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Title: Lessons from the Covid-19 third wave in Canada: shifting demographics and the impact of variants of concern

Authors: Finlay A. McAlister MD MSc, Majid Nabipoor PhD, Anna Chu MHSc, Douglas S. Lee MD PhD, Lynora Saxinger MD, Jeffrey A. Bakal PhD; behalf of the CORONA Collaboration

Reviewer 1:
Name withheld — University in Canada, Medicine

Comments to the Author
RESEARCH articles must be sound, relevant, important and novel

Does the article contribute to what is already known on this topic?
The article adds to existing published literature about the risks of variants over wild-type SARS-CoV-2, specifically within the Canadian context. It also has the ability to add to the literature given use of confirmed cases from both the community and hospital settings. However, it does not contribute to knowledge around the severity of illness in vaccinated vs unvaccinated persons, something that is important to highlight the need for vaccination and to better understand how the disease will continue to affect the majority who are vaccinated.

Reply: Thank you for the kind words on the potential contribution of our work. At the time we originally did this analysis (August 2021) we did not have access to vaccination data but since then we were granted permission to use that data and thus have included information on outcomes in the third wave related to vaccination (note that in Canada waves 1 and 2 occurred before vaccine roll out which was initially very slow and thus we felt it best to restrict this analysis to our third wave data [after Feb 1, 2021]).

Does the background accurately represent current knowledge in this field?
Given the rapid evolution of literature in this field, I believe that there are additional published data in the literature and from government surveillance that corroborate the findings of this study.

Reply: Yes, this is a rapidly evolving field and we have updated our Introduction, Discussion, and reference list to incorporate 6 new studies from China, the US, Ontario, the UK, and Europe published since we submitted this paper.

Do the authors explain why they conducted the study?
Is there a clear research question?
The authors indicate that the Delta variant will rapidly become the dominant strain and phenotypic characterization is important. Unfortunately, since the time of writing I believe this has already come to fruition and, as mentioned above, there are additional publications and public data that already highlight the increased risk of severe/critical illness with the delta variant.

Reply: We agree that our fears that Delta would become the dominant strain did play out very rapidly, particularly in Alberta as our fourth wave (which happened from Sep-Dec) turned out to be larger than any of our prior waves. Unfortunately as there is a 2 month lag between collection of administrative data for hospitalizations and linkage with laboratory testing and vaccination data we were not able to include 4th wave data in this manuscript (indeed, the 4th wave is still occurring and may well last into the late winter or merge with an omicron-driven 5th wave).

Is the study design appropriate?
The use of administrative data for a retrospective cohort assessment is reasonable and informative, but the missing-ness of vaccination status severely affects the interpretation of outcomes in this analysis.

Reply: The silver lining from the 3 month timeframe for initial decision on this paper is it improved the strength of the paper as we finally obtained permission and access to the vaccination data in late November (a process that took over 5 months).

Are the methods described in enough detail? Did you find anything confusing?
The data acquisition, case definition, and outcomes are clearly explained with the exception of why crude and adjusted OR were not both reported.

Reply: As Table 3 already has 7 columns, we elected to present the adjusted ORs within each province as well as the pooled estimates for both provinces rather than the unadjusted ORs as we felt these would be less informative than the adjusted and then pooled values.

Are the results reasonable? Interesting? Novel?
The lack of stratification by vaccination status is a significant limitation and makes the interpretation of results less relevant to current COVID-19 patient and pandemic management.

Reply: Between the time we first submitted this paper to CMAJ (the analysis was completed in mid August) and now, we were finally able to obtain vaccination data in linkable form for both Ontario and Alberta and have now included that information in Tables 1, 2, and 3.

Is the interpretation supported by data in the results?
Yes, their interpretations are supported by both their data and similar published work that was also missing vaccination data.

Do tables and figures accurately represent the data? Would some other visual be more helpful?
The single table included in the manuscript is quite busy and difficult to interpret. There is also consistent mention of odd ratios throughout the text but no summary table for these outcomes that would greatly benefit the reader in terms of their ability to view important highlights of risk estimates from this population.

