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Omicron variant

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# Determinants of reinfection with SARS-CoV-2 Omicron variant

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Dear Editor,

We read with interest the study published by Camacho *et al* in the *Journal of infection* showing that individuals who were vaccinated prior to SARS-CoV-2 infection displayed lower neutralizing antibody titers against both Wuhan-Hu-1 and Omicron BA.4/5 variants than individuals who were vaccinated after experiencing SARS-CoV-2 infection irrespective of when SARS-CoV-2 infection was documented [1]. These findings could imply that vaccination after infection provided better protection against Omicron variant

reinfection than vaccination before first infection. Nevertheless, a recent study that addressed the magnitude of protection conferred by previous infection against Omicron variant reinfection found that both previous infection (alone or combined with previous vaccination) conferred rapidly waning protection against reinfection with the omicron variant [2]. Nonetheless, it remains undetermined whether in "real world" setting the timing of vaccination, before or after first SARS-CoV-2 infection, had an impact on risk of Omicron variant reinfection. To address that, we used nationally collected databases of Clalit health services on documented SARS-CoV-2 infections to study reinfection patterns and factors associated with Omicron reinfection. The study period extended from March 2020 to March 2022. SARS-CoV-2 reinfection was defined as two positive PCR tests or rapid antigen test > 90 days apart. We obtained clinical and epidemiological data including background comorbidities, hospital admission due to COVID-19-related illness, vaccination status against COVID-19, and number of vaccine doses. For the purposes of the study, the cohort was stratified into several groups: i) those who were never vaccinated (NV) ii) those who were vaccinated only after their first infection, referred to as "vaccinated after infection" (VAI) and iii) those who were vaccinated and still got infected at least once, referred to as "vaccinated before infection" (VBI). The vaccinated participants were further divided into: a) partially vaccinated (one vaccine dose); b) fully vaccinated (i.e. two vaccine doses); c) those who received boosters (one or more). Overall, the stratification strategy led to the formation of several groups, each reflecting a distinct epidemiological status in the population, as observed at the end of the study period.

Over a 26-month period 69,370 individuals (5.3%) were reinfected at least once among 1,310,083 documented SARS-CoV-2 infections. Overall, 15,072 (1.1%) people died during the study period but their death could not be specifically linked to COVID complications and were therefore excluded from the main analysis (see supplementary Table S1 for characteristics of the deceased). This study analyzed 1,295,011 SARS-CoV-2 survivors, i.e. people who were infected at least once and survived. Baseline characteristics of documented SARS-CoV-2 infections and reinfections (survivors only) during the study period are shown in supplementary Table S2. Three sequential analysis were carried out. The first showed that vaccination status at time of reinfection was the main factor impacting cumulative hazard of reinfection. At the conclusion of the study period, the cumulative hazard rate for the VBI group was 0.071, meaning that 7.1% of people who are vaccinated before first infection were expected to experience reinfection. In comparison, the expected reinfection rates for the NV group and the VAI groups were 14.0% and 13.5%, respectively. Taking age and health status into account, the NV group had the highest risk of reinfection, while the VBI group had the lowest risk (supplementary Figure S1). Hazard ratios (Cox model) for reinfection among people < 50 years were lowest among those who were healthy and vaccinated before index infection (VBI-healthy) (OR = 0.40, 95% CI; 0.37 – 0.43). However, for those who were vaccinated after index infection and without comorbidities (VAI-healthy) the odds for reinfection was 0.78 (95% CI; 0.73-0.83). The impact of comorbidities on odds of reinfection among the two vaccinated groups, VAI and VBI, was relatively minor (VAI; OR: 0.78 → 0.82, VBI; OR: 0.40 → 0.42) (supplementary Figure S2).

Second, we determined the number of individuals at risk for a second infection during the Omicron surge by determining incidence of reinfection; number of those eventually reinfected divided by number at risk of reinfection for each day from December 15, 2021 till end of March 2022. The data was updated daily until March 31, 2022 (i.e. determined who were reinfected and who remained at risk of reinfection). We found that reinfection incidence during the Omicron surge was higher among those above 50 years old compared to those under 50 (Figure 1). Full Vaccination before index infection (with or without booster doses) was associated with the lowest incidence rates of reinfection during the Omicron surge. People (> 50 years) who were vaccinated after index infection (1 or more vaccine doses) had fewer reinfections than those never vaccinated or partially vaccinated before index infection. Reinfection incidence rates based on health status resulted in similar observations (Figure 1).

