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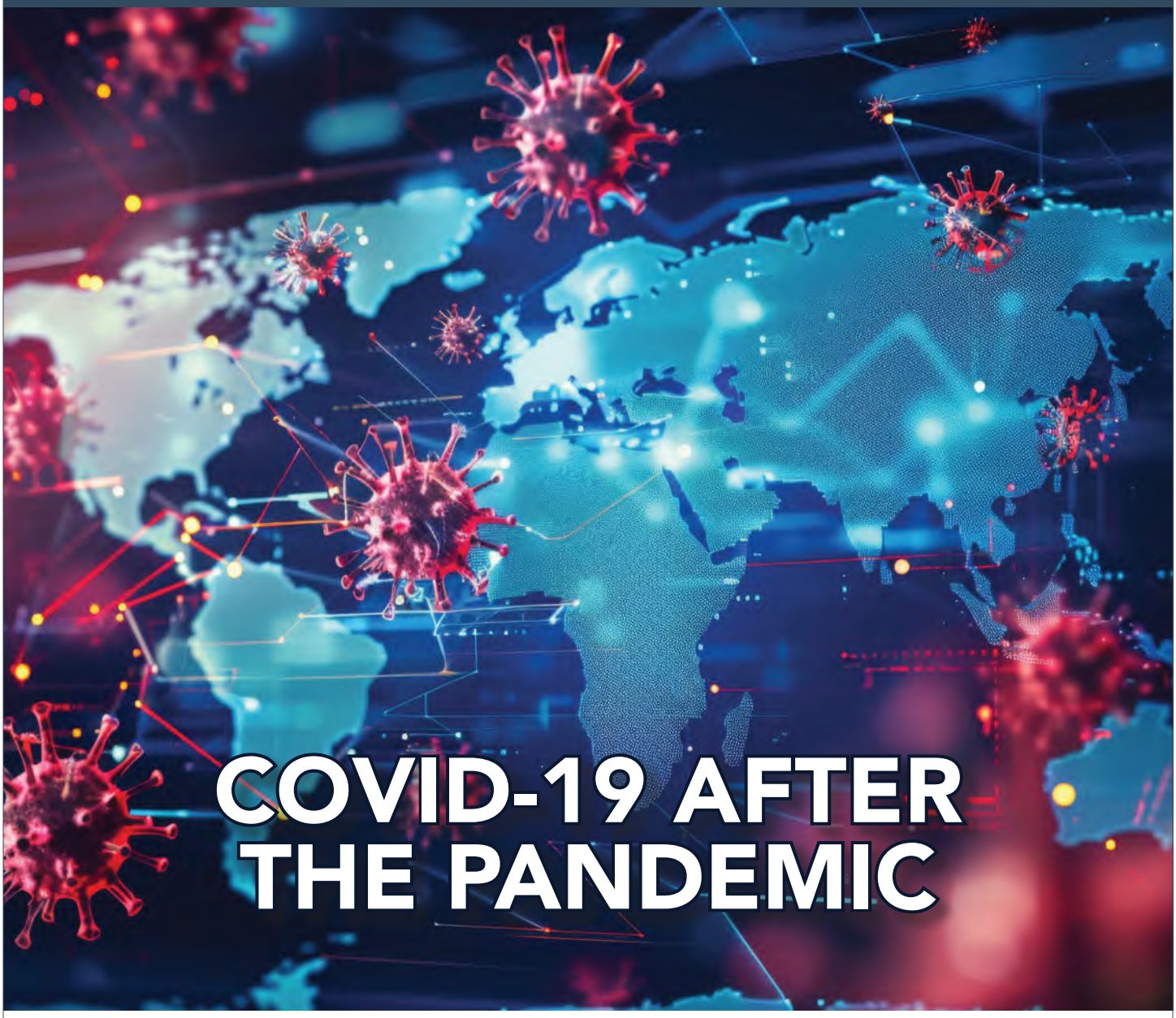

COVID-19 AFTER THE PANDEMIC

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

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The cover photo represents a digital illustration of a virus overlay on a world map, representing the global impact of a pandemic and the interconnectivity of outbreaks. The image was taken from Adobe Stock #772355307.

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COVID-19 AFTER THE PANDEMIC

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EDITORIAL

Lessons learned from COVID-19: Harnessing community insights for better vaccination outcomes

Theresa Tam[1]*

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Keywords: COVID-19, preparedness and response, trusted relationships, community approaches, partnerships and innovations

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Introduction

Vaccination is a cornerstone of public health. The COVID-19 pandemic underscored the importance of local, innovative and equity-oriented approaches to achieve comprehensive vaccination coverage, particularly for populations with complex needs. Community leaders and organizations are uniquely positioned to inform and drive efforts that reduce barriers to access and foster supportive environments. They also play a vital role in the vaccination evidence system by supporting the development of research tools and frameworks that resonate with community needs.

Communities are diverse and intersecting by nature. Individuals may belong to multiple groups with shared geography, interests, lived experiences, cultures or identities. Taking a community-oriented approach to vaccination requires us to build strong relationships within and across communities. These relationships can be leveraged through different levels of engagement, from consulting community leaders on existing vaccination programs to supporting community-led projects.

Existing community-based vaccination initiatives (1) can offer valuable insights for public health planning of routine and pandemic vaccination programs. Established in 2016, the Public Health Agency of Canada's Immunization Partnership Fund (IPF) is an example of an initiative that pivoted during the pandemic to be community-oriented (2). The IPF funded over 100 community-driven COVID-19 vaccine projects aimed at increasing healthcare provider capacity, supporting community-based education and access initiatives and building capacity for evidence-based communication. Given the success of the projects, the IPF has since expanded its community-oriented approach towards routine and respiratory vaccine projects.

Leveraging trusted relationships

We achieve better vaccination outcomes when we support trusted community organizations. The following IPF projects used multifaceted approaches that built on pre-existing programs to offer services that prioritized community needs, trusted relationships and transparency.

Inner City Health Associates

Based in Toronto, Inner City Health Associates (ICHA) employed community health workers (CHWs) with lived experience to facilitate vaccination for individuals experiencing homelessness. These CHWs used destigmatizing approaches to build rapport, foster non-judgemental health discussions, identify high demand clinic locations and adjust scheduling for accessibility. This resulted in 122 pop-up clinics and the vaccination of 1,929 individuals with complex needs from 2023 to 2024.

Inner City Health Associates also relied on community peer ambassadors to co-develop resources, provide training and conduct tailored on-site outreach. Those with medical experience were trained in COVID-19 vaccine administration, enabling peer-led clinics that bridged healthcare and shelter services. Inner City Health Associates are now repurposing these interventions to increase routine and high-risk vaccination services for people experiencing homelessness in Toronto.

Dr. Peter Centre

Between 2021 and 2024, the Dr. Peter Centre (DPC) administered 37 low barrier microgrants to promote vaccination among underserved populations across Canada. Many recipient organizations described the microgrant model as a "game changer" for hyper-local groups experiencing capacity constraints.

From 2023 to 2024, micrograntees organized 42 tailored vaccination clinics, administering over 2,100 vaccinations in accessible and familiar spaces. Micrograntees addressed intersecting health needs through wrap-around approaches informed by harm reduction models, such as offering COVID-19 vaccinations alongside testing and treatment for sexually transmitted and bloodborne infections. Over the next two years, DPC will continue to address access barriers and empower clients with the knowledge needed to make informed decisions about respiratory and other vaccines.

Tailored and innovative community approaches

Community engagement can facilitate our understanding of how health information is accessed and used. Many IPF projects leveraged trusted community leaders to act as community ambassadors and to deliver tailored services that helped to create a supportive vaccination environment.

Alberta International Medical Graduates Association

The Alberta International Medical Graduates Association (AIMGA) used international medical graduates as vaccine navigators during the COVID-19 pandemic to promote vaccination among newcomers in Calgary. These community leaders applied their medical expertise and cultural knowledge to build trust and reduce language barriers for vaccination services. By partnering with Alberta Health Services and other immigrant-serving organizations, they were also instrumental in providing thousands of COVID-19 vaccines to at-risk workers at meat processing facilities in Alberta.

From 2023 to 2024, AIMGA continued to enhance access to evidence-based health information for diverse populations through culturally safe, multi-lingual clinics and social media campaigns in 25 languages. Building on their pandemic efforts, AIMGA is now working to increase vaccine literacy and uptake of routine and respiratory virus vaccines in Calgary's newcomer populations.

Regroupement des centres d'amitié autochtones du Québec

Regroupement des centres d'amitié autochtones du Québec (RCAAQ), a collective providing culturally safe services to urban Indigenous populations in Québec, led the Miro Matisiwin project ("Wellbeing") during the pandemic. This initiative used fixed-site and mobile clinics to increase COVID-19 vaccine uptake among individuals who were not well-served by traditional vaccination services.

Expanding on the learnings of Miro Matisiwin, RCAAQ launched the Mamu project ("Together") from 2023 to 2024 to enhance awareness and uptake of routine and seasonal vaccinations. As part of this program, RCAAQ developed culturally relevant promotional materials to reach 120,000 online users. *Regroupement des centres d'amitié autochtones du Québec* continues to promote routine and seasonal vaccinations in urban Indigenous populations by prioritizing culturally safe and trauma-informed care, decreasing access barriers to vaccination and developing tailored resources.

Conclusion

Now is the opportune time to reflect on how we can sustain the community partnerships and innovations developed prior to, during and post the COVID-19 pandemic. As I raised in my 2023 report, this will require us to consistently integrate community-centred planning across our preparedness and response efforts, including broader pandemic planning, outbreak responses and routine programming (3). We can support the full participation of communities in these efforts through streamlined and coordinated funding mechanisms that meet the needs of community organizations. If we are intentional in our efforts to fortify community relationships and be inclusive of community perspectives, we will be working towards a future in which everyone can experience the benefits of vaccination and, ultimately, better health outcomes against vaccine-preventable diseases.

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Evidence brief on facilitators, barriers and hesitancy of COVID-19 booster doses in Canada

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Abstract

Background: Understanding the facilitators, barriers and hesitancy to accepting COVID-19 booster doses is important for encouraging recommended vaccination. This evidence brief summarizes literature on the intention to accept or reject COVID-19 vaccine booster doses and the factors associated with intention/uptake among individuals in Canada.

Methods: A database of COVID-19 literature established at the Public Health Agency of Canada was searched for articles referencing vaccination and knowledge, attitudes and behaviours towards COVID-19 boosters. A grey literature search of Canadian governmental and academic institutions was also conducted. Primary research conducted in Canada (n=21) and relevant systematic reviews of the global literature (n=8) were included in this evidence brief.

Results: Intentions to get a booster dose in the general population have decreased between 2021–2023, with intentions varying across subpopulations. In Canada and within the global systematic reviews, facilitators, barriers and hesitancy were similar. Older age was the most common factor positively associated with intention/uptake of a booster, and the most common motivators were government/healthcare provider recommendations and helping to protect others. The main reasons for hesitancy were concerns about vaccine side effects and a lack of belief in the vaccine's efficacy.

Conclusion: Intentions to get a booster dose have decreased in Canada. Understanding the reasons for vaccine hesitancy and motivators for obtaining a booster can help guide future public health COVID-19 booster vaccination programs.

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Introduction

Canada has one of the highest vaccination rates for COVID-19 in the world. As of February 2024, more than 81% of the total population had received at least one dose and more than 16% of Canadians had received the most recent XBB.1.5 vaccine, which was released in October 2023 (1). The XBB.1.5 COVID-19 vaccine is the current version as of March 2024 and is recommended for both the primary series and as a booster (additional) dose (2).

Understanding the facilitators, barriers and hesitancy to accept or refuse COVID-19 booster doses among those who have already accepted their primary series is important for encouraging recommended vaccination in the face of waning immunity and more transmissible variants. This evidence brief summarizes literature, available up to January 31, 2024, on the intention and associated factors to accept or reject additional booster doses of COVID-19 vaccine among individuals in Canada. This information is also contrasted with global systematic reviews on the topic. This brief aims to identify whether there are any context-specific roots of vaccine hesitancy in Canada to guide tailored strategies and future public health vaccination campaigns.

Methods

A continuous scan of the COVID-19 literature (published and pre-published) by the Public Health Agency of Canada has been underway since January 2020 (3). Standardized searches to retrieve COVID-19 literature are conducted in PubMed, Scopus

and EuropePMC. The results are maintained in an Endnote™ database and are also accessible in Microsoft Excel®. To develop this brief, targeted keyword searching was conducted within these repositories to identify 1) primary research in Canada and 2) global evidence syntheses (i.e., systematic reviews, scoping reviews, rapid reviews summarizing evidence across multiple countries) on vaccination and knowledge attitudes and behaviours towards COVID-19 boosters. Search terms included: ("vaccin*" OR "immuni*") AND ("third dose*" OR "booster" OR "fourth dose*" OR "fifth dose* OR "additional dose*"). Potentially relevant citations were screened for relevance to the evidence brief question and tagged by country of conduct to identify the Canadian research and global evidence syntheses. Each reference was examined to confirm its relevance and data was extracted by a single reviewer into Table S1 and Table S2 (see **Appendix** for details on the Supplementary Information) using an a priori developed structured format. Data extraction was verified by a senior reviewer. Research that reported only on vaccination in general or reported analysis such that booster results could not be teased apart from primary series results, were excluded. Narrative reviews and other secondary research were excluded. This evidence brief contains research published up to January 31, 2024.

A grey literature search was conducted to complement the bibliographic database search. The grey literature search focused on targeted Canadian governmental and academic institutions (Grey Literature Search S3). The grey literature search was completed on February 1, 2024.

Results

Twenty-one Canadian studies evaluating the attitudes and acceptance of COVID-19 vaccine booster doses between August 2021 and October 2023 were identified and included in this evidence brief (Table S1). Of these, ten were published articles and 11 were reports that had not completed a journal's peer-review process. Many of the studies were observational designs, including longitudinal surveys (n=7), cross-sectional studies (n=9) and a prospective cohort study (n=1). There were also three qualitative studies and one randomized controlled trial. Eight systematic reviews were included in this evidence brief to provide a global comparison (Table S2).

Intention

Intention to accept COVID-19 boosters has decreased. Between January and October 2023, 38%–67% of individuals surveyed intended to receive a booster (4–6), which is lower than the intention from August 2021 to December 2022, when 61%–89% intended to receive a booster (7–18). Two of these studies from October 2021 to July 2022 suggested that 62%–64% of respondents were willing to receive a COVID-19 booster annually (7,17). The most recent study, conducted in October 2023, suggests that intention to get a booster in fall 2023 had decreased substantially since 2021 and was highest in British Columbia (45%) and lowest in Ontario (35%), Saskatchewan/Manitoba (35%) and Atlantic Canada (33%) (5). Across studies, individuals with more doses of COVID-19 vaccines were more likely to accept additional doses (13,17,19). In comparison, booster intention ranged from 56%–98% in studies captured by the global systematic reviews, which included literature published between November 2020 and February 2023 (20–23).

Intention of parents/guardians to vaccinate their children varied across four studies. A survey from Manitoba conducted between August and September 2022 reported that 44% of parents/guardians were likely to have their 12–17-year-old child receive a booster vaccine (18). A Canada-wide survey conducted from November to December 2022 reported that 30% of parents with children aged 12–17 years indicated that their children had received three doses of a COVID-19 vaccine. Among parents with children in this age group that had received two doses, 21% intended to have their child receive a third dose and 24% were unsure (19). The same survey reported that 17% of parents with children 5–11 years old indicated that their children had received three doses, and among parents with children in this age group that had received two doses, 52% intended to have their child receive a third dose and 17% were unsure (19). Intentions to receive a booster were higher during the rollout of the primary series of COVID-19 vaccines to children in a Canada-wide survey; from November 2021 to February 2022, 80.6% of parents/guardians intended for their children aged 12–17 years to receive a booster (12). At the beginning of the COVID-19 vaccine rollout to children, from October to November 2021, parents willing or undecided about vaccinating their children with the primary series reported general acceptance of booster doses (57.8%) and annual COVID-19 vaccination (56.4%) (24). None of the global systematic reviews included intentions of parents/guardians to get a booster dose for their children for comparison.

