Prior infection in an elderly vaccinated population increases the risk of a subsequent infection: An immunological paradox of the COVID-19 era

Ramirez, J.R. [1*], Breznik, J. A. [1-4]; Rahim, A. [5], Pasat, Z. [5,6], Bilaver, L. [1], Kajaks, T. [4-5]; Bramson, J.L. [1-3,7], Bowdish, D.M.[1-4,8]; Costa, A.[1,4-6,9]

* Presenter; ruizamj@mcmaster.ca

[1]Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, Ontario, Canada; [2]McMaster Immunology Research Centre, McMaster University, Hamilton, Ontario, Canada; [3]Michael G. DeGroote Institute for Infectious Disease Research, McMaster University, Hamilton, Ontario, Canada; [4]McMaster Institute for Research on Aging, McMaster University, Hamilton, Ontario, Canada; [5]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Canada; [6]Centre for Integrated Care, St. Joseph's Health System, Hamilton, Ontario, Canada; [7]Department of Biochemistry & Biomedical Sciences, McMaster University, Hamilton, Ontario, Canada; [8]Firestone Institute of Respiratory Health, St Joseph's Healthcare, Hamilton, Ontario, Canada; [9]Research Institute for Aging, Waterloo, Ontario, Canada

Background

- Reduced risk of reinfection has been observed for the Wuhan (ancestral), alpha, beta, delta, and the omicron BA.1 variants[1].
- Having a previous SARS-CoV-2 infection or hybrid immunity (vaccination + infection) provides superior protection in terms of magnitude and duration against omicron when compared against vaccination alone[2].
- 80% of the deaths due to COVID19 between 2020 and 2021 correspond to people aged 60 or more[3].

Objective

To examine the influence of past individual histories of infections and vaccination (including dose type) on Omicron BA.5 risk using adjusted time to event models.

Methods

We conducted a retrospective cohort study of 748 participants [5-7] of long-term care and retirement home residents with four mRNA vaccines. The analysis period corresponds to the exposure period defined below (Figure 1).

Definitions:

Infection: Positive nasopharyngeal RAT/PCR test

Exposure Period: July1st 2022 to Sept 13th 2022

Omicron BA.1/2 period: Dec 15th 2021 to July 1st 2022.

Outcome: An infection during the exposure period.

Time-to-event: Days between the start date and the minimum between the event date, the end date, or date of study withdrawal/death.

Hybrid immunity was defined as the following (mutually exclusive categories):

- One Omicron infection
- Multiple infections (More than one infection before the exposure start date.)
- One Pre-Omicron infection
- No prior infections (No documented infection prior to the exposure start date.)

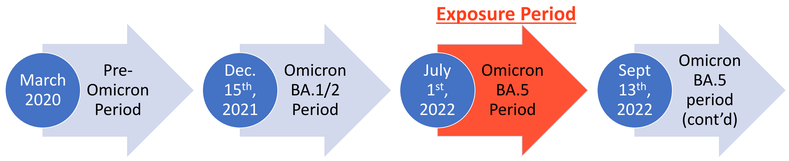


Figure 1: Exposure period timeline.

Differences in outcome were assessed by a χ^2 (proportions) and a Mann-Whitney U test (median). A Cox[4] regression model was used to estimate adjusted hazard ratios (HR) for having an Omicron BA.5 infection during the exposure period.

Results & Discussion

Figure 2 (right, below): Baseline characteristics of study participants, stratified by outcome status. Covariates from top: Hybrid Immunity, Sex, Vaccine Combination, Outbreaks, Days from the 4th dose to the start of the study, Type of Residence, Age.

