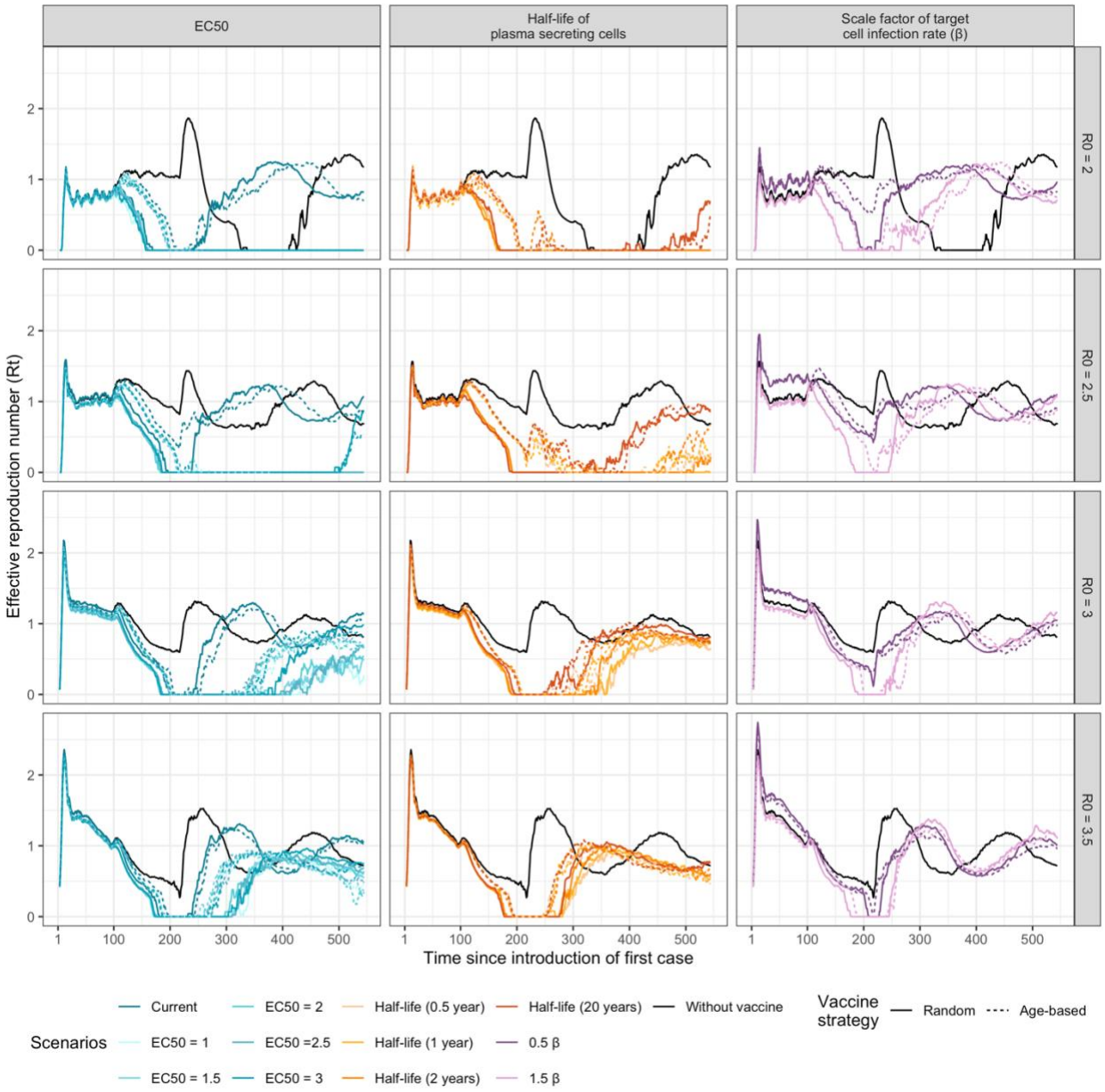

Figure 7.4.3. Time-varying effective reproductive number for each scenario and vaccine strategy.