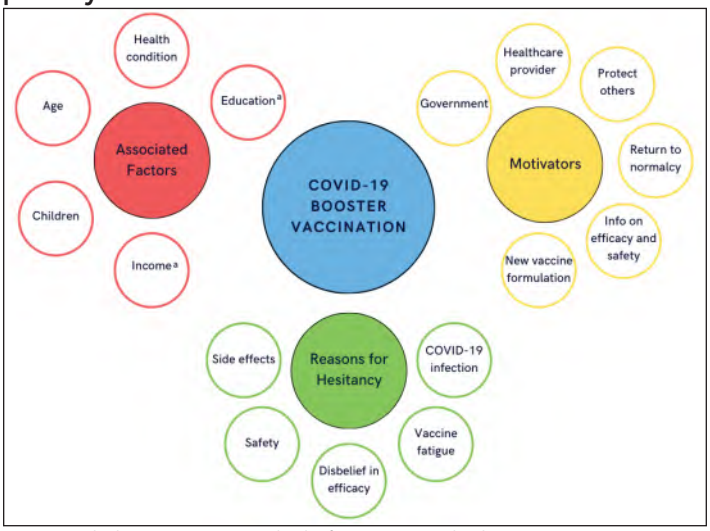
Intention to receive a COVID-19 booster was different across population subgroups, including those that have allergies, use illicit drugs, Indigenous people, immigrants, visible minorities and between sexes. A survey conducted between October 2022 and January 2023 among individuals with allergies 6–18 months post initial COVID-19 vaccination, found that 52%–57% would get a booster dose if the government or a doctor recommended it (25). Among a sample of vaccinated people who use illicit drugs in Canada, intention to receive a booster was 42% between March and October 2022 (26). Two Canada-wide studies (July–December 2022) reported that Indigenous people were slightly less likely to intend to receive additional doses compared to non-Indigenous people (38%–82% vs. 49%–89%, respectively) (12,13). Intention among immigrants and non-immigrants to receive a booster was similar (89.9% vs. 88.9%) between November 2021 and February 2022 (12). The same survey also found that visible minorities that identified as Black (76.9%) and Latin American (78.6%) were

less likely to accept a booster and those that identified as Asian (91.3%–100%) were more likely compared to non-visible minorities (89%) (12). In the same survey, LGBTQ2+ respondents were more likely than non-LGBTQ2+ respondents to intend to receive a booster (93.9% vs. 88.8%) (12). Conflicting results were reported on whether women were more likely to accept a booster compared to men; women had higher intention in one study conducted between November 2021 and February 2022 (12) and men had higher intentions in two studies conducted between September 2021 and March 2023 (4,14). In comparing these outcomes with global systematic reviews, conflicting results on whether men or women were more likely to accept a booster were also reported (22). No other similar outcomes for comparison on intention to receive a booster dose were identified.

Barriers and facilitators

Barriers and facilitators regarding intention and uptake to receive boosters (**Figure 1**) were similar to accepting first and second doses of the vaccine (27). Factors positively associated with intention to receive boosters and uptake of boosters were older age (4–7,12–14,17,28), chronic health conditions (7,12,28), not having children (28,29), belief in vaccine efficacy (29), agreement with government decision-making (29), no history of a previous COVID-19 infection (28), being a past voter for the Liberal/Democrat parties (16), living in a larger/populated area (4) and having less vaccine fatigue (6). Studies between October 2021 and March 2023 reported that higher education (4,7,12,29) and higher income (8,13,29) were positively associated with higher intention and uptake to receive a booster. However, the most recent survey in October 2023 suggested that intention to get a COVID-19 booster was no longer associated with education and income groups (5).

Figure 1: Bubble diagram of the most common barriers and facilitators of getting a COVID-19 booster vaccination, including associated factors[a], motivators and reasons for hesitancy reported in the 21 Canadian primary literature studies



[a] Income and education were reported to be factors associated with intention to vaccinate in studies prior to March 2023, but the most recent survey (October 2023) found no association

Other motivators for booster intention and uptake were government recommendations (7,28); healthcare provider recommendations (7,28); personal and/or family health reasons (7); helping to protect others around them (13,19,26,28,30); emergence of new, more severe, variants (19); likelihood of exposure to COVID-19 (18); a return to normalcy (13,28); having information about efficacy and safety of the vaccine (18,28); and having new variant-specific vaccine formulations (13,19). Social media was identified as a decision influencer in three studies (7,26,30).

The main reasons for being unlikely to accept a COVID-19 booster vaccine included concerns about short and long-term side-effects (5,6,13,19,25,28,30), concern about the safety of receiving multiple/mixed brand doses (4,26), belief that a booster dose would not offer extra protection/help curb the spread (4,6,13,19,26,31), belief that too many doses were required, or vaccine fatigue (4,6,13), and belief they did not need the booster if they already had COVID-19 (4,13). One study (July 2022) reported that those concerned with the long-term effects of boosters were more likely to be female, less than 55 years old and not fully vaccinated or vaccinated but not boosted (11). Recommendations suggested for making booster vaccinations easier to obtain included walk-in appointments, provision of childcare or family appointments and paid time off from work (7).

Findings from the global systematic reviews were similar to that of the Canadian studies. Factors positively associated with booster intention and uptake included older age, male gender, higher education, higher income, being married, White/Asian/Hispanic ethnicity, geography (country, region and residency), history of other vaccinations and history of chronic disease (20–22,32,33). Previous COVID-19 infection was negatively associated with intention to have the booster dose (21,22), but one review found it to be positively associated with actual uptake (21). Motivators for booster intention and uptake were trust in vaccine effectiveness, perceived susceptibility, perceived severity and trust in authorities (21,22,32–34). Reasons for hesitancy included concern about adverse reactions, concerns about safety and efficacy and skepticism/distrust/conspiracy theories (20,22,33). Literature up to November 2022 suggested that a combined influenza and COVID-19 booster vaccine may improve the uptake of boosters (35).

Attitudes and knowledge

In early 2022 (January to April), 60%–81% of Canadians believed that getting booster doses when necessary was effective at providing protection from the virus, protecting against serious illness or death or slowing the spread of virus (11,17,36,37). While both unvaccinated and third dose recipients in January 2022 believed they will be exposed to and infected by Omicron no matter what they do (53% vs. 54%), third dose recipients were more likely than unvaccinated to believe that if they caught COVID-19 it could be severe and/or deadly

(17% vs. 7%) (38,39). In March 2022, a greater proportion of booster dose recipients rated their COVID-19 vaccine knowledge as very good (23%) compared to respondents who had not received a booster dose (14%) ($p \leq 0.01$) (29).

Booster dose recipients between January to March 2022 had higher trust in federal and provincial government decision-making regarding COVID-19 vaccines (29) and COVID-19 restrictions (38). However, between February and August 2022, even among those that were boosted, there was some skepticism of pharmaceutical companies, government and public health decisions and policies (30,40).

A randomized controlled trial looking at strategies to get people booster doses, conducted between January and February 2022, reported that participants would be less likely to get the booster if they were automatically enrolled for an appointment compared to a control condition where they initiate their own booster appointment (41). There was high agreement (75%) for the co-administration of COVID-19 and influenza or other routine vaccines among survey participants who were willing to receive a booster in October to November 2021 (7). None of the global systematic reviews included similar outcomes for comparison.

Discussion

This evidence brief provides insight into the facilitators, barriers and hesitancy to accepting COVID-19 booster doses among Canadians between 2021 and 2023. There were no major differences observed when contrasted with the global systematic reviews. The included Canadian studies consistently reported a reduction in the intention and uptake of COVID-19 boosters between 2021, when booster doses were first recommended, and 2023. The studies captured suggest attributes of the population who are willing to accept boosters but do not give us insight into the attributes of the population whose intentions have changed as pandemic response activities have been scaled back or stopped over the last two years. These insights were also not found in any of the included global evidence syntheses.

Both the Canadian literature and global systematic reviews consistently reported that older age is positively associated with intention/uptake of a COVID-19 booster, and individuals are motivated by government/healthcare provider recommendations and the notion that they are helping to protect others (20,22,33,42). Between 2021 and 2023, federal/provincial/territorial public health response activities have scaled back in Canada and there has been a reduction in the general public's focus on COVID-19. As a result, there has likely been a decrease over time in the positive impact that messaging from trusted sources had on the intentions and behaviours of individuals towards COVID-19 boosters (43). In addition, recommendations for boosters have varied in time and between provinces, which may have had an impact on intention/uptake of the vaccine (2,44). In Canada, hesitancy due to concerns regarding side effects of the vaccine and doubt in the vaccine's efficacy continues to be a challenge and likely did not improve given the reduced public health messaging noted above. Taking these observations into account, as well as the differences in intention noted among various subgroups in Canada, will hopefully guide more tailored strategies and future public health vaccination campaigns to encourage COVID-19 booster vaccination among the Canadian population.

The evidence summarized in this evidence brief is considered to be at high to moderate risk of bias depending on the sample size and whether the sample represents the target population, as well as how well the survey tool can measure the outcome(s) of interest (e.g., whether it was informed by formative research, validated and pretested prior to implementation). Although a formal risk of bias evaluation was not conducted, the representativeness of the sampling frame, low response rates and issues with social desirability bias influencing key results were common across the observational studies. There was limited evidence on intentions and uptakes in underrepresented populations, including visible minorities, Indigenous people, children, LGBTQ2+ individuals and across genders and varying socioeconomic status. Most studies used online or telephone surveys, which may limit participation from segments of the population due to lack of access. Thus, the extent to which the findings can be applied to the target population should be considered. While many studies in this evidence brief show similar trends, the conclusions could change over time and with additional research, larger sample sizes and different sampling strategies and data collection tools.

Key topic areas for future research are intentions and reasons for hesitancy and refusal in high-risk and underserved populations, comparisons between countries and studies that identify effective interventions that would encourage individuals to stay up-to-date on the National Advisory Committee on Immunization's COVID-19 vaccine recommendations (2). As the virus continues to circulate and public health responses have been scaled back to a normal level of service, understanding intentions to get vaccinated and hesitancies for accepting a booster dose remains crucial to improving booster uptake in the face of waning immunity, more transmissible variants and other public health emergencies requiring vaccination strategies.

Conclusion

It is likely that the reduction in COVID-19 booster intentions in 2023 is related to many factors, including pandemic fatigue and the desire to move past the events of the pandemic. There is now less pressure on the community, due to reduced messaging and media coverage, to be aware of COVID-19 and to get boosters when they are recommended, as public health response activities at all levels of government have been scaled back to normal or almost normal operation. Poor vaccine uptake is not a new issue in public health; however, it would be prudent to focus

on improving interventions and communication strategies to provide tailored messaging about what, when and why vaccines are needed to encourage vaccination in the general population and in underserved communities. The result of this evidence brief can inform the development of new public health strategies and prioritization of new research to address the existing knowledge gaps.

Authors' statement

KY — Supervision, data extraction, writing–original draft, writing–review & editing
TC — Conceptualization, methodology, data extraction, writing–original draft, writing–review & editing
KP — Data extraction, writing–original draft, writing–review & editing
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LW — Conceptualization, methodology, writing–review & editing

Competing interests

None.

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Appendix: Data Availability

All relevant data are included in the paper or its Supplementary Information (Supplementary Files 1–3): https://doi.org/10.17605/OSF.IO/8YH7R

Mathematical modelling for pandemic preparedness in Canada: Learning from COVID-19

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Abstract

Background: The COVID-19 pandemic underlined the need for pandemic planning but also brought into focus the use of mathematical modelling to support public health decisions. The types of models needed (compartment, agent-based, importation) are described. Best practices regarding biological realism (including the need for multidisciplinary expert advisors to modellers), model complexity, consideration of uncertainty and communications to decision-makers and the public are outlined.

Methods: A narrative review was developed from the experiences of COVID-19 by members of the Public Health Agency of Canada External Modelling Network for Infectious Diseases (PHAC EMN-ID), a national community of practice on mathematical modelling of infectious diseases for public health.

Results: Modelling can best support pandemic preparedness in two ways: 1) by modelling to support decisions on resource needs for likely future pandemics by estimating numbers of infections, hospitalized cases and cases needing intensive care, associated with epidemics of "hypothetical-yet-plausible" pandemic pathogens in Canada; and 2) by having ready-to-go modelling methods that can be readily adapted to the features of an emerging pandemic pathogen and used for long-range forecasting of the epidemic in Canada, as well as to explore scenarios to support public health decisions on the use of interventions.

Conclusion: There is a need for modelling expertise within public health organizations in Canada, linked to modellers in academia in a community of practice, within which relationships built outside of times of crisis can be applied to enhance modelling during public health emergencies. Key challenges to modelling for pandemic preparedness include the availability of linked public health, hospital and genomic data in Canada.

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Keywords: mathematical modelling, pandemic preparedness, infectious diseases, COVID-19

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, underlined the need for planning for future pandemics. There have been multiple pandemic preparedness initiatives at national and international levels (1,2). Modelling has supported previous pandemic plans, and the World Health Organization (WHO) has included modelling as a source of evidence to support planning (3). In Canada, modelling supported decisions during the pH1N1 pandemic (4–6) and subsequent pandemic

influenza planning (7). During the COVID-19 pandemic, the role of modelling to support decisions was brought into focus. Mathematical models synthesize information on disease transmission in the population, disease severity in different age or population groups, population immunity, effectiveness of non-pharmaceutical interventions (NPIs) and vaccine effectiveness, among other aspects. In so doing, models produce a narrative that is interpretable by decision-makers and the public, and supports evidence-based decision-making, transparency and public trust.

The objective of this article is to describe how modelling efforts can support pandemic preparedness, including a description of the model types, their roles, best practices for their use and the expertise that is required, as informed by past pandemics and our recent experiences with COVID-19. For this article, modelling is considered to include mathematical and simulation approaches to understanding and predicting the introduction, invasion, spread, evolution and control of pandemic-causing pathogens, as well as impacts on healthcare capacity. The focus is on preparedness for pathogens that spread in the human population via human-to-human transmission, with the capability of dispersing through the global travel network. It is likely that such pathogens would emerge from animal reservoirs by zoonotic transmission. While spill back to animal reservoirs, as has occurred with SARS-CoV-2, may be a feature of the transmission and ecology of such pathogens, the significance for pandemic preparedness depends on its impact on human-to-human transmission (i.e., whether ongoing animal-human contact causes the basic reproduction number R_0 to be greater than one). WHO has produced a list of priority pathogens based on their importance to public health, but their criteria are broad and go beyond the capacity to cause a pandemic (8), so this list is too long to consider in its entirety for pandemic planning. For example, zoonoses including MERS-CoV, Nipah, Crimean-Congo haemorrhagic fever and Rift Valley fever are listed, though they often have limited human-to-human transmission, complex transmission cycles and routes of spillover into human populations involving arthropod vectors and wild and domesticated animal reservoirs. Outbreaks of these diseases may be defined by WHO as pandemics because they affect multiple countries. However, the absence of sustained human-to-human transmission, or conditions for zoonotic transmission in Canada, means that, without further evolution, they are unlikely to cause outbreaks in Canada at the scale of COVID-19 or the 1918 and 2009 influenza pandemic, for which pandemic planning aims to prepare us. Modelling supports our understanding of the potential risk from these diseases, particularly in the context of climate change (9), but that is out of scope for this article.

Methods

A narrative review of how modelling can best support pandemic preparedness was developed by members of the Public Health Agency of Canada External Modelling Network for Infectious Diseases (PHAC EMN-ID), a national community of practice on mathematical modelling of infectious diseases for public health. Authors sought and reviewed scientific papers and grey literature published in the last 20 years on pandemic preparedness in Canada, and the use of modelling during the COVID-19 pandemic. As most authors were involved in modelling to support decisions at federal, provincial and/or territorial levels, their expert opinion and lived experiences on how modelling supported public health decision-makers during the pandemic were captured.

Results

There are two components to modelling support for pandemic preparedness:

1. Modelling the transmission of "hypothetical-yet-plausible" pandemic pathogens to support decisions on preparatory activities, such as emergency stockpiles

2. Developing validated modelling methods and tools that are maintained, capable of rapid adaptation to the biology of emerging pathogens and are thus "ready-to-go" to support decisions in the event of the emergence of a pathogen with pandemic potential

In either case, there are considerations of good practices for modelling methods, communication of the results of modelling and data needs for modelling. People trained to recognize and fill modelling needs, embedded with, or having strong relationships with, public health organizations and decision-makers are also essential (10). While not explicitly a part of pandemic planning, modelling can also support resilience to pandemics, which is discussed at the end of this article.