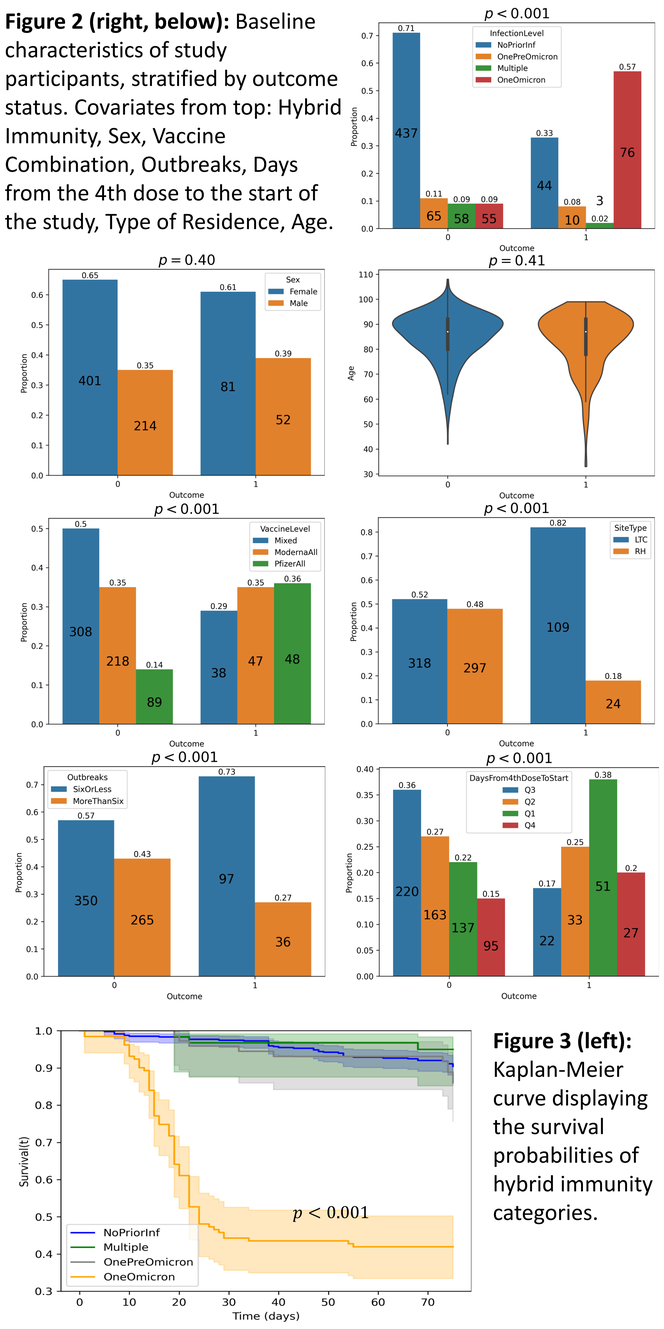


Figure 3 (left): Kaplan-Meier curve displaying the survival probabilities of hybrid immunity categories.

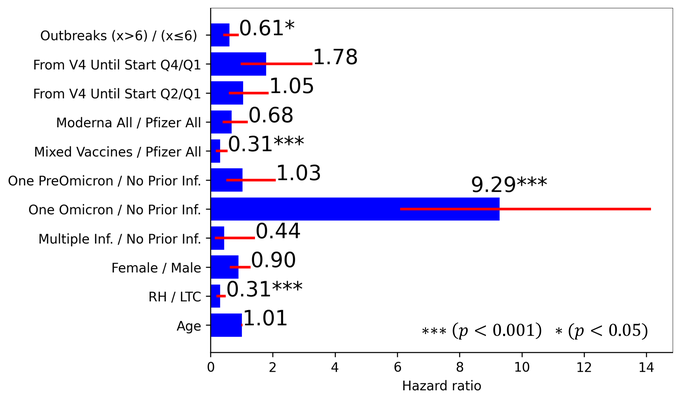


Figure 4 (left): Cox regression model examining the influence of hybrid immunity and vaccination (including dose type) on Omicron BA.5 risk.

Table 1 (below): Hazard ratios for regression analysis with alternative hybrid immunity classification.

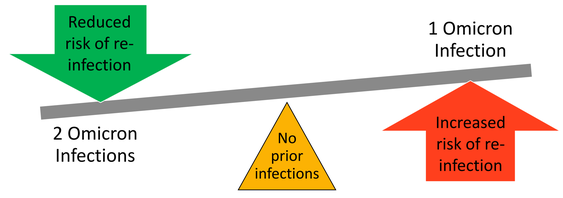
	Alternative Hybrid Immunity Classification	HR	HR lower 95%	HR upper 95%	p-value
	Multiple Inf. vs. No Inf.	0.57	0.08	4.16	0.58
1	**Only Omicron vs. No Inf.**	**6.63**	**4.38**	**10.04**	**p<0.001**
	Only Pre-Omicron vs. No Inf.	1.03	0.53	2.00	0.93
	Only Omicron vs. No Inf.	**5.47**	**3.66**	**8.19**	**p<0.001**
2	1 Pre-Omicron vs. No Inf.	1.08	0.53	2.20	0.82
	2 Pre-Omicron vs. No Inf.	1.00	0.23	4.29	0.99
	Only Pre-Omicron vs. No Inf.	0.96	0.51	1.82	0.90
3	**1 Omicron vs. No Inf.**	**9.27**	**6.08**	**14.13**	**p<0.001**
	2 Omicron vs. No Inf.	0.00	0.00	-	-

$$\text{Concordance} = \frac{\text{concordant}}{\text{comparable}} = \frac{T_i < T_j \Rightarrow \hat{h}_j < \hat{h}_i}{T_i < T_j \Rightarrow E_i = 1} = 0.81$$

Equation 1 (above): Concordance value of the Cox regression model.

Conclusion

- Individuals who had one omicron infection have nine times the risk of getting infected with omicron BA.5 during the exposure period with respect to those that did not have infections. In other words, having one omicron infection is riskier than having no infections at all.
- Interestingly, having two omicron infections reduces the risk of a future omicron BA.5 infection.



***Although two Omicron infections reduces risk of re-infection, it is important to note that vaccination is the most recommended form of protective immunity. There are potentially serious consequences to SARS-CoV-2 infection.**

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