

# **Critique of Mitchell *et al.* JAMA Publication on COVID-19 Patients in Canadian Hospitals**

**Produced by the Scientific and Medical Advisory Committee**

**This is a critical analysis of the article entitled: Trends in Severe Outcomes Among Adult and Pediatric Patients Hospitalized With COVID-19 in the Canadian Nosocomial Infection Surveillance Program, March 2020 to May 2022, by R. Mitchell, J. Cayen, N. Thampi, C. Frenette *et al.* JAMA Netw Open. 2023 Apr 3;6(4):e239050.**

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This recent article presents information from the **Canadian Nosocomial Infection Surveillance Program** (CNISP) regarding the impact of severe COVID-19 outcomes on the health care system almost a year earlier. The authors are primarily clinician scientists from the Public Health Agency of Canada, the Association of Medical Microbiology and Infectious Disease Canada, and sentinel hospitals.

The authors conclude that *“vaccination is important to reduce the burden on the Canadian health care system as well as severe outcomes associated with COVID-19.”*

This conclusion is based on the following results: *“Among 1 513 065 admissions, the proportion of adult (n = 51 679) and pediatric (n = 4035) patients hospitalized with laboratory-confirmed COVID-19 was highest in waves 5 and 6 of the pandemic compared with waves 1 to 4 (77.3 vs 24.7 per 1000 patient admissions).”* With waves 5 and 6 representing the Omicron waves and waves 1 to 4, representing the variants circulating from the beginning of the COVID-19 crisis until the first Omicron variants started circulating in December 2021. So, despite having one of the highest rates of COVID-19 vaccination in the world, Canada experienced 3-times more hospitalizations with the Omicron waves than during earlier waves, which include at least two waves when there were no COVID-19 vaccines, and the SARS-CoV-2 strains were more virulent. Naturally, this higher hospitalization rate in later waves could also be explained (at least in part) as the proportional reflection of a higher infection rate in the general population, especially since incidental positive PCR test were counted as COVID-19 cases by the authors. It may also reflect increased susceptibility to re-infection as a consequence of prior vaccination and negative efficacy.

The authors also state that *“the proportion of patients with positive test results for COVID-19 who were admitted to an ICU, received mechanical ventilation, received extracorporeal membrane oxygenation, and died were each significantly lower in waves 5 and 6 when compared with waves 1 through 4.”*

Remarkably, the authors note that *“the proportion of COVID-19–positive patients admitted to an ICU during waves 1 through 4 combined was 5.3 per 1000 patient admissions compared with 6.8 per 1000 patient admissions for waves 5 and 6.”* So, there was apparently no reduction of ICU admissions per 1000 patient admissions during a time (waves 5 & 6) when there was more natural immunity, more vaccine-induced immunity (>85% double or more vaccinated) and less deadly variants in circulation.

The authors also claim that *“Admission to the ICU and in-hospital all-cause death rates were significantly higher among those who were unvaccinated against COVID-19 when compared with*

*those who were fully vaccinated (incidence rate ratio, 4.3 and 3.9, respectively) or fully vaccinated with an additional dose (incidence rate ratio, 12.2 and 15.1, respectively).” Even if these differences are real, they are minor and of greater concern is the total number of people that were vaccinated that accounted for over 85% of the people that were hospitalized or dead with COVID-19 in 2022.*

The authors considered all-cause mortality as a severe outcome in relation to COVID-19 cases by vaccination status, which gives the advantage of capturing unequivocally the number of dead patients without delving into the specific causes of death. However, when discussing all-cause mortality in relation to an intervention status, there is an implicit weight put on the intervention as a determinant or contributing factor to the death. This is even more so, when the authors avoid all consideration of co-morbidities (either in number or severity) in relation to the intervention status. As readers, we wonder what if the non-vaccinated have a higher number or more severe comorbidities? Could these comorbidities outweigh the vaccination status in the analysis of severe outcomes?

In this article, the authors state/imply that the Health Care System is unduly suffering from an overwhelming number of COVID-19 patients who are occupying the hospitals’ beds and that, more specifically, the unvaccinated are mostly responsible for the substantial burden imposed to the health care system, even in later waves, with more benign variants circulating.