Good practices

Mathematical models currently used to support public health and health policy decisions need to balance biological realism with tractability (11,12). While models should be simple enough to understand and implement efficiently (13), useful realism involves incorporating the biological processes of infection and recovery, outcomes of infection, human behaviour that underpins pathogen transmission and effectiveness of NPIs and pharmaceutical interventions (see below). However, the more complex a model, the more prone it is to undetected errors and inaccurate parameterization (13–15). Overcomplexity may also limit standard model-evaluation methods, such as sensitivity analyses (16) and the ability for models to be calibrated to data (17). However, developments in computing power, data availability and synthesis increasingly allow tractable modelling based on transmission with a digital twin of society to model social contacts in detail (18). Outputs of very simple models can also have value as an adjunct to communicating aspects

of an emerging epidemic to a lay audience, which may be the public or non-expert managers, as was the case during the COVID-19 pandemic (19). Development of criteria that can be universally used to distinguish "good models" from "bad models," discussed as verification and validation of modelling in the broader simulation literature (20,21), remains a work in progress (11,12,22).

Types of models

The main model types relevant to pandemic preparedness are 1) dynamic transmission models of spread of an infectious pathogen within a population, both for prediction, assessment of alternative response strategies and impact of evolutionary changes; 2) importation models that explore the estimated risk of disease importation into and within Canada based on the global network of air and land travellers and knowledge of transmission in source countries (23); and 3) geographic spread models that are capable of identifying spatial pathways of pathogen spread within Canada (24).

Dynamic transmission models typically divide human (or animal) populations into "compartments," such as susceptible-exposed-infectious-recovered (SEIR) models. Flows (or transitions) among these compartments reflect the fundamental processes of the biology of transmission, infection and recovery. They are described by event rates, which can be used to define deterministic, continuous flows between compartments or stochastic transitions.

The simplest SEIR models assume that the population mixes homogeneously. As a result, these models usually overestimate the spread of infections, including the peak size of epidemics. Age-based contact matrices can improve these models by using the results of population surveys (25) or demographic data (26) to estimate the frequency of daily contacts between individuals. Furthermore, SEIR models can be constructed with more complexity to model different sections of the population (27,28) or to model variants and evolutionary changes (29,30).

Agent-based models (ABMs, also called individual-based models) can incorporate even more heterogeneity. Simpler ABMs are conceptually similar to SEIR models but explicitly model individuals in a population (i.e., "agents") who exist in susceptible, exposed, infected or recovered states. Agent-based models allow the integration of contact matrices, the construction of quasi-realistic environments (e.g., home, workplace, schools, leisure venues, public transit) within and between which the agents move according to their demographics, and potentially drawing on more extensive use of socioeconomic data. This structure allows for more realistic exploration of targeted NPIs, such as limited closures (31), and combinations of NPIs with vaccination (32). Both compartmental and agent-based models can be used to study the geographic spread of an infectious disease, in which case transmission can be modelled relatively simply in each grid cell of a landscape with plausible cell-to-cell spread of infection that depends on geographic or other physical constraints (24,33), or more elaborately based on more detailed data synthesis including small area estimation.

At the beginning of a pandemic that has emerged in another country, importation models can be used to estimate the probability of importation and the number of cases that may have recently been introduced into Canada by points of entry (23). Importation models typically consider travel volumes from different countries and/or provinces, and infection prevalence and immunity within those countries and/or provinces. Importation models can also inform travel measures within a country. Once within-country transmission has begun, importation models can provide imported case input to models of community transmission (34,35). As seen during COVID-19, for smaller provinces and territories, importation, rather than community transmission, can be the focus. There may be relatively few travel routes into small jurisdictions, which can be monitored and managed to prevent community outbreaks, at the outset of, and during a pandemic.

Coupling the analysis of geographic spread with genomic analyses is increasingly being used to model transmission and detect sources of new cases for a variety of pathogens, most notably COVID-19 (36–38). A real-time practical use of these methods is Nextstrain (39), an open-source platform and dashboard that allows decision-makers, scientists and the general public to watch, in real time, how the virus is evolving and spreading globally. Underlying phylogeographical and phylodynamic methods are mathematical and statistical models that rely on population genetics models, Bayesian modelling and linked SEIR-type models.

There is an array of modelling and estimation tools to provide intelligence during outbreaks. These include estimation of the instantaneous reproduction number, R_t (40), forecasting based on wastewater signals (41,42), branching process models to explore control methods early in outbreaks (43–45) and analysis of phylogenetic trees of whole genome sequence data to obtain estimates of the basic reproduction number, R_0, of the pathogen and/or emerging variants to compare with estimates from surveillance data (46).

Biological realism

During the COVID-19 pandemic, the importance of models for public health decision-making strengthened, not least because it was recognized that their outputs were biologically realistic (47). To achieve this, the structure of models (i.e., compartments/states and flows/transitions between compartments and states) needs to be realistic in terms of 1) the biology of infection, age and sex-related likelihood of clinical outcomes and recovery (infections being asymptomatic, mild, requiring hospital, or intensive care [i.e., in ICU]), accounting for heterogeneity in different population groups where these are important in

transmission, and data that are available; 2) age and sex-related patterns of contacts between infected and uninfected people, vectors or animal reservoir hosts (48) and how these are likely to change; 3) public health interventions (NPIs and vaccinations); and 4) where possible, realistic direct impacts on healthcare resources and indirect impacts, such as cancelled surgery and avoidance of emergency department visits (**Figure 1**). Parameter values (e.g., the duration of latent and infectious periods, the basic reproduction number, R0, contact patterns within the population) need to be realistic and obtained from prospective studies or inferred from digital twin-style data synthesis and the scientific literature using established knowledge synthesis methods (49). They can also be obtained by fitting models to surveillance or hospital data, particularly for parameters that are difficult to measure in studies, such as the probability of transmission when infected people contact susceptible people. The capacity to fit models to surveillance data (e.g., human cases, hospitalizations and wastewater data) depends on the availability of reliable data, which has been a problematic and largely unresolved issue during and after the COVID-19 pandemic in Canada (50). To achieve biological realism (and ideally socioeconomic realism) useful for public health objectives, modelling must be a multidisciplinary endeavour, synthesizing knowledge and data from a spectrum of scientists and clinicians involved in public health. With these principles in place, evidence provided by models will be more reliable.

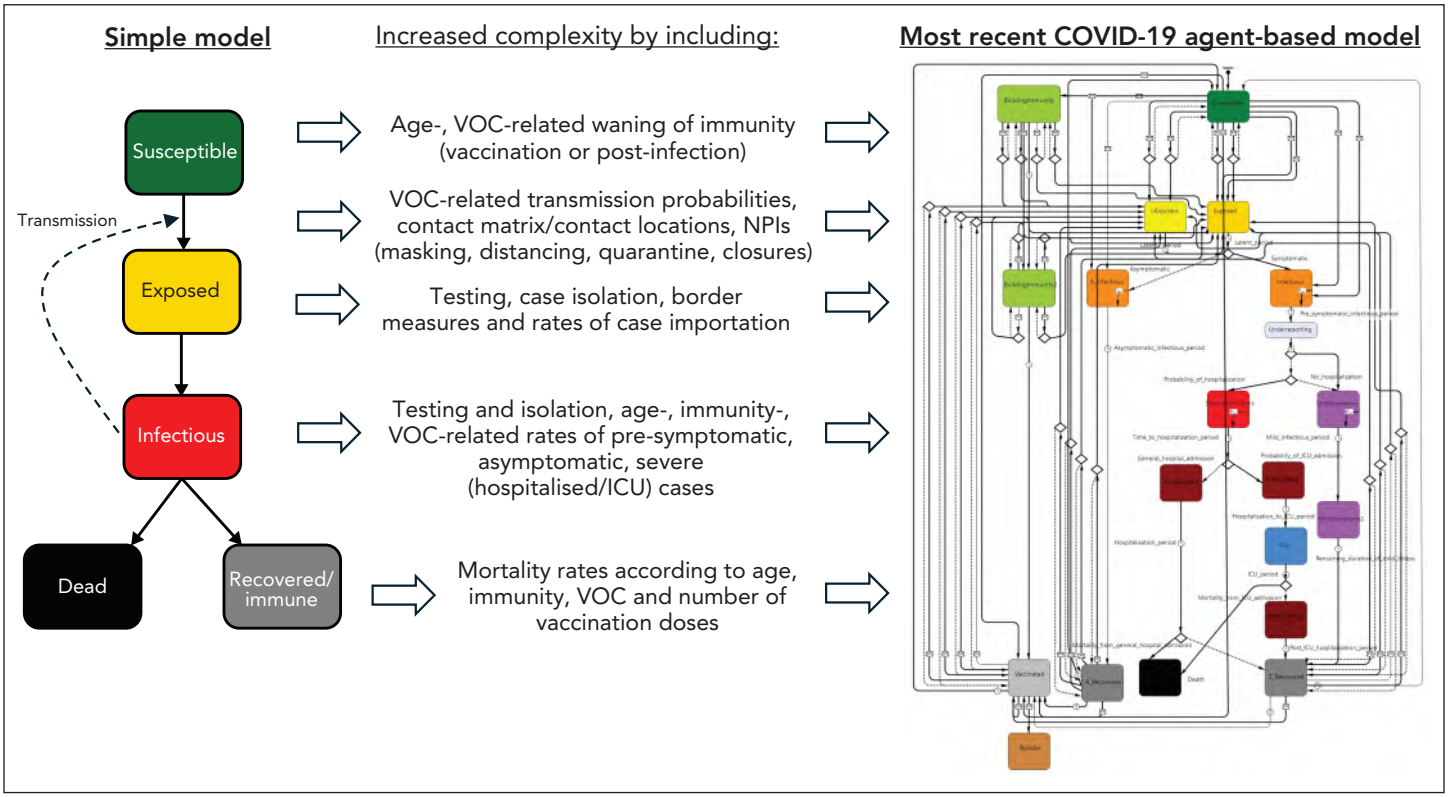
Uncertainty

In general, modelling approaches should account for plausible ranges and distributions of parameter values (e.g., the duration of infectivity) or probabilities of event occurrence (e.g., transmission probability estimates) to allow for exploration and quantification of uncertainty. There are at least three types of uncertainty to consider:

1. Data uncertainty due to measurement error
2. Uncertainty due to inherently variable parameters
3. Uncertainty as to whether the model structure fully represents the true system

Comparing initial model results to observed data may suggest that the model outcomes have very high uncertainty, and the models are insufficiently robust to support decisions without significant changes to model structure, parameters and/or calibration, in order to progress from a development stage. Validation may indicate that model results are robust enough to be useful for decision-making in two ways. If uncertainty is very small, models may have a high enough precision to say, "if public health effort is changed by X%, incidence will change by Y%." However, models may result in outcomes that have a high degree of uncertainty, yet still have enough precision to be useful

Figure 1: Adding complexity to a simple Susceptible-Exposed-Infectious-Recovered (SEIR) model to realistically model public health interventions[a]



Abbreviations: ICU, intensive care unit; NPIs, non-pharmaceutical interventions; VOC, variant of concern

[a] The left hand diagram shows the structure of a simple Susceptible-Exposed-Infectious-Recovered (SEIR) model, next to which are examples of the factors that had to be introduced to realistically model COVID-19 transmission with emerging VOCs, and the use of NPIs and vaccinations, resulting in a complex model structure (right-hand diagram). In this case, the complex model is the Public Health Agency of Canada agent-based model, as described, in an earlier form, in Ng *et al.*, 2020 (30)

in answering less granular questions, such as, "will this be big or small?" or "is it better to do X, Y or nothing?"

Types of modelling projects

There are two main types of predictive modelling projects: 1) forecasting and 2) scenario exploration. Forecasting is the use of mathematical models to predict the trajectory of an epidemic or outbreak in the near or far future (e.g., Slide 7 in (51)). Scenario-based modelling is the use of models to answer "what if?" questions. Common "what if?" questions include the potential epidemiological impact (e.g., on incidence, hospitalizations, deaths) of various interventions (e.g., treatment or vaccination roll out, NPIs) (31,52). Scenario-based modelling often assesses outcomes over the course of multiple generations of infections. Sometimes, forecasts may also have simplified scenarios. For example, PHAC COVID-19 forecasts included a forecast of the current disease trajectory and scenarios of what might happen in a short time scale if NPIs were tightened or relaxed.

Communicating modelling results to decision-makers and the public

Effective communication of modelling results to public health managers and decision-makers is essential. Beyond simply the general need for good oral and visual communication methods that use accessible, accurate and jargon-free language, there are some modelling-specific requirements. First, objectives of modelling need to be clear and placed in the context of decision-maker needs and, ideally, modellers, managers and decision-makers discuss and agree upon what is needed and possible at the outset (12). Assumptions and limitations of models, results of validation, as well as sources and degrees of uncertainty need to be communicated to clarify the degree to which model outputs are actionable by decision-makers (11,53). Communicating the results of models in an early stage of development and models that perform poorly in validation, as well as poorly communicated results, will likely be unproductive or even counterproductive, resulting in managers, decision-makers and stakeholders losing confidence in modelling. A further layer of care needs to be added when communicating model outcomes to the public. For example, scenario-based modelling conducted early in the COVID-19 pandemic was misinterpreted by some members of the public, press and politicians as being a forecast. When the worst-case scenario did not happen (because public health measures were implemented), there was a perception that modelling was simply wrong and that COVID-19 was overblown (47).

Modelling "hypothetical-yet-plausible" pandemic pathogens before pandemics occur

Objective

Pre-pandemic modelling aims to provide a foundation for decisions on pandemic planning, including the healthcare resources that need to be maintained in national stockpiles. Scenario-based modelling is needed to explore the full potential impacts on Canadian health systems of "hypothetical-yet-plausible" pandemic pathogens in Canada. Outcomes of interest are the numbers of cases, hospitalizations, ICU treatments and deaths and the rate at which they occur. With these values, healthcare needs (hospital capacity, ICU capacity, ventilators, personal protective equipment, antivirals) can be estimated (54) and the quantities of healthcare stockpiles (such as the National Emergency Strategic Stockpile (55)) and NPI measures needed, accounting for their negative health impacts, can be evaluated.

Models

Both compartmental models and ABMs can be used for this purpose. Agent-based models may be particularly useful to explore impacts in smaller and/or more heterogeneous communities.

Likely pathogens/disease types

A prioritization of likely emerging pandemic pathogens remains to be done, but zoonotic pathogens that become human-to-human transmissible by contact or the respiratory route (e.g., influenzas, coronaviruses, haemorrhagic fevers) (56,57) are considered likely candidates. At the time of writing, WHO is undertaking a process that is more specifically aiming for a list of priority pathogens of pandemic potential (58).

Data needs

"Most likely" epidemiological parameter values can be sourced from the literature using established knowledge synthesis methods (49).

Development of modelling methods, tools and personnel "ready-to-go" in the face of a pandemic

Objectives

Modelling development in the face of an epidemic should ensure that modelling methods and the necessary highly qualified personnel (HQP) are present and ready to respond to an emerging epidemic in Canada.

Models

Generic, adaptable and preferably validated compartmental models and ABMs need to be developed in advance so that they can be adapted to an emerging pandemic in Canada for the purpose of forecasting and conducting scenario-based modelling to guide public health interventions. Models based on a design for modelling respiratory diseases would likely be readily adaptable to other forms of direct human-to-human transmission, but it would also be valuable to have models that are more explicitly designed for a variety of transmission routes (e.g., sexual transmission (59)). Importation models need to be ready to estimate rates and routes of importation of infectious people into Canada. Ideally, models of geographic spread within Canada, allowing exploration of interventions

that limit spatial spread, would also be ready for adaptation to an emerging pathogen. There is also a need for modelling and estimation methods that enhance analysis of surveillance data, including estimation of the instantaneous reproduction number, R_t, forecasting from clinical surveillance and wastewater data and assessing genomic data to provide estimates of key epidemiological parameters, including R_0 and selection advantage of emerging variants.