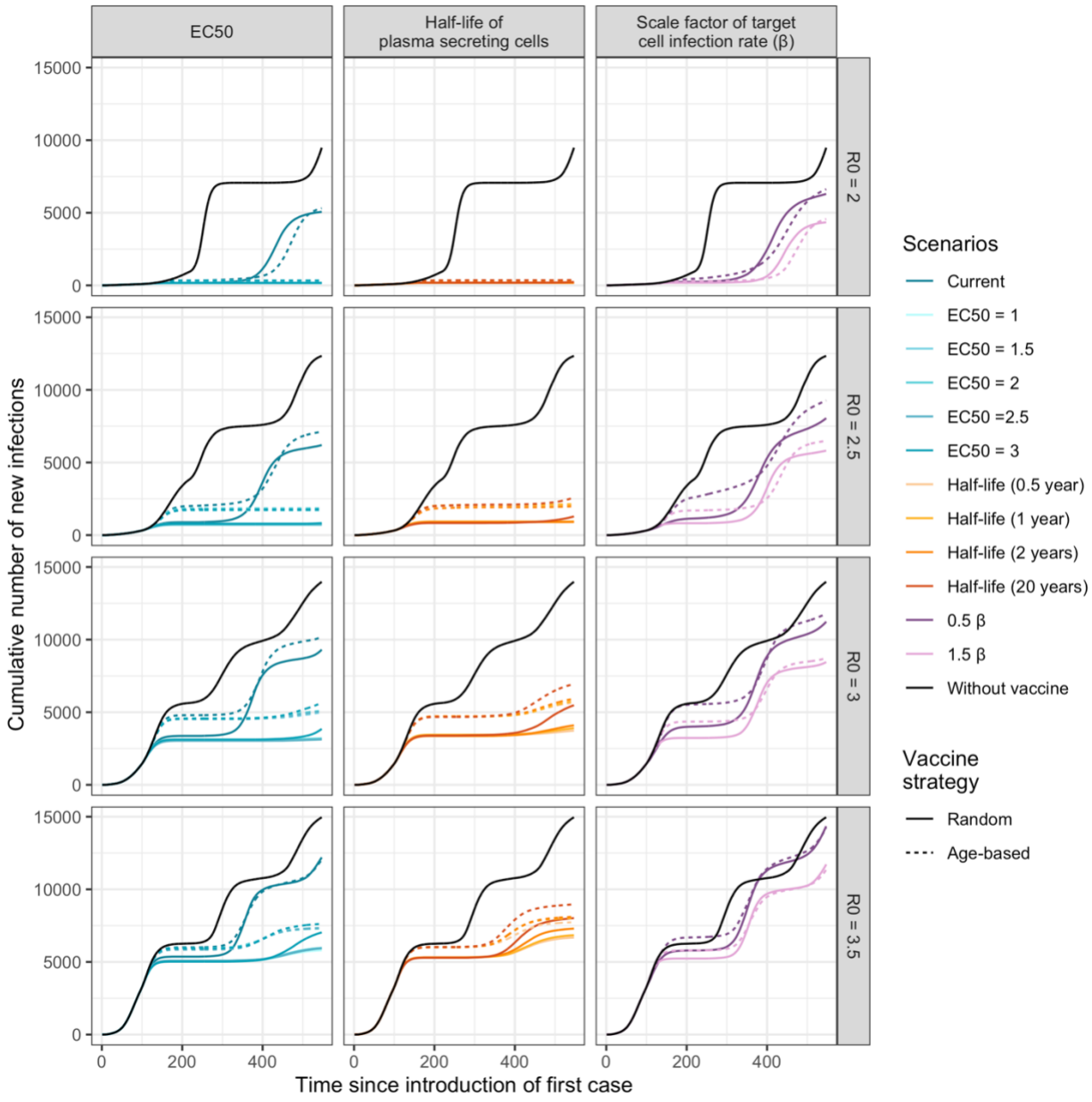

Figure 7.4.4. Cumulative number of infections for each scenario and vaccine strategy.