Finally we determined the impact of time from last vaccination (or first infection for the NV group) on risk of reinfection. We used the time frame of 0-180 days as a reference and analyzed the data using two cohorts; old (> 50 years) with comorbidities, young (< 50 years) and healthy. Hazard ratios for reinfection were highest among those who were vaccinated (or infected) > 180 days in both cohorts (OR=2.3, 95% CI; 2.19-2.41) and (OR=2.1, 95% CI; 2.09-2.19), respectively (Figure 2).

Our findings showed that the most important factor determining risk of Omicron reinfection was time since last vaccination or last infection. These findings were consistent among both age groups (under and above 50 years of age) and comorbid status. The seemingly higher risk of Omicron reinfection

among people who were vaccinated after index infection, compared to those vaccinated before index infection, is likely due to the fact that members belonging to this group experienced their first infection early in the epidemic (see supplementary Figure S3) and with time their risk of reinfection gradually increased. These results are consistent with recent publications addressing the waning immunity of previous infection, with or without vaccination, as the most important factor affecting risk of Omicron variant reinfection [2-4].

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### **Declaration of Competing Interest**

Nothing to declare.

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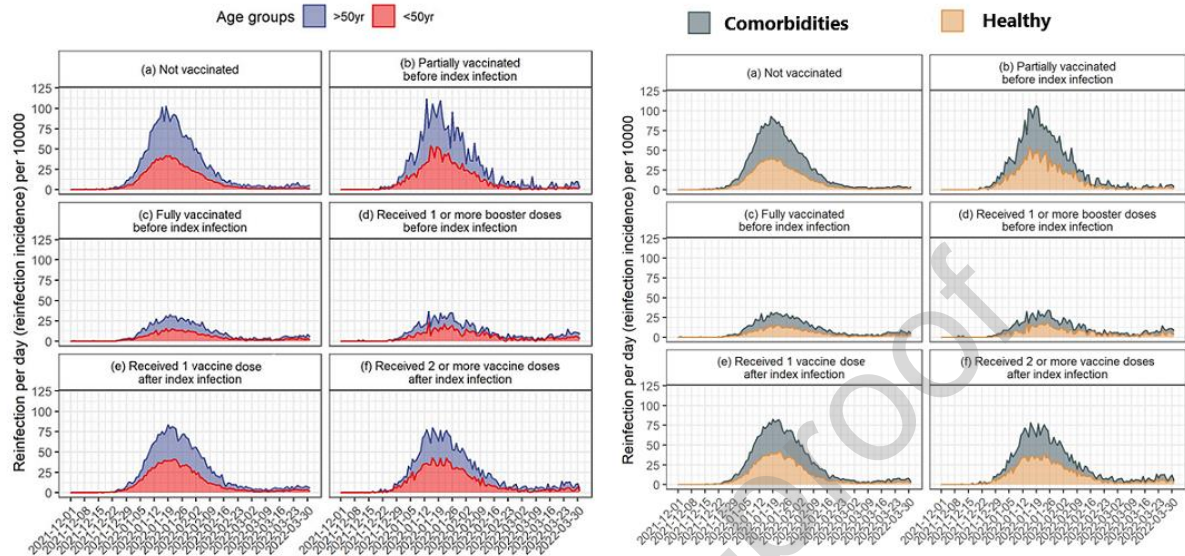
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### **Supplementary materials**

Supplementary material associated with this article can be found in the online version at:



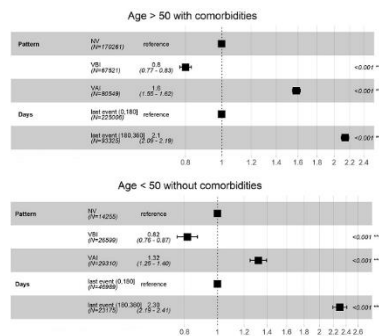
## Legends for figures



**Figure 1: Reinfection per day per 10,000 patients (daily incidence rate) during the Omicron surge based on age, vaccination status, and health status.**

On the X axis time period, from 01.12.2021 (an arbitrary date shortly before the beginning of the Omicron surge) to the end of the study period (30.3.2022). Different color shades represent people younger than 50 years and older than 50 years.

Reinfection incidence rates for non-vaccinated (NV) are shown in (a), for vaccinated before index infection (VBI) are shown in (b), (c), (d), and for vaccinated after index infection (VAI) are shown in (e) and (f).



**Figure 2: Multivariate analysis of hazard ratios for reinfection based on vaccination status and time from last vaccination or infection.**

Cox model results for four independent factors: age (< 50 yrs. vs. > 50 yrs.), comorbidities (healthy vs. > 1 comorbidities), vaccination status (NV; never vaccinated, VBI vaccinated before index infection, VAI; vaccinated after index infection), and time from last vaccination or infection. Two sets are shown; > 50 years of age with comorbidities and < 50 years without comorbidities.

**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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