Data needs

In the face of an emerging pandemic that begins outside Canada, as experienced during the COVID-19 pandemic, key parameter values for modelling emerge in the evolving scientific literature and knowledge synthesis skills are needed to be ready to source them (49). Ideally, estimates of key parameter values for a range of pathogens from the current literature would allow models to be populated with "best estimates" at the start of a pandemic prior to quantification of parameters specific to the emerging pandemic. Canada needs to be prepared in terms of data collection, sharing and linkage of case data with hospitalization and genomic data by learning from the difficulties encountered during the COVID-19 pandemic, along with the success in obtaining and linking case, hospitalization, vaccination and genomic data in countries such as the United Kingdom (50). In particular, Canada would benefit from building a framework of access to linked data for skilled experts, under appropriate conditions of access, well before it is next needed.

The need for highly qualified personnel

A key lesson learned from the COVID-19 pandemic is that public health organizations need in-house HQP to be able to create models, bring together the multidisciplinary skills needed and conduct modelling of utility for public health purposes. Knowledge synthesis teams are crucial for incorporating rapidly evolving evidence into models; geographers and mathematicians are needed for importation, network and spread modelling; epidemiologists and medical, microbiology and immunology experts are required for ensuring biological reality; communication experts are necessary for explaining technical modelling results to the public; methods are needed for bringing these skills together (10). Explicit linkage of these HQP with modellers in academia provides opportunities for modelling within public health organizations to benefit from ongoing innovations, peer review, enhancement of modelling capacity, development of modelling ensemble approaches and transparency that enhances public confidence in the modelling being conducted (60). Without in-house modelling expertise, public health is unprepared to adequately respond to outbreaks and pandemics and must turn to external modellers to undertake the work. The availability and capability of external modellers would not be guaranteed, and without internal experts, public health would not be able to review or adapt the resulting models nor ensure that results are accurately communicated with decision-makers associated with loss of corporate memory of modelling.

The need for a national community of practice of modellers

Many countries have recognized the importance of academic modellers contributing to public health decision-making during the COVID-19 pandemic (47,61). In the aftermath of the SARS-CoV-1 pandemic in 2003, a community of practice of infectious disease modellers formed in Canada and eventually became known as Pandemic Influenza Outbreak Research Modelling, or Pan-InfORM, in 2008 (62). This community aimed to support the use of modelling to inform decisions during pandemics. Although not specifically targeting pandemic preparedness per se, this community of practice did support decisions during the pH1N1 pandemic in Canada (4,63) and had links to public health organizations (62). While this group continued "peacetime" activities of modelling infectious disease transmission in collaboration with public health organizations up to 2018, between that time and the onset of the COVID-19 epidemic in Canada in 2020, links with most public health organizations had been lost, and new communities of practice, such as the Ontario Science Table and PHAC's External Expert Modelling Group (64), had to be created in the face of the pandemic. The loss of Pan-InfORM as a recognized resource for public health in the face of COVID-19 underlines the need for public health organizations to have in-house HQP that can maintain collaborative modelling communities of practice outside of the times when we are responding to infectious disease emergencies.

Modelling to supporting pandemic resilience

Modelling studies can support resilience of public health organizations to pandemics. Such modelling has general application for outbreak management and design of interventions using NPIs. A summary of ways that modelling can support development of resiliency is presented in **Table 1**.

Discussion

Key challenges

Modelling requires computing infrastructure, software and mathematics, but it also requires the multidisciplinary teams of experts in all aspects of disease transmission and public health practice for the modelling to be grounded in the biological reality needed for decision-making in public health. Such teams were brought together in Canada during the COVID-19 pandemic, but they need to be maintained in some form to support future pandemic preparedness. An ongoing issue in Canada is the limitation of collection of granular data on disease cases, hospitalized cases, genomic characterization of causal agents and metadata that are crucial for analyses (75,76). Simultaneously, there is a current incapacity to link surveillance, hospital and genomic data across provinces and territories (50).

Table 1: Examples of modelling studies that may support design of policies to increase resilience to pandemics

Focus area	Example modelling objectives	References
Building design	Enhancing greater ventilation to reduce respiratory pathogen transmission, particularly in locations where large numbers of people congregate.	(65,66)
Estimations to support decisions on public health capacity	Estimation of the surveillance effort needed to detect cases of emerging pathogens.	(67,68)
	Estimation of the test-and-trace effort needed to control transmission, in the absence of restrictive measures, according to different characteristics of pathogens and the diseases they cause.	(31,69)
Tools for strategic decisions	Criteria for determining if elimination of a pathogen in a particular jurisdiction would be successful, or if public health measures should aim simply to "flatten the curve" to limit impacts on healthcare.	(70)
	Estimation of the likelihood of control by test-and-trace versus restrictive measures, according to characteristics of pathogens and the diseases they cause (R_0 and proportions of cases with asymptomatic, presymptomatic or severe manifestations).	(71)
	Criteria for targeting NPIs to specific demographic or geographic sections of the population.	(32,72)
Best practices for use of public health measures	Best practices for the use of restrictive measures if these are needed to control transmission.	(52,73)
	Recommendations for the use of NPIs that reduce the probability or impact of transmission, such as distancing, masking and cohorting at gatherings.	(73,74,78)

Abbreviation: NPIs, non-pharmaceutical interventions

These data issues are the subject of considerable efforts to remedy problems in collection, linkage and sharing within the Pan-Canadian Health Data Strategy (77) and, for health system data, in the Interoperability Roadmap of Canada Health Infoway (78), but they remain the most significant unresolved challenges to effective modelling of infectious diseases in Canada.

Conclusion

Mathematical modelling of infectious diseases is now recognized as a key support to decision-making in public health preparedness and responses to outbreaks, epidemics and pandemics. Judicious use of modelling can support pandemic preparedness in terms of the stockpiles and planning needed to be prepared for a pandemic, while ready-to-go models, methods and HQP will support decision-making early in a pandemic. Modelling resources, particularly HQP, need to be maintained in public health organizations and in academia, and in transdisciplinary collaborative networks with public health-relevant scientists in other disciplines. A key barrier to effective modelling for public health decisions in Canada remains the issue of health data collection and sharing.

Authors' statement

NHO instigated the article and provided a first draft framework into which all other authors contributed. This is a project of the PHAC External Modelling Network for Infectious Diseases (PHAC EMN-ID), a national community of practice on mathematical modelling of infectious disease for public health, of which all authors are members. The authors identify no competing interests.

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An innovative tool to prioritize the assessment of investigational COVID-19 therapeutics: A pilot project

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Abstract

Background: As the COVID-19 pandemic unfolded, hundreds of investigational COVID-19 therapeutics emerged. Maintaining situational awareness of this extensive and rapidly evolving therapeutic landscape represented an unprecedented challenge for the Public Health Agency of Canada, as it worked to promote and protect the health of Canadians. A tool to triage and prioritize the assessment of these therapeutics was needed.

Methods: The objective was to develop and conduct an initial validation of a tool to identify investigational COVID-19 therapeutics for further review based on an efficient preliminary assessment, using a systematic and reliable process that would be practical to validate, implement and update. Phase 1 of this pilot project consisted of a literature search to identify existing COVID-19 therapeutic assessment prioritization tools, development of the Rapid Scoring Tool (RST) and initial validation of the tool.

Results: No tools designed to rank investigational COVID-19 therapeutics for the purpose of prioritizing their assessment were identified. However, a few publications provided criteria to consider and therapeutic ranking methods, which helped shape the development of the RST. The RST included eight criteria and several descriptors ("characteristics"). A universal characteristic scoring scale from −10 to 10 was developed. The sum of all the characteristic scores yielded an overall benefit score for each therapeutic. The RST appropriately ranked therapeutics using a systematic, reliable and practical approach.

Conclusion: Phase 1 was successfully completed. The RST presents several distinct aspects compared with other tools, including its scoring scale and method, and capacity to factor in incomplete or pending information. It is anticipated that the framework used for the RST will lend itself to use in other dynamic situations involving many interventions.

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Keywords: decision support techniques, therapeutic evaluation, investigational therapeutics, COVID-19, prioritization

Introduction

Background

At the beginning of the pandemic, the rapid global transmission of SARS-CoV-2, the virus that causes COVID-19, prompted extensive research into a range of treatment options. As the pandemic unfolded, hundreds of investigational (i.e., prior to market authorization) pharmaceutical COVID-19 therapeutics emerged (1). Maintaining situational awareness of this extensive and rapidly evolving therapeutic landscape represented an unprecedented challenge for the Public Health Agency of Canada (PHAC), as it worked to promote and protect the

health of Canadians (2). A timely and thorough assessment of all investigational therapeutics was not feasible. Therefore, a practical tool to systematically, reliably and efficiently triage and prioritize the assessment of these therapeutics was needed to help inform their potential applicability for Canada.

To identify existing COVID-19 investigational therapeutic assessment prioritization tools, a literature search was conducted in Ovid MEDLINE® with the assistance of a PHAC librarian, using the focused search concepts "decision support techniques," "COVID-19 therapeutic treatment or assessment" and variations of their terms. A total of 302 articles were identified; 46 were deemed relevant and these were reviewed. The search identified no tools designed to rank investigational COVID-19 therapeutics to prioritize their assessments. However, several publications provided criteria to consider when conducting health technology assessments or making therapeutic formulary decisions (3–9). Furthermore, some of these publications and their references featured different therapeutic ranking methods and evaluation frameworks (4,7,9–16). Although they had important limitations (e.g., required a pre-defined list of therapeutics with known properties, complex to implement or adapt quickly), certain elements, such as their assessment criteria and use of positive and negative scoring, were found relevant to incorporate into a tool that PHAC developed in the fall of 2022. This article reports on the first phase of this pilot project to develop what has become known as the Rapid Scoring Tool (RST).

Objective

To develop and conduct an initial validation of a tool to identify investigational COVID-19 therapeutics for further assessment, based on an efficient preliminary review, using a systematic and reliable process that would be practical to validate, implement and update.

Intervention

Setting

During the pandemic, a team of four individuals from the PHAC COVID-19 Therapeutics team was formed to develop the RST. The members had backgrounds in critical appraisal, clinical and research pharmacy, therapeutic evaluation, program evaluation, epidemiology, immunology and public health. Investigational COVID-19 therapeutics were identified primarily from a daily scan of key COVID-19 sources of information (e.g., updates and pre-prints of key COVID-19 trials) and ClinicalTrials.gov. The RST was developed using Microsoft Excel®.

Intervention

The pilot project had two phases:

- Phase 1: Development (stages one and two) and initial validation (stage three) of the RST
- Phase 2: Further validation and enhancement of the RST

Stage one: Design the RST. The RST team developed the RST, which included defining the decision problem it was intended to address (13–15), the broad categories or "criteria" that would be used to assess therapeutics (e.g., safety), and more precise descriptors or "characteristics" within each criterion. The criteria and characteristics were developed based on literature findings, feasibility of implementation and over a dozen internal discussions with stakeholders, both within and outside of the COVID-19 Therapeutics team, involved in the assessment and monitoring of therapeutics (i.e., medical advisors, managers, epidemiologists, policy analysts and research analysts). Next, a "characteristic" scoring scale was constructed based on the decision problem. This universal scale was used to assign a score to each characteristic. For each therapeutic, an overall perceived benefit ("overall benefit") score was calculated by summing the scores of all the characteristics that applied to that therapeutic.

Stage two: Pilot test the RST. During stage two, therapeutics were entered into the RST and ranked by their "overall benefit" score to identify those to assess more thoroughly. Two members of the RST team independently selected the appropriate characteristics (one for each criterion) from the list of possible characteristics, using key sources of information. All discrepancies were resolved through discussion with a third member until full agreement among the three members was reached. When adjustments to the criteria, characteristics and/or their associated scores were required, an iterative consensus approach within the RST team was used, with input from stakeholders, to validate and maintain internal consistency (i.e., alignment and coherence among the RST components). Face validity of the ranking, internal consistency and reliability of the RST were deemed to have been achieved once 10 consecutive therapeutics had been entered without discrepancies (i.e., the need to involve a third member of the team) or the need to adjust the RST and the ranking was deemed appropriate by the members of the RST team.

Stage three: Conduct an initial validation of the RST. This stage consisted of further validation of the RST using the input from three members of the COVID-19 Therapeutics Team who had not used the RST to assess individual therapeutics. Together, they had critical appraisal skills, medical, nursing and public health backgrounds. They were provided with detailed information on 15 randomly selected therapeutics in the RST (using the RAND function of Microsoft Excel) They were given time to ask questions and deliberate, and asked to indicate their level of agreement or disagreement (using a Likert scale) with the RST's ordinal ranking of these therapeutics (i.e., which therapeutic ranked first, second, etc.). They were also asked to provide statements describing the intervals between rankings (e.g., therapeutic A is clearly of greater overall benefit compared with therapeutic B; therapeutics C and D offer very similar overall benefit). The rankings were considered validated (''appropriate") if at least two of the three individuals agreed or strongly agreed (consensus agreement) with the ordinal ranking of

therapeutics and on 75% or more of the 12 ranking statements. This consensus agreement approach was adopted to leverage the benefits of collaborative decision-making, while mitigating risks associated with individual biases; the 75% threshold was considered practical and meaningful to describe substantial consensus.

Outcome measures

Table 1 provides the list of outcome measures and stages during which they were assessed.

Outcomes

Design of the Rapid Scoring Tool

The decision problem pertained to the need to efficiently triage and prioritize the large number of investigational COVID-19 therapeutics for further assessment, based on a preliminary assessment of their perceived benefit, within the Canadian context. The criteria included in the RST at the time of writing, and the elements that were used to develop the characteristics for each criterion, are listed in **Table 2**.

Figure 1 shows the scale developed and used to assign a score to each characteristic, with scores ranging from −10 to +10. In most cases, characteristics had only a moderate effect on the perceived benefit of a therapeutic and, as a result, most scores were in the −5 to +5 range.

Table 1: Outcome measures, description and stage

Objective	Outcome measure	Description	Stage(s)
Development of the RST	Systematic nature of the RST	The RST's systematic nature was assessed based on: the structure (logical and intuitive sequence and configuration), operationality (clarity of definitions), non-redundancy (no duplicates) and mutual independence (without overlap) of the criteria; characteristics and characteristic scores of the RST (15); and its internal consistency.	1 and 2
Development of the RST	Practicality of the RST	The practicality of the RST was assessed based on the feasibility of implementation (whether the RST could be set up using Microsoft Excel), use (ease with which members can select and enter information into the RST) and adaptation (ease with which the criteria, the characteristics and their scores could be modified in accordance with the changing pandemic environment).	1 and 2
Development of the RST	Intra-rater and inter-rater reliability	The intra-rater reliability (consistency in the selection of the characteristics for a same therapeutic by a same RST team member over time, for example, when updating information for a therapeutic) and inter-rater reliability (consistency in the selection of the characteristics for a same therapeutic between members of the RST team for every therapeutic entered in the RST).	2
Development of the RST	The time required to conduct a preliminary assessment of each therapeutic	The time was assessed once the RST team had become accustomed to the RST (after having entered approximately 15 therapeutics in the RST). The aim was for the RST to enable the preliminary assessment of each therapeutic within 30 minutes.	2
Development and initial validation of the RST	Appropriateness of ranking of therapeutics	The appropriateness of ranking of therapeutics was assessed based on face validity of the ranking of therapeutics.	2 and 3

Abbreviation: RST, Rapid Scoring Tool

Table 2: Criteria and elements considered to develop their characteristics

Criteria	Elements considered to develop the characteristics
Quality of evidence	Phase of the study, study design, availability of results and whether they were peer-reviewed and important limitations (e.g., limited generalizability of the results)
Clinical impact	Type of outcomes, the classification of outcomes as either primary or secondary, magnitude of the impact and its statistical significance
Safety data	Adverse events, warnings and precautions, contraindications and drug interactions
Patient preference	Benefits and harms of the therapeutic, route of administration, ease of access to the therapeutic (for outpatient therapeutics) and frequency of dosing
Availability of authorized treatment alternatives for the same broad target patient population	Number of authorized treatment alternatives. Broad target patient populations: outpatients, inpatients not in an intensive care unit, inpatients in an intensive care unit, patients with post COVID-19 condition
Authorization status in Canada	Presence or absence of an authorized indication other than the one being studied
Regulatory status in other jurisdictions	Regulatory status in the United States, Europe, Australia and other select countries with stringent regulatory authorities
Domestic therapeutic development landscape	Current or past Canadian funding, study sites in Canada and geographical location of the manufacturer

Figure 1: Scoring scale of the characteristics

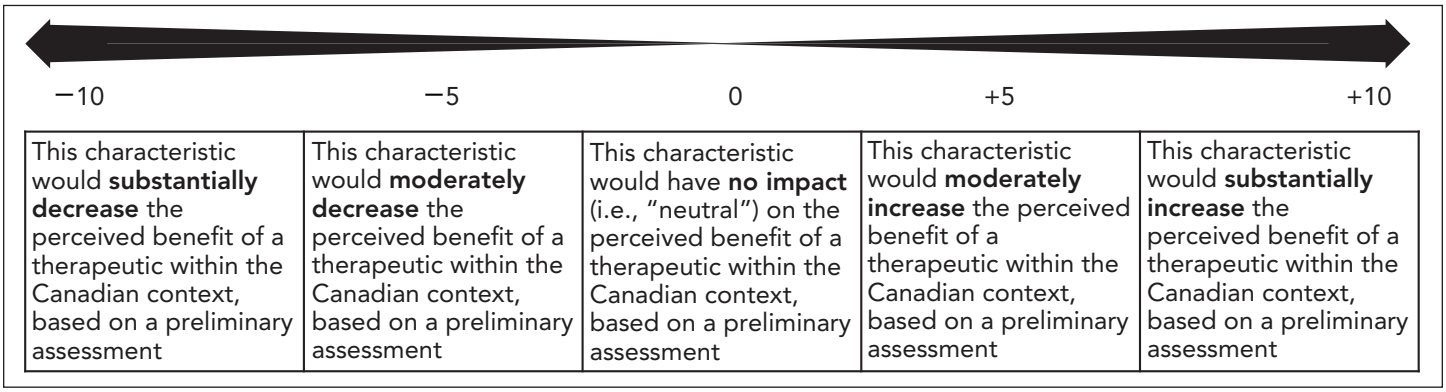


Table 3 provides an example of a criterion, its associated characteristics and their scores from the RST. For example, if a therapeutic was shown to be associated with serious liver toxicity during a Phase 3 trial leading to a serious warning and precaution, characteristic 4, "Serious warnings and precautions (…)" would be the characteristic selected for the safety criterion for that therapeutic. During the development of the tool, it was decided that this characteristic would decrease the perceived benefit of a therapeutic having this characteristic, within the Canadian context and based on a preliminary assessment, and be assigned a score of −2 (as per Figure 1).