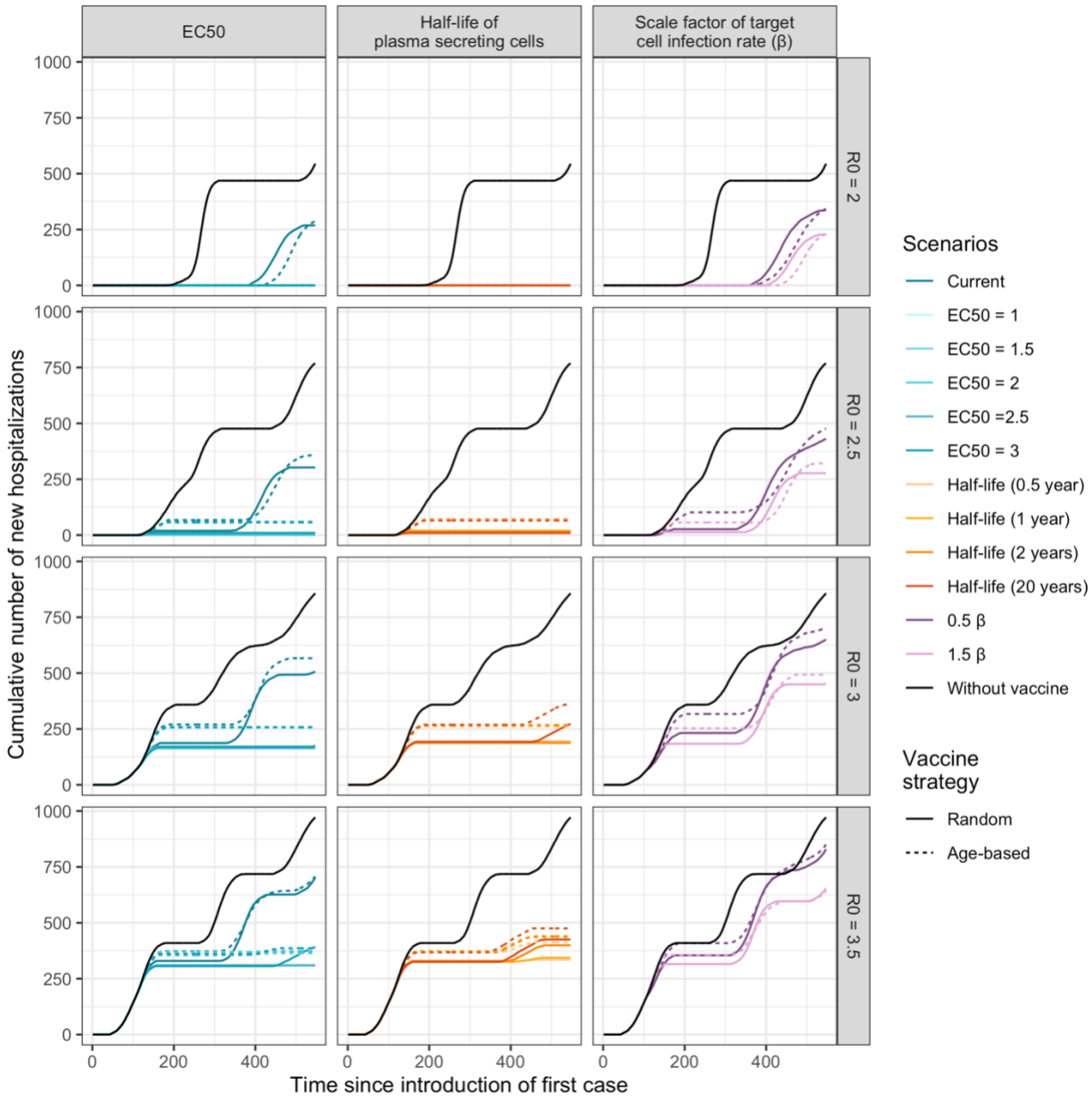

Figure 7.4.5. Cumulative number of hospitalizations for each scenario and vaccine strategy.