**Is the above claim unequivocally true? Is it possible to conclude that COVID-19 patients, and more so the unvaccinated ones, are to blame for the burden on the Health Care System, which is considered by the authors as extraordinary in magnitude?**

To assess the validity of the claim, there are some important considerations regarding the methodology used by the authors that should be highlighted:

- The study considers cases from mid-March 2020 to the end of May 2022, a total period of 26.5 months, which is very long and encompasses most of the COVID-19 crisis. However, the extent of COVID-19 cases prior to mid-March 2020 is not considered, because there was little PCR testing prior to this period that was possible. Consequently, it is unclear when wave 1 of the COVID-19 pandemic really started in Canada. There were already reports of COVID-19 in China in December of 2019.
- The number of admissions comprises 155 hospitals across Canada, but the information of the bed capacity/number of each one is not detailed. The authors omitted presenting the definition of hospital capacity, when a hospital is considered as working “over capacity”, how 2020-2021 compares with previous years, including years with winters dealing with higher

numbers of influenza (*e.g.*, winter of 2009), how frequently these networks of hospitals experience higher-than-normal admissions and in relation with which phenomena.

- Waves 1 to 4 extend between mid-March 2020 to the end of December 2021: period of 21.5 months, where various variants circulated, and the population was mostly unvaccinated during the first 2 waves and highly vaccinated during the last 2.
- Waves 5 and 6 extend between January 2022 and end of May 2022: period of 5 months dealing mainly with the Omicron variant.
- COVID-19 cases were defined as positive PCR tests, regardless of the clinical picture and reason of hospitalization.
- There are no details regarding the PCR protocol tests used in each of the 155 hospitals.
- Different age groups in the adult group were not considered, despite large differences in the severity and lethality of COVID-19 between the age groups.
- The number and type of comorbidities were not considered as part of the analysis.
- The overall degree of severity of COVID-19 that did not require admitting to an ICU was not compared between waves 1 to 4 and waves 5 and 6. Apparently, hospital cases in waves 5 and 6 were milder in general.
- The patients in the first 14 days post-1<sup>st</sup> dose were considered as unvaccinated or excluded for the severe outcome calculation.
- There is no consideration of natural immunity or infection pre-vaccination vs. infection post-vaccination.

The main problems with the methodology of this paper are:

- The authors chose to combine the data from waves 1 and 2 (with no vaccination) with the data from waves 3 and 4 (with partial or full vaccination of over 80% of the Canadian population). This is despite the authors noting that there was significant difference in the proportion of all-cause in-hospital deaths among adult patients between waves 1 and 2 and waves 3 and 4.
- In the calculations of the total number of patient admissions in each of the 6 waves, the numbers are very different, especially between wave 1 and wave 2. In general, the durations of the various waves were somewhat consistent during the first 6 waves (except the first wave that is missing the beginning of the wave). Why there are so many more hospitalizations in Wave 2 in total than Wave 1 (*i.e.*, a difference of 216,979), whereas the hospitalized cases with COVID-19 only increased by 10,141? Where did the extra 206,838 hospital cases without COVID-19 come from?