Methods

Implementation of the Rapid Scoring Tool

Figure 2 depicts a simplified version of the workflow used for developing the RST during Phase 1. Some therapeutics could be excluded from further assessment based on a single characteristic. These characteristics of exclusion were assigned a score of −100 to ensure that therapeutics with these characteristics have low "overall benefit" scores and would not be among the top-ranked therapeutics for further assessment. Characteristics of exclusion are shown in **Box 1**. Given the rapidly changing pandemic environment, all therapeutics were reassessed periodically (whenever new information arose from daily scans of key COVID-19 resources or every six months, whichever occurred first).

Box 1: Characteristics of exclusion

- The therapeutic is unlikely to be active against current COVID-19 variants of concern
- Recommended against by the International Disease Society of America and the National Institutes of Health of the United States
- The manufacturer withdrew their submission to Health Canada (based on publicly available information)
- The manufacturer stopped research in COVID-19/their main COVID-19 trial
- The therapeutic is out of scope (e.g., convalescent plasma, hormones, anticoagulants, natural products, vitamins and human-derived products, such as immunoglobulins)
- There has been no information on the results of the trial for more than six months after the trial completion date or PHAC's last contact with the manufacturer
- No Phase 3 trial results available or expected within one year of the assessment date

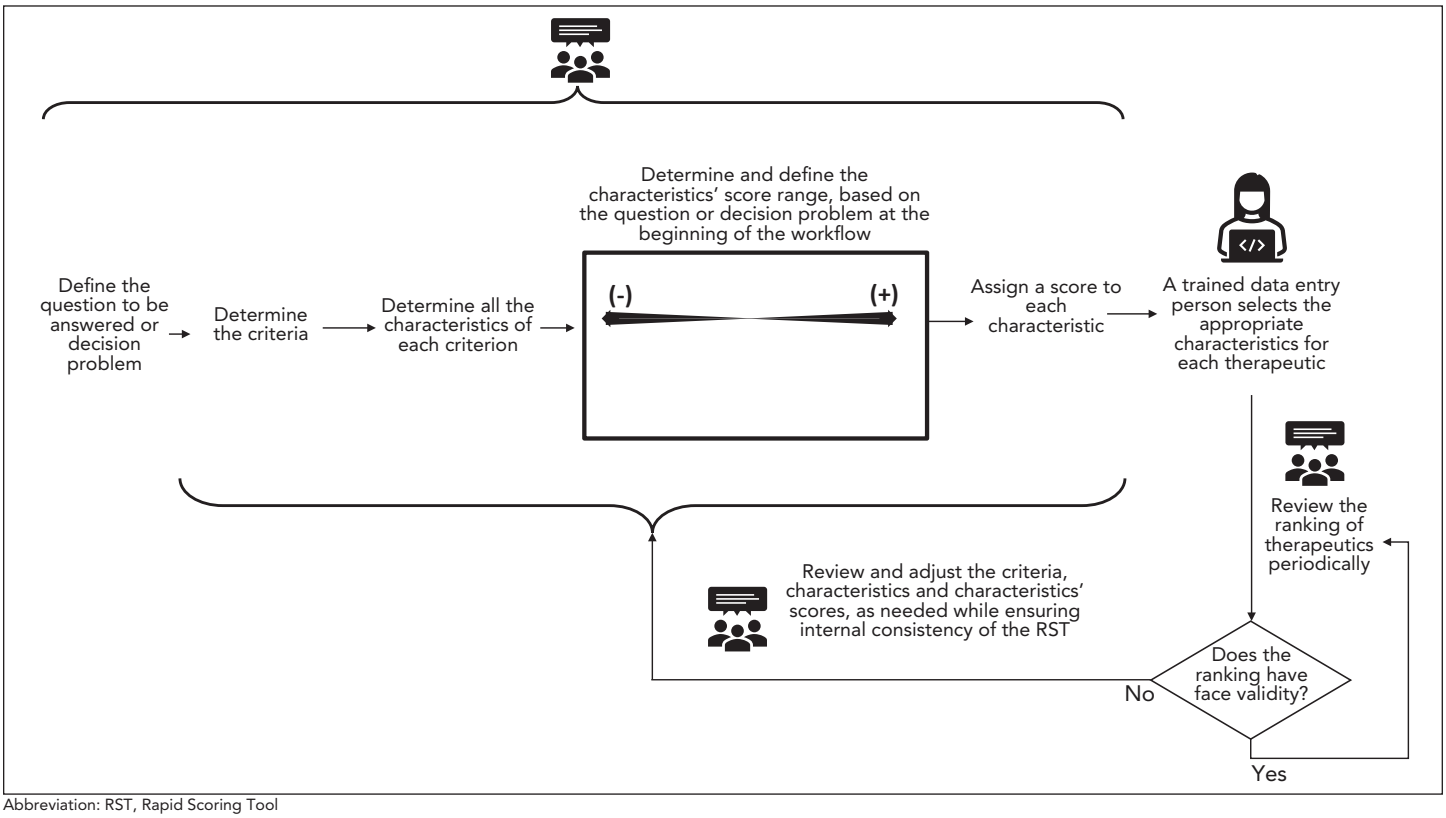
Abbreviation: PHAC, Public Health Agency of Canada

Table 3: Example of the safety criterion, its characteristics and their scores

Safety criterion characteristics	Characteristic's score
Characteristic 1: None of potential significance from a Phase 3 trial or real-world evidence (i.e., no AEs or mild to moderate AEs; no significant type or number of DIs, warnings and contraindications)	2
Characteristic 2: Unknown, but probably no AEs of significance (i.e., no AEs or mild to moderate AEs; no significant type or number of DIs, warnings and contraindications)	1
Characteristic 3: Unknown	0
Characteristic 4: Serious warnings and precautions or indication restricted because of significant safety concerns (e.g., therapeutic authorized for COVID-19 in another jurisdiction, for a non-COVID-19 indication in Canada or for a COVID-19 indication if being assessed for post-COVID-19 condition)	−2
Characteristic 5: Unknown, but probably some of significance (i.e., at least one of: significant AEs, DIs, warnings or contraindications or a serious AE of particular concern)	−3

Abbreviations: AE, adverse event; DI; drug interaction

Figure 2: Simplified overall workflow of the Rapid Scoring Tool



Abbreviation: RST, Rapid Scoring Tool

Results

Outcome measures of the Rapid Scoring Tool

After approximately 30 therapeutics were entered in the RST during stage two, the outcome measures, including appropriateness of ranking and the systematic nature, reliability and practicality of the RST, as well as the time required for completing a preliminary assessment, had been met. A standard operating procedure was developed to ensure ongoing consistency using the RST. Appropriateness of ranking was also met during stage three. Consensus agreement was reached for the ordinal ranking of all therapeutics, and for 10 of the 12 (83%) statements describing the intervals between rankings; disagreements pertained to two therapeutics. Adjustments were made to the RST, and the overall ranking of these therapeutics relative to the others was reviewed until consensus was reached. Ten months into Phase 1, 69 investigational COVID-19 therapeutics had undergone a preliminary assessment using the RST.

Discussion

In a dynamic pandemic environment, it was challenging to identify therapeutics (with incomplete information) in a timely manner for further assessment to enhance situational awareness. The RST enabled this through a continuous iterative process to update and validate the criteria, characteristics and characteristic scores, as well as its unique scoring scale. The RST scoring scale standardized all characteristic scores and directly incorporated the concept of "importance" that other tools typically address by assigning weights to criteria (7,13–15). **Appendix** was developed to provide further details on these key aspects of the RST, as well as some of their benefits compared with other commonly-used tools, such as the System of Objectified Judgment Analysis based tools (7,17–19) and other Multi-Criteria Decision Analysis-based tools (11,16,20).

In addition to its primary role, identifying therapeutics for further assessment, the RST served as a structured repository for key information pertaining to the therapeutics, which facilitated timely updating with new information and monitoring. This further enhanced situational awareness of the investigational therapeutic landscape.

Limitations

The RST has limitations that are inherent to the context in which it was developed and operationalized. How they were considered and mitigated is described below. To optimize the efficiency of the preliminary assessment, the RST relied on a subset of assessment criteria used in more thorough reviews. For example, implementation factors were not part of the RST, as this information was often not available or could not be determined rapidly. A different subset of assessment criteria might have affected the ranking of therapeutics. The initial validation during stage three, however, suggested that the subset of criteria and characteristics selected was adequate for identifying therapeutics for further assessment.

The score assigned to each characteristic was agreed upon by a specific group of individuals. A different group might have assigned different scores, which could have affected the ranking of therapeutics. This limitation is inherent to any decision-making process (18,21) and was mitigated by involving individuals with different backgrounds and roles in the design and validation of the RST.

The initial validation of the RST was led by the RST team, which might have affected the results. Several steps were taken to mitigate this potential limitation, such as using a structured presentation with questions that were carefully worded for clarity and neutrality, and efforts to avoid motivational biases.

Implications and next steps

The RST enabled timely identification of therapeutics to be assessed more thoroughly, as well as efficient tracking of the therapeutic landscape in an evolving environment. Its iterative approach ensured that it integrated the most up-to-date information on the criteria, characteristics, scores, and therapeutics. By nature of this design, stages two and three of Phase 1 will be repeated periodically.

Phase 2 of this pilot project will consist of assessing the validation and reliability of the RST with additional therapeutics and stakeholders, and formal statistical and sensitivity analyses. It is anticipated that an adapted framework would lend itself to other dynamic situations involving many interventions.

Conclusion

Phase 1 of the pilot project was successful. The RST enabled a systematic, reliable and efficient prioritization of investigational COVID-19 therapeutics for further assessment and enhanced situational awareness of the emerging therapeutic landscape during a dynamic pandemic. The RST presents several distinct aspects compared with other tools, including its scoring scale and method, and capacity to factor in incomplete or pending information.

Authors' statement

LB — Conceptualization, methodology, validation, writing–original draft, writing–review & editing
SC — Methodology, validation, writing–review & editing
MA — Methodology, validation, writing–review & editing
ES — Methodology, validation, writing–review & editing
MGR — Validation, writing–review & editing
CM — Validation, writing–review & editing
SGS — Validation, writing–review & editing
JA — Writing–review & editing

Competing interests

None.

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Appendix

Table A1: Key aspects and benefits of the Rapid Scoring Tool compared with commonly used tools[a]

Rapid Scoring Tool	Commonly used scoring tools
The scoring scale includes negative values, zero, and positive values. Negative values are assigned to characteristics that are undesirable (e.g., serious adverse events), and positive values to characteristics that are desirable (e.g., robust clinical trial design). A characteristic that is neither desirable nor undesirable is assigned a value of zero as it would neither increase nor decrease the perceived benefit a therapeutic with that characteristic would have (Figure 1). It is more intuitive to assign negative scores, rather than low positive scores, to undesirable characteristics.	The scoring scales typically start at zero and only include positive values, regardless of whether the characteristic is desirable or undesirable.

Table A1: Key aspects and benefits of the Rapid Scoring Tool compared with commonly used tools[a] (*continued*)

Rapid Scoring Tool	Commonly used scoring tools
The interpretation of a characteristic score remains consistent, regardless of the characteristics involved. The scores of the characteristics are standardized as they always represent the same measure. The scores reflect the impact a characteristic would have on the overall perceived benefit a therapeutic with that characteristic would have (Figure 1). This aspect helps ensure internal consistency of the scores among different characteristics. All the characteristic scores were assigned based on the answer to this question: "How would this characteristic impact the perceived benefit of this therapeutic?" (Figure 1). If a new characteristic is added and assigned a score, one could ensure internal consistency by asking: "Would a therapeutic with this new characteristic have the same perceived benefit as another therapeutic with a different characteristic with the same score?"	The interpretation of a score often varies, depending on what is being assessed. Although these scores are sometimes then converted using a common scale, it is more challenging to ensure internal consistency of the tool. For example, a score of 5 for a safety characteristic may not have the same meaning as a score of 5 for a dosage characteristic, or an undesirable characteristic of a criterion could have the same score as a desirable characteristic from a different criterion.
The RST can include characteristics of exclusion that are assigned a negative score that cannot be balanced out by the scores of other, desirable, characteristics. As a result, a therapeutic with a characteristic of exclusion would get ranked at the bottom of the list of therapeutics. For example, if a therapeutic had no activity against a dominant circulating COVID-19 variant, the RST would rank it very low on the list of therapeutics, regardless of how high its scores are for other characteristics. Therapeutics were periodically reassessed to ensure their selected characteristics reflected the most current information.	Other tools typically do not include characteristics of exclusion. Therapeutics with a very undesirable characteristic could still be ranked among the therapeutics at the top of the list of therapeutics of interest if other, desirable, characteristics override the score of that very undesirable characteristic.
No weights are assigned to criteria. This ensures that the impact of characteristics of exclusion and "outstanding" characteristics have the intended impact on the overall perceived benefit of a therapeutic, based on a preliminary assessment.	Other tools typically assign weights to criteria to indicate their importance relative to that of the other criteria. Criteria are umbrella terms that include several possible characteristics. Assigning weights to criteria can be problematic, especially in an environment where new therapeutics with new characteristics emerge, because the "importance" of a criterion is dependent on its characteristics. A scoring tool that assigns weights to criteria would not fare well in handling therapeutics with a characteristic of exclusion or an "outstanding" characteristic. This is because the impact of these characteristics on the perceived "overall benefit" of the therapeutic would be fixed and pre-determined by the weight of their criterion. For illustrative purposes, we will use a simplified scoring tool with only four criteria: quality of evidence, clinical impact, safety and dosage. Quality of evidence is assigned a weight of 40 points, clinical impact 30 points, safety 20 points and dosage 10 points, for a total of 100 points. The weight of the dosage criterion was determined according to whether the dosage of a therapeutic is, for example, once daily for 10 days, twice daily for five days, or three times daily for three days. This criterion was determined to be of low importance relative to the other criteria and was given a weight of 10% in the assessment. A new dosage, for example once every month, then becomes available and is deemed to be of particular benefit. The impact of this characteristic will be limited by the weight of its criterion (i.e., it will only be able to account for a maximum of 10 out of 100 points). As a result, this new characteristic may not be well-reflected in the overall perceived benefit of this therapeutic.
The RST can incorporate incomplete or unknown information, because of the design of the scoring scale (Figure 1). For example, the RST has a characteristic for therapeutics with an "unknown clinical impact" that was assigned a score of zero because that characteristic had no impact on the perceived benefit of this therapeutic. When results became available, the characteristic (and its associated score) was updated.	Other scoring tools are typically only able to consider a set of therapeutics with complete information on each therapeutic.
The scores of the characteristics could be easily adjusted as the pandemic environment evolved or new information became available, and their impact on the overall ranking relative to other therapeutics, quickly seen.	These tools typically assess therapeutics at a single point in time and updating them based on new information can be cumbersome and a lengthy process.