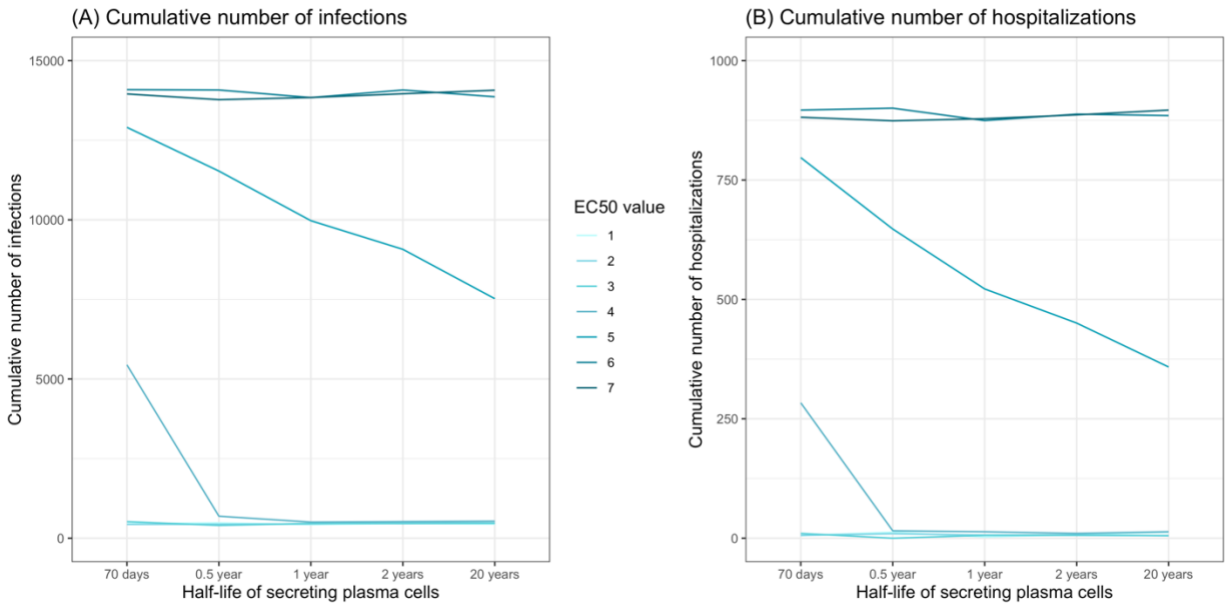

Figure 7.4.6. Changes in cumulative number of infections and hospitalizations by half-life of secreting plasma cells with fixed EC50 values from 1 to 7, assuming a randomized vaccine allocation strategy.

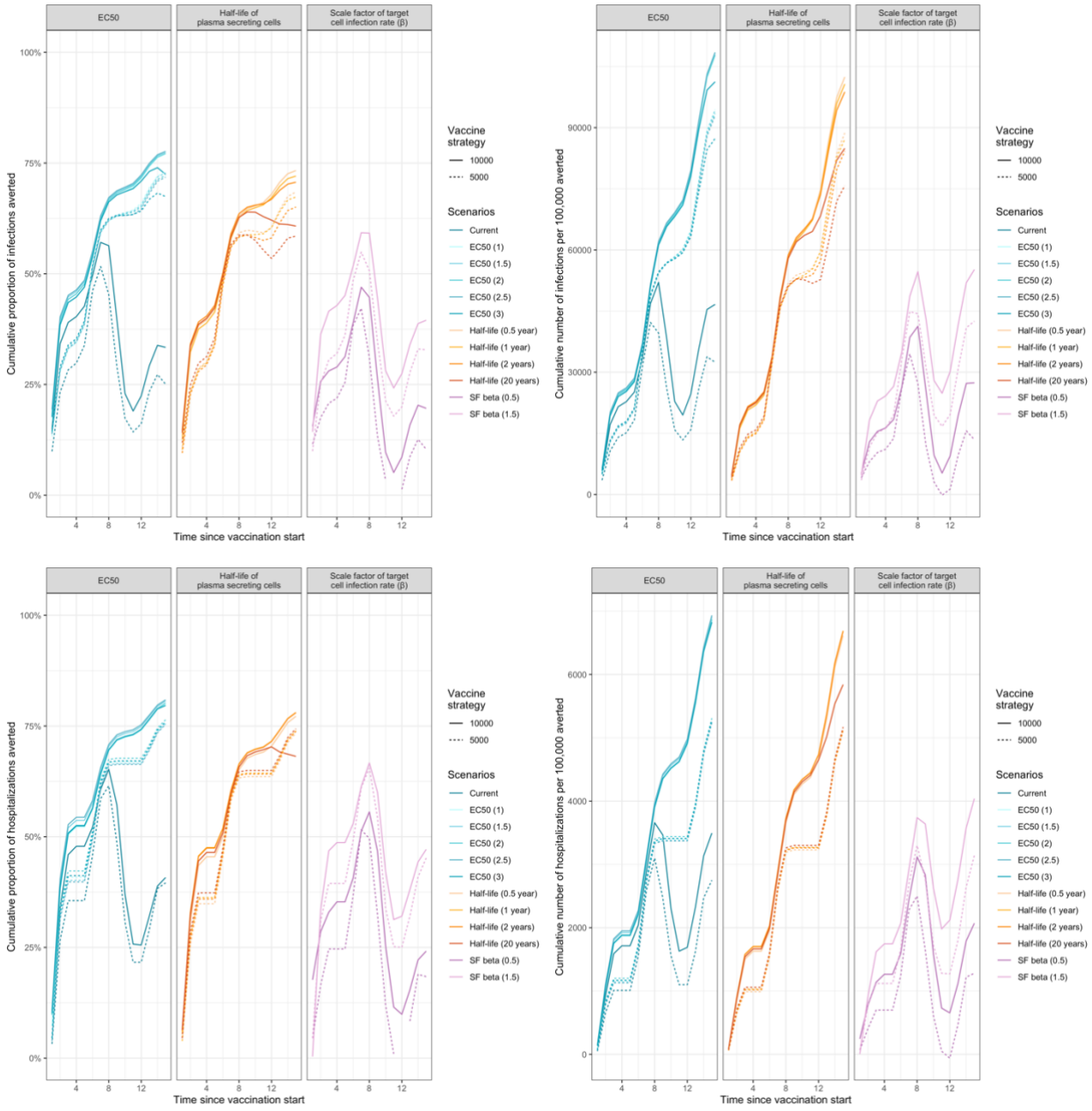

Figure 7.4.7. Comparing the effect of different population sizes (10,000 population vs. 5,000 population).