- COVID-19 cases are defined as PCR+, but it is unclear (not mentioned in the article) whether the protocol of PCR is validated as comparable across the 155 hospitals. Therefore, the number of PCR+ cases may have varied from hospital to hospital, depending on the number of amplification cycles used in each hospital/province, which determines the number of false+ detections.
- The number of PCR+ cases detected in each wave also depends on the number of patients tested, and the frequency of the testing, which may have varied by wave and by vaccination status (more frequent testing in later waves and in unvaccinated patients). This is a key limitation of the study, but it was not mentioned by the authors.
- The number of COVID-19 disease patients vs. COVID-19 incidental cases is not provided, but about half of hospital admissions with COVID-19 appear to be due to other co-morbidities.
- COVID-19 disease cases, which reflect patients with respiratory infections and a PCR+ test, should have been studied for other potential respiratory pathogens (*e.g.*, influenza, parainfluenza viruses, or bacterial infections: pneumococcus, klebsiella, *etc.*) to unequivocally adjudicate the respiratory clinical picture exclusively to SARS-CoV2. There is no mention of such procedural diagnosis in the article. If the ruling out of other infectious diseases was not systematically done, it is difficult to weigh the contribution of SARS-CoV2 to the clinical/symptomatic disease.
- There is no mention of the treatment protocol for COVID-19 patients with a respiratory symptomatic clinical picture, other than the need of mechanical ventilation, or extracorporeal membrane oxygenation. Did all patients receive similar drugs in equivalent doses (*e.g.*, corticosteroids, remdesivir, *etc.*) in all waves? This is highly unlikely, given that the period considered in the article is 26.5 months encompassing 6 waves. The consideration of the overall treatment protocol as a variable is relevant in any analysis considering health outcomes, however it was ignored by the authors.
- The authors claim that the inclusion of incidental COVID-19 admissions underestimates the proportion of severe COVID-19 cases. However, patients with non-COVID-19 severe diseases could easily overestimate the numbers of severe COVID-19. For example, (hypothetically) a congestive heart failure in ICU, with an incidental PCR+ test would be counted as a severe COVID-19 case, maybe even requiring ventilation (which is a potential occurrence in congestive decompensated heart failure patients), contributing to an overestimation more than an underestimation of severe COVID-19.
- Patients in the first 14 days post-first dose were excluded from the severe outcome analysis by vaccination status, but the authors do not justify this choice of analysis. Evidence from Alberta Health demonstrated increased risk for contraction of COVID-19 during this period.

Patients in this category should be counted as vaccinated and adjudicated to one of the outcomes.

- Analysis of severe outcome by vaccination status should consider the number and type of comorbidities, since comorbidities (many of them aggravated due to non-consultation during lockdown periods) may outweigh COVID-19 as a determinant factor of overload of the hospital. Also, patients with terminal pathologies may not be vaccinated due to their frailty and immune system status (*e.g.*, immunosuppressed or immunosenescent) or simply because they are too close to death. For example, (hypothetically) a grade IV glioblastoma in a non-vaccinated teenager with a PCR+ test who dies of the progression of the glioblastoma, could be adjudicated as a severe outcome of COVID-19 using the classification process of the authors, overestimating the cases considered severe.
- Analysis of severe outcome by vaccination status in the adult group seems to be corrected for age, but the data is not presented by smaller age brackets (*e.g.*, >80, 70-to-80, 60-to-70, etc.) which would inform about the type of patients representing the demand/overload in the hospitals. For example, the impact in terms of days of stay in the hospital of an 18-year-old (y.o.) person may be significantly different from that of an 80 y.o.
- Age interacting with number/type of comorbidities (age\*comorbidity) should be used as an interaction term in the statistical analysis of severe outcome by vaccination status, because it could weight more than vaccination status alone.
- The burden of cases affecting the hospitals is reported as Number-Cases/1000 admissions. But this information is not presented in relation to time, so when the authors report 24.7 COVID-19 hospitalizations per 1000 admissions in waves 1 to 4, this number of admissions is taking place during a period of 21.5 months in 155 different hospitals. The key question (not addressed by this article) is, how many cases each individual hospital had at a given week and which proportion of beds those cases occupied. This is the type of analysis that would help determine the real impact of these cases on the health care system.
- Doing an average calculation from the Table of the article, the total number of COVID-19 hospitalizations represent 3.5% of all admissions during a period of 26.5 months, distributed in 155 hospitals, which would translate into 13 cases per hospital per month, and 2 ICU cases and 1.2 deaths per hospital per month. These numbers include incidental PCR+ cases. Are these numbers reflective of a pandemic, and, what percentage of hospital beds were occupied by them so as to consider this as a significant strain in the Canadian health care system?
- Finally, there is no consideration of how many absent health care workers there were in each hospital during each wave, nor the reasons of the absences. Knowing the deficit of workers



per wave per hospital due to contact isolation policies in PCR- or + asymptomatic personnel would be beneficial in the analysis of impact on the health care system.

**In brief, considering the major methodological weaknesses, the authors' main claims cannot be considered as valid.**