Abbreviation: RST, Rapid Screening Tool

[a] For example, the System of Objectified Judgment Analysis based tools (7,17–19) and other Multi-Criteria Decision Analysis-based tools (11,16,20)

Large scale analysis of the SARS-CoV-2 main protease reveals marginal presence of nirmatrelvir-resistant SARS-CoV-2 Omicron mutants in Ontario, Canada, December 2021–September 2023

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Abstract

Background: In response to the COVID-19 pandemic, a new oral antiviral called nirmatrelvir-ritonavir (Paxlovid™) was authorized for use in Canada in January 2022. *In vitro* studies have reported mutations in M^{pro} protein that may be associated with the development of nirmatrelvir resistance.

Objectives: To survey the prevalence, relevance and temporal patterns of M^{pro} mutations among SARS-CoV-2 Omicron lineages in Ontario, Canada.

Methods: A total of 93,082 M^{pro} gene sequences from December 2021 to September 2023 were analyzed. Reported *in vitro* M^{pro} mutations were screened against our database using in-house data science pipelines to determine the nirmatrelvir resistance. Negative binomial regression was conducted to analyze the temporal trends in M^{pro} mutation counts over the study time period.

Results: A declining trend was observed in non-synonymous mutations of M^{pro} sequences, showing a 7.9% reduction (95% CI: 6.5%–9.4%; $p<0.001$) every 30 days. The P132H was the most prevalent mutation (higher than 95%) in all Omicron lineages. *In vitro* nirmatrelvir-resistant mutations were found in 3.12% (n=29/929) Omicron lineages with very low counts, ranging from one to 19. Only two mutations, A7T (n=19) and M82I (n=9), showed temporal presence among the BA.1.1 in 2022 and the BQ.1.2.3 in 2022, respectively.

Conclusion: The observations suggest that, as of September 2023, no significant or widespread resistance to nirmatrelvir has developed among SARS-CoV-2 Omicron variants in Ontario. This study highlights the importance of creating automated monitoring systems to track the emergence of nirmatrelvir-resistant mutations within the SARS-CoV-2 virus, utilizing genomic data generated in real-time.

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Keywords: SARS-CoV-2, Omicron, Paxlovid, nirmatrelvir-ritonavir, main protease gene (M^{pro}), *in vitro* resistant mutations, genomic surveillance, Ontario

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Introduction

Nirmatrelvir-ritonavir (brand name Paxlovid™, Pfizer Inc.) is an orally administered antiviral therapy. This combination received an Emergency Use Authorization from United States Food and Drug Administration in December 2021 (1–3). Nirmatrelvir-ritonavir was subsequently approved by Health Canada for adults with COVID-19 who were at high risk of progressing to severe disease in January 2022 (4,5). Nirmatrelvir (PF-07322332), an active component of Paxlovid, is a novel inhibitor of the SARS-CoV-2 3-chymotrypsin-like protease (3CL^{pro}) or main protease (M^{pro}, also known as non-structural protein, nsp5), which is critical for viral replication and assembly. This inhibitory mechanism prevents the production of new viruses in infected cells (6). Importantly, nirmatrelvir is highly specific to the viral protease, which reduces the risk of off-target effects on human proteases (7). Ritonavir inhibits the cytochrome P4503A4 (CYP3A4) enzyme, a major human hepatic drug-metabolizing enzyme, increasing the plasma concentrations of nirmatrelvir *in vivo* (8).

Clinical efficacy studies on nirmatrelvir-ritonavir reported fewer visits to the emergency department, lower hospitalizations, and lower all-cause mortality in patients infected with SARS-CoV-2 variants of concern (Delta B.1.617.2 and Omicron B.1.1.529, BA.2, BA2.12.1, BA.4 and BA.5) (9–12). A retrospective observational study from Ontario, Canada, reported a significant reduction in hospital admission from COVID-19 and all-cause mortality among outpatients who used nirmatrelvir-ritonavir between April and August 2022, with greater benefits being noted among individuals who were under-vaccinated or unvaccinated and 70 years of age and older (13). The Canadian Nosocomial Infection Surveillance Program found that 13% (n=490/3,731) of adult patients with COVID-19 received nirmatrelvir-ritonavir, either at admission or during hospitalization in Canada, although the results on treatment efficacy remain unreported (14).

The therapeutic effectiveness of nirmatrelvir-ritonavir can be influenced by the emergence of resistant variants. Given the continuous evolution of the SARS-CoV-2 virus and selection pressures from the introduction of nirmatrelvir-ritonavir, resistance is likely to emerge (15). Evidence of *in vitro* nirmatrelvir-resistant SARS-CoV-2 variants (16–18), variable potencies of nirmatrelvir to different human coronaviruses (19) and resistance of other viruses to protease inhibitors (20) support the need for continuous monitoring of SARS-CoV-2 M^{pro} gene sequences to quickly identify mutations that may affect nirmatrelvir's potency. Such genomic surveillance could provide insights into the mechanisms of antiviral evasion that are crucial for policy guidelines and in the development of next-generation M^{pro} inhibitors (18).

The purpose of this study was to survey the prevalence, relevance and temporal patterns of M^{pro} mutations among circulating SARS-CoV-2 lineages in Ontario. First, we conducted a scientific and grey literature review (May 2022 to August 2023) to compile a list of M^{pro} mutations that have been characterized as conferring *in vitro* resistance to nirmatrelvir (21). This complied list was subsequently used to identify the presence of nirmatrelvir-resistant mutations within the dataset. We then analyzed 93,082 M^{pro} sequences derived from SARS-CoV-2 Omicron-positive clinical specimens sequenced in Ontario between December 2021 and September 2023.

Methods

Clinical specimen selection and SARS-CoV-2 whole genome sequencing

Diagnostic laboratories in Ontario provided a proportion of all SARS-CoV-2 positive clinical specimens to designated whole-genome sequencing (WGS) laboratories as part of the Ontario COVID-19 Genomics Network (22). The acceptable criteria for WGS sampling included a SARS-CoV-2 polymerase chain reaction (PCR) cycle threshold (Ct) of 30 or fewer and a sufficient sample volume. The sampling proportion ranged from 10% to 100% and was adjusted over time based on projected case counts and Ontario COVID-19 Genomics Network sequencing capacity from December 2021 to September 2023. The diagnostic PCR testing for SARS-CoV-2/COVID-19 was restricted to high-risk populations (23,24) and, as such, representative surveillance pertains only to those populations tested at the time of sampling.

SARS-CoV-2 main protease sequences

Raw sequence data from the Illumina platform were analyzed using ARTIC pipeline v1.7 (the Ontario Institute for Cancer Research pipelines) and ARTIC primer scheme version 4.1. Post-analysis quality filtering was performed using ncov-tools version 1.8. Samples were annotated for lineage with Pangolin v4.3 using constellations v.0.1.12 (Pangolin-assignment v1.15.1, Scorpio 0.3.17, and usher 0.5.6). The ARTIC nanopolish v1.3.0-dev (+0.3.1 patch) pipeline and associated ncov-tools version were used for samples sequenced on the nanopore platform. All available M^{pro} gene sequences of SARS-CoV-2 Omicron (n=93,082 unique sequences) were collected between December 1, 2021, and September 21, 2023, from Public Health Ontario's SARS-CoV-2 WGS database (PHO-SARS-CoV-2 WGS database). These M^{pro} sequences were screened against the reference SARS-COV-2 genome, Wuhan-Hu-1 (accession no. NC_045512.2), to identify both synonymous and non-synonymous mutations across all Omicron lineages.

Temporal tracking of main protease mutations in Omicron lineages

An in-house data science pipeline was developed in Python v.3.9.16 to track the temporality and prevalence of observed M^{pro} mutations among Omicron lineages in Ontario. A generalized additive model with restricted cubic spline was fit on the log transformed mutation count. We examined the patterns of the M^{pro} non-synonymous mutations over the study time-period; based on these patterns, a negative binomial regression (R package mgcv v.1.9-0) was used to model the decline of the number of non-synonymous mutations over time.

Results

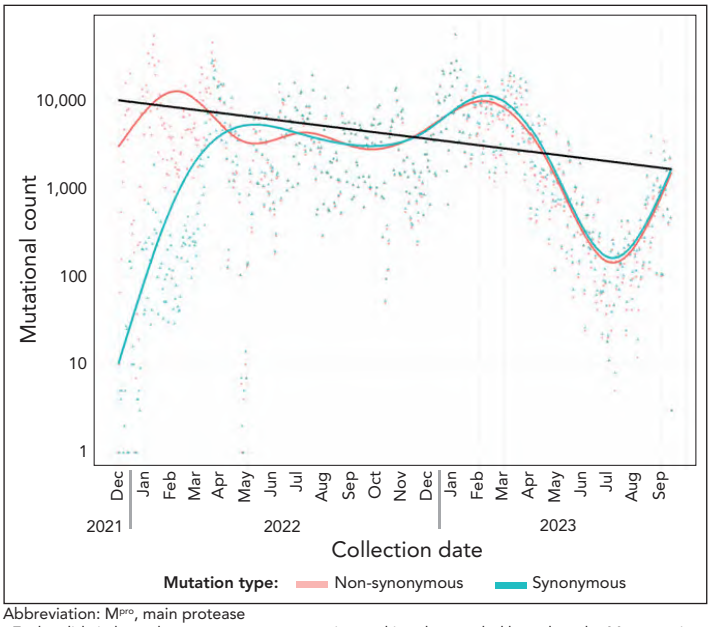
A total of 93,082 M^{pro} gene sequences corresponding to 929 Omicron lineages of SARS-CoV-2 from Ontario were analyzed. Omicron lineages were grouped by their prevalence of total sequences analyzed as low (less than one percent) or high (greater than or equal to one percent). Twelve SARS-CoV-2 lineages were categorized with high prevalence. The five lineages with the highest prevalence during defined period were: BA.1.1 (9.3%), XBB.1.5 (8.3%), BQ.1.1 (7.8%), BA.2 (7.4%) and BA.5.2.1 (6.0%).

We studied the evolution of M^{pro} nucleotide sequences of SARS-CoV-2; we observed cyclic variations for total counts for both synonymous (no change in protein sequence) and non-synonymous (change in protein sequence) mutations. The negative binomial regression on M^{pro} non-synonymous mutations showed a 7.9% (95% CI: 6.5%–9.4%; $p<0.001$) decrease in mutation counts every 30 days (**Figure 1**). The non-synonymous mutational burden, with sequences carrying at least one mutation across the M^{pro} protein sequence, accounted for approximately 67.7% (207 AAs/306 AAs of M^{pro}) (**Figure 2**). **Table 1** presents details of low and high prevalent lineages with M^{pro} non-synonymous mutations reported in at least 10 sequences of the total sequence data collected for each lineage. For example, the T21I mutation is observed in 31 of 2,801 total BA.2.12.1 sequences during the study period. Only six mutations, L67, L75, K90, A116, P184 and R279, were found to be common in both high and low-prevalent lineages; however, none of these mutations were relevant to the reported *in vitro* nirmatrelvir-resistant mutations.

Pattern of documented highly prevalent mutations in SARS-CoV-2 Omicron lineages, Ontario

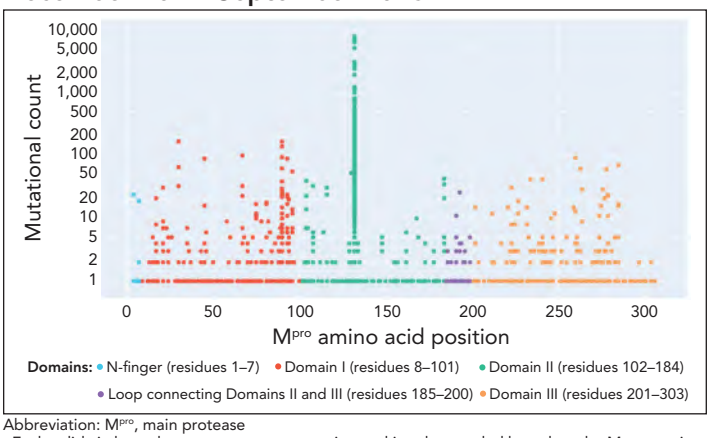
Of the nine most prevalent M^{pro} mutations in SARS-CoV-2 (G15S, T21I, K88R, L89F, K90R, P108S, P132H, L205V and A260V) (17,26,27,32), albeit with unaltered susceptibility to nirmatrelvir (2,3), only P132H accumulated at a noticeable frequency, eventually accounting for more than 95% in the Omicron lineages in Ontario (27). The K90R mutation

Figure 1: Temporal trends of non-synonymous and synonymous mutations using restricted cubic spline across mutations observed in the main protease (M^{pro}) nucleotide sequences of SARS-CoV-2 Omicron lineages circulated in Ontario, Canada, December 2021–September 2023[a]



Abbreviation: M^{pro}, main protease
[a] Each solid circle or dot represents one mutation and is colour-coded based on the M^{pro} protein structural details (25). The mutational count is the observed absolute value of mutations at each position. Log transformed Y-axis presents mutational counts

Figure 2: Burden of non-synonymous mutations observed in the main protease (M^{pro}) of SARS-CoV-2 Omicron lineages circulated in Ontario, Canada, December 2021–September 2023[a]



Abbreviation: M^{pro}, main protease
[a] Each solid circle or dot represents one mutation and is colour-coded based on the M^{pro} protein structural details (25). The mutational count is the observed absolute value of mutations at each position. Log transformed Y-axis presents mutational counts

was observed in the following Omicron lineages: BA.1.1, BA.2, BA.2.12.1, BA.5.2, BA.5.2.1, BQ.1, BQ.1.1 and XBB.1.15 (within lineage rates ranged from 0.37% to 2.14%). While the A260V substitution was observed in 1.41% (n=92/6,513 sequences) of BQ.1.1 variants circulated in 2022, the T21I mutation accumulated in BA.2.12.1 lineage with 1.1% (n=31/2,801 sequences) mutational frequency.