Panel A: cumulative fraction of infections averted. Panel B: cumulative number of infections averted per 100,000 population. Panel C: cumulative fraction of hospitalizations averted. Panel D: cumulative number of hospitalizations averted per 100,000 population.

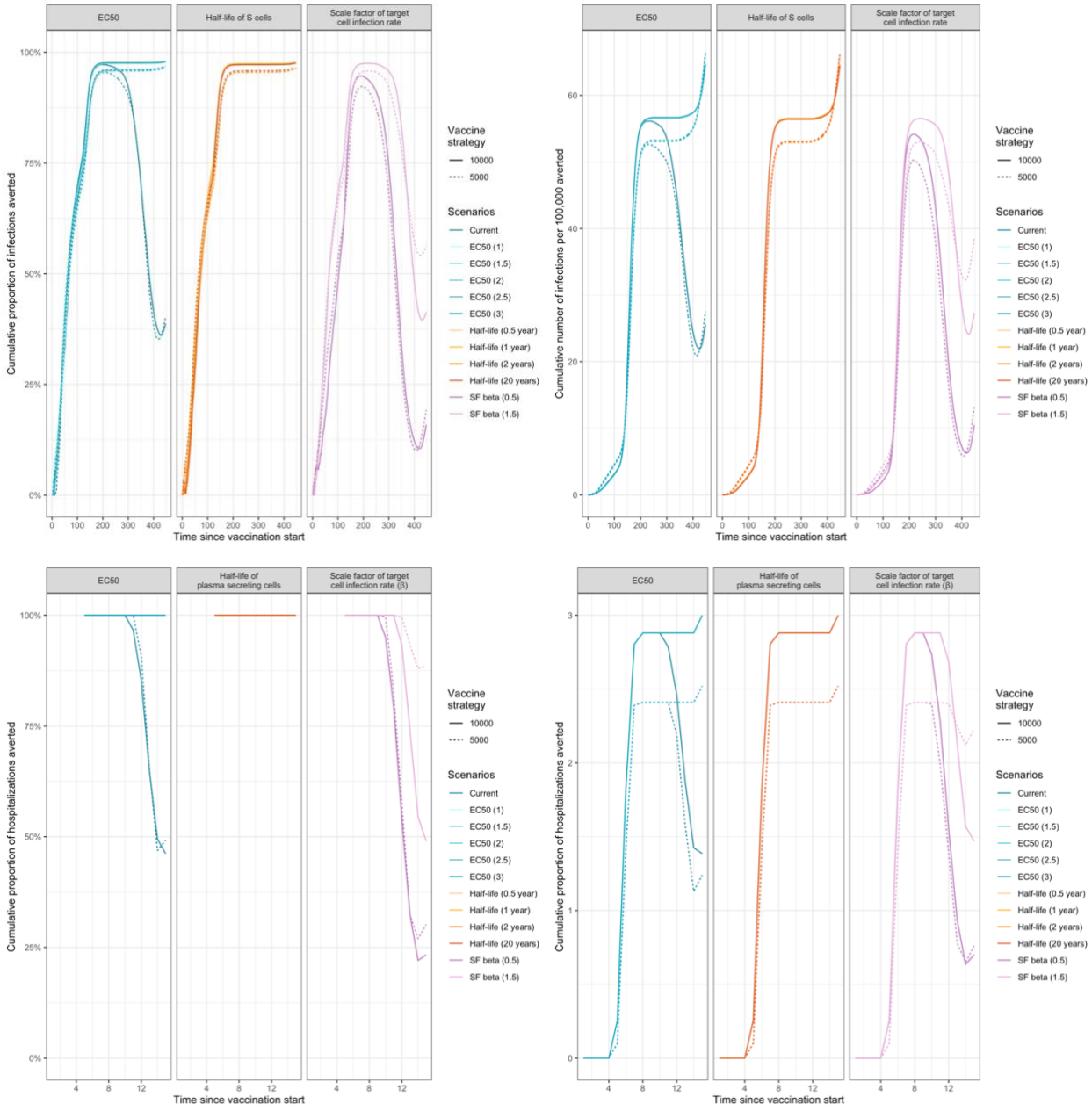

Figure 7.4.8. Comparing the effect of different population sizes (10,000 population vs. 5,000 population), when assuming all contacts are non-household members.
Panel A: cumulative fraction of infections averted. Panel B: cumulative number of infections averted per 100,000 population. Panel C: cumulative fraction of hospitalizations averted. Panel D: cumulative number of hospitalizations averted per 100,000 population.