Reply: To improve clarity we elected to break the old Table 1 into Tables 1 (comparing demographics and outcomes for patients infected in waves 1, 2, and 3) and Table 2 (restricted only to wave 3 and comparing demographics and outcomes for patients infected with VOC vs. wild-type/original strain SARS-CoV-2). We have now put the relevant multivariable aOR results into a new Table 3 as per the reviewer suggestion.

Are any important limitations not mentioned?
None are readily apparent.

Did you spot any fatal flaws? That is, errors you do not believe the authors could overcome. Please explain clearly.
Vaccination status, as explained above.
Reply: As detailed above, we were now able to include vaccination status data in Tables 1, 2, and 3.

Is the topic relevant for CMAJ's clinical readers?
The topic is relevant but missing data limits the applicability to current management of COVID-19.

Reply: As outlined earlier, our ability to now include vaccination data we believe improves the impact of our paper.

Do the authors place their findings in the context of the literature?
Yes.

Reviewer 2
Name withheld — Taiwan

Comments to the Author
Thank you for the opportunity for me to review this paper. The cohort seems well-designed and analytic methods are appropriate. Canadian healthcare system has provided a very good linkage of healthcare datasets to identify all-cause hospitalizations or deaths within 30 days after a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction test from March 1, 2020 until June 30, 2021, with genomic confirmation of variants of concern (VOC).However I have the following suggestions:

1. First, I appreciate that the authors present the data in two of Canada's most populous provinces. While there have been several studies done in Europe, the Canadian experience with VOC has provided some view about differences in the epidemiology of infection and in vaccine roll-out across countries.
As the World Health Organization has recognized 4 variants of concern (VOC) for SARS-CoV-2 as they are more transmissible, I wonder if a table showing the difference between the current studies and the previous studies might help the readers get more from the current cohort study?

Reply: We have revised our Introduction and Discussion sections to incorporate information from the newly published studies.

2. The third wave of COVID-19 in Canada occurred between February and June 2021 and was driven by VOC, particularly Alpha (B.1.1.7) and emerging Delta (B.1.617) variants, with Gamma (P1) and Beta (B.1.351) largely seen only in returning travelers.
I wonder if a health policy change (by Canadian health authorities) had happened in comparison with the first two waves (such as vaccination eligibility criteria, ending isolation and precautions for People with COVID-19)? Do the authors consider this might have an impact on the outcomes?

Reply: The first and second waves of the pandemic in Canada occurred before vaccination became an option and yes there is no doubt that the various government mandated restrictions that changed through the pandemic and individual compliance with these had an influence on infection rates but that would be the topic for a different paper as in this paper we wanted to focus solely on changes in the features of those becoming infected and their outcomes. We have added the following limitation on page 12 to acknowledge the potential impact of such factors on who became infected in each wave: "We also cannot account for potential differences in uptake of public health guidance (particularly with respect to social distancing and masking guidelines) between different groups over the course of the pandemic.***"**

3. The authors find out that affected younger patients more than the first two waves.
Third wave patients were more likely to be hospitalized (aOR 1.57 [95%CI 1.46-1.70]), but had shorter lengths of stay (median 6 vs. 7 days)
However, it is difficult to exclude the possible confounders such as people's health habits change between the different periods.

Reply: Given this is an observational study we can only comment on changes in the features of those infected in the various pandemic waves and cannot account for changes in health and social distancing/masking habits between the different time periods. We have added this limitation to page 12.

We thank the editors of CMAJ and the reviewers for their helpful comments which helped improve our manuscript. Given the 3 month timeframe for the initial decision (during which time several similar studies were published in CMAJ and other journals), I hope a decision on this revision could be reached sooner please, particularly since I have consistently turned around request reviews from CMAJ within 1-2 weeks. All of my co-authors are aware of this resubmission and have agreed. Thank you for your consideration of our work.