Table 1: M^{pro} non-synonymous mutations with at least 10 observed in the SARS-CoV-2 Omicron lineage sequences, Ontario, Canada, December 2021–September 2023

M^{pro} structure region	Mutation[a]	Pango lineage	Lineage prevalence[b]	Total sequences	Count of sequences with mutation	Frequency[c]	Observation from prior literature (reference)
N-finger (1 to 7 AA)	R4K	BQ.1.2	Low	267	24	8.99	Mutation contributes to M^{pro} dimerization (26)
	A7T	BA.1.1	High	8,143	19	0.23	Mutation contributes to M^{pro} dimerization (27–30)
Domain I (8 to 101 AA)	M17V	XBB.1.5	High	7,281	18	0.25	-
	T21I	BA.2.12.1	High	2,801	31	1.11	*In vitro* study reported as founder or precursor mutation (18)
	L30I	BQ.1.3	Low	33	33	100	L30F, an *in vitro*-reported nirmatrelvir-resistant mutation (9) but L30I has not been tested
		BQ.1.3.1	Low	170	170	100	
		BQ.1.3.2	Low	66	66	100	
	T45N	BE.4	Low	90	90	100	-
		BE.4.1	Low	16	16	100	
		CQ.2	Low	16	16	100	
	L67S	BA.5.2.1	High	5,312	23	0.43	-
	L67V	BF.14	Low	46	32	69.57	-
		BQ.1.1.40	Low	448	101	22.54	
	L75F	BA.1.1	High	8,143	11	0.14	-
		BA.2	High	6,551	12	0.18	
		BA.4.6	High	1,250	17	1.36	
		BA.5.5	Low	705	10	1.42	
	S81C	XBB.1.5	High	7,281	18	0.25	-
	K90R	BA.1.1	High	8,143	95	1.17	Prevalent mutation in Beta (B.1.351) variants (27)
		BA.2	High	6,551	140	2.14	
		BA.2.12.1	High	2,801	23	0.82	
		BA.5.2	High	3,083	24	0.78	
		BA.5.2.1	High	5,312	25	0.47	
		BQ.1	High	1,987	12	0.6	
		BQ.1.1	High	6,513	39	0.6	
		XBB.1.5	High	7,281	27	0.37	
		BA.2.3	Low	751	166	22.1	
		BA.5.9	Low	70	10	14.29	
		BF.14	Low	46	29	63.04	
		BF.21	Low	104	12	11.54	
		BQ.1.1.51	Low	133	15	11.28	
	T93I	BA.2.12.1	High	2,801	11	0.39	-
		XBB.1.5	High	7,281	6	0.08	
	A94V	BU.1	Low	20	20	100	-
	P96S	BQ.1.1	High	6,513	56	0.86	-
	P96L	XBB.1.5	High	7,281	14	0.19	-
Domain II (102 to 184 AA)	V104I	BN.1.4	Low	15	14	93.33	-
	P108T	BA.5.2.1	High	5,312	33	0.62	-
	A116V	XBB.1.5	High	7,281	31	0.43	-

Table 1: M^{pro} non-synonymous mutations with at least 10 observed in the SARS-CoV-2 Omicron lineage sequences, Ontario, Canada, December 2021–September 2023 (*continued*)

M^{pro} structure region	Mutation[a]	Pango lineage	Lineage prevalence[b]	Total sequences	Count of sequences with mutation	Frequency[c]	Observation from prior literature (reference)
Domain II (102 to 184 AA) (*continued*)	A116T	BQ.1.2	Low	267	24	8.99	-
	M130L	BA.5.2.9	Low	534	53	9.93	-
	P168S	BA.5.1	High	2,452	10	0.41	Prevalent mutation in pre-Omicron lineages (17)
	P184S	BA.1.1	High	8,143	21	0.26	-
		BA.2.3	Low	751	43	5.73	-
	P184L	BQ.1.14	Low	250	35	14	-
Loop (185 to 200 AA)	A193V	XBB.1.16.1	Low	227	4	1.76	-
Domain III (201 to 303 AA)	V202I	BQ.1.2.3	Low	289	15	5.19	-
	V212I	FL.7	Low	17	12	70.59	-
	N221S	BQ.1.22	Low	112	15	13.39	-
	F223L	BN.1.3.1	Low	31	31	100	-
	L227F	BA.5.2.1	High	5,312	19	0.36	-
		BF.7	High	999	12	1.2	
	L232F	BA.5.2	High	3,083	14	0.45	-
	A234V	BQ.1.13	Low	435	42	9.66	-
	P241L	XBB.1.5	High	7,281	42	0.58	-
	H246Y	BA.5.1.15	Low	10	10	100	-
	D248N	BU.1	Low	20	12	60	-
	A260V	BQ.1.1	High	6,513	92	1.41	No impact shown on the reducing drug potency in biochemical assay (2,3)
	D263A	BQ.1.1	High	6,513	62	0.95	-
	M264I	XBB.1.5	High	7,281	29	0.4	-
	N274T	BQ.1.1	High	6,513	11	0.17	-
	N274S	BQ.1.14	Low	250	10	4	-
	G275S	BN.1.5.2	Low	18	16	88.89	-
	M276I	BA.5.1.2	Low	154	28	18.18	-
	N277I	BA.5.1.23	Low	236	21	8.9	-
	G278R	BF.7	High	999	58	5.81	-
	R279C	BF.7	High	999	23	2.3	-
		BA.5.5	Low	705	22	3.12	-
		BF.1	Low	95	11	11.58	-
	A285T	BA.2	High	6,551	16	0.24	Mutation contributes to M^{pro} dimerization (26) and potential decrease in M^{pro} catalytic efficiency (31)
		BF.1	Low	95	11	11.58	-

Abbreviations: M^{pro}, main protease; -, not applicable

[a] P132H, given its predominance in Omicron lineages, has been excluded from this table

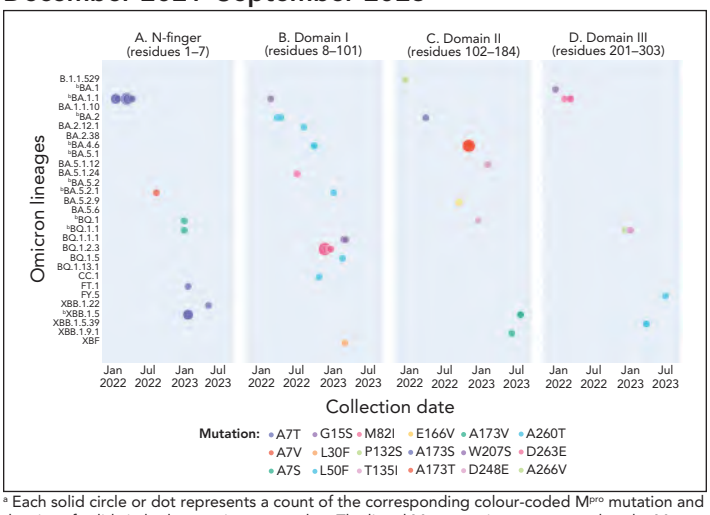
[b] Lineage prevalence: Omicron lineages were grouped by their prevalence of total sequences analyzed as low (less than one percent) or high (greater than or equal to one percent)

[c] Formula used to calculate the frequency is: (count of sequences with mutation/total sequences)*100

Low prevalence and no temporality of nirmatrelvir drug resistance in SARS-CoV-2 Omicron lineages, Ontario

Sixteen of 34 *in vitro* characterized nirmatrelvir-resistant mutations (2,3,32,33), corresponding to A7T/S/V (M^{pro} N-finger), G15S, L30F, L50F, M82I (M^{pro} Domain I), P132S, T135I, E166V, A173S/T/V (M^{pro} Domain II), Q189K, T196A (loop that connects M^{pro} Domains II and III), W207S, D248E, A260T, D263E and A266V (M^{pro} Domain III), were observed with lineage-specificity (3.12%, n=29/929 lineages) (**Figure 3**). The burden of these mutations ranged from 1 to 19 counts, with A7T being the most frequently observed in BA.1.1 (within lineage rate=0.23%, n=19/8,143 sequences; observed only once in FT.1, XBB.1.22 and XBB.1.5), followed by M82I in nine sequences of BQ.1.2.3. The rest were observed in n=4 sequences of BA.4.6 for the A173T mutation, according to **Appendix**, **Table A1**. Only A7T and M82I exhibited some temporality; A7T was notable during weeks three, four and 10 to 15 in 2022 among the BA.1.1 lineage and M82I during weeks 46 to 51 in late 2022 among the BQ.1.2.3 lineage (Figure 3).

Figure 3: *In vitro* characterized nirmatrelvir-drug resistant mutation accumulation in SARS-CoV-2 Omicron lineages and its temporal patterns in Ontario, Canada, December 2021–September 2023[a,b]



[a] Each solid circle or dot represents a count of the corresponding colour-coded M^{pro} mutation and the size of solid circle denotes its count value. The listed M^{pro} mutations correspond to the M^{pro} structural regions of the mutation (25)
[b] Denotes highly prevalent lineages. Appendix, Table A1 provides counts of each mutation and associated lineages in time

We also examined our database for double (18,21,33–35), triple (2,3), quadruple and quintuple (2,3) mutants, as have been reported in the literature, since these multiple mutations have the potential to confer synergistic resistance to nirmatrelvir. However, none of these mutations were identified within SARS-CoV-2 lineages circulating at the time of sampling in Ontario.

Discussion

A comprehensive analysis of SARS-CoV-2 Omicron lineage M^{pro} sequences from Ontario revealed that approximately 3% of lineages (n=29/929) exhibited *in vitro* characterized nirmatrelvir-resistant M^{pro} mutations, without any discernible temporal pattern.

Consistent with the global literature (26,27,32), the missense mutation P132H in the M^{pro} structural Domain II region was the most widespread with higher than 95% prevalence in all Ontario Omicron lineages. In addition, K90R, the most prevalent mutation of Beta variants, was observed with modest prevalence in the Ontario Omicron lineages (27). However, despite their predominance, these two mutations were not reported to reduce nirmatrelvir potency (2,3). Structural assessments of M^{pro} revealed that both mutations (P132H and K90R) are distal to the nirmatrelvir binding site and, thus, do not alter structural conformation at or around the binding site (34). The A260V substitution, another highly prevalent M^{pro} mutation observed in BQ.1.1 variants reported as an infrequent natural polymorphism, was flagged in the EPIC-HR clinical trial with impact on nirmatrelvir-resistance pending (2,3).

In our dataset, we observed a low frequency of M^{pro} point mutations, such as T21I, P252L and T304I, which are known to function as "precursor" mutations for the emergence of nirmatrelvir resistance in SARS-CoV-2 (18). These three mutations may independently limit the replication of the SARS-CoV-2 virus (32), but no data are available on their potential contribution to resistance. None of the low prevalence mutations observed in our dataset, including A7T and M82I, are implicated in nirmatrelvir-resistance (35). Notably, A7 is situated within the N-finger region, known to play a role in dimerization which is crucial to M^{pro} enzyme activity (28,29). According to Iketani *et al.* (30), variants with mutations of A7 to V/C/S/T have comparable protease activity to wild type. Consistently, structural studies suggest that the alanine substitution by threonine at position 7 only has a modest effect on protease activity of M^{pro}, a reduction in efficiency by 1.5 times (29). Altogether, these studies suggest that the A7V/S/T mutations observed in BA.1.1 variants in early 2022 were unlikely to contribute to nirmatrelvir-resistance or protease activity. No known *in vitro* nirmatrelvir-resistant mutations were found (as of September 17 to 30, 2023) in Ontario's recently circulating variants, EG.5.1.1, FL.1.5.1, HV.1, HK.3 and XBB.1.16.6 (36).

The declining pattern seen in non-synonymous M^{pro} mutations (Figure 1) suggests the possibility of either a reduced heterogeneity among Ontario's circulating viral variants or a decreased propensity for the M^{pro} protein to evolve in response to selective pressure (27). Alternatively, Schwartz *et al.* (13) reported only 5% of patients (n=8,876/177,545) had been treated with nirmatrelvir-ritonavir between April 4, 2022, and

August 31, 2022, in Ontario. These data, although specific to a brief study period within the timeframe of our study, suggest limited selection pressure, potentially contributing to the lower prevalence of antiviral-resistant Omicron variants observed in the population studied. Overall, our observations suggests that Omicron variants analyzed at the time of study period have not yet developed significant and widespread resistance to nirmatrelvir (37).

Strengths and limitations

A major strength of the study is the large scale of the analysis of the M^{pro} sequences from the Omicron lineages that circulated between December 2021 and September 2023 in Ontario. A comprehensive analysis led to insights related to *in vitro* mutations relevant to nirmatrelvir resistance (both mutational frequencies and temporality), protease activity and the identification of mutations of unknown function unique to our dataset that may be investigated further in experimental studies. A key limitation of our study is its generalizability, because only a defined sampling proportion was sequenced at given time (i.e., targeted population for COVID-19 diagnostic testing, proportions of specimens sequenced that vary in time, specimens with PCR Ct of fewer than 30). Because of this stringent criteria for sequencing samples, our study dataset may not be directly representative of M^{pro} sequences of Ontario. Furthermore, a lack of availability of sociodemographic, clinical and treatment data limited the interpretation of our findings in the context of nirmatrelvir-ritonavir treatment.

Conclusion

Overall, we found very low presence of nirmatrelvir-resistant mutant strains with lack of temporality. Our data suggest that the current use of nirmatrelvir-ritonavir targeting specific populations in Ontario may not provide selective pressure for the emergence of resistant mutants (37). Finally, this study underpins the need for continuous genomic surveillance and also forms the foundation for the creation of an automated monitoring system designed to track the emergence of nirmatrelvir-resistant mutations within the SARS-CoV-2 virus, utilizing real-time genome data. The ability to track, in near real-time, the frequency of mutations associated with antimicrobial resistance can inform the antimicrobial stewardship necessary to maintain drug efficacy over a longer period.

Authors' statement

VD — Conceptualization, software, formal analysis, writing–original draft, writing–review & editing
FS — Software, formal analysis, writing–review & editing
SI — Formal analysis, writing–review & editing
TB — Writing–review & editing
SC — Formal analysis, writing–review & editing
AMA — Writing–review & editing
AE — Writing–review & editing
HB — Writing–review & editing
NV — Writing–review & editing
YL — Software, formal analysis, writing–review & editing
KS — Writing–review & editing
HH — Writing–review & editing
KC — Writing–review & editing
AS — Writing–review & editing
AL — Writing–review & editing
AZ — Writing–review & editing
KR — Writing–review & editing
JK — Writing–review & editing
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The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

JB Gubbay is a paid consultant scientific editor for GIDEON Informatics, Inc., which is unrelated to the current work. All other authors have no competing interest to declare.

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Appendix

Table A1: Cumulative detection of nirmatrelvir-resistant M^{pro} mutations observed in SARS-CoV-2 Omicron lineages circulated in Ontario, Canada, December 2021–September 2023

M^{pro} mutation	Current evidence	Associated lineage	Year of lineage circulation	*In vitro* reported nirmatrelvir-resistant mutations in each lineage
A7T	Post-treatment emergence	BA.1.1	2022	19
		FT.1	2023	1
		XBB.1.22	2023	1
		XBB.1.5	2023	2
A7V	Post-treatment emergence	BA.5.2.1	2022	1
A7S	Post-treatment emergence	BQ.1	2023	1
		BQ.1.1	2023	1
G15S	Biochemical assay, resistance selection study	BA.1.1	2022	1
		BQ.1.1.1	2023	2
L30F	Post-treatment emergence	XBF	2023	1
L50F	Resistance selection study	BA.2	2022	2
		BA.2.12.1	2022	1
		BA.4.6	2022	2
		CC.1	2022	1
		BA.5.2.1	2023	1
		BQ.1.5	2023	1
M82I	Post-treatment emergence	BA.5.1.24	2022	1
		BQ.1.2.3	2022	9
T135I	Biochemical assay	BQ.1	2022	1
		BA.5.1.12	2023	2
E166V	Biochemical assay, post-treatment emergence	BA.5.2.9	2022	1
A173S	Biochemical assay, cell culture assay	BA.2	2022	1
A173T	Biochemical assay, cell culture assay	BA.4.6	2022	4
A173V	Biochemical assay, cell culture assay	XBB.1.5	2023	2
		XBB.1.9.1	2023	1
Q189K	Biochemical assay	XBB.1.5	2023	1
T196A	Post-treatment emergence	BA.2	2022	1
		BA.2.3	2022	1
		BA.4.1	2022	1
W207S	Post-treatment emergence	BA.1	2021	1
D248E	Biochemical assay	BQ.1.1	2023	3
A260T	Post-treatment emergence	FY.5	2023	1
		XBB.1.5.39	2023	2
D263E	Post-treatment emergence	BA.1.1	2022	3
A266V	Post-treatment emergence	BQ.1.1	2022	1

Abbreviation: M^{pro}, main protease

EPIDEMIOLOGIC STUDY

Opportunities and lessons learned from a retrospective analysis of administrative billing data to understand the language profile of high-risk close contacts of COVID-19 cases in Ontario

Andrea Chambers[1]*, Mark A Cachia[2], Jessica P Hopkins[1,2]

Abstract

Background: During a public health emergency, it is vital to have access to data sources that can identify communities disproportionately affected and to ensure public health communications are meeting the needs of diverse populations.

Objective: To explore how administrative billing data for language interpretation services could be used as an additional source of information to understand the language profile of high-risk close contacts of COVID-19 cases.

Methods: A retrospective descriptive analysis was conducted using administrative billing data from Public Health Ontario's Contact Tracing Initiative from May 2020 to February 2022. Data from the Contact Tracing Initiative were utilized to identify drivers that could have influenced patterns in language interpretation requests. Trends were compared with community language profiles using 2021 Canadian Census data.

Results: Interpreters responded to 2,604 requests across 38,518 interpretation minutes and provided information in 50 different languages. The top five requested languages were French, Arabic, Spanish, Punjabi and Mandarin. Five distinct periods were identified of different language predominance including Spanish in spring/summer 2020, French in summer/fall 2020 and Arabic in spring 2021. Overall, these trends aligned with the language profile of health units contributing most submissions.