Chapter 8. Discussion and Conclusions

8.1. Discussion

Canada had lower SARS-CoV-2 case counts, COVID-19 mortality, and excess deaths, and higher vaccination coverage than most G10 countries (i.e., a group of 11 advanced economy countries)–but also experienced some of the most restrictive public health measures (237). However, Canada performed worse on these same measures compared to nations like China and South Korea, where stricter measures were employed (82, 238). Moreover, Australia, a peer nation with a federated healthcare system similar to Canada, was able to achieve local control and had better health outcomes (239). Important lessons need to be drawn from Canada's COVID-19 response. These include improvements in data-sharing between provinces and territories and the federal government, enhancement of mathematical modelling capacity, alleviation of health inequities that worsened during the pandemic, avoidance of an exhausted healthcare workers force that limited hospital capacity, and restoration of trust from long-term care homes, among others (240-242). By comprehensively examining the elements of the Canadian COVID-19 response–from mathematical modelling, health inequities, and drivers of in-hospital COVID-19 mortality–my thesis provides an in-depth understanding of some of the most salient pandemic challenges and outcomes. Moreover, it offers evidence-based insights to inform future vaccination strategies and improve pandemic preparedness.

In my first manuscript, I highlighted the diversity of modelling approaches and collaboration structures employed across provinces. These reflected regional variations in COVID-19 transmission dynamics, data availability, and modelling capacity. Importantly, I identified in this article several challenges faced by modellers and which have put particular emphasis on the necessity of timely availability of high-quality surveillance data that are linkable across different healthcare datasets. "*A mathematical model is as good as the data it uses*" (243) and quality of the data determines the accuracy of the model's projections (244). At the federal level, a recent publication by members of the *PHAC External Modelling Network for Infectious Diseases* (PHAC EMN-ID) on the role of mathematical modelling for pandemic preparedness arrived at a similar conclusion, highlighting the important challenges related to the "*availability of linked public health, hospital and genomic data in Canada*" (95). More specifically, data on new

cases with sociodemographic information (including sex, age, are of residence, ethnicity, social determinants of health, and genotype of the pathogen) and epidemiological information (including date of symptom onset, travel history, and contact information), with linkage to hospitalization and mortality databases are required in response to future pandemics. In addition, regular seroprevalence surveys with representative samples should be performed to better understand the population-level prevalence, adjust for under-detection of surveillance data, and better inform the models. With regard to the structure modeling teams, it would be beneficial to establish frameworks that encourage enhanced collaboration among government, academic, and community partners. This could be achieved through greater transparency, open dialogue, and clear justification of decisions to ensure alignment and mutual understanding among all stakeholders.

An editorial entitled "*COVID-19 data and modelling: We need to learn from and act on our experiences*" accompanied my first manuscript (245). This editorial by Michael Wolfson agreed on the importance of improving data availability, linkage, and quality, addressing inequalities, supporting on-going collaborations, and increasing the modelling expertise in Canada. However, he criticized my statement that "*there was no one size fits all modelling approach*" as being "*rather anodyne*". Instead, he would have wanted me to draw lessons on the modelling approaches and team structures that were the most effective. I argue that this criticism does not appreciate that the effectiveness of modelling approaches depends on the type and quality of the surveillance data, which differed greatly by provinces and through time. The same can be said about team structure: some regions do not have enough modelling capacity to set up larger teams, such as the one established in Ontario for instance. The last criticism mentions that I did not address the federal role in modelling and data flows. However, provinces and territories were responsible for implementing and lifting the majority of NPIs (e.g., school closure, stay-at-home), often applying them to some selected local health regions only. Further, when surveillance data gets harmonized and aggregated across jurisdictions, there can be loss of granularity and information which could limit federal modelling efforts. Such a centralized system could risk losing the nuances that are necessary for effective regional public health interventions.

My second manuscript quantified and compared the geographical concentration of SARS-CoV-2 cases by social determinants of health across 16 cities in four Canadian provinces–British Columbia, Manitoba, Ontario, and Québec–using Gini coefficients and Lorenz curves. Overall,

half of the cumulative cases in each city were concentrated in areas where only 21%-35% of their population resided. Additionally, the results showed disproportionate burden of cases in disadvantaged communities with lower income and educational attainment, and in areas with higher proportion of visible minorities, recent immigrants, high density housing, and essential workers. Besides the fact that these population were generally vulnerable (i.e., more likely to experience adverse health outcomes than general population) (246, 247), the public health interventions during the COVID-19 pandemic might have aggravated the inequalities in SARS-CoV-2 transmission by impacting the population differently. For example, essential workers were not able to work from home, along with the limited and poor condition of personal protective equipment (248), imposed on these individuals a greater risk of SARS-CoV-2 infection.

Inequalities in SARS-CoV-2 case burden stemming from social determinants of health has been noted by previous studies conducted in Canada and other countries such as the United Kingdom and the United States (227, 249-254). The overall patterns observed in my paper are consistent with the findings from similar contexts in Canada, the United Kingdom. However, those studies focused on fewer locations. Presenting estimates for 16 Canadian cities provides compelling evidence that inequalities were important across the country, even if the unique contribution of specific SDOH varied by city. The results from my paper later assisted in the adoption of the "hotspot strategy" for the vaccine rollout in Toronto. Nevertheless, early pandemic responses in Canada overlooked health inequalities, neither did the COVID-19 research investments (255). As the lessons of COVID-19 has shown, social determinants of health should be integrated as part of the pandemic response strategies and research priorities.

In my third manuscript, I leveraged population-based databases from Ontario and Québec and examined mortality trends and length of stay among hospitalized patients with COVID-19 during the first three epidemic waves using logistic regressions and marginalized standardization. In both provinces, mortality was initially very high but declined by 22%-point in Québec and by 11%-point in Ontario, after adjusting for patient profiles and facility characteristics. This highlighted the impact of improved clinical management and patient treatments (256-258). For instance, advancements in treatment protocols such as corticosteroid use, anticoagulation therapy, and vaccination, likely played a significant role in reducing mortality (259-261). On the other hand, patient load appeared to be a critical factor influencing the in-hospital mortality risk during the

pandemic: the adjusted odds of morality in the highest patient load quintile were 1.2 and 1.6 in Ontario and Québec, respectively. Hospitals operating near or beyond capacity led to significant challenges in providing optimal care, strained healthcare resources (e.g., staff, ventilation equipment), and thus contributed to the higher mortality risks (262). Moreover, the regional differences in length of stay between Ontario and Québec might have reflected differences in healthcare capacity, as Ontario consistently had longer stays and higher proportion of patients admitted directly to the ICU throughout the study period. The latter might explain the lower mortality risk in Ontario early in the pandemic. These findings underscore the importance of healthcare capacity on COVID-19 outcomes.

Mathematical modelling can contribute not only to the informing the response during an ongoing pandemic, but also for pandemic preparedness. The use of vaccines during the COVID-19 pandemic has highlighted the feasibility of rapidly developing, testing in clinical trials, and distributing vaccines at scale to effectively combat emerging pathogens (9). Integrating dynamics of viral load, antibody, and virus transmission, my fourth manuscript examined the desired vaccine features against future Disease X pandemic caused by a SARS-CoV-2-type of virus. Specifically, my paper highlighted the importance of increasing the potency ($EC50 \leq 3$) and the persistency (half-life of S cells≥ 1 year) of the vaccine to reduce the need for frequent dosing and booster vaccinations. This approach not only improves convenience for individuals but also optimizes healthcare resource utilization by minimizing logistical challenges and associated costs.

Achieving the desired vaccine feature needs to use appropriate technology to deliver these features. During the COVID-19 pandemic, messenger RNA (mRNA) vaccines showed the highest efficacy to prevent symptomatic infection compared to vaccines developed using other platforms (263). More importantly, mRNA vaccines stand out compared to traditional vaccine technologies for their superior manufacturing and scale-up efficiency, as well as their adaptability to emerging variants (264, 265). These characteristics make mRNA vaccines one of the most promising platforms for developing vaccine candidates in future pandemics, enabling rapid responses to evolving pathogens. My fourth paper addresses this priority research area for pandemic preparedness.

8.2. Strengths and Limitations

Limitations

The main sources of information I leveraged for my thesis included primary data collection, administrative databases, and surveillance data. While the latter two were the most authoritative and comprehensive databases available, the findings were inevitably subject to the limitations inherent to the nature of these data sources. For instance, my narrative review of provincial modelling efforts could have missed some teams or models that were not part of the modelling networks I surveyed. Regarding the administrative and surveillance databases, for instance, they lacked critical variables (i.e., ethnicity, occupation), sometimes had coarse granularity (i.e., aggregated), and missingness in existing variables.