Conclusion: Public health agencies could benefit from using existing secondary data sources to understand the language interpretation needs of their communities. This study also demonstrated how existing data sources could be used to help assess how communities are being disproportionately affected by public health emergencies and how this might change over time.

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Keywords: contact tracing, COVID-19, SARS-CoV-2, language concordance, pandemic

Introduction

The use of case and contact management is a foundational public health approach to control the spread of infectious diseases. Conducting case and contact management was an important priority for many jurisdictions during the early phases of the COVID-19 pandemic (1). Forward contact tracing involves cases identifying people ("contacts") who may have been exposed to the SARS-CoV-2 during their period of communicability. Public health agencies then communicate with high-risk contacts to advise them of the exposure and provide information on testing, isolation requirements and enabling

supports. For the delivery of case and contact management to be effective and equitable, information and support needs to be delivered in a community's preferred language (2–4).

Socioeconomic data collected early during the COVID-19 pandemic in Ontario helped describe how some communities were disproportionately impacted and early results emphasized the importance of looking at language ability (5,6). In Ontario, approximately 16% of the population predominantly speaks a non-official language at home (7). An analysis of patterns of testing and test results early during the pandemic found that lack of English or French language ability was associated with lower testing but higher percent positivity among recent adult immigrants and refugees in Ontario (6).

Collection of individual-level socioeconomic data from COVID-19 cases in Ontario was not extended to collection of information from high-risk close contacts of COVID-19 cases. We see this as a gap as the disproportionate impacts of the pandemic extend to other outcomes and experiences, including the mental health and financial impacts of multiple and prolonged periods of isolation associated with being identified as a high-risk close contact (8). Moreover, primary data collection efforts were time-intensive and several factors impacted data completeness, accuracy and sustainability (9).

Given the gaps in understanding how language interpretation services have been utilized among high-risk contacts during the COVID-19 pandemic, this study aimed to 1) outline the steps used to leverage secondary data sources to understand the language profile of high-risk close contacts and 2) describe how this type of analysis can help investigate disproportionate impacts of the COVID-19 pandemic.

Methods

Setting

This study leveraged data from Public Health Ontario's COVID-19 Contact Tracing Initiative (CTI). Between April 2020 and February 2022, Ontario's 34 local public health units (PHUs) could use the CTI to help manage the volume of work associated with contact notification.

Provincial and federal government agencies provided support for initial and follow-up phone calls to high-risk close contacts of confirmed or probable cases of COVID-19 (10). If a contact required interpretation services or requested if services were available, the interviewer would dial the interpretation service provider to provide simultaneous interpretation in the contact's preferred language. How this program was developed and used by local PHUs in Ontario has been described in more detail in a separate publication (10).

Below, we have outlined the four-step process used to conduct a descriptive retrospective analysis of secondary data sources and a visual analysis of trends to describe the language profile of high-risk contacts.

Step 1: Analyze language interpretation services data

We obtained administrative billing data from the interpretation services vendor from May 4, 2020 (first billing date), to February 25, 2022 (last day of operations and possible billing date). The billing data included a line listing reflecting interpretation requests, the language requested and the call duration with no missing data across the variables of interest. We computed the frequency of encounters with language interpretation services, the cumulative total interpretation time in minutes and the median interpretation time and interquartile range (IQR) for each language and overall. A visual analysis of time trends was used to identify shifts in language predominance.

Step 2: Identify drivers that could be influencing patterns in language interpretation requests

Data from the CTI were utilized to examine trends over time in the volume of high-risk contacts, independent of translation requests, submitted to the program. We described changes over time in which health units were submitting the majority of contacts to the CTI.

Step 3: Compare trends with region-specific census data

For comparison purposes, data from the 2021 Canadian Census were extracted to summarize information about the primary languages spoken most often at home for Ontario and regions supported by Ontario's 34 PHUs (11). Specifically, we focused on the number of single responses (i.e., the number of people who gave only one language) for the language spoken most often at home.

Step 4: Identify patterns and discrepancies

After completing steps 1 to 3, comparisons were made across data sources. Two primary questions helped identify patterns:

- Do the top languages requested for interpretation align with the language profiles (according to the 2021 Census) for regions contributing the most submissions to the program?
- Do changes in the top languages requested over time align with changes in which local PHUs were submitting a high volume of contacts?

Results

There were 972,625 calls to high-risk contacts over 21 months (May 14, 2020, to February 7, 2022) with fewer than 1% of calls requiring language interpretation support. Interpreters responded to 2,604 requests, totaling 38,518 interpretation minutes (**Table 1**). Overall, there were 50 different languages requested (Table 1). For the entire observation period, the top five languages were French, Arabic, Spanish, Punjabi and Mandarin, accounting for 69.2% of all interpretation minutes. Among the top five languages requested, median interpretation time varied from 7.0 minutes (French) to 13.5 minutes (Arabic), with IQRs ranging from a low of 4.0 minutes (French) to a high of 25.0 minutes (Arabic).

Table 1: Requests for language interpretation support during phone calls with high-risk contacts of COVID-19 cases supported by Public Health Ontario's Contact Tracing Initiative, May 14, 2020, to February 17, 2022

Language	Number of encounters	Cumulative minutes	Median (IQR)
Akan	2	15	7.5 (6.8–8.3)
Albanian	14	222	8.0 (4.3–16.8)
Amharic	3	43	16.0 (9.5–20.0)
Arabic	370	6,642	13.5 (7.0–25.0)
Bengali	3	49	20.0 (10.5–24.0)
Cantonese	73	1,166	13.0 (5.0–23.0)
Croatian	4	78	22.0 (12.3–29.3)
Czech	2	43	21.5 (20.8–22.3)
Dari	11	213	19.0 (11.0–23.0)
Estonian	1	5	N/A
Farsi	41	528	8.0 (5.0–17.0)
French	803	9,203	7.0 (4.0–16.0)
German	30	175	6.0 (4.0–7.8)
Greek	4	80	20.5 (9.3–31.3)
Gujarati	2	8	N/A
Hindi	53	768	10.0 (4.0–20.0)
Hungarian	9	132	7.0 (5.0–15.0)
Indonesian	2	54	27.0 (22.5–31.5)
Italian	27	322	10.0 (6.0–15.5)
Japanese	3	21	5.0 (5.0–8.0)
Karen	2	53	26.5 (19.3–33.8)
Khmer	1	18	N/A
Korean	24	456	15.5 (6.3–31.3)
Laotian	2	13	6.5 (4.8–8.3)
Mandarin	133	2,146	9.0 (5.0–20.0)
Nepali	5	90	18.0 (15.0–21.0)
Pashto	1	11	N/A
Polish	25	497	20.0 (10.0–24.0)
Portuguese	51	968	16.0 (7.5–25.5)
Punjabi	221	3,657	10.0 (5.0–22.0)
Rohingya	3	15	2 (1.5–7.0)
Romanian	1	69	N/A
Russian	10	167	14 (5.0–19.5)
Serbian	12	221	15 (11.3–25.0)
Shanghainese	1	10	N/A
Somali	27	379	9.0 (5.0–22.0)
Sorani	3	14	5 (4.0–5.5)
Spanish	316	5,009	13 (5.0–23.0)
Sudanese Arabic	2	53	26.5 (18.3–34.8)
Swahili	5	35	4.0 (4.0–12.0)
Tagalog	11	165	6.0 (5.0–24.0)
Taiwanese	1	5	N/A
Tamil	62	915	9.0 (5.0–23.0)
Telugu	2	9	4.5 (4.3–4.8)
Thai	16	409	17.0 (13.8–24.5)
Tigrigna/Tigrinya	42	810	12.5 (7.0–25.8)
Turkish	14	168	12.5 (5.3–14.8)
Ukrainian	10	163	16.0 (11.8–18.3)
Urdu	38	434	7.0 (4.0–14.8)
Vietnamese	106	1792	12.5 (4.0–23.0)
Total	2,604	38,518	10.0 (5.0–20.0)

Abbreviations: IQR, interquartile range; N/A, not applicable

We noted that overall time trends for language interpretation minutes aligned with trends in the volume of contacts submitted to the CTI, with some exceptions (**Figure 1**). For example, there were periods where the number of interpretation minutes was high relative to contacts submitted, including the period from January to July 2021.

We examined time trends to assess how the top requested languages for interpretation services changed over the observation period. Four periods of interest were identified to investigate further.

Observation 1: In September 2020, there was a rise in French language interpretation requests (**Figure 2**). The following local PHUs submitted approximately 94% of the contacts to the CTI during this month (number of contacts): Ottawa (n=1,204), Halton (n=710), Durham (n=666), York (n=509) and Niagara (n=346) (Table 1) (supplemental data available from the corresponding author). According to the 2021 Canadian Census,

Figure 1: High risk-contacts submitted to Public Health Ontario's COVID-19 Contact Tracing Initiative and language interpretation requests (in minutes), November 2020 to December 2021

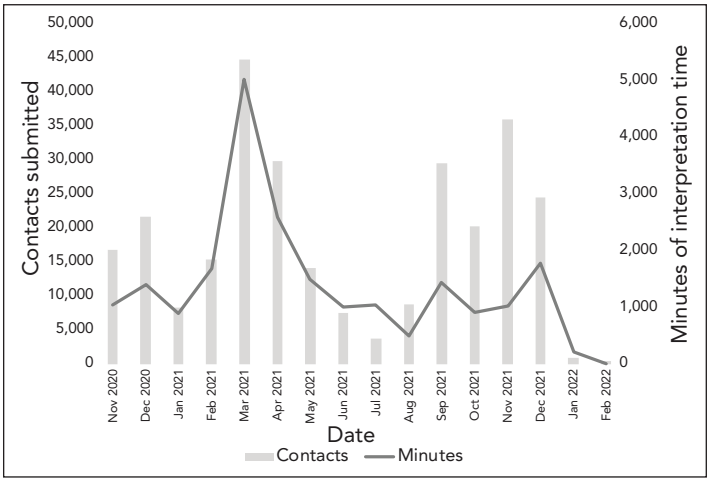
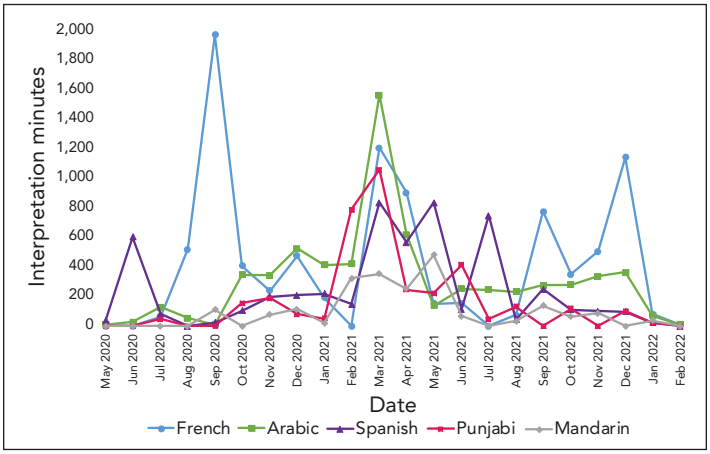


Figure 2: Language interpretation minutes for the top five requested languages over the study period



French was the most common non-English language spoken most often at home in Ottawa, accounting for approximately 40% of all non-English languages reported (supplemental data available from the corresponding author).

Observation 2: Arabic was the most common language requested for interpretation between November 2020 and March 2021 (Figure 2). The following PHUs submitted approximately 60% of the contacts in March 2021 (number of contacts): Durham (n=6,325), Peel (n=5,804), Sudbury & Districts (n=4,890), Halton (n=4,059), Hamilton (n=2,657) and Niagara (n=2,452) (supplemental data available from the corresponding author). Peel had the highest percentage of individuals reporting a non-official language spoken at home (33%) according to the 2021 Census (supplemental data available from the corresponding author). Punjabi was the most common language spoken at home in this region (32%), with Arabic coming in third (5.3%) (supplemental data available from the corresponding author).

Observation 3: In the early spring of 2020 (May 2020) and between March and July 2021, there was a rise in language interpretation requests for Spanish (Figure 2), with this language becoming predominant in the spring-summer period when Waterloo, Peel, Halton and Grey Bruce PHUs continued to submit high volumes of contacts (supplemental data available from the corresponding author). Halton and Waterloo regions also submitted high volumes of contacts in May 2020 (supplemental data available from the corresponding author). We noted that Spanish was not among the top three non-official languages spoken most often at home in these regions according to the 2021 Census.

Observation 4: In the final months of the program (September 2021 to December 2021), French became the predominant language requested for interpretation (Figure 2). This could be attributed to the sudden rise in submissions from Eastern Ontario and Sudbury & Districts (supplemental data available from the corresponding author). These PHUs have a large proportion of the population that speaks French most often at home (supplemental data available from the corresponding author). Public health units that submitted a high volume of contacts during these four months included (number of contacts): Durham (n=18,146), Waterloo (n=15,150), Niagara (n=12,363), Sudbury & Districts (n=8,236), Peel (n=6,437) and Eastern Ontario (n=6,159) (supplemental data available from the corresponding author).

Discussion

Interpreters provided over 38,500 minutes of interpretation services in 50 languages for the CTI. Some of the shifts in language predominance could be explained by changes in which local PHUs were submitting a high volume of contacts to the CTI and the associated language profiles of those communities.

There were two periods when the patterns in language interpretation requests could not be explained by examining which health units were driving submissions and their community's language profiles. The predominance of Arabic interpretation requests is an interesting finding that could represent the disproportionate impact of COVID-19 pandemic on Arabic-speaking communities. This observation is consistent with the findings of an analysis of race-based data collected by Ontario PHUs, where Middle Eastern communities experienced disproportionality high crude per capita rates of COVID-19 infection (9).

The increase in Spanish interpretation requests is another interesting finding as Spanish is not among the top three non-official languages spoken most often at home for the health unit regions that were driving submissions. This observation is consistent with the findings of the analysis of race-based data collected by Ontario PHUs, where Latino communities

in Ontario experienced the highest crude per capita rates of COVID-19 infection in Ontario (9). In the absence of systematic collection of race-based data, lack of concordance between language interpretation requests and a community's language profile could prompt further investigation to identify potential disproportionate impacts of disease that should be addressed.

Our work shows there is extreme variability between the average lengths of interpretation encounters. Interpretation is more than a direct translation. There is a need to incorporate cultural contexts and unique characteristics of the target language into scripts that were written in English. We believe this this is an important area for future study with opportunities to continue to build on work that aims to improve technology and training for effective communication that is mediated by an interpreter.

Strengths and limitations

Key strengths of this study were the novel use of administrative data for understanding public health communication needs and completeness of the data set spanning the full program duration. There are important limitations and caveats to the data available for this exploratory analysis that we made note of. Individual encounters could have involved calls to households with one or more persons or a proxy (e.g., parent for a child); therefore, we were unable to identify the number of unique contacts.

This was also an exploratory descriptive study with limitations in being able to control for potential confounding factors. The contacts supported by the CTI are a subset of high-risk contacts in Ontario that were submitted by PHUs based on program criteria, which changed over time in response to PHU needs and provincial policy directions. There will be a less accurate picture of interpretation needs during periods when there was a high volume of COVID-19 cases when some case and contact management activities were modified to prioritize other COVID-19 response activities.

The use of administrative billing data for requests for interpretation services from an external vendor may not fully capture all language interpretation needs. The need for interpretation services may not have always been requested by the contact or recognized by the interviewer. The effectiveness of training on accessing interpretation services and the consistency in which these services were recommended by interviewers was not assessed. It is important to further understand barriers to effective communication and other factors, including cultural preferences, to continue to improve language services and the overall delivery of public health information.

Conclusion

Public health agencies could benefit from using existing secondary data sources to understand the language interpretation needs of their communities. This study also demonstrated how existing data sources could be used to help assess how communities are being disproportionately affected by public health emergencies.

Authors' statement

AC — Methodology, formal analysis, interpretation, writing–original draft, writing–review & editing
MAC — Methodology, interpretation, writing–review & editing
JPH — Conceptualization, methodology, interpretation, writing–review & editing

The content and view expressed in this article are those of the authors and do not necessarily reflect those of the Government of Canada.

Competing interests

None

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