The findings of my thesis should be interpreted considering following limitations. Firstly, underreporting of cases in surveillance datasets of SARS-CoV-2 infections might have led to underestimation of case counts. The surveillance datasets were able to catch all cases that were diagnosed at testing facilities through mandatory reporting. A study conducted in Toronto found that individuals who were visible minorities or had a lower household income were less likely to be tested (250). In this case, the estimates of my second paper might have underestimated the inequalities of SARS-CoV-2 case burden in those vulnerable communities. However, my qualitative conclusions would not have changed. On the other hand, underreporting is unlikely to have affect the databases related to COVID-19 hospitalizations given their complete population coverage.

Secondly, when comparing results across provinces, caution is necessary due to the slight differences in case definition, available information, and protocols. For example, in Québec, due to the restrained testing capacity especially during the early phase of the epidemic, SARS-CoV-2 cases identified through epidemiological links (e.g., close contact of a laboratory confirmed case and showing symptoms of SARS-CoV-2 infection) were also included in the official reported number of cases, while the rest of the provinces included in my analyses did not include these individuals in their counts. Additionally, some hospitalization variables in Ontario lacked disaggregation, which might have obscured the patterns such as the trend of mortality risk by

patient load observed in Québec. However, these heterogeneities did not affect the province-specific estimates, ensuring their validity within provincial analyses.

Moreover, the hospitalization datasets we used included all patients with a positive COVID-19 diagnosis, but we do not know if the reason for the hospitalization was due to their COVID infection (i.e., incidental). In other words, not everyone included in the analysis of my third manuscript was hospitalized due to COVID-19. If patients were hospitalized for other reasons, they might have milder symptoms and thus less likely to die. This might lead to underestimation of the mortality risk. Finally, errors during data entry and pre-processing by medical archivists are inevitable. While some errors were corrected during subsequent transmissions, others might remain. However, according to expert opinion, these errors are likely random rather than systematic which would not bias my results.

The findings of my fourth manuscript should be contextualized given some of the assumptions I had to make. Both the within-host and between-host models were based on the natural history of SARS-CoV-2 and parameterized as such, albeit I explored a wide range of basic reproduction number. Further, while it is likely that a future Disease X pathogen will share some characteristics similar to that of SARS-CoV-2, they may differ significantly in some respects (i.e., morbidity, mortality). However, targeting prototype pathogens remains a strategic approach. Importantly, the model is flexible and can be adjusted for other respiratory pathogens, enhancing its applicability in future scenarios.

Strengths

In terms of strengths, my thesis adopted a multi-province lens to examine the Canadian COVID-19 pandemic. I offered a detailed comparison of the disparities in SARS-CoV-2 transmission, severe outcomes, healthcare capacity, and public health strategies across the country. For instance, my first manuscript included mathematical modelling teams from six provinces, together encompassing >90% of the total Canadian population. My second manuscript included four provinces with accessible DA-level SARS-CoV-2 case data, while the third used population-based cohorts of hospital admissions in Ontario and Québec (covering approximately 60% of Canada's population), improving the precision and generalizability of previous studies that focus on a single city or facility. My work delivered nuanced insights into Canada's COVID-19 epidemic

and response strategies. To my knowledge, my first three manuscripts are rare examples of research on COVID-19 that combined insights from multiple provinces in Canada.

Furthermore, my thesis leveraged a diverse range of methodologies across the four manuscripts. These included a narrative review, descriptive epidemiology and inequality measurements, regression analysis, and mathematical modelling of disease transmission as well as within-host viral load and immune response dynamics models. This methodological diversity highlights the multifaceted contributions of public health and epidemiology to both pandemic response and preparedness.

8.3. Conclusions

Mathematical modelling is a useful tool to guide pandemic response and assist preparedness. Efforts need to be made to overcome data limitation, increase pandemic response capacity, and smooth collaboration barriers during non-crisis period. Pandemic responses should consider heterogeneities and tailor the interventions based on local context. Continued investments should be devoted to developing a more resilient healthcare system capable of effectively planning capacity and allocating resources during public health emergencies. Additionally, optimizing vaccine features, and leveraging adaptable platforms such as mRNA technology are critical to designing effective vaccine candidates for future pandemics, if distributed equitably at global and national levels.

Chapter 9. References

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